Now on to this weeks discussion. As usual I will discuss a case that a Lipidaholic sent to me for analysis. Once that is out of the way I am issuing a "rant" on the idiotic terms that we must now bury, namely good or bad cholesterol. When I hear TV adds talk about good and bad cholesterol my head feels like exploding. Read on! And as you read try and figure out if the patient below has a good or bad cholesterol problem

I received the following questions from a respected clinician (lipidologist) regarding a case. My comments are in bold face

Hello Tom: I thought it would be nice for you to hear how your teachings do not fall on deaf ears. This is a classic case of what you always talk about. The patient is a 65 y/o patient who was seen for risk evaluation. His concern was that he had a brother with CABG at age 67. The patient with a sedentary lifestyle has the following vitals: BP 122/84, BMI 27.

Original lipid profile -

TC = 187, LDL-C = 137, HDL-C = 35, Trig = 73. Non HDL-C = 152

Glucose = 99, HgbAIC is 5.4%. I did a coronary calcium score which was 167 putting him into the 69th % by MESA tables. The goal was to get his LDL-C < 70, especially since his LDL-C was somewhat low to start. On Crestor 10mg daily and Zetia 10mg three times a week (for cost reasons), and a low glycemic index, high fiber Mediterranean diet, his most recent lipids were as follows

TC = 110, LDL-C = 56, HDL-C = 42, and Triglycerides = 59. VLDL-C = 11.8
Non-HDL-C = 68 TC/HDL-C = 2.6 TG/HDL-C = 1.4

Every other day ezetimibe (Zetia), although off label, is pretty efficacious because it has a 48 hr hepatobiliary recirculation and in clinical trials 5 mg every other day was pretty efficacious at improving lipid concentrations.

I thought this looked pretty good, but told him we needed to do an NMR to make sure his LDL-P was at goal. Now this is when I decided that you walked on water. In the old days, I would have said that with his TG being that low, he is not going to have an excess of small LDL particles, and so his LDL-P is most likely at goal.

Once again proving my mantra that <u>even skilled lipidologists</u> cannot predict lipoprotein parameters with any serious degree of accuracy.

The LipoScience (we are just getting hooked up with HD Lab) numbers:

TC = 93, LDL-C = 49, HDL-C = 37, TG = 34.
LDL-P = 1230 nmol/L
Small LDL-P = 1063 nmol/L
LDL size is 19.6 (pattern B).
Total HDL-P = 35.3 umol/L (75th %)

HDL size 8.6 nm (very small),
Large HDL-P = 2.2 umol/L (very low)
Large VLDL-P <0.7 nmol/L (normal)

My interpretation (after the surprise resolved) was that his LDL's were primarily small and therefore not being cleared appropriately by the liver LDL-receptors (because of their size). Instead of just pushing on with the statin, I opted to start niacin with instructions to titrate up to 2000mg per day.

I assume you were surprised because the TG was perfect but the particles were still quite small. Yet overall you had good thinking, because the cholesterol-depleted LDLs are the result of statin therapy. It takes a lot of cholesterol-depleted LDLs to traffic even low levels of LDL-C. That is why statins lower LDL-C fare better than they due LDL-P. Cromwell demonstrated this nicely in the FOS paper. (Journal of Clinical Lipidology 2007;1:583–592).

The thought is this will increase the LDL particle size, and may result in better clearing of the LDL particles with resultant drop in LDL-P, hopefully to goal (<1000).

That is the hope: but like everything else in therapeutic medicine it does not always work and there can be individual differences in response to therapies.

I'm not sure that the niacin will improve HDL size in this case since the VLDL particles are nearly nonexistent so CETP inhibition and hepatic lipase inhibition may not do much to increase the particle size.

We are also learning that CETP activity can be present at previously considered normal TG levels. Lipoprotein remodeling with exchange of core lipids is apparently a normal physiologic process to balance lipids. So the statin-induced CE deficient LDLs attract TG.
What is interesting is that he has an adequate number of HDL particles so it doesn't really matter. Now if LDL-P doesn't drop with this plan, then I can increase the statin, but with that many small LDL-P I think the statin response might be blunted, and therefore difficult to get to goal.

