

LIPID CASE # 203 PCOS and TG/HDL Axis Disorder

Recently I received the following case: A 26 yrs old woman presents with amenorrhea and questions about conceiving. She has a history of polycystic ovary syndrome (PCOS) since age 16. Her height is 5'1, and her weight is 210. BP is 116/92. Her provider obtained the following labs

Original (over a year ago): TC = 221 TG = 286 HDL-C 49 LDL-C = 115 FBS 82.

The patient started metformin a month later. Her most recent labs are:

TC = 203, TG = 379, HDL-C = 37, LDL-C = 90 and fasting insulin 26.

NMR LipoProfile (lipoprotein concentrations)

LDL-P = 1820 (desirable < 1300 perfect < 1000)

Small LDL-P = 1556 (perfect < 600) However likely not a problem if total LDL-P is OK

LDL particle size = 19.5 (quite small) Cutoff between Pattern A (normal) and Pattern B (small is 20.5)

Large HDL-P 3.9 Quite low

Small HDL-P not provided (Likely it is quite high)

Large VLDL-P 23.1 Extremely high (normal <0.5)

I was asked to discuss the lipid metabolic pathways that create this high risk profile in these young patients? Since the preponderance of lipid/lipoprotein abnormalities we all currently see are related to insulin resistance it does make sense to fully understand why patients such as this may have significant risk for CHD yet have perfect or borderline LDL-C levels. In my mind it is unfortunate that the majority of risk prediction and therapeutic goals (as well as provider behavior) is so LDL-C centric. For those that deal with PCOS patients (a diagnosis that is extremely under diagnosed) this is an opportunity to better understand women as to their CHD related metabolic abnormalities.

The key to understanding CV risk attributable to lipids is to recognize the crucial fact that lipids like TG, phospholipids and cholesterol and other sterols go nowhere in the human body unless a lipoprotein traffics them somewhere. Thus, comprehension of atherogenesis and its prevention or treatment must be focused on lipoproteins. The only way sterols penetrate the arterial wall is as passengers inside of lipoprotein particles. It really does not matter how much cholesterol is in a given lipoprotein, it is the number and the various qualities of that vehicle (particle) that determines the lipoproteins destiny. We need to know which of the various lipoproteins are potentially atherogenic (capable of arterial wall entry and macrophage ingestion) and knowing that, how best to measure them in the laboratory: using lipid or lipoprotein parameters. Also, since particles have to penetrate the endothelial barrier before getting to the arterial intima, what do we need to know about and measure endothelial dysfunction?

Although there are many ways to separate lipoproteins in research labs, in the real world it is for the most part done by ultracentrifugation (VAP), nuclear magnetic resonance spectroscopy (NMR) or electrophoresis (Berkeley & others). A convenient way of classifying lipoproteins is to identify them by their surface "apolipoproteins" that provide the particle with structure, stability and solubility. ApoA-I (1-4 molecules thereof) wrap each HDL particle (classically called the alipolipoproteins) and a single molecule of apoB surround each of the betalipoproteins: Chylomicrons, VLDLs, IDLs and LDLs as well as another type of LDL termed Lp(a). Before we recognized the concept of dysfunctional or proatherogenic HDLs it was thought that the apoB particles are atherogenic whereas apoA-I particles were always cardioprotective (which unfortunately turns out not to be true). Multiple epidemiological and therapeutic trials have shown that ApoB or the apoB/A-I ratio is the best predictor of CV risk. It should be apparent that measuring apoB or apoA-I is one method of collectively quantitating how many of the lipoproteins exist in a dL of plasma. If one uses NMR instead of apoB, we get actual concentrations of the

individual lipoprotein species: VLDL-P, IDL-P, LDL-P, and HDL-P. Although the apoB "dump trucks" are the potential killers, because of its very long half life LDL particles make up > 90% of the betalipoproteins in most people, making LDLs the prevalent "illegal dumpers" of sterols into our patient's arteries. Many consider apoB to be synonymous with LDL-P, but several studies now exist where LDL-P was a better predictor of risk than was apoB and one might conclude that if we are to spend extra healthcare dollars on lipoprotein testing, LDL-P, rather than apoB is the way to go.

Multiple studies have shown that it is particle number, not particle size and not necessarily how much cholesterol is in the various particles, (LDL-C, VLDL-C, HDL-C) that are the best correlates of CV risk. Patients with too many betalipoproteins or worse yet, too many beta and too few alpha have the highest CV risk. If one is stuck with doing traditional lipid profiles, the lipid concentration surrogate(s) (predictors) of apoA-I is HDL-C and that of apoB is: TC, LDL-C and best of all, Non HDL-C. VLDL-C is a notoriously poor predictor of apoB since VLDL-C is calculated as TG/5 --- patients with high TG might simply have TG-rich particles rather than too many TG containing particles: thus VLDL-C goes up but VLDL-apoB or VLDL-P may or may not. In recent data from Framingham Offspring Trial, Non HDL-C was a better predictor of risk than LDL-C, but LDL-P was the best of all. Since >90 % of the apoB particles are LDLs, the real reason Non HDL-C is a better predictor of risk than is LDL-C is that Non HDL-C correlates better with LDL-P than does LDL-C. Interestingly from that same population (Framingham Offspring) apoB was no better than the TC/HDL-C ratio in predicting risk.

Back to the Case: This woman, with her insulin resistance, certainly related to her androgen excess so typical of PCOS, is greatly over producing TG-rich VLDLs (Note the large VLDL-P of 23.1. Of course if her liver is making too many large VLDLs, her serum TG will be high and de facto her VLDL-C (TG/5) is quite high at (379/5) 74 (normal < 30). As they are exposed to lipoprotein lipase (LPL), the TG-rich VLDLs ultimately undergo lipolysis (hydrolysis or breakdown of its lipid contents). Once TG depleted the majority are rapidly removed by hepatic LDL receptors: some go on to form LDLs.

However in patients with insulin resistance, the lipolysis is significantly delayed, lasting 8-12 hours or more, rather than 2-6 hours as is normal. As the TG-rich VLDLs circulate they create endothelial damage by increasing blood viscosity, impairing endothelial nitric oxide production, upregulating inflammatory, and coagulable proteins. Also by existing in plasma longer than they should, the VLDLs can be acted upon by cholesteryl ester transfer protein (CETP) which happily takes their TG and exchanges it for cholesteryl ester (CE) from HDLs and LDLs. This radically changes the composition of the VLDLs, HDLs and LDLs, with the former become CE-rich and the latter two becoming TG-rich and CE-poor. HDLs and LDLs that now carry too much TG, also undergo lipolysis as they pass through the liver: hepatic lipase hydrolyzes both their TG and surface phospholipids, resulting in much smaller HDLs and LDLs. The HDLs can become so small they pass through the glomeruli and are excreted (clearly explaining the very low large HDL-P, and presence of predominantly small HDL-P as well as the reduction in HDL-C). Of course the VLDL-C goes even higher as it is receiving CE that used to be in LDLs and HDLs (cholesterol-rich VLDLs are called remnants). Because the LDLs are so much smaller (in this case 19.5 nm) it takes extremely large numbers to traffic (carry) the 90 mg/dL of cholesterol that is in this woman's plasma. It should be no surprise that her LDL-P (both total and small) are quite high. So in the future when you see patients with elevated TG and low HDL-C, strongly suspect increased apoB (LDL-P). A TG/HDL-C ratio of > than 3.8 indicates an 80% chance or higher that small LDLs are present (the woman under discussion has an extremely high TG/HDL-C ratio).

Therapeutically one needs to get rid of the TG: Lifestyle can be extremely effective, but unfortunately for lots of reasons known to all providers it seldom gets done. What are the pharmacologic solutions to the lipoprotein abnormalities in this case? Well let's summarize: The lipoprotein pathology is:

Too many LDLs, most of which are quite small (High apoB or Total LDL-P)

Too few HDLs (Low apoA-I, HDL-P and low HDL-C) (Elevated TC/HDL-C, Elevated Non HDL-C)
Too many large TG-rich VLDLs (elevated VLDL-C) (Elevated Non HDL-C) (Elevated TG/HDL-C)

But please realize the illegal dumper, potentially generating atherosclerosis in this woman is the LDL-P! So initial therapy must be directed at slowing the synthesis of, increasing the catabolism of or removing the existing LDLs from plasma. The most potent lowering LDL-P monotherapy drugs are statins (with rosuvastatin or Crestor, having the best ability): statins upregulate LDL receptors which by attaching to apoB clear LDL-P. However if one adds ezetimibe or a bile acid sequestrant to the statin, there will be upregulation of many more LDL receptors than the statin can upregulate by itself: hence combo-therapy as an initial choice can make great sense in folks with very high apoB and LDL-P. The patient's glucose is OK on the metformin: if it were not colesevelam might be an interesting add-on to the statin as it has recently shown an ability to improve glycemic parameters (a subject of a future newsletter). Ultimately I think one will have to significantly diminish TG synthesis and that is where fibrates, niacin and N-3 fatty acids can help out. By reducing production of hepatic TG, one will produce less TG-rich VLDLs which will have downstream benefits on HDL and LDL composition: LDL size increases making the LDL more amenable to LDL receptor removal and the larger HDLs are not subject to renal excretion. Blood viscosity and the other aforementioned rheological abnormalities improve. In this case the TG are clearly the problem and I'd go with fenofibrate first or feno plus N-3 FA if need be. Since this is a young women we hope she really tries the lifestyle so we can minimize the drugs. Also take note that if N-3 fatty acids are prescribed for TG-benefit, one must use 4000 mg daily. Lesser doses are ineffective.

Final caution: since metformin can improve her fertility, one must address contraception before using the above lipid-modulating drugs in such a patient. Often such women are prescribed OCs for a variety of reasons which would cover that problem. If the patient wants to conceive: lifestyle, N-3 FA and re-evaluate after delivery.

Two references of interest were just published. The first is perfect for this case and is from the ERA (Estrogen Replacement in Atherosclerosis Study): The conclusions: The degree of coronary atherosclerosis in postmenopausal women is linked to a dysregulation of the TG/HDL metabolism. Subpopulations of TG-rich and HDL lipoproteins are better predictors of disease than TG and HDL cholesterol concentrations. (Arterioscler Thromb Vasc Biol. 2008;28:000-000: available on line as a prepublication). The paper is entitled Plasma Levels of HDL Subpopulations and Remnant Lipoproteins Predict the Extent of Angiographically-Defined Coronary Artery Disease in Postmenopausal Women. Stefania Lamon-Fava, David M. Herrington et al.

The second sheds light on which women may be responsive to estrogen administration with respect to atherosclerosis: Conclusion: Estrogen and SHBG are associated with reduced subclinical atherosclerosis progression in healthy postmenopausal women. These associations are partially mediated by their beneficial effects on lipids. Among women taking estradiol, the most beneficial hormone profile for CIMT progression was increased free estradiol and SHBG with concomitant decreased free testosterone. (J Clin Endocrinol Metab 93:131–138, 2008): Relationship between Serum Levels of Sex Hormones and Progression of Subclinical Atherosclerosis in Postmenopausal Women Roksana Karim, Howard N. Hodis et al. In the case above, a PCOS patient it is likely she has increased testosterone and decreased SHBG and this may help explain why such patient have increased CV risk.

LIPID CASE 204 Gonads and Cholesterol

Hi Lipidaholics: Hope the dust is settling in your practices from the ENHANCE data and the hysterical reaction by the press (expected) and some few thought leaders (unfortunate and unscientific). I will be discussing a case today and will work some of the challenges raised by

ENHANCE into the discussion. At the very end of the newsletter is the position statement of the National Lipid Association on the ENHANCE trial as well as that of the ACC for those who have not seen them. The NLA conclusion is the statin/ezetimibe therapy remains a reasonable option to achieve goal (I have certainly continued my daily dose). Now, to the case:

A provider contacted me about a 42 year old male with hypogonadism being treated with Testim (1% testosterone gel). He was only recently started on testosterone therapy and his testosterone levels are on the low side of normal now. He is not overweight and does get regular exercise. No other health problems. He has a previous history of anabolic steroid use and now states he does not use them now. He also has hyperlipidemia which is characterized by low HDL-C. He states that his HDL-C used to be as high as 60 and is now quite low.

His most recent Berkeley Heart Lab showed an LDL-C of 215, HDL-C of 19 (no other lipid concentrations sent to me). Everything else was normal except for an ApoB of 157 (perfect < 90 mg/dL). His CIMT was very good (no plaque and values placing him in only the 40th percentile for his age) and his Lp-PLA2 PLAC test) was <100. Based on the high apoB, the provider is recommending statin therapy, but the patient is not interested. He is clinging to the idea that, because cholesterol is used to make testosterone, that his cholesterol is high because his testosterone is low. The clinician asks: Is there anything I am missing?

DAYSRING ANALYSIS

This patient, as one would expect, with any illegal anabolic steroid user is totally misinformed, and totally ignorant of cholesterol and hormonal biology, and I suspect he may not be entirely truthful about continued steroid use. HINT: when you see a well built man with acne and low HDL-C suspect anabolic steroid abuse). His hypogonadism level is almost certainly too exogenous androgen use causing suppression of the hypothalamus/pituitary/testicular axis. These patients often have clinically obvious testicular atrophy on examination. Indeed, steroid hormones do have cholesterol as a precursor molecule (with multiple in between steps including estrogen). The question is then: where do steroid producing organs (adrenals and gonads) get their cholesterol supply: In healthy people it is a combination of de novo cholesterol synthesis and lipoprotein mediated cholesteryl ester (CE) delivery. Surprisingly, as it is not taught, it is HDL particles, not necessarily LDL particles that deliver the majority of the needed cholesterol to steroidogenic tissues (forward cholesterol transport).

The immature alpha or prebeta HDLs or unlipidated apoA-I attach primarily to ABCA1 (ATP binding cassette transporters) at the liver and proximal small intestine, acquire cholesterol and then perform "forward cholesterol transport" to adrenals, gonads and adipocytes (which require cholesterol for their extensive cell membranes). These tissues upregulate the scavenger receptor B1 (SRB1) to delipidate the mature HDLs of their cholesteryl ester content. LDL particles can deliver cholesterol to these tissues but are not absolutely required and we know this because persons with genetic hypoalphalipoproteinemia (who have LDL-C between 5 and 40), newborn babies (with mean LDL-C of 40) and people with statin-induced low LDL-C do not have hypogonadism or hypoadrenalism or any other cholesterol deficiency problem. Under urgent situations (adrenal crisis secondary to some body insult) the adrenal can upregulate LDL receptors and internalize LDL particles. Under normal physiologic conditions it is still debatable how much cholesterol arrives via HDLs or LDL and it probably varies between individual patients. One of LDL particles major function is to return CE to the liver (indirect reverse cholesterol transport) as does HDL (direct RCT). Perhaps also surprisingly the HDL-C level necessary to support endocrine function is in the 10-20 mg/dL range. In summary, persons with reductions of HDL-C or LDL-C do not suffer cholesterol deficiency problems or have production problems in their steroidogenic tissues. This patient who believes that by lowering plasma cholesterol he will have even greater hypogonadism is sadly mistaken. The amount of cholesterol needed to ensure steroid hormone production when HDL-C is very low is at most an LDL-C of 20-40 mg/dL. If HDL-C drops, then the steroidogenic tissues can upregulate LDL receptors and use them as a cholesterol source.

This person's apoB level of 150 establishes him as Familial Hyperbetalipoproteinemia and he thus is surely at terrible risk for CV complications. An apoB of 150 is in the 90th percentile of humans: i.e. 90% of humans would have a lower apoB. The 50th percentile is 115-120 and desirable to keep arteries healthy is < 90 (20th percentile). Readers of my newsletter know that, atherogenic particle number is what determines whether a particle enters the artery or not. Thus our mission is to diagnosis high apoB (because of long half life, LDL particles make up 90% of the apoB-containing lipoproteins). Our therapeutic mission is to lower apoB.

It is good news that his CIMT (hopefully done by people competent to do such testing) is so good. The next question is relevant with the news of last week about statin/ezetimibe and effect on CIMT. Why do we treat people? So many have lost site of the fact that we are trying to reduce future cardiovascular events, like MIs, stroke, angina, bypass, etc. Just about the only proven lipid-related parameter associated with outcome reduction is apoB (or its lipid concentration surrogates like LDL-C and Non HDL-C). So I would assume if we get this patient to goal he will have less chance of a future event and that is pretty much not arguable. I'm not sure at this time what we have to do to IMTs or any other imaging procedure to link it to event reduction. My guess is if we halt progression and stabilize existing plaque we will reduce events. Why would regression on an image guarantee any more event reduction than lack of progression?

Pravachol (pravastatin), a statin with as much if not more outcome data than any other existing lipid drugs has never failed to reduce events in a placebo-controlled clinical outcome trial (ALL HATT was not placebo controlled - it was heavily statin contaminated in the placebo group). Yet in the REVERSAL study, over time, coronary atheroma progressed in patients on event-reducing Pravachol. The atheroma did not progress in those taking high dose (80 mg) of Lipitor (atorvastatin). Of course Lipitor lowers events, but obviously it does so by halting progression (without regression). In the PROVE IT trial of Lipitor 80 vs. Pravachol 40, there were fewer events in the Lipitor arm. So it seems both drugs with a known ability to reduce clinical events (our desired endpoint) even though the arterial plaque increases with Pravachol. The event reducing superiority of Lipitor 80 over Pravachol 40 was directly related to the amount of apoB (LDL-C) reduction and secondarily the hs-CRP reduction. Indeed in the patients in whom Pravachol reduced those 2 parameters as well as the Lipitor, event reduction was the same with either drug (who knows what was happening to the atheroma in the folks with the most outcome reduction). I'd make the case that events are reduced by preventing plaque progression and perhaps more importantly in stabilizing any existing plaque. There is an IMT trial in patients with FH, called ASAP where high dose atorva (80 mg) was tested against lower dose simvastatin (40 mg). In those with atorva there was regression of IMT parameters which did not occur in those on simva. Of course no outcomes were looked at in this small trial, but in IDEAL, Lipitor 80 did not statistically significantly reduce events (primary endpoint) more than did the lower dose simvastatin (20 mg) used in that study (secondary endpoint were in atorva's favor). However simva 20 will not get as many people to goal as atorva 80, so most would use the atorva if needed to get to goal despite the failure to hit that primary endpoint with atorva. One other interesting thing to ponder: All of the above cases clearly point out we have to be very, very careful in extrapolating endpoint benefits from what a drug does to some imaging endpoint, especially carotid where there is really nothing. One other note: despite what folks are being told: the patients in ASAP have virtually nothing in common, except cholesterol levels, with the patients tested in ENHANCE. The two trials are not comparable in any way.

Back to the case: The patient needs a lot (over 50%) of apoB/LDL-P (LDL-C, Non HDL-C) lowering and as most patients with FH will need a powerful statin with a helper drug if not two helper drugs. Since there is no TG abnormality it is unlikely one would choose fenofibrate or N-3 FA as an add -on therapy. Because of the low HDL-C many might add Niaspan which would help improve apoB/LDL-P and Non HDL-C. Other options would be Zetia (ezetimibe) or WelChol (colesevelam). I do not have glucose data but if it were elevated then WelChol might be an attractive option as it has glucose improving effects mediated through the farnesoid receptor. I'd go with Crestor 20 mg (ultimately titrated to 40 if needed) and Zetia 10 mg and almost certainly

Niaspan (in a titrated fashion) would have to be added. We will soon get a new combination product called SimCor (simvastatin and Niaspan) but this man is not getting to goal as rapidly with simvastatin as he would with rosuvastatin. If he is still abusing anabolic steroids his HDL-C will not change.

A small dose of Testim to restore his free testosterone level to physiologic levels is indicated and not likely aggravate (reduce) apoA-I and HDL-C but larger doses might and illegal doses will. Of course his LDL-C will drop significantly if he uses lipid modulating meds (like statins or statin/ezetimibe) but there is zero worry that the drop will be associated with further inability to make testosterone and the patient must be so educated. If his previous steroid use was chronic and he has significant testicular atrophy, his testicles may never again be able to use cholesterol to make testosterone. No matter what you do to the HDL-C/apoA-I the real way to prevent atherosclerosis is to normalize his apoB/LDL-P. If one is simply looking at lipid concentrations rather than particle measurements, one would have to blow away the TC level. If his HDL-C is in the 20 range, one could get him to NCEP Non HDL-C goal by dropping the TC to 150 mg/dL (good luck and I think impossible without ezetimibe added to the statin).

Lastly although androgens (in a dose related effect) drop HDL-C by reducing apoA-I production in the liver and inducing hepatic lipase which by enhancing lipolysis (hydrolysis of TG and surface phospholipids) will reduce HDL particle size what do androgens do to CV events, or arterial walls. Of course we do not have (and likely and unfortunately never will) level 1 prospective CV outcome data related to androgen administration.

A recent editorial (Circulation. 2007;116:2658-2661) in Circulation by Baseria and Dobs had a discussion of androgens and CHD well worth reading. They state: "low total and free testosterone levels were inversely linked to coronary artery disease, even after adjusting for age and adiposity. This observation still holds true, as was recently supported by a study showing that men with angiographically proven coronary artery disease had lower levels of testosterone than those of controls." They were commenting on the following data: Endogenous Testosterone and Mortality Due to All Causes, Cardiovascular Disease, and Cancer in Men European Prospective Investigation Into Cancer in Norfolk (EPIC-Norfolk) Prospective Population Study which concluded: Conclusions—In men, endogenous testosterone concentrations are inversely related to mortality due to cardiovascular disease and all causes. Low testosterone may be a predictive marker for those at high risk of cardiovascular disease. (Circulation. 2007;116:2694-2701.)

In a nice meta-analysis review of existing data the Haddad et al. concluded: Testosterone use in men with low testosterone levels led to inconsequential changes in blood pressure and glycemia and in all lipid fractions (total cholesterol: odds ratio [OR], -0.22; 95% confidence interval [CI], -0.71 to 0.27; high-density lipoprotein cholesterol: OR, -0.04; 95% CI, -0.39 to 0.30; low-density lipoprotein cholesterol: OR, 0.06; 95% CI, -0.30 to 0.42; and triglycerides: OR, -0.27; 95% CI, -0.61 to 0.08); results were similar in patients with low-normal to normal testosterone levels. The OR between testosterone use and any cardiovascular event pooled across trials that reported these events (n=6) was 1.82 (95% CI, 0.78 to 4.23). The final conclusion was: testosterone use in men is not associated with important cardiovascular effects. Patients and clinicians need large randomized trials of men at risk for cardiovascular disease to better inform the safety of long-term testosterone use (Mayo Clin Proc. 2007;82(1):29-39).

LIPID CASE 205 Lipids Perfect but Arteries Worse

I wish I could issue CME credits for this newsletter because if you have the courage to read the whole thing you deserve them. Before we get into the case, I would like to start with some quotes from a 2 part article (Circulation 2008;117:560-568), which I strongly suggest everyone read. It is a debate on what is more important lowering LDL-C or raising HDL-C. H Robert Superko makes the case for niacin and as usual Scott Grundy (Chairman of NCEP ATP I,II and III) has a sound and evidence based retort. Superko states: "The purpose of this article is to challenge healthcare

workers to consider the possibility that the cholesterol-lowering program has in large part failed to stem the epidemic of CHD and that the well-meaning focus on LDL-C reduction has deflected interest in other therapeutic aspects of lipoprotein treatment that provide equal or greater benefit. This myopic focus on LDL alone is not surprising because, so far, guidelines have not adequately addressed other evidence." ----- "In the subsequent 10 years, important advances have been made in the understanding of **lipoproteins** that have clinical relevance for patient management and improved clinical outcomes beyond LDL-C reduction alone." ----- What clinicians must now consider is the possibility that LDL-C reduction alone is not adequate to stem the epidemic of CHD events when LDL-C values are below "hypercholesterolemic" levels. Although laudable, a 25% relative risk reduction is insufficient to treat this disease --- Professional individuals have the misleading impression that if they just get their LDL-C low enough, they will be free of CHD risk. The results of 5 large statin trials show that this is a dangerous misconception in that it leaves large numbers of patients still at risk for cardiovascular events." Dr Superko then goes on to speculate about using combination therapies that focus on HDL modulation and focuses on niacin as an HDL-C raising drug and points out that the real benefit of niacin is probably in inducing macrophage reverse cholesterol transport (delipidation of arterial wall foam cells).

Dr Grundy sticks to the tried and true: "elevated low-density lipoprotein (LDL) is a cause of atherosclerotic cardiovascular disease (ASCVD) and that lowering of LDL levels will reduce risk for ASCVD." He then talks about HDL as a target: "First, a low HDL commonly reflects an increase in atherogenic lipoproteins (e.g., triglyceride-rich lipoproteins and small LDL particles). Second, a low HDL level is associated with other risk factors of the metabolic syndrome (e.g., insulin resistance, elevated blood pressure, and prothrombotic and proinflammatory states). Third, a low HDL per se may directly promote atherogenesis; if this is true, HDL could be a direct target of therapy. **To date, however, the efficacy of HDL-raising therapy to reduce ASCVD risk has not been proved.** With respect to HDL influencing drugs: "In particular, lowering of atherogenic triglyceride-rich lipoproteins likely will be efficacious. **Whether raising HDL by pharmacological intervention that directly targets HDL will reduce cardiovascular risk remains to be proven.** This idea is attractive to many investigators because of the known association between low HDL levels and cardiovascular risk. On the other hand, it is possible that a low HDL is primarily a marker of risk caused by other factors (e.g., metabolic syndrome) and that direct HDL raising will not substantially modify risk. To resolve this question, 2 things are needed: development of a drug that will effectively raise HDL (without a confounding lowering of apolipoprotein B-containing lipoproteins) and demonstration of the efficacy of such a drug in a morbidity/mortality outcome trial. Until these have been accomplished, **the benefit of raising HDL per se remains in the arena of speculation.**"

Well let me chime in: Unfortunately what goes unmentioned by Dr Superko is that macrophage RCT (a likely crucial atheroprotective process influenced by not only niacin, but also other drugs)) has little if any effect on plasma HDL-C. Thus any ability niacin has to be cardioprotective through macrophage RCT would not raise HDL-C. He cites the known imaging data on niacin: impressive, small angiographic trials and of course the outcome data from some of those angiographic trials. Although it is not level I evidence it is pretty much all we have at present with respect to what any lipid-combination therapy offers (in them niacin was always combined with resins or statins or both). There is in actuality no prospective, empowered outcome data with any combo using statins other than some of the new statin/N-3 FA trials out of Japan which have little transference to westerners. There is nothing on outcomes with statins/sequestrants, statins/fibrates or statins/ezetimibe. Of course all of those therapies help us get to lipid/lipoprotein goal and all are recommended by NCEP as effective lipid drugs and the hope is the combos will reduce events better than the very limited benefit with statins and LDL-C reduction. With drug monotherapy, residual risk remains unacceptable.

I agree with Dr Superko, the answer lies not in the lipids but rather in the lipoproteins trafficking the lipids. The sooner we get away from lipid concentrations and what drugs do to them the sooner we will eradicate atherosclerosis. Of course I believe and have been teaching for

some time that lipids are simply passengers within lipoproteins and only by better focusing our therapies on lipoproteins (instead of how much cholesterol is in them) will we begin to truly impact atherosclerotic events in a spectacular way. We need to diagnose and then reduce atherogenic lipoproteins (mostly apoB, the majority of which are LDL particles, but realize that HDLs can also be atherogenic). In reality there is a limit in predicting beyond a certain point much about lipoproteins by using lipid concentrations. So we need to both count atherogenic particles (vast majority of which are LDLs) and then figure out the functionality of the particles: both the apoBs and ApoA-I (HDLs). You see a lot about HDL functionality in the current literature but do not see much if anything written about apoB functionality. What is apoB functionality??? TG-rich lipoproteins create all sorts of vascular havoc that has nothing to do with particle number: they aggravate coagulation and inflammatory markers, increase blood viscosity, traffic inflammatory enzymes, types of sterols (esterified, unesterified, noncholesterol) and pathological phospholipids. All of those variables can affect atherosclerosis. We are hearing more and more about phospholipids, including sphingolipids as mediators of atherosclerosis. Lipoproteins also traffic numerous other molecules like vitamins that are also involved in vascular health. Of course all of these factors have little to do with how much cholesterol is within the particles or particle numbers. Normal trafficking of these molecules indicate normal lipoprotein function. Any pathology of these molecules or the lipoproteins trafficking them might render those particles dysfunctional perhaps even making them proatherogenic in spite of their normal cholesterol content.

Let's get to the case at hand and see if we can apply the above concepts: I was asked for an opinion on a patient who is male, late 60's with hyperlipidemia and no other risk factors. He is on Crestor 20 mg and Zetia 10 mg. His latest blood work shows

Total C = 161 LDL-C = 65, HDL-C = 84, and triglycerides = 59. VLDL-C = 11 Non HDL-C = 77

NMR LipoProfile:

LDL-P (LDL particle concentration) = 762 nmol/L (Perfect < 1000)

Small LDL-P number at 663 nmol/L (perfect < 700)

LDL particle size is large (size not provided)

Large HDL-P 9.3 (normal) Other HDL (medium and small) subparticles not provided

Large VLDL-P at 0.

The patient is showing increasing plaque both on IMT and Heart Scans. His latest heart scan shows a calcium score of 520 with most of the calcium in the left anterior descending artery. The score is up in one year from 313 despite a good lipid panel. I was asked for my thoughts on this anomaly and treatment?

DAYSRING ANALYSIS

Don't you just love it when patients do not play by the book! Crestor/Zetia is a powerful 1-2 combo therapy to reduce apoB or LDL-C, etc. The EXPLORER trial, using that combo, showed the vast majority of participants got to lipid goals. Indeed this patient, using that therapy has perfect lipid and lipoprotein concentrations. So why is his IMT and CAC worse? Theoretically at a total LDL-P of < 800, those LDL particles should not be entering the vessel wall, unless there is serious endothelial dysfunction. So I'd be interested to see inflammatory markers like hs-CRP and especially the atheroma specific lipoprotein phospholipase A2 (Lp-PLA2 or PLAC test). How about fibrinogen and homocysteine? Should we measure noncholesterol sterols (sitosterol, campesterol) if LDL-P is excellent? Or maybe this case is going to come down to the functionality of the lipoproteins rather than their concentration or cholesterol content. Could he have dysfunctional lipoproteins?

Cromwell et al in recent data from Framingham showed that some folks with very low LDL-C, have cholesterol depleted particles and have risk due to increased LDL-P. That is obviously not the case here as both LDL-C and LDL-P are perfect. The HDL-C is fine as is the large HDL-P. So

maybe we have to ask about the functionality of both the apoB and apoA-I particles. Well TG are physiologic and I do not think we can ascribe much risk to them in this case. There is little else I can measure on other aspects of apoB functionality speculated about in earlier paragraphs. So it looks like we are left with the HDL particles. Do we have an HDL functionality problem at play? I have to believe so. Obviously this patient has no macrophage RCT as his arteries are worsening. So bear with me lipidaholics as the molecular biology behind this process is high level! I'll try my best to keep this simple.

Brief Review: HDLs are small lipoproteins containing apoA-I as well as many other apoproteins. Unlipidated apoA-I is phospholipidated and becomes prebeta HDL. As these acquire cholesterol then are termed alpha HDLs (small at first). As more cholesterol is acquired and as it is esterified into cholesteryl ester (CE) by LCAT (lecithin cholesteryl acyl transferase) the particles mature (become spherical) and become the larger HDL species. As those particles then delipidate (give up their cholesterol), they become the small species all over again. Real world docs cannot measure the prebeta species: small alpha HDLs correlate with HDL3 (H1, H2 on NMR) and the larger alpha species with HDL2 (H4, H5 on NMR). We have no way of measuring prebeta or unlipidated HDLs outside of research facilities. Measuring apoA-I provides no information as to which particles it is associated with.

Arterial wall macrophages (derived from monocytes) endocytose, using scavenger receptor A or CD36, oxidized apoB particles and become laden with sterols, mostly cholesteryl ester (CE) and cholesterol but also noncholesterol sterols. Once inside the macrophage the free cholesterol can be converted to cholesteryl ester (the storage form of cholesterol) via acyl Co-enzyme A cholesterol acyl transferase (ACAT1) or using cholesterol hydroxylase to oxysterols like 25 or 27 hydroxycholesterol or a variety of other species). Both unesterified (free) cholesterol and oxysterols are more likely to cause macrophage apoptosis than is CE, contributing to unstable lipid cores in plaque, .

Oxysterols are powerful ligands of the nuclear transcription factors (NTF) that regulate cholesterol homeostasis, especially the liver X receptor (LXR). The function of LXR is to prevent cholesterol toxicity. Too much cholesterol will crystallize and cause cell death: thus all cells have many ways in which to keep intracellular cholesterol levels from accumulating. These methods are 1) exporting cholesterol out of the cell, 2) slowing synthesis of cholesterol or 3) converting the cholesterol into something else (bile acids, steroids). LXRs facilitate all of these processes.

Foam cell handling of cholesterol, cholesteryl ester and oxysterols: As macrophage cellular cholesterol pools increase the LXR is activated, heterodimerizes with the retinoid X receptor and that dimer then attaches to specific response elements on genes. Messenger RNA is formed and goes to the protein making apparatus, the endoplasmic reticulum. Several of the proteins that are subsequently synthesized are those belonging to the ATP binding cassette (ABC) transporter family of sterol efflux proteins. These proteins help efflux cholesterol out of the cell onto acceptor proteins, the best known of which are apoA-I and apoE. Unesterified cholesterol or oxysterols, along with phospholipids are effluxed to prebeta or more mature alpha HDL, especially the smaller (empty) alpha species. A small amount of cholesterol can also pass by passive diffusion through the cell membrane into mature HDLs. Some studies also show macrophages can upregulate scavenger receptor B1 (SRB1) which effluxes CE into more mature alpha HDLs. This ability of HDLs and perhaps poorly lipidated apoE to extract cholesterol from foam cells has been termed, by Dan Rader and colleagues, macrophage RCT. He states it to be the most important part of the reverse cholesterol transport system. In reality it is the only thing that an HDL can do to cholesterol in plaque that is cardio-desirable or reduce plaque volume due to sterols. If all goes well, plaque regression or at least stabilization will occur.

Here is the paradox: Macrophage RCT has no effect on plasma HDL-C levels. Although the amount of cholesterol removed from foam cells (plaque is very beneficial to their artery, the amount of cholesterol removed is so small compared to the amount of cholesterol that all of the other HDL particles are simultaneously removing from the enterocytes of the proximal small

intestine or hepatocytes, that the process of Macrophage RCT will not change (raise HDL-C). A drug that induces macrophage RCT might be very cardio-beneficial but this benefit will not be reflected with a rise in HDL-C.

However other aspects of HDL lipidation and delipidation do have profound effects on HDL-C concentrations. The majority of HDL lipidation in most people occur at the liver and the proximal gut. These tissues usually have endless supplies of cholesterol, and the LXR in those locations go to work forcing ABCA1 upregulation and HDL lipidation. Hepatic and to a lesser extent intestinal or other peripheral cell ABCA1 is the primary regulator of HDL-C. There are rodent studies where upregulated hepatic ABCA1 raises HDL-C profoundly but if fed cholesterol the animals still get atherosclerosis. Yet if the macrophage ABCA1 are upregulated, serum HDL-C does not change and atherosclerosis does not occur. To further confuse the situation, let's not forget the liver, gut and steroid tissue are also capable of delipidating mature HDLs via the SRB1 receptors. As the liver delipidates HDL, HDL-C will drop. The liver can recycle that cholesterol to bile acids, excrete it in bile or relipidate new HDLs. Therefore, any drug inducing hepatic SRB1 will reduce HDL-C. In animals upregulation of hepatic SRB1 is associated with very low HDL-C and cardioprotection. Probuocol induces SRB1 and is associated with reducing HDL-C but also cardioprotection. Fibrates induce both hepatic ABCA1 and SRB1, thus we see no major increase in HDL-C in many patients using them (see VA HIT and FIELD HDL-C changes of 6% or less). Niacin is discussed below.

So the unvarnished truth is: Total HDL-C is due to 1) apoA-I production (PPARs, FXRs), 2) apoA-I lipidation (LXRs) and 3) apoA-I delipidation or removal/catabolism. HDL-C levels vary from patient to patient because different patients have differing rates of 1,2 and 3. A patient with a lot of 1 and 2 will have very high HDL-C and a patient with very active 3 will have low HDL-C. Different drugs affect processes 1,2 and 3 in very different fashions, explaining why drugs have different ability to affect HDL-C. Consider a patient with very active process 3: lots of SRB1 --- that patient would have excellent macrophage RCT, excellent hepatic delipidation of mature HDLs (and subsequent excretion of cholesterol in bile), very low HDL-C and no risk of CHD!!!!!! A person with very active process 2 (hepatic lipidation of HDL) but diminished process 3, might have very high HDL-C but dysfunctional HDLs that cannot return their cholesterol to the liver. Is your brain hurting yet or is this starting to make sense??

Macrophage RCT is a major part of HDL functionality. If an HDL cannot perform macrophage RCT, it is considered dysfunctional or proatherogenic. What might make the HDL incapable of performing macrophage RCT? Well maybe the macrophages in some people cannot upregulate the sterol efflux transporters? If amyloid is present in the HDL (inflammatory state) the HDL lose certain surface apoproteins some of which may be necessary to attach to the ABCA1 transporter. Amyloid or other inflammatory proteins render the HDL incapable of performing macrophage RCT! David Herrington of Wake Forest has shown that in women with CHD, oral estrogen-induced amyloid infiltrates the HDLs potentially making them dysfunctional: yet estrogen raises HDL-C by increasing apoA-I production, inhibiting hepatic lipase (keeping particles larger) and down-regulating hepatic SRB1. In a women without CHD estrogen would not create this potential problem: this is another reason why estrogen seems to benefit women without existing plaque yet aggravate those that do.

Other things affecting HDL's ability to bind to cells and macrophage sterol efflux transporters are their surface phospholipid makeup. Especially sphingolipids are crucial to whether an HDL binds properly or not. Thus the lecithin (phosphatidyl choline)/sphingolipid makeup of HDL particles is important: we have no way of measuring that or knowing how prescribed drugs affect that! One person with high HDL-C and the proper phospholipid surface coat has functional HDLs and another person with the same high HDL-C without the proper phospholipid makeup make have dysfunctional, useless HDLs and be subject to CV risk. This gets even more complicated when we realize that hepatic and endothelial lipase, which have phospholipase activity, are both crucial to HDL remodeling (size), lipid and especially phospholipid content. Yet again we cannot measure their activity. Functional CETP activity is also crucial to HDL remodeling: although this is driven by

TG, other factors including apoC-I and apoF (lipid transfer inhibitory protein) regulate its activity -- another aspect of HDL function we cannot measure. Lastly, LCAT is necessary to esterify cholesterol into CE, a step which is crucial to HDL particle maturation. Decreased LCAT activity will hinder HDL particle maturation from small to large. Clearly, interrupted HDL remodeling may not be desirable!

Guess what NTF upregulates CETP, LCAT, as well as ABCA1. Our friend the LXR! As you know we do not have LXR agonists meds yet. Fortunately other NTF cross talk to LXR and affect its activity. PPAR alpha and PPAR gamma agonism (drugs) help the LXR upregulate ABCA1 in macrophages and thus induce macrophage RCT. Fibrates are PPAR alpha agonists that through LXR activity promote ABCA1 yet so does niacin through its metabolite prostaglandin J2, which is a powerful PPAR-gamma agonist. The farnesoid X receptor (FXR) regulates bile salt synthesis but has lots of other abilities. It induces something called short heterodimer protein 1 (SHP1) which acts as an LXR antagonist. Yet FXR inhibition (bile acid sequestrants and estrogen) would reduce SHP1 and induce LXR activity (macrophage RCT). LXR upregulation of macrophage ABCA1, stimulation of CETP and LCAT would also promote proper HDL remodeling.

OK, enough of cellular processes. Let's translate this back to the real world patient at hand. Despite spectacular control of LDL-P and lipid markers of LDL-P (LDL-C and Non HDL-C) plaque is progressing in this man. Consider the following -- The low LDL-P is desirable as it keeps sterols out of the artery -- yet the very low LDL-C and perhaps very low cellular cholesterol content significantly down regulates the LXR. LXR inactivity would down-regulate macrophage ABCA1 and reduce macrophage RCT -- not desirable --- could this explain the rising CAC? All this is speculation! But we have animal studies showing statins can down regulate macrophage RCT. Now I do not think we should stop the statin or statin/ezetimibe or LDL-P skyrockets and would no longer be at goal. So how about adding a drug that will upregulate macrophage ABCA1 and induce macrophage RCT: This is exactly what Dr Superko suggests in the article quoted above. Our therapeutic choices are adding fenofibrate, niacin or a sequestrant like colestevlam (WelChol).

The patient is not insulin resistant and has no TG problem, so for me that rules out fenofibrate use. LDL-P and LDL-C are perfect, so even though WelChol could likely help HDL functionality, I really see no need to drop LDL-P or LDL-C further. However, one could stop the ezetimibe (Zetia) and substitute WelChol. There is rabbit data attesting to the efficacy and the macrophage RCT seen with this combo (Davidson M et al. The Journal of Applied Research • Vol. 6, No. 1, 2006 pp4-13 -- also see Toth editorial in same journal pp 1-3).

Finally, we are left with niacin. Niacin is unlikely to drop apoB down any further in a patient with such a normal TG but it would increase HDL-P (by delaying hepatic endocytosis of large HDL particles through its inhibition of the hepatic HDL holoparticle receptor). However, it's only good to have increased apoA-I or HDL-P if the HDLs are functional. Well niacin through PPAR-gamma/LXR agonism upregulates macrophage ABCA1 and induces macrophage RCT (Biochemical Pharmacology 67 (2004) 411-419). And niacin has at least imaging trials showing it helps regress plaque (at least in angiographic trials which of course cannot quantitate plaque as can IVUS).

So I would follow Dr Superko's recommendation and add Niaspan, titrated to 2000 mg) to this man's regimen! I cannot imagine what other option exists in this man. I'll bet many would have decided on that exact same therapeutic addition without any understanding of what I just described above. Fine -- patient wins --- you just couldn't pass the lipid boards without some of that mechanistic knowledge! I would not reduce the Crestor or stop the Zetia: His LDL particles are perfect and I want no increase in a person whose CAC is rising that quickly. Our battle requires us as Grundy points out in the review is to attack both apoB (LDL-P not necessarily LDL- and its lipid surrogates). Attacking the functionality of our HDLs and apoB particles is as he states, speculation --- quite true -- but one thing that is not speculative is the dramatically worsening CAC. Please note that in none of the studies showing niacin plus statin would help

arteries on an angiogram did the patients have perfect lipid and lipoprotein concentrations as did this man. So my speculation is way beyond evidence based medicine.

LIPID CASE # 206 HDL-C is dropping - Is this a concern?

I want to get back to the most common lipid disorder you all see every day: TG/HDL axis disorders, but with an unusual twist: the therapy prescribed reduced HDL-C! I received a request from an old friend in the Midwest to review his lipid profiles and help guide his therapy. Multiple salient points are demonstrated in this case. The patient and his clinician were very concerned when his therapy dropped the HDL-C, but I was not so alarmed.