Correct: But beware: the few additional LDL receptors you get with statin titration may have a hard time recognizing and clearing the small LDLs with their reconfigured apoB. Also it is now being recognized increasing statin or adding Zetia to the statin increases proprotein convertase subtilisin kexin type 9 (PSCK9) activity which would also blunt additional LDL clearing. PCSK9 is a protease that carbolizes LDL receptors (LDLr). With less PCSK9 there are more LDL receptors and vice versa. That is why most of the statin apoB reduction occurs with the lower statin dose and much less with subsequent increases (i.e. as the statin causes more an more upregulation of LDLr, their half life decreases: so the more LDLr are upregulated, they are far more rapidly catabolized by PCSK9). You will get far

more apoB (LDL-P) reduction by adding ezetimibe to a statin than doubling a statin dose.

Questions: 1. Am I wrong with my concept of the niacin response regarding the LDL and the HDL? Will it increase the LDL size?

Responses are very individual, but in the majority one would expect it to do both. Niacin by inhibiting TG synthesis through many mechanisms reduces VLDL-apoB or VLDL-P production. It also inhibits CETP and thus the LDLs and HDLs stay larger. Niacin also effects HDL size via multiple other mechanisms including ABCA1 lipidation and hepatic lipase inhibition.

What about the HDL size?

One should not really care about on therapy HDL size as various therapies can cause very different types of HDL remodeling and be very efficacious. I simply try to keep HDL-P levels adequate (sometimes not easy). As you know we have no HDL functionality assays. Niacin because of CETP inhibition and hepatic lipase inhibition will typically increase HDL size: but some of that is TG-dependent.

2. In this type of patient is the mechanism for small LDL the same as for small HDL? In other words, are they both the result of excessive CETP and HL action which seems unlikely in view of the minimal amount of VLDL particles?

Some of the MOA is the same (as you describe), but a lot is not. HDL remodeling is also much more susceptible than are LDLs to endothelial lipase and perhaps other secretory lipases. ApoA-I is also subject to renal excretion via the megalin and cubilin pathways: LDLs are not. ApoA-I remodeling is very dependent on apoE content: LDLs, since they do not carry apoE are not. Since we cannot assay most of these, it is a very difficult exercise to explain HDL size change in specific individuals and what they mean. Because of little evidence based marketing, docs put way to much emphasis on LDL and for sure HDL sizes.

Or is the LDL small since the cholesterol pool is small so the LDL composition has been altered by the liver,

As discussed above, that is certainly possible: When TG are so low, livers may make very few VLDLs (and those made are less lipidated and small: they have less TG to exchange via CETP. Such livers also make IDLs and some have speculated even LDL sized particles.

and the HDL is small because of reduced lipidation by the liver and enterocyte due to a low cholesterol pool and reduced fat intake?

Again this is complicated and related to genes, but HDL lipidation is related more to apoA-I concentration and hepatic ABCA1 expression than hepatic cholesterol pools.

ABCA1 upregulation is regulated by the nuclear transcription factor called the liver X receptor (LXR) and depleted hepatic cholesterol pools would reduce LXR activity and expression of both ABCA1 and bile acid synthesis (which would both result in the liver maintaining its cholesterol)

DAYSPRING DISCUSSION:

In addition to the comments made above I want to rant a bit about cholesterol. In the above patient the original lipid profile was TC = 187, LDL-C = 137, HDL-C = 35, Trig = 73, Non HDL-C = 152 (all in mg/dL). Of these cholesterol measurements, which were indicative of either endogenously or exogenously produced cholesterol and which represents either good and/or bad cholesterol? My guess is the bad cholesterol, defined as that existing in his plaque is not measurable using any serum test: one would have to strip all plaque from his arteries and measuring it.

One of the joys of being a physician is to realize much of what we learned early in our career was nonsense. As research continues we discover new facts that either support previous believes or refute them. For instance despite what was previously taught, we now know reverse cholesterol transport is not all about HDLs, but just as much LDL mediated as HDL. We now know HDLs acquire most of their cholesterol from the liver, not peripheral tissues and they bring it elsewhere, not back to the liver per se. Who knew the intestine was just as important in lipid homeostasis as is the liver. So what about the concept of good and bad cholesterol. In fact there is nothing more asinine than to refer to cholesterol with those adjectives.