The patient is in his late 30s and is active with no history of smoking or hypertension. Like so many he had put on a few pounds over time but is not very obese. Let's examine the lipid profiles over time:

October 2007--no meds

Triglycerides: 306 (>200 is high risk)
VLDL-C (TG/5) = 61 (desirable well under 30)
HDL: 34 (no NCEP goal of therapy exists): low HDL-C in drug naive patients is a major risk factor
LDL: 135 (goal is 130)
Total cholesterol: 230 (>200 is risky)
Total Cholesterol-to-HDL ratio: 6.76 (normal < 4.0)
Non HDL-C = TC - HDL-C = 196 (goal is 130)
TG/HDL-C = 9.0 (should never be above 3.8)

Basics: Lipids like cholesterol and TG are trafficked within protein enwrapped vehicles called lipoproteins: the surface proteins are called apolipoproteins. For cholesterol to generate atherosclerosis a lipoprotein has to carry it into the artery wall where it is ingested by macrophages (generating foam cells). The atherogenic lipoproteins are those that carry a single molecule of apoB. It is particle number, not particle size that determines whether they enter the artery wall or not. Lipid profiles provide lipid concentrations (the lipid within the particles) and we can use that information to "guess" what type and how many lipoproteins are present. If you are not counting particles using apoB or NMR LipoProfiles (nuclear magnetic resonance spectroscopy) you have to use lipid concentrations or ratios, etc., to make the guess.

Since the majority of cholesterol is trafficked within the apoB (not the HDL or apoA-I particles), TC is an apoB surrogate as is LDL-C. The profile above reveals a TC of 230, so right away we are concerned too many apoB particles are present. In multiple trials the TC/HDL-C ratio has been very predictive of CV risk: indeed when doing Framingham Risk Scoring, the only lipids used are TC and HDL-C. The latter is a lipid surrogate of apoA-I and the former (TC) is an apoB surrogate. Thus the TC/HDL-C ratio is the "poor man's" apoB/apoA-I ratio.

Our patient's TC/HDL-C ratio of 6.76 indicates high CV risk as it suggests the patient has too many apoB and too few apoA-I particles. Next we look at the TG/HDL-C ratio. If it is > 3.8 (and this patient has a 9.0): there is an 80% chance the predominant LDL species is small. Although the LDL-C does not look so scary at 135, we know the volume of a spherical lipoprotein is related to the third power of its radius. Thus it takes many, many more small LDLs to traffic a given level of cholesterol than it does larger LDLs. Since it appears like this man has very small LDLs, the odds are overwhelming that he has a rather high LDL-P or apoB (over 90% of apoB particles are LDLs due to their long half life). His elevated VLDL-C (a risk factor as important as is LDL-C) is indicative of what are called remnant lipoproteins: chylomicrons, and mostly VLDLs that have lost a lot of their TG, but replaced some of it with cholesterol. Although their number is very small compared to the number of LDLs (i.e. VLDL-P vs. LDL-P), remnants injure the endothelium,

increase blood viscosity, aggravate coagulation and inflammatory markers and thus are considered to be atherogenic particles.

Of course, by far the most serious atherosclerosis lipid-related risk factor we know is LDL-P (LDL particle concentration). The best surrogate of LDL-P that exists in the lipid profile is Non HDL-C, which is very elevated in my friend. When you see someone with very high Non HDL-C and an unremarkable LDL-C, you can strongly suspect the patient has way, way too many small LDLs (high total LDL-P or apoB) as well as some remnants. Although the LDL-C does not look so bad, the LDL-P (because of the small size of the LDLs) would likely have been in the top 20th percentile of humans (high risk). Thus a quick glance and rapid analysis of the lipid profile tells us we are dealing with too many small LDLs, some remnants and a lack of HDL particles. Of course that is a high risk profile.

The NCEP goals of therapy in this patient is to reduce (normalize) LDL-C and Non HDL-C. At that time, in addition to restriction of simple sugars and saturated fat, and increased exercise, a powerful statin (our best apoB lowering drug) or a lower statin dose with ezetimibe (Vytorin), would be the logical first step. The provider who was managing the patient, elected to start TriCor 145 mg daily instead of a statin. I suppose the very high TG drove that decision. You should realize the primary risk associated with elevated TG is too many LDLs: The high TG is usually associated with the overproduction of VLDLs and IDLs, many of which ultimately become LDLs. Since statins or statin/ezetimibe upregulate hepatic LDL receptors, which clear apoB particles (especially LDLs) before they crash the artery wall and statins have so much outcome benefit, most would not have started the TriCor first (with the TG being < 500). However, based on VA-HIT (high TG, low HDL-C, unremarkable LDL-C) there is reason to think a fibrate will help this man. I think we all know he will need combination therapy, so in reality terms, it really does not matter which drug is started first as long as one is prepared to add a second drug if necessary.

December 2007--taken after two months of TriCor 145 mg Also lost > 10 lbs

Triglycerides: 92
VLDL-C = 18
HDL: 46
LDL: 134
Total cholesterol: 198
Cholesterol- to-HDL ratio: 4.30
Non HDL-C = 152
TG/HDL-C < 2.0

Lifestyle and TriCor did a very good job on inhibiting triglyceride synthesis, resulting in significantly less VLDL production and a much better VLDL-C (a risk factor as important as is LDL-C). Dropping VLDL-C is a good way to reduce Non HDL-C. As often happens when very high TG are reduced, VLDLs carry less TG and there will be less cholesteryl ester transfer protein (CETP) activity (exchange of TG for cholesterol between VLDLs and LDLs/HDLs). With reduced VLDL-TG content, TG are no longer transferred via CETP to HDL particles: The HDLs stay larger and HDL-C goes up. Likewise, with reduced VLDL-TG content, TG are no longer transferred via CETP to LDLs enabling them to keep their cholesterol resulting in larger (but not more numerous) LDLs. LDL-C goes up, but LDL-P actually may go down (if less VLDLs are produced there will be downstream be less LDLs). Indeed the LDL-P is way down (as reflected by the much reduced Non HDL-C) the LDL-C has not changed. Again, this phenomenon is explained by an increase in LDL size that occurs when TG are lowered by fibrates or other drugs (niacin, high dose N-3 fatty acids) that inhibit TG synthesis. The profiles of October 2007 and December 2007 really demonstrate how useless LDL-C can be: LDL-C is the same on both dates, but the LDL-P and CV risk is much lower in the second profile. The biggest change between the two profiles is big improvement in TG/HDL-C (indicative that small LDLs are disappearing and being replaced with lesser amounts of larger LDLs) and Non HDL-C (indicative of reduced LDL-P). The latter of course is the NCEP goal of therapy for such patients with TG/HDL axis disorders.

The patient was then started on Crestor 5 mg daily and 1000 mg of N-3 Fatty acid in addition to the TriCor 145 mg. I presume the Crestor was started because the LDL-C was not reduced by the TriCor, but the real reason should be that the Non HDL-C (LDL-P surrogate) is still too high. NCEP states that when the Non HDL-C is still elevated on a statin, one should consider a fibrate or niacin product. Zetia/statin also has a non HDL-C indication. Now that the LDL size is larger, one would expect LDL receptors upregulated by statins to dramatically further reduce LDL-P (LDL receptors more easily recognize the apoB and preferentially remove larger than smaller LDLs).

February 2008-taken while continuing the TriCor and adding Crestor 5 mg and fish oil 1000 mg. (Crestor and fish oil were taken for one month prior to these labs.)

Triglycerides: 45
HDL: 36
LDL: 62
Total cholesterol: 107
Cholesterol-to-HDL ratio: 2.97
TG/HDL-C = 1.25
Non HDL-C = 71

Wow, everything is picture perfect except HDL-C is low. Someone not astute in the understanding of lipoprotein biology might be alarmed that the HDL-C is lower than it was previously. In reality there is a tremendous lipoprotein benefit in the profile as far as one can judge using lipid concentrations. The best predictor of risk as far as lipids are concerned is the TC/HDL-C ratio which for the first time is normal. The best goal of therapy that correlates with apoB (atherogenic particle number) or better yet LDL-P is Non HDL-C which is now 60 points below the goal of 130 mg/dL. For what it is worth the LDL-C is also excellent. The TG for the first time are physiologic (< 70 mg/dL). The TG/HDL-C ratio again confirms the vast majority of the LDLs are normal sized (no longer small). Thus one does not need as many LDLs to traffic their cholesterol in plasma. Depending on the LDL size, it takes 40-70% more small LDLs than large to traffic a given amount of LDL-C. Persons with smaller LDLs usually have very high LDL-P (apoB) counts and are at high risk. It is particle number, not particle cholesterol content that determines if an LDL will invade the artery wall. Despite the very low HDL-C, Cromwell in using data from Framingham Offspring Trial, did show that some people with very low LDL-C, have cholesterol depleted particles and thus still may have high LDL-P. So in reality the only way to truly know the risk in this patient is to check LDL-P.

Lastly why did the HDL-C go down? Part of what an HDL does is termed reverse cholesterol transport: i.e. it returns unwanted cholesterol (not needed by steroidogenic tissue or adipocytes) directly to the small intestine (where it is excreted), directly to the liver (where it becomes a bile acid or is excreted in the bile to the stool) or indirectly by transferring cholesterol to LDL particles which return it to the liver for utilization or excretion (indirect reverse cholesterol transport). But do not forget that HDLs also do a lot of forward cholesterol transport from liver and gut to steroidogenic tissue. Thus in therapeutic situations when one uses a drug, like fenofibrate, that enhances the liver's ability to empty the HDL cholesterol content (via upregulation of hepatic scavenger receptor B1 or SRB1), HDL-C can go down especially if used with a statin that also dramatically lowers TC. Unfortunately many clinicians are unaware of these concepts and they look at the decreasing HDL-C as a bad sign when it is not. Indeed in last week's Journal of the American College of Cardiology data was published (reference 4 below) showing that as HDL-C starts to go very high and HDL size is significantly increased, CVD risk can increase. Cardioprotection from fibrates is often seen therapeutically with the generation of small HDL particles (that carry less cholesterol) and that also have the best ability to remove cholesterol from arteries (Robbins S, et al. JAMA 2001;285:1585-1591). In effect the decreasing HDL-C in this case reflects both a systemic depletion of cholesterol and hepatic delipidation of HDLs and increased reverse cholesterol transport.

Lastly this case explains perfectly why in many insulin resistant patients with TG/HDL axis disorders it makes so much sense to combine fenofibrate or niacin with a statin. Abbott and AstraZeneca is now partnering to bring a combination rosuvastatin/fenofibric acid tablet to market. Just last week the FDA approved Simcor (Niaspan and simvastatin combo tab).

LIPID CASE # 207 Counting Particles

For this issue I wanted to deal with a classical type of lipid disorder that seems all too uncommon in our insulin resistant TG/HDL axis disorder clinical world.

I was asked, via e-mail to comment on the following patient: 62 year old Caucasian woman with a strong family history of lipid disorders. Her father had an aortic aneurysm and her mother had CAD with a PTCA (age not specified). No other clinical details available. The laboratory values were as follows:

TC = 301 LDL-C = 214 TG = 105 HDL-C = 66

NMR (nuclear magnetic resonance spectroscopy) LipoProfile performed:

Total LDL particle concentration: LDL-P = 1571 nmol/L (ideal < 1000, Concern > 1300)

Small LDL-P = 0

LDL particle size is very large at 22.6 nm (Pattern A or buoyant > 20.5 nm)

Large HDL-P = 13.1 umol/L

Small HDL-P = 25.4

Medium HDL-P not provided

Large VLDL-P = 0.2

Small VLDL-P = 67 (90th percentile)

IDL-P = 0

DAYSRING ANALYSIS:

At first glance most of us looking at an LDL-C of 214 would think we are dealing with an extremely high CV risk patient: but is that assumption correct? Guidelines set risk and goals by looking at lipid/lipoprotein concentrations in the public (patients in epidemiological trials). The 50th percentile of LDL-C in the US is between 130 and 140 mg/dL. Thus 50% of folks have a higher LDL-C and 50% lower. At an LDL-C > 190, only 20% of the population would have such levels. Thus if one happens to be in the top 20th percentile, one is considered high risk. However several studies, to the point of no longer being debatable, have shown that it is particle number (apoB or LDL-P) that determines risk, not how much cholesterol is within the particle. The LDL-C may or may not be an accurate predictor of particle number depending on other variables (especially size and lipid composition).

I thought I would use this case to illustrate exactly what all of the above numbers mean and get into a different type of discussion of the mediators of atherosclerosis: lipoproteins. Remember no cholesterol molecule would ever find its way into the arterial wall unless a lipoprotein deposited it there. I wonder how many providers look at atherosclerosis as a lipoprotein-mediated disease? When you look at the NMR results of the various particle concentrations, have you ever stopped to ask how many lipoproteins are actually circulating in plasma. The following numbers should give insight into the immensity of the task before us:

Total LDL-P is the number of all of the LDL particles that exist in a liter of plasma (not a deciliter as standard lipid concentrations are reported: LDL-C = 214 mg/dL). The LDL-P of 1571 does not mean there are 1571 LDL particles per liter. One nanomole of LDL particles actually represents 6×10^{14} or six hundred trillion individual LDL particles. Of course no human has an LDL-P of 1 nmol/L. If one has a desirable LDL-P of 1000 nmol/L (the 20th percentile in population

studies: i.e. 20% of people will have < 1000 and 80% of people will have > 1000) then there is 1000 times six hundred trillion or 6 hundred quadrillion LDL particles per liter (a quadrillion is 1000 billion). If one has five liters of plasma, then we would expect to find three quintillion (18 zeros) LDL particles circulating in their plasma. In a diabetic or FH patient with an extremely elevated LDL-P of 2000 nmol/L (very high risk as it is well above the 90th percentile in population studies) there would be six **quintillion** LDL particles. So my question is how many LDL receptors do you have to upregulate to restore body LDL-P to 3 quintillion?

HDL particles are reported in micromoles/L: add three zeros to a micromole to convert it to a nanomole. 1 umol of HDL-P represents 6×10 to the seventeenth power (6 hundred quadrillion particles). If you go through the same exercise with HDL as described above and a desirable HDL-P is 30 there are one hundred five quintillion HDL particles floating in 5 liters of plasma. Few realize it, but in actuality there are many more HDL particles in plasma than LDL particles.

Why then is LDL-C so much higher than HDL-C if there are more HDL particles? This is explained by both size and lipid composition. LDL size using NMR varies between 18 and 23 nm, whereas HDLs vary between 6-12 nm. Since the volume of a sphere is related to the third power of the radius, LDLs being 2-4 times bigger than HDLs carry more lipids. So even though there are less of them, the LDL cholesterol load is usually considerably more.

VLDLs are reported in nanomoles and you can easily see by their very low nanomolar concentration that they contribute very little to total apoB particle concentration. However VLDLs contribute to atherosclerosis as both precursors to LDLs and as suppliers of TG which when transferred by cholesteryl ester transfer protein (CETP) create TG-rich, cholesterol-depleted LDLs and HDLs leading to small LDLs and HDLs: The former (cholesterol-poor LDLs) greatly increase total LDL-P and the latter (cholesterol-poor HDLs) facilitate HDL excretion. TG-rich VLDLs also increase blood viscosity, are associated with abnormal hemostasis and generate endothelial dysfunction and inflammatory markers. Although VLDLs and other remnants smaller than 70 nm can enter the arterial wall, their concentration is trivial compared to LDLs. So look at LDL-P as the major risk factor but realize large VLDLs have everything to do with LDL-P, LDL size and LDL composition.

IDLs because of their very short half life and concentration are not major players other than in certain infrequent lipid disorders (Type III Dyslipidemia, Hepatic lipase deficiency)

Back to the case: With an LDL-P of 1571, and very large LDLs (22.6 nm being humongous) and TG not being terribly high, it is no wonder the LDL-C is 214 and the TC is 301. However an LDL-P of 1571 is just shy of the high risk flag of 1600 nmol/L (only 20% of the population will have an LDL-P more than 1600). LipoScience lists an LDL-P of 1300-1600 as borderline high. So despite the LDL-C of > 200, perhaps the CV risk is not as high as the LDL-C suggests. If this person had cholesterol depleted particles, (small, or TG-rich) the LDL-P would be well above 2000 (very high risk). Is it shocking to see no small LDLs? No: this patient has none of the findings usually associated with small LDL size.

Is the extra cholesterol in this person due to over synthesis from saturated fat substrate or is it hyperabsorption of cholesterol the hepatobiliary system is trying to excrete or is it an inability of the liver to clear the LDLs or some combination of all three. Since up to one third of total HDL-C may originate via enterocyte loading (lipidation) of HDL, a high HDL-C can be seen in hyperabsorbers of cholesterol. Many people with FH just have so much cholesterol in their system, it is easy for HDLs to lipidate (acquire cholesterol) and often most of the lipoproteins have increases in their cholesterol content.

Other things contribute to the elevated LDL-C. Many people with Familial Hypercholesterolemia (FH) have dysfunction LDL receptors (LDLr) that just do not recognize and bind well with the apoB on the LDL particle. In others the apoB itself is defective and is not recognized by normal functioning LDLr. LDL size matters: On LDLs that are not normal sized (very large or small) the

apoB conformation changes and the LDLr binding domain on apoB gets distorted and the particle loses some of its affinity for the LDLr. There is an enzyme (a peptidase) that helps catabolize LDLr called Proprotein Convertase Subtilisin Kexin Type 9 (PCSK 9). If one over-expresses this enzyme LDLrs have short half life's and LDL particles are not cleared (LDL-P, LDL-C and CV risk are high). If one under-expresses this enzyme, LDLs are aggressively cleared and the patients actually have hypobetalipoproteinemia (and very low CV risk).

Using Framingham Risk Scoring (FRC) this woman (assuming she is normotensive and does not smoke) is in the intermediate risk category. Of course NCEP suggests an LDL-C of > 190 mg/dL always qualifies for treatment. The AHA Women's Guidelines states that any menopausal women > 50 with a single risk factor for CHD has a > 50% lifetime risk of a CV event. So, FRS does not really help in this patient and I would recommend pharmacological treatment.

Mission number one is to increase upregulation of LDLr: This is done via depleting the liver of cholesterol by inhibiting synthesis (statins), impairing chylomicron delivery of cholesterol (ezetimibe and plant stanols), or forcing the liver to make bile acids using cholesterol (bile acid sequestrants). There may be a problem with the very large LDL size: the apoB on its surface may not have the most ideal conformation to be recognized by the LDLr, but if we take out enough cholesterol via the above mechanisms the LDL size may reduce making it more receptor compliant. So I'd probably go with Crestor 20/Zetia 10 or give Vytorin 20 a try to save a co-pay if that's an issue. If there was a glucose issue WelChol (colesevelam) would be attractive. If the statin plus ezetimibe did not get to goal, then WelChol would be the logical addition.

LIPID CASE # 208 Get to Goal But How?

This issue's case is pretty typical of what you see every day and there are several approaches to get to goal. Here is the patient profile.

Male Age: 60 Has CAD, and has had angioplasty

2004 lipid profile:

TC = 224 LDL-C = 156 HDL-C = 30 TG = 190 VLDL-C = 38 (all in mg/dL)
Non HDL-C = 194 TC/HDL-C = 7.4 TG/HDL-C = 6.3
LDL pattern or phenotype is B (small: less than 20.5 nm using NMR indices)

Was titrated up to Lipitor 80 mg and Niaspan 3000 mg daily and clinically has had no CVD events.

Nov 2007 lipid profile:

TC = 196 LDL-C = 140 HDL-C = 33 TG = 118 VLDL-C = 23
Non HDL-C = 163 TC/HDL-C = 5.9 TG/HDL-C = 3.5
LDL pattern remains type B

Despite the good clinical course, the provider was still concerned about the above profile, especially the low HDL-C and Pattern B phenotype. The provider added TriCor 145 mg to the regimen and wonders if that was a correct choice.

DAYSRING DISCUSSION:

This is a great case, that many providers might have trouble managing. Before we start, never forget that sterols are carried into the artery as passengers within lipoproteins. Thus lipoproteins

are the mediators of atherosclerosis. We always have to think in terms of does the patient have or not have atherogenic lipoproteins. Only the former are at CVD risk.

In this case, it is the low HDL-C that scares everyone, but there are multiple clues other than the low HDL-C in the lipid profile that are equally scary. Low HDL-C in most people (especially those that are insulin resistant) is a major independent predictor of risk even in most patients on lipid-modulating drugs (especially statins). Although NCEP ATP-III does not provide a specific HDL-C goal of therapy (and that fact amazes lots of clinicians) it does not discourage raising HDL-C with lifestyle and FDA approved drugs. However, it does not recommend Dilantin or estrogen even though they both significantly raise HDL-C. Few also realize there is also no specific TG goal of therapy in NCEP ATP-III, although NCEP clearly advocates reducing risk in patients with high TG by lifestyle and if necessary drugs. NCEP points out that most patients with CV risk who have low HDL-C and/or high TG (TG/HDL axis disorders, mixed dyslipidemia, etc) have too many atherogenic apoB particles: typically these patients have the metabolic syndrome. Of course the lipid surrogates of elevated apoB (LDL-P) are LDL-C and especially Non HDL-C. Thus NCEP suggests the proper way to reduce risk in patients with TG/HDL axis abnormalities is not per se to raise HDL-C to a specific level or drop TG to a specific level but rather to normalize the apoB (LDL-P) lipid surrogates (LDL-C and Non HDL-C).