Cholesterol is a 27 carbon molecule that is absolutely required for human life, so how bad can it be? Without cholesterol there are no cell membranes, no lipoproteins, no steroidal hormones including vitamin D, no bile acids, or in other words without cholesterol there are a lot of dead people. However the cholesterol measurable in the plasma has little real reflection of total body cholesterol stores. Persons with hypobetalipoproteinemia might have an LDL-C of 10 -15mg/dL and lead long and healthy lives which no clinical cholesterol deficiency problems. Many members of the animal kingdom have very low LDL-C values. In the Get with the Guidelines Study 18% of people with CAD issues had an LDL-C < 70 mg/dL (bad cholesterol?), some as low as 20-40 mg. Cholesterol is so crucial that not only does every cell in the body have the power to manufacture it de novo, the proximal small bowel can absorb it. Indeed the average person absorbs into the enterocyte about 50% of the intestinal cholesterol and noncholesterol sterols that present at its microvilli brush border. So therefore is all cholesterol good? Well the answer is yes if all of the cholesterol is put to use in the functions described above. However as the editor of the American Journal of Cardiology (Bill Roberts) recently stated in an editorial - "It is the cholesterol stupid!" (Am J Cardiol 2010;106:1364–1366). By that he meant there is no atherogenesis without cholesterol build up in arteries. So I guess any cholesterol that is diverted to plaque is indeed "bad." Typically and those TV commercials have implied LDL-cholesterol (LDL-C) is bad and HDL-cholesterol (HDL-C) is good. Unfortunately a lot of clinicians repeat that nonsense to their patients. It has to stop. Please follow me closely:

Cholesterol is trafficked within plasma as a passenger in a protein enwrapped particle called a lipoprotein, which are classified by their buoyancy in a centrifuge tube (very low density, intermediate density, low density or high density). Particle density depends on the weight of the lipids and protein each particle has (proteins being heavier than lipids. Also within any lipoprotein class, the smaller particles are always denser than the larger so it is very redundant to call a particle small and dense. There is no difference between a small or a dense LDL and thus no need to call it a small, dense LDL. Lipoproteins can also be classified by the apolipoproteins on their surface. HDLs have apolipoprotein A-I (apoA-I) and chylomicrons, VLDLs, IDLs and LDLs contain a single apolipoprotein B (apoB) molecule. Hence the terms beta and alpha lipoproteins.

Definitions:

Total cholesterol is the sum of the cholesterol trafficked within all of the lipoproteins per deciliter (100 cc) of plasma. In the US it is reported in mg/dL and elsewhere in mols/L. In reality:

TC = chylomicron-C + VLDL-C + IDL-C + LDL-C + HDL-C
LDL-C actually is IDL-C + LDL-C
VLDL-C is typically calculated as TG/5
LDL-C is typically calculated as TC - [HDL-C + VLDL-C]
TC = VLDL-C + IDL-C + LDL-C + HDL-C (no chylomicrons are present if fasting)

So is total cholesterol bad or good? Likewise are the "parts" VLDL-C, LDL-C or HDL-C trafficking good or bad cholesterol. How about this question: some speak of cholesterol or even lipids as endogenous (produced in the body cells) or exogenous (absorbed fro the jejunum), presumably from eaten sources. Off the top of your head do intestinally produced chylomicrons only carry exogenous (eaten) cholesterol? Do LDLs only carry endogenously produced cholesterol? Where the heck do HDLs acquire their cholesterol? In fact as much as 30% of the cholesterol within HDLs is from enterocytes.

Let's say someone eats cholesterol or cholesteryl ester (which will be de-esterified in the intestine): this would be considered as exogenous cholesterol. It will rapidly make its way to the jejunum and enters bile acid enwrapped "intestinal lipid transportation vehicles" called biliary micelles: micelles also carry noncholesterol sterols, fatty acids, monoacylglycerol and phospholipids. The micelles make their way to the enterocyte microvilli where delipidation and sterol absorption via the Niemann Pick C1 like 1 protein (membrane sterol influx transporter) occurs. Typically 50% of the sterols are absorbed into the enterocyte. Noncholesterol sterols are returned to the intestinal lumen via the ATP binding casette transporters G5 and G8 (ABCG5, ABCG8). Most of the free cholesterol in the enterocyte will be esterified by the enzyme ACAT and become cholesteryl ester (cholesterol to which a long chain fatty acid is attached) and incorporated with TG and phospholipid into chylomicron particles. So is all of the CE in chylos from the diet? In fact only a very small portion is. The enterocytes can also transfer cholesterol into unlipidated apoA-I or prebeta HDLs vis the ABCA1 transporter.