Since Non HDL-C is in reality LDL-C plus VLDL-C, I really see no need to any longer look at LDL-C (as Non HDL-C includes LDL-C). Liu and Grundy published Framingham data (Am J Cardiol 2006;98:1363–1368) that at all levels of Non HDL-C, LDL-C has no statistical relation to CVD risk. They also demonstrated that VLDL-C is as important a risk factor as is LDL-C and most importantly, that Non HDL-C always out predicted LDL-C regardless of the TG level (i.e. Non HDL-C is a better parameter whether or not TG are above or below 200 mg/dL). That new data is crucial to know because in the 2001 and 2004 NCEP papers, it was suggested Non HDL-C is especially important when TG are > 200. We now know that the TG level per se does not really tell us when the Non HDL-C is important. Non HDL-C is always important, as it is always the best lipid surrogate of apoB or LDL-P. Do not get lost in reality: in more recent Framingham data (Journal of Clinical Lipidology 2007;583–592), Non HDL-C was a better surrogate of LDL-P than was LDL-C, but Non HDL-C certainly was nowhere near as good as measuring LDL-P (using NMR LipoProfile).

So let's go back and examine the before treatment lipid profile:

TC = 224 LDL-C = 156 HDL-C = 30 TG = 190 VLDL-C = 38 (all in mg/dL)
Non HDL-C = 194 TC/HDL-C = 7.4 TG/HDL-C = 6.3

The elevated TC (>200, LDL-C > 100, TG >150, Non HDL-C > 130, high TC/HDL-C all indicate elevated apoB (LDL-P). The elevated TG/HDL-C strongly suggests small LDL particles are predominant. What is impossible to know by looking at those numbers is - How high is the apoB (LDL-P): mild, moderate or severe. If indeed the LDLs are small or TG-enriched there is a potential for extremely high LDL-P levels.

Now let's look at the on-treatment lipid profile:

His VLDL-C is 23 (calculated by dividing TG by 5). His Non HDL-C is 196 - 33 or 166. The NCEP ATP-III goals for a high risk person are an LDL-C of 100 (with an option for 70). Since his TG are < 200, a literal reading of NCEP ATP-III means looking at Non HDL-C is not needed. However we now know better (based on Liu and Grundy) and the goals of therapy indeed should be an LDL-C < 100 (70) and a Non HDL-C < 130 (100).

Bottom line is that atherosclerosis is caused by too many apoB particles entering the arterial wall: because of their 3 day half life, 90-95% of apoB particles are LDLs, not VLDLs or IDLs. It is always best to measure apoB (available in any lab) or better yet LDL-P (LDL particle concentration by NMR LipoProfile). If that is not possible, the best lipid surrogate or predictor of apoB (LDL-P) is non HDL-C (not LDL-C). And of course, Non HDL-C is usually calculated by

subtracting HDL-C from TC (neither of which require fasting), or by adding the calculated VLDL-C to the calculated LDL-C.

The lipid surrogates of small LDL particles are elevated TG (not present in the second profile), low HDL-C (still present), TG/HDL-C ratio > 3.8 (in this case it is 3.5) and a high Non HDL-C with a normal LDL-C. In this case, although the Non HDL-C is high so is the LDL-C. In other words the high Non HDL-C is driven by an elevated LDL-C, not VLDL-C. So there is no way to be sure what size LDLs are present without doing advanced lipoprotein testing. We may think that the LDLs are likely small but it is just a guess.

Question: How can LDL-P be elevated (a major risk factor) if LDL-C is at goal? The answer is the LDL would have to be a cholesterol-depleted LDL particle (i.e. it does not contain many molecules of cholesterol). This is seen if the LDL particles are small but it also can be seen in patients with large LDLs if the LDL particle is TG-rich. If it is TG-rich it will have to be cholesterol poor. **It always takes many more cholesterol-depleted LDLs to traffic (carry) a given amount of cholesterol than it does cholesterol-enriched LDL particles.** The patients with the highest LDL-P (apoB) concentrations are those that have LDLs that are both small and TG-rich. Those particles can only carry a few molecules of cholesterol per particle and thus lots of LDLs are necessary to traffic a given level of cholesterol.

So back to the case: on Lipitor 80 mg plus Niaspan 3000 mg, the LDL-C and Non HDL-C are not at goal (studies show that Niaspan doses > 2000 mg are not much more efficacious than the 2000 mg and side effects increase). I am sure the provider escalated the Niaspan dose to reach some imaginary HDL-C goal, when in reality Non HDL-C is the goal of therapy. So if one is on Lipitor 80 and Niaspan 2000 mg and still not at HDL-C goal, I believe the proper choice is to do something else.

Let's take a close look: $\text{Non HDL-C} = \text{VLDL-C} + \text{LDL-C}$

On the combo Rx, the VLDL-C is normal (< 30) but the LDL-C is still high. Fibrates and Niacin because of their ability to inhibit TG synthesis (something a statin cannot do) drastically reduce VLDL-C more than does a statin. However in this patient the problem is the high LDL-C, not a high VLDL-C. Niacin has done its job on the VLDL-C. To lessen the remaining LDLs, I think we need to upregulate more LDL receptors: thus I would D/C Lipitor and substitute Crestor 40 (a more powerful statin) and because VLDL-C is normal, reduce the Niaspan dose to 2000 mg (for Crestor/Niaspan data see Am J Cardiol 2003;91:1304–1310). If Non HDL-C did not get to goal with Crestor 40/Niaspan 2000 mg, I would add Zetia 10 mg to get additional upregulation of LDL receptors. I would be surprised if Crestor/Zetia/Niaspan (2000 mg) did not correct the lipid profile. If it did not, then WelChol should be added for additional LDL receptor upregulation. I do not see a role for TriCor here as the benefit of fibrates are usually seen in folks with TG > 200 (high VLDL-C). However, since the provider started TriCor, one might just ride it for 8 weeks and then see what happens to Non HDL-C even though the TG are not in the range where the fibrate usually works best. One can always hope for the unexpected. The 3000 mg of Niaspan has potential to elevate the uric acid: at least TriCor might help correct that! I see no role for N-3 FA in this patient with a TG of 118, other than all high risk patients should be on 1000 mg for their non TG benefits.

Simple Treatment Algorithm:

$\text{Non HDL-C} = \text{TC} - \text{HDL-C}$ or alternatively $\text{LDL-C} + \text{VLDL-C} (\text{TG}/5)$

NCEP states that if Non HDL-C is still high on a statin and lifestyle: add a fibrate or niacin. Zetia/statin also has a non HDL-C indication from the FDA. High dose N-3 FA (4000 mg) do not have the Non HDL indication but have the data that they can also reduce Non HDL-C when added to a statin (Clin Therap 2007;29:1354-67).

So if Non HDL-C is being driven by LDL-C: add Zetia or WelChol to the statin

If Non HDL-C is driven by VLDL-C (high TG): add TriCor or Niaspan or high dose N-3 FA: Fibrate data is best when TG >200. Fibrates and niacin have outcome data in patients with high TG/low HDL whereas N-3 FA do not.

If the TG is < 200 and the high Non HDL-C is being driven by mild VLDL-C elevations and low HDL-C add Niaspan

If Non HDL-C is being driven by high LDL-C and VLDL-C despite the statin: Add TriCor/or Niaspan, high dose N-3 FA and Zetia if needed

A new drug combo hit the market last week: Simcor (Niaspan/simvastatin). It is available in 20/500 mg tabs, 20/750 and 20/1000 mg tablets. Since most patients will require two Simcor tabs (taken together), they will wind up on simvastatin 40 mg and Niaspan 1000, 1500 or 2000 mg daily. If you get to goal, great: if not one could add Zetia, switch to Crestor/ Niaspan or attack Non HDL-C in extreme cases (severe familial combined hyperlipidemia) by adding TriCor, or high dose N-3 FA. As we all have heard there is a fibrate/Crestor tablet in development). So we continue to have nice, cost-saving combo therapies available which also helps compliance.

LIPID CASE # 209 Abandoning Ezetimibe

Of course I have received lots of e-mails about the recent ENHANCE study and how it should affect real world lipid management. Here is a case I received from a frustrated lipidaholic: "Sometimes I feel like I am swimming against the tide! Let me share a patient who validates the conflict between cardiology and lipidology conceptualization."

The patient is a 57 yr old man who had his first MI 8 yrs ago (age 49!!) He was stented and his EF (2005) was only 45%! His current LDL-C is 94 and his non-HDL is 111 mg/dL. He was on Vytorin 10/40 and his cardiologist, reacting to recent news switched him from the Vytorin to Simvastatin 80. The clinician is fine with increasing the statin dose, as he would like to see him in the LDL-C range of 70. He cannot find a piece of research that shows 80 mg of Simvastatin will do that. He states that that Crestor 10 or 20 would have been a better choice, and that he believes that Zetia is still appropriate in combination with the statin. But, of course, he laments, a cardiologist gets more respect than a Family Practice NP.

DAYSRING DISCUSSION

Well I'll bet this scenario is happening all over the place since the one-sided ACC discussion of the ENHANCE trial (a panel of 3 discussed their opinions without offering any time for those who disagree). I also have no problem with using a more efficacious statin if need be. What the cardiologist fails to appreciate is that Vytorin 40 mg is a more potent lipid/lipoprotein-modulating drug that is Simvastatin 80 mg (see package insert which reveals simva 80 lowers LDL-C by 49 % and apoB by 39% and Vytorin 40 LDL-C by 55% and apoB by 44%). Harold Bays nicely demonstrated in a head to head trial that Vytorin 40 is better than simvastatin 80 on LDL-C by 55 to 48% (Clin Ther 2004;26:1758-1772). In another one of the first classic studies of Vytorin, Dr Ted Feldman concluded that: "Ezetimibe plus simvastatin was well tolerated, with an overall safety profile similar to that of simvastatin monotherapy. So Thus, through the dual inhibition of cholesterol absorption and synthesis, ezetimibe plus simvastatin allowed more patients to reach LDL cholesterol <100 mg/dl at a lower simvastatin dose and with fewer dose titrations than simvastatin monotherapy (Am J Cardiol 2004;93:1481-1486)." So I ask why is anyone using simvastatin over simva/ezetimibe in patients not at goal?

As far as thinking you have to be on a gorilla (max dose) statin to maximize outcome improvement, well that is just silly (even though it seems to be accepted as fact by so many). In both PROVE IT (J Am Coll Cardiol 2005;45:1644-8 and TNT (Am J Cardiol 2007;100:747-752), the patients who achieved the best outcomes were those who had the best lipid (LDL-C) improvement. Pravachol 40 mg was as efficacious as Lipitor 80 mg in several patients in PROVE IT if they both got the LDL-C < 70 mg/dL and CRP < 2.0. One did not need to use the powerful

Lipitor (with its significantly higher incidence of LFT elevations compared to Pravachol) if the generally weaker Pravachol got the patient's LDL-C down. Ditto in TNT: if the smaller dose (10 mg) of atorvastatin achieved the same LDL-C reduction as the 80 mg dose (as it did in several patients), outcomes were identical. So as every trial in the last 20 years has demonstrated: getting to goal, regardless of statin dose, is the primary predictor of event reduction with statins.

Now that the ACC/ADA in its brand new consensus statement about patients with cardiometabolic risk has signed on to the fact that the only way we are ever going to solve CHD is to quantitate lipoprotein concentrations (i.e. apoB or LDL-P assays - not apoB calculations) we really need to abandon lipid concentrations (especially LDL-C) as a way to judge the efficacy of our lipid modulating drugs (Reference 1 below). The above cardiologist might be stunned to know that in the STELLAR trial of metabolic syndrome (Am J Cardiol 2005;95:360-366) patients, 80 mg of simvastatin failed to get 67% of patients to non-HDL-C goal (never mind apoB or LDL-P where it would have even less efficacy). As the new ACC/ADA guidelines point out statins are nowhere as good at reducing apoB (LDL-P) as they are LDL-C. Indeed even Crestor 20 mg only got 2/3 of patients to non-HDL-C goals in STELLAR MS study (the other statins including atorvastatin were nowhere close). So it really baffles me that anyone thinks statins alone have any real chance to wipe out the lipoprotein risk of cardiovascular disease in more than a handful of patients. For those who think the statins are the champs at CRP reduction: in the ENHANCE trial ezetimibe added to statin reduced hs-CRP 25% greater than the statin monotherapy. So if you give up the Vytorin and many cardiologists believe that lowering CRP is important (as is suggested by data from PROVE-IT and likely JUPITER) that you are in even bigger trouble (i.e. not close to goal) by stopping the combo therapy.

NCEP ATP-III in the 2004 addendum paper suggested two ways of achieving LDL-C and non-HDL-C goals. First they declared that the standard dose of a particular statin is the dose that is able to reduce LDL-C by 30-40%. I like to look at it this way. The standard statin dose will upregulate enough LDL receptors to remove enough LDL particles to reduce LDL-C by 30-40%. Clearly the number of LDL receptors (LDLr) that a statin is capable of upregulating is related to its ability to inhibit HMGCoA reductase, Thus 5-10 mg of Crestor inhibits as much cholesterol synthesis as does 20-40 mg of atorvastatin and upregulates as many LDLr. The more LDLr that are expressed the greater the apoB (LDL-P) lowering. Thus the standard dose of Crestor is 5-10 mg and that of atorva is 20-40 mg. NCEP in 2004 suggested that instead of taking forever to titrate a statin to achieve goal it makes much more sense to immediately start the dose of the statin that will achieve the desired apoB (LDL-C, non-HDL-C) reduction. Why putz around and wait?? Thus if one needs a 40-50% reduction, it is silly to start a standard statin dose: one should immediately go to the gorilla dose. If only those big statin doses did not increase the chance of myalgic symptoms this might be practical.

NCEP ATP III 2004 gave us another option to get to goal. Instead of using a large statin dose, they told us it makes just as much sense to use a smaller (and likely better tolerated) statin dose and combine it with a bile acid sequestrant (colesevelam or WelChol preferred), niacin (extended release or Niaspan preferred), ezetimibe (Zetia) or a plant stanol (absolute last choice). As you all know and as NCEP ATP-III signees knew, there is absolutely no Level I evidence, outcome data with any combination lipid drug regimens: yet NCEP still strongly endorses combination therapy because they know the only thing that has ever correlated with outcome reduction is getting to lipid/lipoprotein goal (not repeating any imaging procedure).

NCEP ATP III also states that if one is using statin monotherapy and non HDL-C is not at goal, then combination therapy benefits outweigh any risk deemed to be associated with such combination therapies.

So if we want to follow NCEPs advice on getting to goal lots of combo therapy is going to be required, especially in our insulin resistant world where statins are notoriously poor at achieving lipid and especially lipoprotein goals, The new ADA/ACC consensus panel guidelines now give us an apoB goal of 80 in very high risk patients. I hate to be the bearer of bad news, but that is just not going to happen (be achieved) very often with statin monotherapy.

In the case at hand, the patient is not at lipid goal (and likely nowhere near lipoprotein goal) with Vytorin 40 mg. Thus it is irrational to think simvastatin 80 mg has a prayer in this case. The numbers will actually worsen by taking this high risk patient of Vytorin and going to generic simvastatin. So how does any provider come to that therapeutic conclusion to replace Vytorin 40 with simvastatin 80?? There are a couple of options getting closer to goal in this case. One is to abandon Vytorin 40 mg and as the NP suggests switching to Crestor. However it would take 40 mg, not 10 or 20 mg of Crestor (a non-approved starting dose) to equal or surpass Vytorin 40 mg apoB-lowering ability. Thus one would have to go to Crestor plus ezetimibe which is the world's best apoB lowering dual combo therapy: see EXPLORER Trial (Am J Cardiol 2007;99:673– 680) or Crestor plus WelChol. The other option is to keep the patient on Vytorin 40 mg and simply add Niaspan. In this week's Journal of the American College of Cardiology is a nice study demonstrating that Vytorin plus Niaspan is an incredibly potent lipid/lipoprotein modulating triple combo- therapy (Am Coll Cardiol 2008;51:1564–72). There was an incredible 48% reduction in apoB and 52% reduction in the apoB/apoA-I ratio. Obviously one could also use Simcor and add Zetia to it instead of adding Niaspan to Vytorin. I have no idea which triple therapy might be cheaper.

Since we do not have the TG or HDL-C values in this man one can only speculate as to the proper therapy: If he is a pure Fredrickson Type II Hyperlipdemia patient (no TG/HDL abnormalities), then Crestor/Zetia or Crestor/WelChol is the way to go (or all three if he has severe familial hypercholesterolemia). Crestor, a hydrophilic statin is not only far more powerful than simvastatin it also does not have the multiple drug-drug interactions that the very lipophilic simvastatin 80 mg has. These drug-drug interactions are much less of a worry at lower simvastatin doses. Crestor at all doses is likely safer in a polypharmacy world than simvastatin 80 mg. The bad news is that even Crestor at 20 mg fails to get 30-40% of metabolic syndrome patients to apoB/LDL-P, Non HDL-C goal and you will have to still add ezetimibe (EXPLORER Trial) or a different secondary drug to Crestor to achieve goal. If this patient has a TG/HDL axis abnormality (Fredrickson Type IIB, or IV) than Simcor might be the best way to goal and then add Zetia if needed as the just published data in JACC demonstrates. Statin/fenofibrate could also be another option if the TG are high. For very high TG (>500 mg/dL) high dose N-3 FA enter into the picture.

LIPID CASE # 210 No HDL Particles

A cardiologist recently shared a fascinating case with me. The patient is an elderly (80 y/o) male, with no history of diabetes who has well controlled non ischemic cardiomyopathy/CHF condition. He has a low coronary calcium score. He is also being treated for a lymphoma with a drug called Targretin (bexarotene). The lipid/lipoprotein analysis left the cardiologist shaking his head and that is how I got involved.

Previous 2008 lipid profiles

TC = 285 TG = 480 HDL-C = 7 TSH normal No lipid meds - Started on TriCor 145 mg afterwards

TC = 174 TG = 376 HDL-C < 5.0 LDL-C cannot be calculated Glucose 97 BUN 26 Creatinine 1.4

TC = 177 LDL-C = 120 HDL-C = 11 TG = 232

As now advised by the ADA/ACC Consensus statement on managing lipoproteins in patients with cardiometabolic risk, an NMR LipoProfile was performed. Here are the findings:

LDL-P = 3192 nmol/L (perfect < 1000, high risk > 1600): This puts him in the 99th percentile or higher of the human race in terms of how many LDL particles he has.
Small LDL-P also very high at 1928 (perfect < 600)
LDL size 21 nm (Pattern A - Large)

Large VLDL-P = 0.9 (30th percentile)
Medium VLDL-P = 76 (95th percentile)
Small VLDL-P = 22 (20th percentile)
IDL-P = 0 (25th percentile)

Large HDL-P = 0
Medium HDL-P = 0.2
Small HDL-P = 0.4
Total HDL-P = 0.6 $\mu\text{mol/L}$

So Lipidaholics what are the diagnostic possibilities and what would your therapeutic plan of attack be?

DAYSRING DISCUSSION:

At first glance it looks like another patient with cardiometabolic risk (CMR) with an insulin resistant, TG/HDL axis disorder but the HDL-C is significantly lower than that seen in most CMR patients. Indeed this qualifies as a hypoalphalipoproteinemia, many of which are genetic and some of which have no association with CHD despite extremely low HDL-C. It would be very informative to know if he has had this very low HDL-C throughout his life or not or is it of recent onset. As far as the lipoprotein particles are concerned, when is the last time you saw someone with almost no detectable HDL particles. How are the steroidogenic tissues receiving their cholesterol? The answer: LDLs to the rescue. In lipidology lingo this case would be classified as extreme hyperbetalipoproteinemia (way too many apoB particles) with severe hypoalphalipoproteinemia (very few alpha or apoA-I particles)..

How can we explain this hypoalphalipoproteinemia? Certainly as TG elevate, they leave TG-rich VLDLs and invade HDL particles, via cholesteryl ester transfer protein (CETP), creating TG-rich, cholesterol poor HDLs which after exposure to hepatic lipase remodel into small or very small HDL species, the latter subject to renal excretion. Yet I cannot remember ever seeing that result in such a low HDL-C and HDL-P. Thus I do not think we can explain the extremely low HDL-C on a TG of 232 and we have to come up with another reason.

One possible explanation for the hypoalphalipoproteinemia (in a man without known serious CHD despite the nightmare LDL-P) is lecithin cholesterol acyl-cholesterol transferase (LCAT) deficiency. People with the heterozygous form of this disease usually have HDL-C levels around 10, but usually do not get CHD as they usually do not have high apoB levels. They often have elevations of TG as does this patient. Often they have lens clouding (this disorder has been called fish eye disease).

This paragraph for advanced students: LCAT is an enzyme that traffics on lipoproteins (mostly HDLs). It regulated genetically by liver X receptors (LXR) that induce esterification of the free (unesterified) cholesterol that HDLs acquire from cells changing cholesterol (by transferring a fatty acid from particle phospholipids to the number 3 position of the cholesterol molecule) to the trafficked form of cholesterol called cholesteryl ester (CE). When a long chain fatty acid attaches to the cholesterol the entire CE molecule is quite hydrophobic. The CE migrates deep into the core of the small, discoid prebeta-HDL transforming it into a larger, spherical particle (alpha HDL). Without LCAT the HDLs cannot manufacture CE and they cannot mature into large HDL species. The resulting very small HDLs are subject to renal excretion, explaining the absence of HDL particles and very low HDL-C so typical of this syndrome. Since there is also LCAT activity in apoB particles (VLDLs and LDLs), those particles also have lipid compositional abnormalities

often manifest as TG-rich particles. Lipoprotein X (Google it) is often seen in LCAT patients and is diagnosable using NMR, although it was not reported on the NMR analysis in this patient.

What about the extreme LDL-P, which is almost always associated with severe CHD. Also how can his LDL particles be very large when TG are high and HDL-C is low. Usually such patients have very small LDLs. Usually but not always. If this man's large LDLs are TG-rich and thus cholesterol depleted he will need a lot of those large LDLs to catty his cholesterol load. People with cholesterol-depleted LDLs usually have very high LDL-P levels: the two main causes of cholesterol-depleted particles are small LDLs or LDLs of any size that are TG-rich (and thus cholesterol-poor). Hepatic lipase deficiency can cause such LDL compositional abnormalities.

It is very likely that the cancer medication is a contributor. Targretin (bexarotene) is a retinoid and as all lipidologists know these drugs aggravate lipids, especially TG. The mechanism is not well understood but they clearly affect nuclear transcription factors such as the RXR (Retinoid X receptor) and the RAR (retinoic acid receptor). There is one report showing these drugs can induce apoC-III. ApoC-III is a hepatic produced apoprotein that traffics on HDLs but is rapidly transferred to TG-rich lipoproteins such as chylomicrons and VLDLs. By interfering with the attachment of apoC-II to lipoprotein lipase and apoE to the VLDL receptor or by displacing apoCII and apoE from TG-rich particles, lipolysis will be slowed resulting in increased plasma residence times of these TG-rich lipoproteins -- postprandial and fasting hypertriglyceridemia occurs.

Teleologically it is essential that TG-rich lipoproteins have the necessary time to deliver TG (fatty acids) to energy requiring cells (muscles). It would not be desirable for lipoproteins carrying TG to be rapidly removed before delivering the TG and yet it is not desirable for them to have a long existence as they can create endothelial dysfunction, etc. Their rate of catabolism (lipolysis) is controlled by a delicate balance of apoE/apoCII and apoC-III. The former two expedite lipolysis and the latter delays lipolysis. Thus the surface content of these apolipoproteins regulates the rate of lipolysis. A low apoCII/CIII ratio delays lipolysis. Retinoid by increasing apoC-III will delay lipolysis of TG-rich lipoproteins which in part explains their TG effects.

Targretin is well reported to cause severe lipid abnormalities: 55% of patients have levels > 800 with a median of 1200. Decreases in HDL-C to less than 25 mg/dL were seen in 55% and 90% of patients and TC > 300 in 60 and 70% of patients. These changes are reversible upon drug upon drug discontinuation. Thus it is quite likely the cancer drug is aggravating this man's lipids. Note the tremendous increase in medium sized VLDL-P on the NMR report. Many of these VLDLs with their increased residence in plasma are converted to LDLs. When apoC-III is high it can also bind to LDL particles, further increasing their half-life. Yet it cannot explain an HDL-P of near zero and HDL-C of < 10 mg/dL. That is why I believe there are two problems at work.

If the oncologist will not allow discontinuation of the Targretin, because of the lymphoma, one would have to treat the lipids. With the extreme LDL-P, we will have to be aggressive. I'd start with Crestor (rosuvastatin) 20 mg plus 4000 mg of N3 fatty acids (Lovaza). Normally I'd go with fenofibrate (TriCor) first, but in elderly, complex patients with CHF and potential less than optimal renal function, I'd try there N-3 FA first. With an LDL-P of >3000, I do not think Crestor can upregulate enough LDL receptors to lower the LDL-P enough so ezetimibe (Zetia) will almost certainly also be required. One must always consider how much pharmacy to use in an 80 year old and that is a clinical decision that can only be made after talking to the patient and family: risk vs. benefits!

The HDL-C levels as they cannot be changed with therapy if LCAT deficiency is the correct diagnosis. Of course lowering TG often has a beneficial effect on HDL-C and HDL-P: so if his hypoalphalipoproteinemia is more TG dependent and not related to an LCAT deficiency, then an HDL response may occur. However as noted in the new ACC/ADA guidelines, the proper way to treat low HDL-C is to lower LDL-P (apoB). I would not lose sleep over his low HDL-C.

LIPID CASE # 211 CAD with seemingly perfect lipids

Time to chase those particles again. This case up for discussion involves a 57 year old male with morbid obesity (305 lbs) and significant atherosclerosis which was diagnosed in 2005 with the discovery of hypertension and the onset of heartburn (angina pectoris) and led to a coronary stent in March 2006. The total cholesterol had ranged from 210 +/- 10 for a decade prior to the disease discovery. The angiogram at the time of the stent, revealed a 95% lesion of the "widow maker" (left anterior descending artery). Family history reveals a father who died at age 68 during coronary bypass and a bother with 2 vessel CABG at age 60. A "very fit" cousin died suddenly. A CT-angio (16 slice) was performed in November 2007 suggesting an 80% blockage of the LAD and a high calcium score (not provided). The cardiologist repeated a coronary angiogram which revealed the blockage to be 50% with no intervention performed. Since the time of the stent, the patient has been managed with Crestor (rosuvastatin) 20 mg and Zetia (ezetimibe) 10 mg daily. Other past history includes chemical (aminase) and ultrasound findings showing hepatic steatosis. The patient states: "my weight seems to be stuck at 305 lbs despite an intake of 1500-2500 cal a day I have been exercising very regularly (3-5 times a week 45-75 min), as my biggest challenge is to lose weight, while loving great food and great wines"

Current labs are:

Creatinine was at 0.7 mg/dl (norm 0.6-1.3), and BUN 11 mg/dl (norm 7-22),
Uric acid 6.1 (3.3-8.0)
TSH = 3.4
Fasting glucose = 102
Lipid/Lipoprotein numbers

TC = 103 TG = 62 HDL-C = 40 LDL-C = 51
NMR LipoProfile
LDL-P = 1193 (for a high or very high risk patient desirable is < 1000 nmol/L)
Small LDL-P = 1017 (normal < 600)
LDL size = 20.0 nm (Pattern B)
Large HDL-P = 2.9 (quite low)
Large VLDL-P = 1.7 (normal < 0.5)

Is the patient at lipid/lipoprotein goal or is there room for further CV risk reduction?

DAYSRING ANALYSIS

First of all anyone consuming 1500-2500 calories a day eating great foods and wine would need to exercise 75 minutes every day to break even never mind lose weight. As an overweight lipidologist myself, I can also proclaim that anyone who admits they enjoy eating great foods and wines is likely consuming well over 3000 calories a day. So clearly there is room for much more aggressive therapeutic lifestyle here, almost certainly with the advice of a skilled nutritionist/exercise physiologist. If weight loss is not going to happen, bariatric surgery should be seriously considered for those very high risk CV patients with BMIs well over 40.

This case is one of so many showing how misleading lipid concentrations can be. It is the reason the new ADA/ACC consensus statement of lipoprotein management for patients with cardiometabolic risk now advises assayed apoB or LDL-P be the goal of therapy beyond lipid concentrations (JACC 2008;51:1512-24 or Diabetes Care 2008;31:811-22). It would be hard to imagine a more perfect lipid profile, yet the lipoprotein (NMR LipoProfile available at www.lipoprofile.com) analysis still demonstrates distinct lipoprotein pathology. First of all one must determine is this man at high or very high risk of a clinical event? When you add up morbid obesity, family history of CAD, abnormal lipoproteins despite a powerful Crestor/Zetia combination regimen, hypertension, angina pectoris history, stent, current 50 % LAD lesion,

hepatic steatosis, impaired fasting glucose, I think we can all agree such a patient is a very high risk, vascular nightmare who is very likely to have a MACE (major atherosclerotic cardiovascular event). Another way to even better estimate risk is to perform a very specific marker of coronary inflammation, namely lipoprotein associated phospholipase A2 (Lp-PLA2), available commercially as the PLAC test. If elevated that would be another reason to worry and to become much more aggressive with medication. I'd also do a urine microalbumin screen and a HgbA1c to see if there is more of a glucose problem than indicated by the IFG.

Hopefully neither the cardiologist nor the patient is downplaying the 50% LAD lesion. As you all know, the risk of a clinical event (heart attack, stroke, angina, bypass, etc) has very little to do with the degree of arterial lumen blockage. The predominant disease is in the wall of the artery and thus angiography demonstrating nonthreatening lesions offers little in the way of prognosis as it tells us little about the presence of unstable plaque. What causes clinical events is rupture of a nonobstructive plaque (lipid-rich, thin cap) leading to the sudden appearance of a thrombus which partially or totally occludes the artery. Therefore despite the good looking lipid profile, because of still abnormal lipoproteins I would get significantly more aggressive with several aspects of treatment.

Before discussing further pharmacological modulation of the lipoproteins: what lipoprotein disorder are we dealing with? Despite two drugs that together significantly upregulate LDL receptors (LDLr) and thus induce indirect reverse cholesterol transport (hepatic removal of apoB containing particles - VLDLs and especially LDLs) the total LDL-P is still too high for a very high risk person. Part of the reason is that the LDLs are Pattern B (small or < 20.5 nm). LDLr are more efficacious at recognizing the apoB protein shape on larger, normal sized particles, than the distorted apoB configuration on smaller LDLs. By far the most common factors causing small LDL size are insulin resistance, glucose and triglyceride abnormalities, apolipoprotein abnormalities (especially high apoC-III), CETP activity, lipase activity (especially hepatic and endothelial), and particle cholesterol content. In the recently published data (J Clinical Lipidology December 2007) from Framingham Offspring Study (Journal of Clinical Lipidology (2007) 1, 583–592), lipidologist-extraordinaire Bill Cromwell describes the phenomenon that when cholesterol levels are very low (as in this case) LDL particles may be cholesterol depleted and thus it will take many more of them to traffic (transport) even trivial levels of cholesterol: the LDL-C is spectacular, yet the LDL-P remains high. In this study such patients were still at considerable risk for CHD events despite perfect LDL-C levels.

Did everyone look very carefully at the NMR results above. When used properly this profile is full of all sorts of clues regarding lipoprotein pathology, beyond LDL-P. There is little doubt this man has significant insulin resistance as demonstrated by small LDL phenotype, increased large TG-rich VLDL-P and significantly reduced large HDL-P (not induced by an HDL-delipidating drug such as a fibrate or probucol). Despite the TG level being perfect, there is obviously a delay of VLDL catabolism as large VLDL-P is elevated. Why? Something has to be delaying the catabolism of these TG-rich lipoproteins (better known as fat balls): the two most likely culprits are lipoprotein lipase impairment (not uncommon in T2DM or IR patients) or increased hepatic production of apolipoprotein C-III (lipidologists - go read about hepatic nuclear factor 4 alpha and how it regulates apo-CIII: please see Diabetes 1999;48:423-425). Too little LPL or reduced LPL activity or increased amounts of apoC-III (by hindering the C-II activation of LPL) would delay particle TG hydrolysis (lipolysis) and keep the VLDLs larger and TG-rich. The half-life of the large VLDL is thus increased, which will activate apolipoprotein D (better known as cholesteryl ester transfer protein or CETP) that traffics on the surface of HDLs. Increased CETP activity will facilitate swapping of neutral lipids (one molecule of CE for one of TG) between the large VLDLs and LDLs/HDLs. The ultimate result is creation of TG-rich, CE depleted HDLs and LDLs which are very amenable to the lipolytic action (hydrolysis of core TG and surface phospholipids) of hepatic lipase as they pass through hepatic sinusoids, leading to the creation of smaller HDL and LDL species (exactly what this patient has). So no one should be surprised that this man has small, CE depleted LDLs despite the perfect TG level. And of course as discussed above, most folks with cholesterol-depleted LDLs will almost always have elevated LDL-P (apoB). If you found

this paragraph intimidating, please re-read it slowly. It is packed full of just about everything you need to know to understand lipoprotein abnormalities in IR patients.

Ok- let's consider adjusting the lipid medications: Bottom line is we need to do the following: 1) Further reduce total LDL-P and 2) if possible make the HDLs more numerous and functional and hopefully induce macrophage reverse cholesterol transport (RCT) which is Dan Rader's descriptive term describing the HDL-mediated delipidation of arterial wall foam cells (macrophages) responsible for the plaque.

Step 1) Increase (upregulate) more LDLr to further lower LDL-P --- One could increase Crestor to 40 mg and of course continue the Zetia (See EXPLORER Trial: Am J Cardiol 2007;99:673–680). Anyone considering stopping the Zetia is going to further increase LDL-P, so that would be irrational. Upregulating more LDLr also might induce increased removal of the large VLDL-P as these particles are usually apoE enriched and apoE is a ligand for LDLr. If however, the particles are apoC-III enriched, the apoE is blocked from attaching to LDLr and removal of VLDLs will be difficult. The real problem with simply increasing the Crestor dose is that: Going from Crestor 20 to 40 in actuality upregulates very few additional LDLr: most of that LDLr upregulation came with the small dose of the statin - doubling statin doses does not provide a lot of further LDLr upregulation. This explains why most of the LDL-C (apoB) reduction with statins occurs with the starter dose. The 40 mg of Crestor might have more powerful anti-inflammatory actions than the 20 and perhaps using speculation that can help HDL functionality. Note: There is no increase in HDL-P or apoA-I in going from Crestor 20 to 40 mg.

2a) Patient has significant CAD on a statin/ezetimibe combo: LDL-P is high and LDL size is small. HDL-P is low. How about adding extended release niacin (Niaspan). Niacin/statin have excellent angiographic data supporting its use. Niacin would shift LDL size through its inhibitory effect on hepatic lipase and CETP, activity and the larger LDLs would be more amenable to removal by the statin/ezetimibe upregulated LDLr. Niacin, being an excellent drug to help reduce TG through multiple PPAR mediated actions (decrease FA synthesis, inhibition of DGAT) would reduce large VLDL formation. Niacin by impairing hepatic removal of HDLs by downregulation of the hepatic holoparticle receptor would increase HDL half life and increase HDL-P (apoA-I): please see the just published article entitled Niacin inhibits surface expression of ATP synthase beta chain in HepG2 cells: implications for raising HDL: J. Lipid Res. 2008. 49: 1195–1201. Niacin is also known to stimulate macrophage RCT through PPAR gamma effects of one of its intermediaries (Biochemical Pharmacology 67 (2004) 411–419). A recent study (J Am Coll Cardiol 2008;51:1564–72) showed superb lipid control using simvastatin/ezetimibe/extended release niacin: option include Vytorin/Niaspan or Simcor/Zetia.

2b) If apoC-III is the culprit responsible for the large VLDL-P, increased CETP activity and Pattern B LDL phenotype, fenofibrate (TriCor) might be a perfect choice. Fibrates through an inhibitory effect on hepatic nuclear factor 4 alpha inhibit apoC-III production. This would expedite VLDL lipolysis and clearance of VLDLs and LDLs. The fibrates via PPAR alpha effects also reduce hepatic TG synthesis as well as upregulation of LPL which would further enhance VLDL lipolysis and in turn reduce CETP activity. Fibrates more than any other drug increase total HDL-P, especially the small HDL species so adept at macrophage RCT. Fibrates improve insulin sensitivity which would be desirable in this patient and might impact beneficially on possible future microvascular disease.

The AHA would also strongly recommend 1000 mg of omega-3 fatty acids (Lovaza) daily as well as some type anti-platelet medication. The glucose level is impaired and it is possible that it also has to be attacked with medication (like metformin) to delay the onset of Type 2 diabetes. Aggressive BP control is clearly mandatory.

LIPID CASE #212 LowHDL-C To treat or not

The National Lipid Association's Annual meeting was a big success in Seattle. The attendance was the largest ever to attend an NLA event. Time to start planning for next year's in Miami (see www.lipid.org). There was a lot of buzz about the establishment of NCEP ATP-IV with the hope that they will join the ACC/ADA in advocating non-HDL-C and especially apoB/LDL-P testing. Everyone had their favorite lecture but mine was an advanced lipoprotein tutorial lecture by John Guyton who brought the chemical structures of lipids, lipid membranes and lipoproteins alive like few can.

I hope you got a chance to read the article published in JAMA this week on the risk associated with low HDL-C? **It is one of these mandatory reads if you manage lipids.** It is entitled "Association of Loss-of-Function Mutations in the ABCA1 Gene With High-Density Lipoprotein Cholesterol Levels and Risk of Ischemic Heart Disease" by Ruth Frikke-Schmidt et al. Using data from over 50,000 people in 3 major studies in Copenhagen, the conclusion is that lower plasma levels of HDL cholesterol due to heterozygosity for loss of-function mutations in ABCA1 were not associated with an increased risk of IHD. JAMA. 2008;299(21):2524-2532. Say what????

My readers know that unlipidated apoA-I acquires unesterified (free) cholesterol from cells via the ATP Binding Cassette Transporter (ABCA1) which drives cholesterol from within the cell into unlipidated apoA-I or Prebeta (very small) HDL species. Once acquired the cholesterol is esterified by an enzyme called LCAT: the much more hydrophobic CE drives from the surface to the center of the particle (the core), freeing surface space for more free cholesterol and making the HDL particle spherical and larger. If one does not have the gene (homozygotes) for ABCA1, it is called Tangier's disease and their HDL-C level is very low or nonexistent (zero), because the apoA-I cannot be lipidated and is excreted by kidneys. Heterozygotes have some ABCA1 function and thus their HDL-C levels are often somewhat low but not to the extreme of a homozygote. If such patients present to your office all you would observe is the low HDL-C and you would likely think they are at risk and treat them accordingly as high risk patients. We now learn, that these folks with ABCA1 down regulation with low HDL-C are not at increased risk of atherosclerosis.

The overall heterozygote frequency in the general population was approximately 3:1000. Unadjusted plasma levels of HDL cholesterol were reduced by 17 mg/dL in heterozygotes. As expected, not all heterozygotes had a low plasma level of HDL cholesterol, but 25 of 28 heterozygotes (90%) in the CCHS study and 69 of 76 heterozygotes (91%) in the CGPS study had levels of HDL cholesterol below the 50th percentile for age and sex. ---- The principal finding of this study is that heterozygosity for loss-of function mutations in ABCA1 associated with substantial, lifelong lowering of plasma levels of HDL cholesterol, but not with corresponding higher levels of plasma triglycerides or atherogenic remnant lipoproteins, did not predict an increased risk of IHD. ----- these data including 3 different genes suggest that **low HDL cholesterol is associated with increased risk of IHD ONLY in combination with a simultaneous increase in triglycerides and atherogenic remnant lipoproteins**

My Translation: The vast majority of cholesterol carried in our HDLs is pumped from hepatocytes and enterocytes into unlipidated HDLs using ABCA1 proteins. If we do not genetically manufacture enough ABCA1 proteins, our hepatocytes and enterocytes will not fill our HDL particles as much and we will have low HDL-C! So what --- why would a reduced hepatic capacity to fill HDL particles be a CHD risk factor? The major coronary risk factor is too many illegal dumpers of cholesterol - our apoB, primarily LDL particles. A liver not filling my HDL particles would not raise apoB (atherogenic particle concentration).

Low HDL-C is not **the universal, absolute risk factor** that we all have been taught. We now see studies where low HDL-C is not a risk factor and studies where high HDL-C is. There are genetic conditions affecting both HDL-C, HDL remodeling and HDL function that are not associated with CHD and the one discussed above is not that rare. The clinical pearl that you need to know is that the vast majority of folks who get CHD associated with low HDL-C have elevated TG which leads to lots TG-rich (cholesterol depleted) LDLs and remnants (high apoB or LDL-P). You and I have been calling these patients "TG/HDL-C axis disorders. Bottom line: Next time you see "isolated low HDL-C" do not assume you have to treat. Best bet is to check apoB or LDL-P. I have been saying for years that TG are big part of the evil in an insulin resistant America (no matter what the LDL-C) because high TG are very often associated with overproduction of apoB (atherogenic particles) and study after study supports it. So yes in most of our patients low HDL-C is a big risk factor, but not in all. You have to think about whom with low HDL-C warrants Rx, and who does not. High TG is the clue: respect low HDL-C more in patients with abnormal TG. Let's "segway" this new study into the following patient:

This issue's case deals with a common problem: low HDL-C in young folks: Few young people have a high ten year risk (Framingham) of CHD but they may well have a very high lifetime risk of an atherosclerotic event. At one point does one get serious with pharmacological therapy -- right away and totally prevent the disease, or let the disease get established and then treat with the hopes of preventing the established disease to cause a clinical event. Do ten year risk assessment tools have any real use in young people or are they a disservice?

Professor John Kostis of UMDNJ (President of NELA) wrote a spectacular piece in the Journal of Clinical Hypertension: 2006 Volume 8 Issue 7 Page 519-520 and some of what he stated is:

"Age is the strongest determinant of absolute risk. The algorithms under emphasize modifiable risk factors by emphasizing age. The guidelines are based on vague estimates of cost effectiveness, assumptions of individual and societal values that have not been explicitly debated and accepted, and on the implicit conviction that preclinical asymptomatic functional and structural abnormalities are irrelevant before they lead to cardiovascular events. These functional and structural cardiovascular abnormalities are caused by risk factors and precede the occurrence of morbid and mortal events. Prevention of these asymptomatic functional and structural abnormalities by controlling all risk factors will result in the prevention of cardiovascular events. Age should be removed from the algorithms used to decide whether to treat risk factors. Physicians should treat risk factors in all patients, regardless of age. Lifestyle changes to decrease risk factors are advised for the young and old. Why should physicians avoid prescribing pharmacological treatment of risk factors because of young age? The target of therapy should not be to postpone events, but to avoid the disease. To wait for a person to become a high risk by getting older and developing target organ damage before treating is committing "an impossible sin"—"this is madness."

So how did I answer a clinician concerned about a 22 y/o male, who is a senior in college with a history of dyslipidemia, ADD (treated with Adderall), and a complaint of palpitations on exertion. He drinks 3-4 beers per week, denies tobacco use and exercises only 1-2 days per week (for maybe 30 minutes per day). His family history reveals his mother and father are in the mid 50s with low HDL-C between 25 and 32 mg/dL. His height is 5'10" and weight 165 lbs.