About 85% of the cholesterol in the gut awaiting absorption derives from the hepatobiliary system. Excess systemic cholesterol makes its way back to the liver via direct or indirect RCT and of course the liver synthesizes plenty of cholesterol. The vast majority of that cholesterol is endogenously produced. Much of it is excreted via hepatobiliary ABCG5, ABCG8 into the bile or converted to bole acids which enter the bile via ABCB11 (bile salt export transporter). Ultimately those sterols make their way to the gut. So after a meal (gall bladder contraction and evacuation) the vast majority of the cholesterol in the gut is of endogenous not exogenous origin. So despite what almost everyone thinks the vast majority if the cholesterol within a chylomicron is of endogenous origin not exogenous. However some small amount is exogenous. Is the cholesterol in chylomicrons good or bad? That will depend on where the chylomicron brings the cholesterol.

At the liver the cholesterol pool is derived from endogenous production (by hepatocytes or acquired from peripheral cells and delivered to the liver in VLDLs, IDLs, LDLs and HDLs. However some exogenous cholesterol makes its way to the liver in chylomicron remnants. Some of the cholesterol returned to the liver in HDLs might be of intestinal origin. What does the liver do with all that cholesterol?

1) Secretes it to the bile
2) Coverts it to a bile acid which enters the bile
3) Lipidates (using the ABCA1 efflux transporter) small HDL particles
4) Uses it in hepatocyte cell membranes
5) Incorporates it into VLDL particles which are excreted into plasma

So is the cholesterol that enters HDLs (the majority of cholesterol within HDLs is of hepatic origin) and VLDLs of exogenous or endogenous origin? Well most is endogenous but some could be exogenous. Under physiologic conditions the VLDLs deliver TG to muscles (where the FA are used for energy) or to adipocytes (where FA are stored as TG for future energy needs) and become IDLs which are rapidly cleared by hepatic LDL receptors. Some (~30-40%) of IDLs are converted to LDLs which hang around few a few days before they are cleared by hepatic LDLr. A few LDLs may deliver some cholesterol to peripheral tissues but the majority of our cells endogenously produce all of the cholesterol they need and hence do not require cholesterol delivery. That explains why folks with very low LDL-C have no difficulties: most cells don not require cholesterol delivery. Of course as the LDLs hang around for several days they acquire CE from HDL particles via CETP exchange of TG for CE. Therefore although not commonly appreciated a large amount if not the majority of CE within LDLs had an HDL origin. Where did the HDL get its cholesterol: as mentioned above, mostly hepatocytes, but also enterocytes, some from peripheral cells including arterial wall sterol-laden macrophages (foam cells). So in reality we have no clue how much of the cholesterol within our HDLs is of endogenous or exogenous origin. Likewise we have no clue what percentage of the cholesterol in our LDLs is of what origin. The CETP mediated exchange of lipid between lipoproteins is complex:

Chylos exchange TG for CE with IDLs, LDLs and HDLs
VLDLs exchange TG for CE with IDLs, LDLs and HDLs
HDLs exchange TG for CE with each other (small and big HDLs)

The point is that lipoproteins carry lipids including CE which are being exchanged all day long and thus endogenous and exogenous cholesterol becomes completely mixed. Thus it makes no sense whatsoever to talk about endogenous or exogenous cholesterol. However which cholesterol is good and which is bad?

If a lipoprotein traffics its cholesterol into the arterial wall and that cholesterol becomes part of a plaque, I guess that is bad. But if cholesterol enters a cell membrane, becomes a steroid or a bile salt or is excreted in a bowel movement, that I would presume is good! So what particles carry cholesterol to where it might do good. The answer is all of them. Which particles carry cholesterol to the artery where it will do harm? The answer is all of them if you realize HDLs transfer some cholesterol to an LDL which can bring it to the artery. If you look at a given HDL-C value, how much of that might be transferred to an LDL and wind up in an artery? I think I just taught you that all of the cholesterol in HDLs is not destined to wind up where it will not harm you

Chylos, VLDLs, IDLs and LDLs if present in physiologic concentrations take most of their cholesterol to the liver where it can be used or excreted into bile in one form or another (cholesterol or bile acid). LDLs might deliver a tiny amount of the cholesterol they carry to some cells that need it. All of that LDL-cholesterol would be good. So only a moron would say LDLs carry only bad cholesterol. But wait, if an apoB containing chylo, VLDL, IDL or LDL entered the artery wall, then the cholesterol they carry would indeed be very bad! But it is particle number that drives them into the artery, not particle cholesterol content. But even in patients with very high VLDL-P and LDL-P some LDLs are being cleared by the liver. So I guess in those patients with elevated LDL-P some of the cholesterol is good and some bad???