His lipid profile revealed a TC of 139, LDL-C of 75, TG of 174, VLDL-C of 34 and an HDL-C of 29. The non-HDL-C calculates to 110 mg/dL. The TG/HDL-C was: 4.1. The provider also performed lipoprotein testing using the NMR LipoProfile and the results are:

LDL-P 1340 (borderline risk): The bottom 20th percentile of the population is < 1000 nmol/L
Small LDL-P 1111
LDL particle size is small at 20.1 (Pattern B)
Large HDL-P 3.1 (low value with > 9 expected)
Large VLDL 8.5 (very high: <0.5 is normal)

He was apparently tried on Niaspan at that time by a primary care provider he was seeing then, but per his mother was never told about the flushing, taking Aspirin, taking it at bedtime with low fat snack, etc....and as often is the case, he flushed significantly and stopped the medication immediately.

2 months later he shows up at a new provider now wanting to know what he can do for his cholesterol. He refuses to take Niaspan again, even though with a few modifications his likelihood of flushing would be reduced. So, the patient was started on TriCor 145 mg daily to try and increase the production of apolipoprotein A-I (apoA-1) to increase his HDL-C.

He then had his NMR profile repeated 6 weeks later (not 12 weeks) b/c he was home from college then The new profile was:

TC = 145 LDL-C = 100 HDL-C = 23 TG 112 VLDL-C = 22 Non HDL-C = 122 TG/HDL-C = 4.9
LDL-P 1621 with small LDL-P 1438 (both increased from previous)
LDL particle size 20.0 (Pattern B)
Large HDL-P 0.4
Large VLDL 1.4

So following 6 weeks of a fenofibrate HDL-C and large HDL-P dropped, LDL-P went up, concentration of large HDL dropped also. TG were reduced as expected, but the clinician wanted to know what is going on with the rest of his panel? He stated that he commonly sees LDL-C go up in patients like this, esp after treating their TG, but does not see their LDL particle number go up. The clinician states: Once finals are over we will try and re-challenge Niaspan if he is willing, but in the meanwhile, what should be done regarding his therapy?

DAYSRING THOUGHTS

The TG/HDL-C axis abnormality (high TG with low HDL-C) is typical of an insulin resistant patient with cardiometabolic risk but he is not obese and as far as I know there is not a problem with BP or glucose so he cannot be diagnosed as the metabolic syndrome. Looking at his history and the first lipid/lipoprotein results he would be classified as low risk and indeed one could make the case he did not need any further therapy other than lifestyle (especially stopping the alcohol). Despite an HDL-C that NCEP calls high risk, he is clearly at NCEP ATP-III lipid goals (LDL-C and Non-HDL-C). Never forget there is no specific HDL-C goal of therapy in NCEP ATP-III (low HDL-C is a risk factor but not a goal of therapy). In at risk patients with low HDL-C, the therapeutic mission using lifestyle and drugs if necessary is not to increase HDL-C per se but rather to lower the atherogenic apoB particles. In the patient at hand both LDL-C and non HDL-C were fine.

The LDL-P in that first profile is around the 50th percentile of the population instead of the desirable below 20th percentile mark. Thus I suspect there is long-term CV risk and as per the Kostis editorial above I do not believe it can be ignored despite NCEP lipid guidelines. Of course increased exercise and a South Beach or DASH type diet will be advised. A trial called MELANY was published last year (Ann Intern Med. 2007;147:377-385) and pretty much ignored. It was a five year study of over 13,000 men age 22-46. A rise of TG from below 60 to > 164 over 5 years was associated with a four-fold risk of atherosclerosis (diagnosed via routine stress testing followed by coronary angiography).

My readers know that TG, a pathetically ignored risk-factor by far too many clinicians, is associated with CV risk for many reasons: Hepatic fat (TG) drives apoB (risk factor #1) by increasing hepatic production of TG-rich VLDL particles many of which become IDLs and especially LDLs after lipolysis (lipase induced hydrolysis or removal of their TG). Increased residence time of TG-rich lipoproteins increases CETP activity, whereby TG are swapped for cholesteryl ester molecules between VLDL and HDLs and LDLs. The latter become TG-rich and cholesterol depleted (explaining the reduced HDL-C and LDL-C so typical of patients with high TG) and ultimately after further lipolysis via hepatic lipase the HDLs and LDLs lose their TG and become small. ApoA-I breaks off of small HDLs and is excreted and the small LDLs have prolonged half-life's leading to increased LDL-P. The TG-rich particles also disturb coagulation, inflammation, endothelial function and increase blood viscosity. These pathological effects of TG begin at levels as low as 70-100 in some people and for sure by levels of 150-200 mg/dL. The NMR profile in this man showed increased large VLDL-P concentrations and although it was not provided to me, there may have been increases in the smaller VLDLs and IDLs as well.

Also not reported to me was the total HDL-P: we see that he lacks proper amounts of large HDL-P (so typical of patients with IR and high TG. When looking at the NMR report, one has to add up the large, medium and small HDL-P numbers to get total HDL-P (not possible with the truncated LabCorp NMR report). NMR also does not count unlipidated apoA-I or prebeta HDLs (the most important HDLs) but they are usually no more than 5% of total HDL-P because of their extremely short half-life. The provider mentioned apoA-I: that is another way of estimating HDL-P (as there are 2-4 apoA-I proteins on HDL particles, unlike apoB where there is only one molecule per beta-lipoprotein particle). Epidemiological studies have consistently shown low apoA-I to be a powerful risk factor as has low HDL-P (especially large HDL-P) in NMR studies. Of course most (not all) people with low HDL-P or low apoA-I also have low HDL-C.

In the patient under discussion, we know his lack of large HDL-P and likely low total HDL-P is TG induced through the mechanisms explained above. But please never forget AND THIS IS SO CRITICAL, TG-induced low HDL-C levels are almost universally associated with high apoB (LDL-P) and that explains a lot of the CVD risk in patients with low HDL-C (as indicated in the JAMA study quoted at the top of the newsletter). It also is why statins, not niacin or fibrates or N-3 fatty acids are always the first line drug to treat low HDL-C or high TG between 150-500). However it is unlikely that the statin will get all patients to apoB or LDL-P goal even though it will get patients to LDL-C goal.

In this case when the original provider saw the lipid profile he clearly recognized the low HDL-C associated with high TG, was a major risk factor. Unlike the cases described in JAMA, this man does not have an ABCA1 mutation and we know that because his TG are high! This is a low HDL-C that we have to very seriously respect. He then made the therapeutic mistake of not first-line prescribing a statin. As described, Low HDL-C is an apoB problem and the best apoB monotherapies are statins (proven in numerous trials). Statins upregulate LDL receptors (LDLr) inducing indirect reverse cholesterol transport (RCT) i.e. hepatic endocytosis of apoB particles. The more potent the statin (rosuvastatin is the most potent) the greater the apoB (non HDL-C and LDL-C) reduction. For patients with very high apoB or LDL-P levels, adding ezetimibe to the statin will upregulate more LDLr than will the statin monotherapy. Certainly additional drugs may be needed, especially when TG/HDL-C axis abnormalities are present: The STELLAR trial showed statins to be not very good at getting non HDL-C to goal in patients with cardiometabolic risk, and published apoB studies show statins to be downright lousy in getting apoB to goal in higher risk patients (despite achieving LDL-C goals). One of the reasons is simple: upregulated LDLr are far less efficacious at removing small, rather than normal sized LDLs. Since patients with high TG have small LDLs, we need therapies that shift LDL size (often at the expense of raising LDL-C) added to statins: fibrates, niacin, properly dosed N-3 FA.

In the case at hand had a statin been prescribed (much easier for a college student to take) LDL-P goal might have been achieved. Was it a terrible error to start with Niaspan? Not really. Niaspan is approved as a monotherapy and niacin monotherapy has outcome evidence. The driving force

behind the apoB (LDL-P) problem in this man is TG. Niacin, properly dosed (1500-2000 mg) can be an excellent TG-lowering and apoB lowering drug. The error was not spending time with the patient detailing the proper way to administer Niaspan. Without such instructions there is little chance most patients will comply with the therapy. This man may ultimately require statin plus Niaspan. Should such a combo have been started? Simcor is now available and I think it would have been an excellent choice. There also seems to be significantly less flushing when Niaspan is coated with the simvastatin (as is the case with Simcor).

So in this patient with moderate LDL-P elevations, treatment **if needed after lifestyle** could have been 1) statin monotherapy, 2) Niaspan monotherapy with proper instructions mandatory or statin/niacin (Simcor). How about Advicor (lovastatin plus Niaspan): maybe, but the flushing is less with the Simcor than any other extended release niacin preparation and simvastatin is a more potent statin than is lovastatin..

With respect to the use and follow up profile on TriCor (fenofibrate):

Was this an unusual response to TriCor: yes. Like the provider I have not seen fenofibrate increasing LDL-P. It does not always lower it but there is no viable explanation of how it would increase it. There are certainly some people do not respond to PPAR alpha agonism. Was the patient truly compliant? His alcohol use may be higher than he lets on in which case drugs may not work well on lowering TG as alcohol inhibits hepatic beta-oxidation of FA (the main substrate for TG production).

Yet, other than the LDL-P rise, in this case it looks like the TriCor did what it is supposed to do: namely get rid of the TG-rich VLDLs and shift HDLs from large to small (which was associated with outcome benefit in VA-HIT). Usually the fibrates increase the HDL-C a mg or two, but in some patients fibrates will lower HDL-C because they significantly upregulate hepatic SRB1 and delipidate HDL particles (the smaller HDLs do not carry as much cholesterol). Inducing hepatic delipidation of mature HDLs allows the cholesterol to subsequently be excreted in the bile: Unfortunately the LabCorp version of NMR does not give you the critical increase in small HDL-P number seen with fibrate therapy (I think that is a must if a patient is on a fibrate and I would order a LipoScience performed NMR in such patients henceforth). An increase in total HDL-P and shift of HDL size from large to small is a sure sign the fibrate is doing what it is supposed to be doing to an HDL. If one were measuring apoA-I there would be an increase.

Therapy: Stopping alcohol and continued use of TriCor should normalize his still slightly elevated TG-rich lipoproteins (large VLDL). Most data show fibrates work best when there TG are > 200 mg/dL. Alcohol (occasionally used by college students despite their denial) inhibits beta-oxidation of FA thus enhancing TG synthesis. As the new ADA/ACC consensus statement clearly emphasizes the first line treatment for this young man and all patients with cardiometabolic risk is lifestyle and a statin, not a fibrate or niacin. If the alcohol avoidance and lifestyle and statin do not normalize his lipoproteins then niacin is the recommended add on. Clinical trial data support fibrates when metabolic syndrome or T2DM are present and the TG are > 200 mg/dL. That was not the case in this man. In the above case could one simply keep the patient on TriCor and add a statin? I guess, but because of the low HDL-C, and a TG < 200 mg/dL, as discussed one might prefer the Niaspan and statin (Simcor).

How about statin and N-3 FA - Sure the COMBOS study (see Lovaza package insert) shows that simvastatin and Lovaza (4000 mg) significantly, lowered non-HDL-C more than did the statin alone. We do lack outcome data in patients with high TG using N-3 FA, but we all use drugs mostly to get to goal as there is very little combination therapy outcome data in existence.

It is my belief that in patients with TG-rich lipoproteins we often (sooner or later, especially if lifestyle is not happening) have to add drugs that inhibit TG synthesis (fibrates, N-3 FA and niacin). If the patient would agree to extended release niacin again (titrated and taken properly), I would go there. For cost and compliance reasons, Simcor makes the most sense since it is the

most tolerable form of prescribing niacin: it would work well (reduce LDL-P) because it will also get rid of his TG-rich lipoproteins (if he stops drinking).

However because the niacin partially retards the liver from delipidating the HDLs and it inhibits hepatic lipase, the HDLs will enlarge and the HDL-C will be higher than it would be on the TriCor. But if one checks HDL-P it will be the same on the TriCor or Niacin despite the vastly different HDL-C. Both fibrates and niacin have the potential to also increase the HDL functionality. Although what a drug does to HDL-C is not that important (see reference 1 below), there is emerging evidence that it may be important to increase HDL-P and especially HDL functionality (which of course we cannot assay). Usually fibrates do increase total HDL-P (although they reduce large HDL-P, they dramatically raise small HDL-P). The smaller alpha and prebeta HDL particles of course are the best at performing macrophage RCT.

LIPID CASE # 213 Postprandial TG elevation

The premature CV death of Tim Russert, may he rest in peace, was a reminder that we clinicians must do a better job in screening patients and that we have to be incredibly aggressive in treating any risk that is discovered. The sooner all providers, not just lipidologists adopt the new ACC/ADD Consensus statement on Lipoprotein Management on making all therapeutic decisions using atherogenic lipoprotein concentrations (apoB or LDL-P) rather than lipid concentrations (especially LDL-C) the sooner CVD morbidity and mortality will improve.

I originally had no clinical information on Mr. Russert, but I shuddered at the thought that he might have been managed using LDL-C and that he was being followed and reassured using stress testing. Phenotypically he looked like a metabolic syndrome (had LVH on autopsy indicative of hypertension) and if so statin monotherapy (even at large dose) was most unlikely to get him to LDL-P goal for high or very high risk patients. Now yesterday, on the net I find out that indeed he did have the metabolic syndrome as he had obesity, impaired fasting glucose, a low HDL-C (37) and an LDL-C of 68. His physician commented that the lipid profile is acceptable! Neither non-HDL-C or apoB (LDL-P) was reported and one can only assume they were not considered. When does not following the ACC/ADA consensus statement become substandard care?

Ever since ENHANCE I have been hearing the following from too many folks who should know better: "I'm going back to statin monotherapy." That would be like a hypertension specialist stating he was going back to HCT! How silly! ApoB immediately raises 15-20% when one stops a second drug like Niaspan, fenofibrate, ezetimibe, high dose N-3 FA or BAS. 2/3 of the events still occur even on high dose statin therapy. If one really wants to bail on a secondary therapy ezetimibe, for whatever silly reasons, one has to immediately add niacin or fenofibrate or colesvelam --**THERE IS NO GOING BACK TO STATIN MONOTHERAPY FOR HIGH RISK FOLKS. It is an absurd premise**

The following is a challenging case I was asked about and the discussion is pertinent to Mr. Russert. A 46 yrs old male having recurrent chest pain for the past 6 yrs. He had a baseline coronary angiography in January 2001 which revealed scattered coronary ectasia. Height is 5' 3/4" and weight 188 lbs (BMI =29).

His lipid and lipoprotein analysis from January 2002 was as follows while using Pravachol 40 mg & Altace 10 mg daily:

TC = 166 LDL-C = 116 HDL-C = 37 Triglycerides = 61 VLDL-C = 12 Non HDL-C = 127

LDL particle concentration (LDL-P) = 1141
LDL Particle size 21.4 nm (Pattern A or large)
Large HDL-P = 18
Large VLDL-P = 4.

Subsequently he had recurrent chest pain in 2007; He had a normal Cardiolute stress test as well as elective coronary angiography which revealed normal left ventricular function with ejection fraction of 55-60%; diffuse three vessel ectasia, especially in the LAD and right coronary artery; coronary vessels seemed to fill in a somewhat delayed fashion. He also had CT Coronary Angio October, 2007 which revealed right dominant, coronary ectasia in the LAD, circumflex, and large first diagonal artery; minimal nonobstructive plaque in the right posterolateral branch. At this time he takes Diovan Hct 160/12.5 and Vytorin 10/20 (for one year).

Very recently he had some recurrent chest pain. Stress/echo normal. Coronary Calcium is zero. The most recent lipids and NMR analysis is:

Non fasting: TC = 164 LDL-C = 85 HDL-C = 29 TG = 249 VLDL-C = 49 Non HDL-C = 135
Fasting the TG dropped to 83 with a VLDL-C = 16
LDL-P = 1646
Small LDL-P 1637
LDL size 19.1 nm
Large HDL-P = 2.2
Large VLDL-P = 4.6 (n<0.5)
hs-CRP = 4.93
Lp-PLA2 pending

He met with a nutritionist who recommended an aerobic and weight lifting program and 20 lb weight loss as well as taking N3-FA daily (1000mg EPA and DHA). The provider advised adding Niaspan 500 mg daily and possibly 500 mg BID and aspirin. I was asked to comment

DAYSRING DISCUSSION

The first problem is what is the risk of this patient? He has no major atherosclerosis other than the small nonobstructive disease described on last angiogram. The angina is thought to be due to the coronary artery ectasia not atherosclerosis. Using Framingham Risk calculator (FRC) he is low risk for an event over the next ten years. However it is inappropriate to use FRC since he is on lipid medication. The FRC was developed from drug naive folks in Framingham and as noted in NCEP ATP-III should not be used to ascertain risk in patients on medication. Thus the only thing I can use as a lipidologist are his lipid and lipoprotein concentrations. He does not meet the criteria to diagnose the metabolic syndrome although the, high BMI, low HDL-C, elevated hs-CRP and postprandial hypertriglyceridemia strongly suggest insulin resistance. Despite the low HDL-C, which is a major independent risk factor for CHD, he is at NCEP ATP-III goal for a low or moderate risk patient. If for whatever reason you think he is high risk, he is still at LDL-C goal and just 5 mg/dL above the desired non-HDL-C goal, so the nutritionist is correct in her weight loss advice.

But let's get real: It is 2008 and this patient would be much better served if his provider followed the recommendations of the new ADA/ACC Consensus Statement on Lipoprotein Management for patients with cardiometabolic risk. LDL-C, since it is fine cannot help us in this man. The Non-HDL-C is unremarkable. Of course as is clearly evident on the lipoprotein analysis he has way to many atherogenic apoB (LDL and VLDL particles). Indeed the LDL-P of 1646 nmol/L puts him in the top 20th percentile of the population (high risk): in other words 80% of the population have a lower LDL-P). In the ADA/ACC statement they clearly pointed out that while non-HDL-C is a significantly better predictor of risk and goal of therapy than is LDL-C and while he has a high correlation with apoB (LDL-P), there is only moderate concordance between Non HDL-C and apoB (i.e. they are discordant). What this means is that in the individual patient, one cannot rely on non-HDL-C to totally explain risk. This is why they stated that all pharmacological decisions should be made using apoB (LDL-P). All of this is founded on one principle: The determining factor on whether an apoB particle (>90% of which are LDLs due to its longer half life) will, with its

load of cholesterol and cholesteryl ester, enter the artery wall is particle number (apoB or LDL-P), not how much cholesterol is within the particle (LDL-C)

If you look at the changes in the lipid/lipoproteins over the five years between tests he was clearly becoming more and more insulin resistant: the rise in TG, especially postprandial TG, worsening HDL-C suggest it and the rising small LDL-P, large VLDL-P and dropping large HDL-P confirm it. Although I have discussed it many times before, let's go over why these lipoprotein changes occurred and why there is such a disconnect between LDL-C, non-HDL-C and atherogenic particle number.

The liver produces apoB containing VLDL (apoB) particles to carry TG from the liver to the muscles and adipocytes (for energy use or storage respectively). The more TG that are in the liver, the more the VLDL secretion number will be and the more TG-rich the individual VLDL particles will be. Hence one will notice an increase in the large VLDL-P number. Multiple studies confirm large VLDL-P is an independent predictor of risk. Why? In IR patients, the over-secretion of apoB VLDLs will raise TG and VLDL-C levels: note VLDL-C is calculated using the Friedewald formula where $VLDL-C = TG/5$. Normally the VLDL particles undergo rapid hydrolysis of their TG upon exposure to lipoprotein lipase (LPL) in muscle and adipocyte capillaries. For this to happen, the apoA-V on the VLDLs anchors the VLDL to areas of LPL expression. Next apoE (several molecules of which are on VLDLs) bind to the VLDL receptor in this same vascular beds. Finally apoC-II binds to the LPL and the TG are rapidly hydrolyzed to fatty acids (FA). Obviously if one had low apoA-V, abnormal apoE or low apoC-II, hypertriglyceridemia would be present. ApoC-III is another surface protein, often present in excess amounts in IR patients. Too much C-III displaces or camouflages A-V, C-II and E which would also delay lipolysis of the TG-rich lipoproteins, contributing to fasting and PP hypertriglyceridemia.

If a large TG-rich VLDL (or chylomicron) has delayed lipolysis (increased half life) it will begin to swap TG for CE with cholesterol and CE trafficking particles that normally carry less TG (LDLs and HDLs). Cholesteryl ester transfer protein (CETP) swaps neutral lipids: one molecule of TG for one of CE. The longer the half life of the TG-rich particle the more swapping of CE for TG will occur. This process creates TG-rich, CE-poor LDLs and HDLs and VLDLs (chylols) that are less TG rich and more CE-loaded. This will be reflected in the lipid profile with increasing VLDL-C, reducing HDL-C and variable (often reducing) LDL-C. These particles have in effect had their internal lipid composition changed. As the now CE-rich VLDLs are subjected to further LPL exposure they lose additional TG, changing them into smaller VLDL species or even IDLs that are now CE-rich: these are referred to as remnants (considered as quite atherogenic) and their presence is suggested by elevated VLDL-C.

Now let's deal with the altered LDL particles: normal LDL particle composition is 80-90% CE and 10-20% TG. After exposure to CETP and swapping of TG for CE, the LDL composition changes in that there will be less CE and more TG inside the particle. In effect the LDL becomes a cholesterol-depleted particle. It will take many more, CE-depleted LDL particles to traffic a given level of cholesterol (LDL-C) than it would particles that are not CE-depleted. Many of the TG-rich, CE-poor LDLs undergo further lipolysis as they pass through the liver where they are exposed to hepatic lipase (HL). HL has the ability to not only hydrolyze TG, but also surface phospholipids: the loss of TG and phospholipids creates much smaller LDLs. It takes many more small LDLs to traffic a given amount of CE than it does large LDLs. The conformation of the apoB on small LDLs is changed and it is less readily recognized by LDL receptors. Thus small, LDLs will have increased plasma residence time, further elevating LDL-P (the number 1 risk factor for CHD).

SUMMARY OF THIS CRITICAL CONCEPT

Four patients (A, B, C and D) have the exact same atherogenic particle count (apoB or LDL-P): That means, other issues being equal (BP, smoking age, etc) they have the exact same CV risk.

Patient A: Has normal sized LDL particles with normal LDL composition (90% CE, 10% TG)

Patient B: Has normal sized LDL particles that are TG-rich and CE poor (50% CE and 50% TG)
Patient C: Has small LDL particles that are TG-rich and thus CE-poor.
Patient D: Has very small LDL particles with normal LDL TG/CE composition

The LDL-P and apoB are the same in all patients: If you measure those parameters you would rapidly see that and treat them aggressively if the count was high. However if you were only looking at the lipid profile and especially LDL-C:

LDL-C (A) < LDL-C (B) < LDL-C (C) < LDL-C (D)

Thus the LDL-C levels are all over the place, yet the lipoprotein related risk is identical in all. If the LDL-C was OK (at goal) one might not realize they need Rx unless you order apoB (LDL-P). Because if the apoB is high despite the normal LDL-C, treatment is indicated (see new ADA/ACC statement).

Finally what about the HDLs whose composition was also changed to a TG-rich, CE poor particle. As it passes through the liver, HL also transforms it into a small dense HDL: as the HDL gets very small it loses surface apoA-I which rapidly passes through the renal glomeruli and is excreted. This over time will obviously lead to reduced apoA-I, HDL-P and HDL-C. It also explains why this patient has a very low level of large HDL-P. Since the vast majority of HDL-C is trafficked on the larger HDL species, persons who lack large HDL particles will have low HDL-C (< 40 mg/dL). Since there are so few large HDLs, the predominant HDL species that will be present in this patient is the small HDL. This does not mean the small HDL is bad, it is just that in patients with rising TG, one will simply convert their large HDLs to smaller species, some of which are excreted. The most important thing to remember is that these patients with low HDL-C, caused by the presence of elevated TG and CETP activity will all have high LDL-P and Remnant-P counts. Take home point: In those with CV risk who have low HDL-C, high LDL-P (apoB) will almost certainly be present and thus the proper way to treat low HDL-C on those at risk is to normalize LDL-P (apoB, or its lipid surrogate non-HDL-C). Finally the TG concentrations at which CETP activity increases and starts to create the havoc described above is 70-130 and it worsens as the TG rise further. It should now be clear why patients with PP TG abnormalities have high apoB and low apoA-I.

This man clearly have a high risk LDL-P, and almost all of the particles are quite small. 80% of the population would have less LDL particles than him. His large VLDLs which are carrying the excess TG out of the liver are also quite abnormal. I'll bet if one looks at the NMR graph on the report, the smaller VLDLs are also increased. Therapy is to reduce the numbers of LDL-P. Statins like Pravachol or statin/ezetimibe like Vytorin simply upregulate hepatic LDL receptors (LDLr) (with ezetimibe making all statins much better at LDLr upregulation). Unfortunately LDLr are not very good at recognizing and removing small LDLs. Thus the LDL-P remains high even though the patient is taking Vytorin a powerful LDLr upregulating drug. In this case, one needs to shift (increase) LDL size, making the particles more likely to be removed. This requires a drug that inhibits TG synthesis (fibrates or niacin or high dose N-3 FA).

Because the fasting TG are < 200 mg/dL, it is likely that niacin will work better than a fibrate (fenofibrate or TriCor would be the preferred fibrate to add to a statin). Thus I would add Niaspan 500 mg daily for 3 weeks and then immediately escalate to 1000 mg daily. The NMR (an absolute must for future follow up) should be repeated in 8 weeks adding the third drug. The fibrate outcome data is usually best when IR is present and the TG are > 200. However fibrates are very effective in reducing PP hypertriglyceridemia which is a big part of this patient's [pathology]. Since fenofibrate and ezetimibe work synergistically together, if I added TriCor I would continue the Vytorin.

LIPID CASE # 214 Looking at HDL-P

Not the greatest weather weekend here in Jersey. Thus time can be put to focusing on lipid education and not outdoor lipid cooking. Hope Tim Russert's tragic death despite and LDL-C of 68 on a statin has made all providers start seeking the real cause of atherosclerosis - elevated apoB or LDL-P by assays or at least by dwelling on non-HDL-C instead of LDL-C.

This issue's case involves a 40 year old 3 times weekly aerobically exercising, nonsmoking, insulin sensitive (fasting glucose=70), minimally overweight (BMI 25.15, waistline=30 inches) white female. She is described an anxious woman who knows just enough to be dangerous to herself (reads various diets, Googles too many things to pick up disinformation). She is concerned because she just turned forty and has a family history of CAD: her diabetic globally vasculopathic nonsmoking father (at age 47 with an MI, age 58 had a CVA, age 55 bilateral BKAs due to nonhealing wounds from his PAD, also had two CABGs in that time window) who died at age 64 of an infarcted bowel from ischemic colitis.

Her meds include: Yaz which is an oral contraceptive containing estradiol and drospirenone. OTC fish oil, name brand unknown. Zoloft 100 mg po daily for anxiety. Desyrel 50 mg po QHS for insomnia and Lunesta 2 mg po qhs for insomnia

Her lipid/lipoprotein parameters (not on any lipid meds) shows:

TC = 275 LDL-C = 92 mg/dl HDL-C = 107 TG = 64 VLDL-C = 12
TC/HDL-C = 2.6 Non HDL-C = 168

NMR LipoProfile from LipoScience

Total LDL-P = 968 Considered ideal when < 1000 nmol/L (Bottom 20th percentile of population)

Small LDL-P = 0

LDL particle size: 22.6 nm Pattern A >20.5 nm Pattern B < 20.6 nm

Large HDL-P = 19.2 micromol/L (high)

Medium HDL-P = 12.8

Small HDL-P = 14.6

Large VLDL-P = 1.0 nmol/l (normal < 0.5 nm)

Lipoprotein associated phospholipase A2 or Lp-PLA2 (PLAC test) despite the high HDL-C and undetectable small dense LDL is elevated at 254. The hs-CRP is also elevated.

The provider had the following questions:

1-Is the elevated Lp-pLA2 attributable to her OC use?

2-Do we need to worry that her elevated HDL is in some way conformationally dysfunctional? Are there any tests I can do to further stratify this, and do you have any literature you think would be relevant in this regard.

3-What do you know about people who produce zero small dense LDL?

4-Would you treat her with any particular agent since her Lp-PLA2 is elevated, or would you simply stop OC use and retest in a couple months?

DAYSRING DISCUSSION

Despite the High HDL-C in the case under discussion, the woman is rightly concerned because of premature heart disease in her father and the elevated Lp-PLA2 and hs-CRP. Each by itself is a strong predictor of clinical CHD events. The good news is her LDL-P is normal (in the bottom 20th percentile) and this is the most important lipoprotein predictor of events. What do HDL-C levels really mean with respect to risk in a given individual, especially women? In general low HDL-C

is major risk factor and high HDL-C is less associated with CHD in both genders: However in individual patients that may not always be the case. Baseline lipid data from HERS (Heart and Estrogen/Progestin Replacement Study) showed 20% of women with CHD (before taking HRT) had HDL-C values between 60 and 80 mg/dL (Am Heart J 2001;288-96).

A few weeks ago JAMA published a study dealing with ABCA1 mutations showing how easy and common it is to have low HDL-C and no CV risk (JAMA. 2008;299(21):2524-2532). The authors noted that most folks with low HDL-C who get CHD also have elevated TG. And indeed recent data from IDEAL and EPIC Norfolk trials have shed light on who with high (even very high) HDL-C gets CHD ((J Am Coll Cardiol 2008;51:634-42).

So let's look at closely at her HDL-C of 107 mg/dL. A total HDL-C value simply tells us how much cholesterol is being trafficked within all of the HDLs in a deciliter of, plasma. The cholesterol is distributed within all of her HDL subspecies (small and large) and the NMR profile shows us a large HDL-P of 19 (high), a medium HDL-P of 12.8 (high) but very few small HDL-P of 14.6. Therefore her total HDL-P is $19 + 12.8 + 14.6$ or 46.4. This is a high total HDL-P. So not only does she have lots of HDL-C she also has lots of HDL particles. That means even though she has predominantly large HDLs that are not super large (which tend to be dysfunctional). In the recent data from IDEAL and EPIC Norfolk study quoted above, the people with High HDL-C who had CHD had lower HDL-P levels and very large HDLs (it is presumed the very large HDL is actually a cholesterol donor to foam cells, not a cholesterol acceptor ---- such HDLs make the plaque worse). Those that did not get CHD in the study had lots of HDLs but they were not as big. So HDL-P and not HDL-C is the more important parameter (sound like what we now know about LDLs) and this patient has lots of HDLs and they are not so gigantic.

Note: The NMR technique does not capture unlipidated apoA-I or pre-beta HDLs, which many believe to be the most cardioprotective HDLs (as they have the maximum ability to delipidate tissues, especially foam cells). These can be captured by ordering apoA-I. However apoA-I has weaknesses as maturing HDLs carry 2-4 molecules per HDL particle so apoA-I also cannot accurately tell us HDL-P. In most folks the unlipidated apoA-I or pre-beta HDLs only represent about 5% of total HDL-P, so NMR is the best way to accurately count HDL particle number. The EPIC Norfolk, IDEAL studies used apoA-I as their way of quantifying HDLs. It thus would be interesting to order apoA-I on this patient.

Ultimately all HDL discussion comes down to HDL particle functionality: do the HDLs have the capacity to delipidate sterol-laden macrophages in the arterial wall and are they trafficking all of the potentially cardioprotective proteins like paraoxonase, etc. on their surface: of course we have no way in the real world of measuring this. For a current state of the art discussion on HDL functionality testing please see: (de Goma E et al. J Am Coll Cardiol 2008;51:2199-211 and Mowa R, et al. Clinical Chemistry 54:5;788-800 (2008): Both are part of what I call the Dan Rader classics on HDL.

More and more it appears people with dysfunctional or proatherogenic HDLs have underlying inflammation. Inflammatory proteins especially amyloid which has a high affinity for apoA-I, "assault" the HDL particles and displace many of the beneficial surface proteins. Indeed the above patient has significant elevations of two powerful inflammatory markers - hs-CRP and Lp-PLA2. This raises the question, even though the patient has lots of HDLs -- are they useless or even worse proatherogenic HDLs? I cannot answer that. In case you think this is not real I have another powerful study for you: Corsetti JP et al. Atherosclerosis 187 (2006) 191-197 -- In the THROMBO study they looked at people with very high total cholesterol levels and very elevated hs-CRP (sound exactly like this patient). The only lipid parameter that predicted clinical events was elevated HDL-C due to very large HDL particles. So much for those who believe one has to have large HDL particles! The authors believe oxidative forces make the apoA-I nonfunctional and these HDLs cannot perform macrophage RCT (delipidate foam cells). Based on this study I think this woman might have a lot to worry about.

The oral estrogen is not at play here in explaining the marked elevation of inflammatory markers. Although it can very slightly raise hs-CRP -- it cannot put it at the levels present in this case. Estrogen also does not affect Lp-PLA2. However, although oral estrogen is associated with an increase in HDL-C, it also via a first pass hepatic effect raises serum amyloid. The amyloid associates with apoA-I and renders the HDL dysfunctional in women with CHD. HDL-amyloid levels increase! (Arterioscler Thromb Vase Biol. 2004;24:1866). In a classic editorial David Herrington and John Parks reminded us "all that glitters is not gold!" He correctly states "the data emphasizes the folly of relying simply on HDL cholesterol concentration to infer a clinical effect of hormone therapy. It is questionable whether we actually have such complete knowledge about any cardiovascular risk factor, which is **why the assessment of interventions always requires confirmation with properly designed clinical end point trials**. In the case of hormone therapy, it appears that we were previously blinded by the glittery array of favorable effects on intermediate end points, such as HDL cholesterol. As a consequence, we failed to recognize the lack of proven efficacy or safety for cardiovascular disease prevention." (Arterioscler Thromb Vase Biol. 2004;24:1741-1742).

With respect to the zero small LDL-P. If you do a lot of NMRs, it is not uncommon to have predominantly large and very few if any small LDLs. Classic example is familial hypercholesterolemia or FH (lots of large LDLs), which this patient does not have. She may have minor some hepatic lipase variant (deficiency) which explains not only the absence of small LDL-P but the high HDL-C and high large HDL-P and a reduction of small HDL-P. If there is an HL problem, it has to be minor because usually those patients have some degree of TG elevation which is not present in this case (although there is a slight increase in the large VLDL-P). As we now know, CHD risk primarily depends on the number of LDLs, not the size of the LDLs. Interestingly Lp-PLA2 usually attaches to (has a much greater affinity for) the small LDL and persons with high Lp-PLA2 usually have lots of small LDLs. Lesson: When assessing risk, divert your attention to the total LDL-P not the phenotype of the LDLs. I am not sure if any of her psych meds can aggravate inflammatory markers or LDL size. They are not the ones classically associated with metabolic syndrome. Zolof has been described as a culprit sometimes associated with elevated LDL-C.

So what to do with a lady with some serious risk factors but a very normal LDL-P. I would do a serious search for subclinical atherosclerosis: Coronary calcium scoring and carotid ultrasounds to start with. If she has CHD I would stop the estrogen based contraceptive (normally I do like YAZ because of the drospirenone, a progestogen that can lower BP through its antialdosterone effects). If CHD is present, I'd also run noncholesterol sterol levels.

Her atherogenic particle numbers are perfect - should they be further reduced? Your guess is as good as mine. But if she had CHD, I'd try and lower the LDL-P further with a statin or stain ezetimibe combo: If she has CHD, despite her good LDL-P, her LDL-C is not at goal if she is considered to be in the very high risk category. So try and drive the LDL-C to < 70 mg/dL -- that would also drive her total LDL-P lower. The statin/ezetimibe would reduce hs-CRP more than would the statin alone if you believe it is important to reduce inflammatory markers. This also brings up another consideration: There are readily available tests that measure oxidized LDLs - Might this shed some light on this woman's CV risk? See (Circulation. 2008;118:75-83.)

What drugs can improve HDL functionality? Fibrates and niacin for sure. One might speculate that fibrates, by upregulating Scavenger receptors B1 (SR-B1) increase hepatic delipidation of large HDLs so prominent in this lady. By delipidating and reducing the size of her HDLs, they might be better able to perform macrophage RCT. Fenofibrate would also increase her HDL paraoxonase. If hepatic lipase deficiency is present fenofibrate would help. Although niacin might further increase her HDL-C and HDL size, niacin can induce arterial macrophages to secrete lipolytic proteins which frees up apoA-I at the macrophage surface, where it can attach to the macrophage ABCA1 (also upregulated my niacin) and induce macrophage RFCT.

Would statins improve HDL functionality by reducing inflammation? Interesting new data also demonstrates ezetimibe by reducing enterocyte lipidation of HDLs, may make the HDLs better delipidators of arterial macrophages, by inducing macrophage RCT (discussed in Bays et al. Expert Rev Cardiovasc Ther 2008;6:447-470 and Arterioscler Thromb Vasc Biol.2008;27:1296-1297).

). Total guesswork, but if CHD is present in this patient I'd prescribe a statin and go from there. Perhaps I might advise it even if I could not find subclinical CHD. I am uncomfortable with this woman's risk factors. How else to treat? ASA for sure if for no other reason to reduce the risk of stroke or CVA of which high Lp-PLA2 is a powerful predictor.

Everything I have suggested is miles out of the world of evidenced based medicine and one would have to have a very thorough discussion with the patient - benefits vs. risk - and then proceed.

LIPID CASE # 215 Using hormones in an MI patient

Recently we saw WHI data where although oral estrogen reduced LDL-C, it did not reduce LDL particle concentration (LDL-P) and this is why the drug did not prevent CHD in the women studied (available on line ATVB: Lipoprotein Particle Concentrations May Explain the Absence of Coronary Protection in the Women's Health Initiative Hormone Trials published July 3, 2008, 10.1161/ATVBAHA.108.170431). This paradox of estrogen (reduces LDL-C but not apoB or LDL-P) has actually been known for several years but is almost never mentioned in discussions of estrogen and lipids. Indeed I wrote about this 6 years ago in an article entitled Coronary Heart Disease in Women: Triglycerides and Lipoprotein Biology. Journal of Gender-Specific Medicine 2002;5:27-33. However there are many reasons to prescribe estrogen to menopausal women and of course premenopausally for contraception. However can it ever be dispensed to a woman who has had an MI? Get ready for a controversial newsletter.

The case for discussion is just such a case. I was asked about a pre or perimenopausal 45 year old normotensive woman, nonsmoker, who had a recent myocardial infarction with stent placement into the LAD. Her LDL-C elevation was modest but had a normal NMR LipoProfile (i.e. normal LDL-P). Her Lp(a) was normal and she has no other risk factors. She has significant dysmenorrhea and menorrhagia since stopping her oral contraceptive after her MI. She and her gynecologist would like to prescribe a hormonal manipulation-- but estrogen use in an MI patient seems to be a contraindication. What can we advise?

DAYSRING DISCUSSION

Ever since the Heart and Estrogen/Progestin Replacement study, EPT lost its luster as a cardioprotective therapy. They enrolled women with significant CHD and randomized them to placebo or Prempro (combined continuous conjugated equine estrogen and medroxyprogesterone acetate and there was no benefit. Over the initial year there was a worsening in clinical events in the EPT users. In subsequent analyses there seemed to be benefit from estrogen in women who had elevated Lp(a) and there was no CV adversity in the women who were receiving statins. Interestingly women on either statins or ASA also had significantly less VTEs. So there is some evidence that in menopausal women with CHD, using proper CVD treatments, including a statin, seems to negate any vascular adversity that EPT brings to the table. Of course such data does not exist in younger women taking OCs and the doses of estrogen used in OCs are higher than that used in postmenopausal hormonal therapies. But occasionally we as physicians have to make tough real world decisions that have not been addressed in clinical trials. Clearly this woman's menstrual symptoms are quite significant and making life miserable or we would not even entertain estrogen use. She has been carefully worked up by the GYN and some type of hormonal therapy is the solution.

We of course have to aggressively manage any lipoprotein disorder that exists as well as other CV risk factors that may be present. Interestingly her NMR profile is described as normal (at goal), but there is a modest LDL-C elevation. So what to do? Atherosclerosis is present despite the good LDL-P. Probably makes sense to drop her LDL-P by 30% which would likely also get her LDL-C to goal and a statin or statin/ezetimibe would be the drug of choice to achieve that. There is no TG/HDL-C axis disorder so fibrates or niacin are not indicated. I presume after her stent she is on ASA or Plavix.

What about the approach to her menstrual symptoms? First, the patient would have to received informed consent that estrogen has a back box warning and a contraindication against such use. Coagulation studies are in order to make sure everything is kosher there. What would be the best approach? There is a nonestrogen solution and also some estrogen possibilities I'd consider **if she is on a statin, ASA and/or Plavix.**

1) Mirena IUD: Might solve the problem without estrogen administration. This is a progestogen (levonorgestrel 52 mg) carrying IUD that serves as contraception and is used to improve dysmenorrhea. It can take several cycles to control periods but it has no estrogen or contraindication in women with CHD.

2) NuvaRing: This is a vaginal ring administered (by patient) contraceptive that containing etonogestrel/ethinyl estradiol and delivers 0.120 mg/0.015 mg per day. It is inserted and left in for three weeks and then removed for one week. It like any estrogen carries a contraindication for use in a woman with CHD.

3) Ortho Evra: The estrogen (ethinyl estradiol 0.75 mg & norelgestromin 6 mg) OC patch: Might make sense as transdermal HRT use is not as adversarial to TG and CRP, amyloid and other inflammatory proteins. This might be important as amyloid (which has a high affinity for apoA-I) induced by oral estrogen has been described as a potential cause of HDL dysfunction. However the estrogen dose in contraceptives is higher than that in menopausal hormonal therapies and even with transdermal application the OC patch can increase such proteins. (Contraception 2006 74:293-296). There may also be a significant increase in VTE with OrthoEvra but the hope is the statin and platelet drugs might lessen that risk. Use for three weeks, then have one week off the patch. Then repeat the cycle. Again, It like any estrogen carries a contraindication for use in a woman with CHD.

2) YAZ: 0.2 mg of ethinyl estradiol and 3 mg of drospirenone (a progestogen with aldosterone antagonist properties-). Higher doses of drospirenone have antihypertensive effects. Take for 24 days and then 4 days use a placebo tab. It also carries a contraindication for use in a woman with CHD.

Other possibilities: In an attempt to use lower doses of estrogen, there are menopausal HRT therapies that do have contraceptive abilities (off label use). FemHRT used at the 5 mcg ethinyl estradiol/1 mg norethindrone dose is one such product. However, it is questionable whether this will address the menorrhagia. One would have to discuss all of this with the GYN and see what his/her preference would be.

The data from the WHI (referenced above), did not support cardioprotection form HRT despite a significant estrogen induced reduction in LDL-C. Interestingly the NMR LipoProfiles in these women showed LDL-P was not reduced, creating an LDL-C/LDL-P disconnect. Such a therapy would not be expected to reduce risk via a lipid/lipoprotein mechanism despite the seemingly benefit of lowered LDL-C. So what exactly could we expect in the above woman if estrogen was administered:

Increased hepatic TG production leading to increased TG-rich VLDL-P production (increasing apoB). These TG-rich particles would increase CETP activity mediating exchange of TG and

cholesteryl ester molecules between LDLs and VLDLs. The LDL particles become cholesterol depleted, and some would reduce in size which would lower LDL-C. However the increase in VLDL-P should lead to an increase in LDL-P. Fortunately estrogen upregulates LDL receptors in the liver and thus there is not an increase in LDL-P. In essence oral estrogen creates apoB particles as well as removes them leading to no net reduction in apoB which is necessary to reduce events. In the woman above, the hormonal therapy would not affect her LDL-P but the statin therapy would significantly lower it from where it is.