HDLs after filling up (lipidating) in the various places mentioned above take their cholesterol to the adrenal cortex, gonads, adipocytes, liver or intestine: that would seemingly be good. So HDL-C is good? Wait - what if the HDL transferred its cholesterol via CETP to an apoB containing LDL, IDL, VLDL or chylo and those particles wet into an artery. Then in effect the cholesterol an apoB particle acquired from an HDL is in effect bad! If your adrenal cortex just produced a corticosteroid molecule, did it make it using endogenous or exogenous cholesterol? You have no clue! Did the HDL that delivered the cholesterol to the adrenal cortex acquire that cholesterol from the liver, intestine or an artery wall? You have no clue, do you?

Are you ready to scream yet? We literally have several quadrillions of lipoproteins in our plasma that exist anywhere from minutes, to hours to days. As they float around they are constantly exchanging their core lipids. No one has any idea in an individual patient what percentage of the cholesterol within any lipoprotein is of endogenous or exogenous origin and what percent might be good (serving a useful purpose) or bad (entering a plaque). So can we please retire the concept of good and bad

cholesterol once and forever and stop confusing ourselves and out patients. I believe Tim Russert is still dead with his good and "at goal" cholesterol level in the 60s mg/dL range. Can that dope in the TV commercials stop talking about good and bad cholesterol. Bill Roberts was right, it is the cholesterol stupid: but he is too smart to use useless terms like good and bad cholesterol. His editorial did not state It's the Bad cholesterol stupid." All he meant is you cannot have atherosclerosis without cholesterol in your artery. Dean Ornish showed a long time ago in his angiographic studies that if we simply and dramatically lower TC, plaque improves, even though HDL-C sometime drops big time. Thus Dean Ornish saved lives by reducing "good" cholesterol! Or one might say the folks experiencing torcetrapib related mortality sure had a lot of "good" cholesterol or maybe we should just avoid such silly terms.

Moral of the story: (take home points)

1) Every lipoprotein carries free and esterified cholesterol: most of the cholesterol they carry is endogenously produced but ALL carry some exogenously sourced cholesterol

2) All lipoproteins are constantly exchanging their core and surface lipid content

3) Chylomicrons and HDLs lipidate at the jejunal enterocyte

4) HDLs lipidate mostly at the liver and intestine but also a bit from peripheral cells including the artery wall.

5) The cholesterol removed from the arteries (macrophage RCT) does not contribute to serum HDL-C levels. Such cholesterol in the HDL could wind up at the adrenal gland, gonads, liver, intestine or given to an apoB particle which can return in to the liver or redeposit it in the artery wall!

6) As much as half of the cholesterol in LDLs originated from HDLs

7) No cholesterol measurement has any relationship to the complex reverse cholesterol transport system.

8) Much of the cholesterol in all lipoproteins is good: meaning going to peripheral cells (especially steroidogenic tissues) or intestine or liver. Some could be "bad" meaning going to the artery wall. **NO** clinician has a clue on whether any of that "bad" cholesterol is of exogenous or endogenous origin (although most is of the latter) and that "bad" cholesterol could have spent time in every single circulating lipoprotein before it enters the artery! If I can sort of paraphrase Rodney King: Can we all just move on? Is it time to stop making silly statements regarding cholesterol measurements or indeed time to stop relying solely on cholesterol measurements?

Interesting with respect to this topic: yesterday I saw the following: **'Bad' Cholesterol Not As Bad As People Think, Shows Texas A&M Study.** Check it out:

http://www.kbtx.com/home/headlines/Bad_Cholesterol_Not_As_Bad_As_People_Think_Shows_Texas_AM_Study_121274804.html?utm_source=twitterfeed&utm_medium=twitter