LIPID CASE 216

I have been contacted about a 60 year old white menopausal female with known CAD with a 2 vessel bypass 4 years ago. Recently she developed atypical chest pain in and had a normal Cardiolyte ETT. Shortly thereafter she had a non-Q wave MI and had 2 vessel PTCA. So, her "noncardiac" chest pain was probably cardiac. She is on Lipitor 10mg, and Evista 60 mg, along with Quinapril/HCT, ASA 325, and atenolol 25 BID. She is 5'2" tall and 144 pounds. Her BMI = 26.

Lipid/Lipoprotein results

Her previous NMR LipoProfile revealed:

TC = 118 mg/dL LDL-C = 38 HDL-C = 65 TG = 75 VLDL-C = 15 Non HDL-C = 53
Total LDL-P = 760
Small LDL-P = 413
LDL particle size 21.3 Pattern A (large) is >20.5 nm
Large HDL-P = 13.3
Large VLDL-P = 1.6 (normal < 0.5)

Her most recent profile is:

TC = 149; LDL-C = 77; HDL-C = 52; TG = 99 VLDL-C = 19.9 Non-HDL-C = 97
Total LDL-P = 901
Small LDL-P of 533
LDL particle size of 21.1 (Pattern A)
Large HDL-P = 12.7
Large VLDL-P = 1.9

The provider thought her numbers had crept up some probably due to increased cholesterol reabsorption although her weight did increase from 139 to 144 and commented the patient is scared and was frustrated that they haven't been able to keep her from having events. Neither Lp-PLA2 nor hs-CRP has been checked, but will be next time.

I was asked several specific questions:

1. Are there any clues in her labs to tell us she was at increased risk? Can a large # of large HDL-P be a bad thing if they are not performing RCT?
2. What can I use as a therapy goal now that her LDL-P is less than 1000?
3. How low can we go to get her LDL-P to "physiologic" levels.
4. Should I add Zetia to further lower LDL-P, or would Niaspan help the HDL do a better job with RCT?

DAYSRING ANALYSIS

This is an interesting case and a major league dilemma. The patient has achieved goal with respect to the lipid parameters (LDL-C and non-HDL-C) as put forth in NCEP ATP-III as well as the AHA/ACC secondary prevention guidelines. Although apolipoprotein B was not measured, the new ADA/ACC consensus considers LDL-P to be an acceptable substitute and the total LDL-P is

quite good. Consider this: A classic way of determining CV risk is to equate the patient's levels with those seen in epidemiological trials of large amounts of patients. Normally it is desirable to be in the bottom 20th percentile of atherogenic lipid or lipoprotein concentrations -- this would mean 80% of humans would have a worse level. Using Framingham Data:

The first LDL-C of 65 was in the bottom 1% and the second LDL-C of 77 is in the bottom 5th percentile

The first LDL-P of 760 was bottom 3% and the second LDL-P of 901 is in the bottom 7th percentile

Thus even with the slight worsening on the second analysis, the laboratory measures of atherogenic LDLs are quite good. What if any CV benefit would be achieved by further reductions? This cannot be answered using clinical trial data. There certainly is no worry that these numbers are too low. Her LDL-P is physiologic: She is in the bottom 5th percentile of the human race. Many animal species have lifelong levels of extremely low LDL-C and they do just fine. Humans with hypobetalipoproteinemia of varying etiologies have longevity and suffer no consequences of their extremely low LDL-C. It is certainly not required that LDL particles deliver cholesterol to any peripheral tissues. Every cell in the body has the ability to de novo synthesize cholesterol from acetoacetyl Co A (a derivative if fatty acids). Steroidogenic tissues which do require substantially more cholesterol than they synthesize receive it primarily from HDLs (forward cholesterol transport) not LDLs. In the recent ADA/ACC consensus on Lipoprotein management (if you have not read this yet ---- WHY NOT), the experts noted the following:

"When human fibroblasts are grown in cell culture, they take up media LDL via the LDL receptor pathway until sufficient cholesterol is internalized to meet cellular needs, leading to the downregulation of LDL receptors. The amount of LDL cholesterol that is needed in such cultures is only 2.5 mg/dl. Because there is a 10:1 gradient between plasma and interstitial fluid LDL levels, this implies that a plasma level of 25 mg/dl LDL cholesterol would be sufficient to supply peripheral cholesterol needs."

The provider suspected the rise in LDL-C and LDL-P that occurred between the two profiles is a statin induced over absorption of sterols. Years ago before this action was understood it was referred to as statin tachyphylaxis. Why does the same dose of a statin seem to lose some efficacy in some people over time? Statins of course inhibit cholesterol synthesis in every cell they get into. Cellular homeostatic mechanisms rapidly come into play to restore the "statin-created" cholesterol deficiency. The sterol regulatory element binding proteins (SREBPs), whose job it is to prevent cholesterol deficiency 1) increase lipogenic enzymes (such as HMGCoA reductase) which is futile if the patient is on a statin and 2) upregulate production and expression of LDL receptors. These receptors of course internalize apoB particles with their cholesterol content. However, the statin created cellular deficiency, also suppresses the "sterol toxicity" nuclear transcription factor called the Liver X receptor (LXR) which down regulates sterol efflux proteins such as ATP binding cassette transporters A1,G5 and G8: (ABCA1: the protein which lipidates HDLs) and (ABCG5, ABCG8: the hepatocyte and enterocyte sterol efflux proteins often called sterolin -- hepatocytes efflux sterols into the bile and enterocytes into the gut lumen). These proteins collectively decrease cellular efflux of cholesterol and noncholesterol sterols. The statin induced cholesterol deficiency in hepatocytes and enterocytes also cause an upregulation of the Niemann Pick C1 Like 1 (NPC1L1) protein that facilitates sterol entry from the gut lumen into enterocytes or from the bile back into the hepatocyte. The LXR also induces (via the upregulation certain enzymes - 7 alpha cholesterol hydroxylase) the conversion of cholesterol into bile acids which can be excreted into the bile via the ABCB11 transporter. The final piece of the puzzle is that PPAR-alpha and delta are major regulators (inducers) of the NPC1L1 protein and thus play significant roles in cholesterol absorption. Fenofibrate (a PPAR-alpha agonist) has now been shown to significantly decrease the absorption of cholesterol. By the way the synergistic reduction in cholesterol absorption may explain why Zetia and TriCor (an FDA approved combo therapy) is such a fantastic combination therapy of lowering apoB or non-HDL-C (over 60% to goal).

To summarize: **GOOD**: Statins inhibit cholesterol synthesis in cells: In the liver this causes LDLr upregulation and internalization of apoB particles. **BAD**: Statins by suppressing LXR increase intestinal absorption of cholesterol, increase hepatic reabsorption of biliary cholesterol and decrease the conversion of cholesterol to bile acids. These "bad or negative" actions on cholesterol thus partially negates some of the good actions. Of course these genetic actions vary considerably from patient to patient. This explains the "tachyphylaxis" concept described above. I believe these actions are contributory reasons why statins very often cannot normalize apoB or LDL-P by themselves and the provider above was "spot-on" with his assessment that the statin therapy partially defeated itself in this patient. That is why the addition of ezetimibe (Zetia) or bile acid sequestrants such as colestevlam (Welchol) or fibrates can help a statin overcome some of these "bad" actions. Ezetimibe blocks the action of the NPC1L1 protein in the gut as well as the hepatobiliary interface preventing intestinal or biliary sterols from entering enterocytes or hepatocytes. The sequestrant by reducing plasma and hepatocyte bile acids inhibits the farnesol X receptor (FXR) which has a "cross-talk" effect (via the short heterodimer protein or SHP) of stimulating LXR (partially undoing the statin suppression the LXR). Fibrates will likely reduce the statin-induced cholesterol absorption via downregulation of the NPC1L1 protein. (Valasek, MA Clarke, SL and Repa, JJ: Fenofibrate reduces intestinal cholesterol absorption via PPAR α -dependent modulation of NPC1L1 expression in mouse. J Lipid Res 2007;48:2725–2735).

Should the provider measure inflammatory markers such as hs-CRP or lipoprotein-associated phospholipase A2 (Lp-PLA2). This woman is already in the high risk category. Would we treat her any differently if her inflammatory markers are up or not? I doubt it. If they are elevated it confirms what we know: she is in a very high risk category: However based on the PROVE IT study, people have better outcomes if you not only normalize lipids and lipoproteins, but hs-CRP and presumably Lp-PLA2. But again: every lipid-modulating drug we write improves these inflammatory markers, so in this case I do not see how they would help management. Please see reference 5 under references of the week if you really think statin pleiotropy has a lot of meaning.

Can a large # of large HDL-P be a bad thing if they are not performing RCT? The answer is maybe, if the large particles are associated with decreased HDL functionality . Recent data from the IDEAL and EPIC Norfolk trials showed that people with large HDL particles who have low HDL particle counts or apoA-I (who because of the large HDL size have elevated HDL-C) are at risk for CHD. In that same analysis patients with elevated HDL-P with particles not so large were protected. This is just one of many studies shooting down the belief that one must have large HDLs. We need to look at her total HDL-P (the sum of small, medium and large HDL-P) or apoA-I level to get a better handle on this. J Am Coll Cardiol 2008;51:634–42

How low can we go to get her LDL-P to "physiologic" levels.

Should the clinician add Zetia to get her LDL-P down, or would Niaspan help the HDL do a better job with RCT? I would add Niaspan to this patient, because of its multiple (albeit small) studies that it significantly improves arterial health: but readers of my newsletter know that although niacin can significantly induce macrophage RCT and HDL functionality, neither of those actions have anything to do with the HDL-C increase seen with niacin. Niacin raises HDL-C by inducing **hepatic** lipidation of prebeta HDL via ABCA1 (Rubic et al. Biochemical Pharmacology 2004;67:411-419) or SRB1 transporters, by reducing CETP activity and by inhibiting hepatic lipase. Next week on www.lipidcenter.com will be a very current review of niacin's MOA, much of which was in a former issue of this newsletter. Statins reduce macrophage RCT by suppressing the ABCA1, so my hope is that in this patient niacin will do positive things to HDLs that statins cannot. There is new evidence that ezetimibe can also induce macrophage RCT (Bays HE. Expert Reviews Cardiovascular Disease 2008;6:447-470). The fact that niacin lowers Lp-PLA2 is nice, but no one has any idea what that means (i.e. there is no serious evidence that improves

outcomes). Virtually every other lipid-modulating drug lowers Lp-PLA2 also. Thus I do not see that as an advantage unique to niacin.

What can the provider use as a therapy goal now that her LDL-P is less than 1000?

There is nothing you can use as a goal of therapy that is any better than LDL-P. Some speculate that in persons with recurrent events, perhaps an LDL-P of 700-750 is more desirable than 1000 nmol/L. You just have to also be more aggressive treating things we cannot measure: inflammation and HDL functionality. I think this patient needs a high dose statin (Crestor 40 mg) and should titrate the Niaspan to 2000 mg as tolerated. I would not object if one stayed with a lower dose of rosuvastatin and added ezetimibe, but I really think Niaspan is a key addition in this patient.

LIPID CASE 217

I hope this edition of the newsletter will be fascinating as it will teach you many of the things you simply must understand to be successful in CV risk recognition and management using advanced lipoprotein testing. As useful as the lipid profile has been, it has numerous shortcomings that are preventing all of us from doing a better job with atherosclerosis. It is unarguable that atherosclerosis is simple an illegal dump job of sterols in the artery wall and the illegal dumpers are atherogenic lipoproteins. Thus the million dollar question is what is the best available laboratory test indicative of which patients have atherogenic lipoproteins in their plasma: Should we have the lab assay or calculate lipid concentrations (the lipids within all or some of the particles), use those values as ratios or additional calculations, should we size the atherogenic particles or should we enumerate the particles: if we do the latter should we be using apolipoprotein measurements or nuclear magnetic resonance spectroscopy or newer (and far less adjudicated) methodologies of assaying lipoprotein particle concentrations. As my readers know, in April 2008, the ADA/ACC issued a consensus statement advocating that for patients with cardiometabolic risk in high or very high risk categories measured (not calculated) apoB assays (using the protein immunoassays available) or LDL-P using NMR be the new standard. They certainly encouraged calculation of non-HDL-C but reminded all that although it correlates with apoB that correlation is moderately discordant in individual patients.

To elucidate several concepts I will discuss two patients, the Professor and his Provider, both males. The former is 77 years old with a history of an MI and hypercholesterolemia treated with a statin for many years. His current regimen is Crestor (rosuvastatin) 20 mg and Zetia (ezetimibe) 10 mg daily. The provider is 50 years old, overweight with a history of the metabolic syndrome taking Crestor 20 mg, Zetia 10 mg and TriCor (fenofibrate) 145 mg daily. Just with this history most of us would suspect these patients must be at goal using such powerful treatment regimens. Let's look at the numbers in stepwise fashion:

Professor	Provider
TC = 171 HDL-C = 56 LDL-C = 101 TG= 72	TC = 125 HDL-C = 48 LDL-C = 65 TG= 59
VLDL-C = 14 Non-HDL-C = 115	VLDL-C = 5 Non-HDL-C = 77
TC/HDL-C = 3.05 TG/HDL-C = 1.3	TC/HDL-C = 2.6 TG/HDL-C = 1.2

Are these values: Great? Average? Poor? What is your response? Do they need more or less therapy?

What risk categories are the patients in? Well the professor is an MI survivor and thus must be considered high risk. I do not think he meets any of the criteria for a very high risk patient. The Provider would be considered at moderate risk or moderately high risk by most because of his metabolic syndrome. On therapy, are they at NCEP ATP-III guideline goal?

For a high risk patient (the Professor) NCEP would want the LDL-C to be < 100 mg/dL. Non-HDL-C would not be a factor because the on-treatment TG are < 200 mg/dL (newer data from Framingham have shown that Non-HDL-C is always as good or out predicts LDL-C whether TG are elevated or not: Am J Cardiol 2006;98:1363-1368). NCEP 2004 addendum offered an optional LDL-C goal of 70 in these high risk patients. The AHA secondary prevention guidelines strongly advocates an LDL-C < 70 in this high risk patient. The Provider meets all lipid goals of every known guideline that exists. In fact he is every way, significantly below goal. Could that be harmful or simply unnecessary? No: People with hypobetalipoproteinemia (very low apoB and LDL-C levels) have longevity.

Of course we now realize quantitating atherogenic lipoproteins is the best way to assess lipid risk. Apolipoprotein B testing (a protein immunoassay) was performed. The professors level was 74 and the Providers was a spectacular 44 mg/dL. There is one apoB molecule on every beta-lipoprotein (chylous, VLDLs, IDLs and LDLs). Because of the much longer LDL half-life compared to the other apoB particles the vast majority of the apoB measurement represents LDL-P (LDL particle concentration). In the immunoassay the antibody attaches to certain specific areas of the apoB molecule called epitopes. Epitopes are the three dimensional surface of the apoB molecule. With respect to data from the Framingham offspring study, let's see where both the lipid concentrations and the apoB levels position each patient. Normally lower risk is associated with concentrations that are in the bottom 20th percentile of a population and higher risk is in those with levels above the 80th percentile (top 20th percentile).

Professor: LDL-C = 101 (20th percentile) Non-HDL-C = 115 (20th %tile) apoB = 74 (15th %tile)
 Provider: LDL-C = 74 (15th percentile) Non-HDL-C = 77 (2nd %tile) apoB = 44 (2nd %tile)

Clearly both patients are at measured apoB goals and measured apoB is a far superior goal than are any lipid concentrations. Although non-HDL-C correlates well with apoB levels, that correlation is moderately discordant in individual patients. However in these two people, the values seem concordant. Thus can we assure these gentlemen that we have done all that is possible for their lipid-related CV care or are there circumstances where apoB can provide a false negative value. Well, if the immunoassay depends on specific epitopes binding to the antibody (the part of the antibody that binds to the epitope is termed the paratope), what would happen if the configuration of the apoB molecule changed (as could happen when apoB assumes a different configuration on very small LDL particles) or was damaged as might happen when exposed to reactive oxygen species, glycosylation, tyrosination, etc.

A way to settle the question would be to perform LDL-P using nuclear magnetic resonance spectroscopy which has nothing to do with apoproteins. The NMR technology analyses spectral signals produced by methyl groups on the lipids within the particles (the number of methyl groups on TGs, cholesterol and phospholipid molecules are constant. Indeed, such testing was performed:

	Professor	Provider
Total LDL-P (<1000 nmol/L)	1428	1647
Small LDL-P (<600 nmol/L)	1191	1628
LDL Size (<20.6 = small or Pattern B)	20.3	19.1
Large VLDL-P (<0.5 nmol/L)	0.5	0.6
Large HDL (> 9.0 umol/L)	8.6	2.4

My goodness: Those LDL-P values are far from acceptable and strongly suggest there is residual risk despite the decent lipid and apoB concentrations. So which do we believe. It would be easy to say the NMR is wrong and simply dismiss the findings. However in the VA-HIT trial data as well as the Framingham Offspring trial (as well as other studies), LDL-P was more accurate in predicting events than was apoB. Both of these patients had Pattern B LDL phenotype (small

particles). This is one situation where configuration changes happen to apoB that might reposition the apoB epitopes making it less likely to be found by the paratope creating a falsely low apoB reading.

Where do the LDL-P readings position the patients within population cut points:

Professor's LDL-P of 1428 is in the 45th percentile of the Framingham population and the Provider's LDL-P of 1647 is in the 65th percentile. That is unacceptable and both are potentially at continued risk despite the nice lipid and apoB readings. How could they have so many LDL particles despite having such good LDL cholesterol concentrations (LDL-C). Keep in mind LDL-C simply is the amount of cholesterol in mg that are transported within all of the LDL particles that exist in a deciliter of plasma. LDL-P is a measure of how many LDL dump trucks there are and LDL-C is how much cholesterol is in the back of all of them. LDL particles are circular or spherical: the volume of a sphere is $\frac{4}{3}(\pi)\text{Radius cubed}$. Therefore very small diameter (radius) reductions can translate into significantly less ability to carry cholesterol molecules.

Let's calculate the volume of the LDLs of each patient:

Professor

LDL diameter is 20.1 nm Radius = 10.15 nm

LDL volume = $\frac{4}{3}(3.14)(10.15)^3$

LDL Volume = 4377 cubic nm

Provider

LDL diameter = 19.1 nm R = 9.55 nm

LDL volume = $\frac{4}{3}(3.14)(9.55)^3$

LDL volume = 3642 cubic nm

Clearly the Provider's LDL particles will hold significantly less cholesterol molecules than the Professor's which have 16% more volume. This makes it easy to understand why patient's with smaller LDLs need more particles to traffic the cholesterol load. Now let's take it to a higher level -- How many actual cholesterol molecules are in each of these patients LDL particles. We can calculate this rather easily if we convert their LDL-C value to a molar concentration and then simply divide it by the particle number (also in molar concentration).

To calculate how many cholesterol molecules are in ones LDL particles: you simply divide LDL-C (in mol/L) by LDL-P in mol/L. To convert mg/dl of cholesterol to mols multiply by .0259. Keep in mind a mmol is 10 to the minus third and nanomoles are 10 to the minus 9th mols.

Professor: LDL-C of 101 X .0259 = 2.61 mmol = 0,00261 mol/L His LDL-P of 1428 nmol/L converts to 0.000001428 mol/L. Divide the former by the latter and one sees that the Professor's LDLs each carry 1864 molecules of cholesterol.

If you do the same calculations to the Provider you will discover that his LDL particles each carry 1056 cholesterol molecules. Thus the provider's LDLs are significantly more cholesterol depleted than the Professor's. Paradoxically the provider requires significantly more LDL particles to traffic his LDL-C of 65 mg/dL than does the professor with a much higher LDL-C of 101. The Professor's LDLs are capable, because of their 30% larger volume of trafficking significantly more (56%) cholesterol molecules per particle. I hope this geometric description of LDL particle size and number allows all of you lipidaholics to understand how easy it is for patients to have tremendous disconnects between LDL-P (apoB) and LDL-C. Since what drives the LDLs into the arterial wall is particle number (not particle size or particle cholesterol content) it is easy to see how these two patients with good (Professor) and fabulous (Provider) LDL cholesterol concentrations still can have residual risk ---- which cannot be understood or recognized by their LDL-C or even Non HDL-C levels. Why are the Provider's LDLs so much smaller than the Professor's? Metabolic syndrome, obesity, impaired fasting glucose, increased hepatic and endothelial lipase activity, increased CETP activity are all associated with increased lipolysis of LDLs leading to both size reduction and cholesterol depletion. Also keep in mind that if either of these men had higher TG levels, TG entry into their LDLs would have further lowered their LDL cholesterol molecule

concentration -- i.e. TG-rich, cholesterol depleted LDLs (no matter what the LDL size) will be associated with elevated LDL-P.

A quick word about the HDL situation in these patients. I think you are going to be surprised. Looking simply at the HDL-C (The Professor has 12 mg/dL more of HDL-cholesterol than the Provider), who would you suspect has more HDL particles in their plasma? Look at what we know and look at exactly how much wonderful information is there if you really know your way around the NMR LipoProfile. :

Professor	Provider
HDL-C = 56	HDL-C = 48
Large HDL-P = 8.6 umol/L	Large HDL-P = 2.4
Medium HDL-P = 4.6	Medium HDL-P = 10.8
Small HDL-P = 25.1	Small HDL-P = 27.9
Total HDL-P = 38.3	Total HDL-P = 41.1

Using MESA (Multiethnic Study of Atherosclerosis) data: A total HDL-P is in the 90th percentile of the population: i.e. they have plenty of HDL particles. Also notice since HDLs are measured in micromoles (umol/L) humans have significantly more HDL particles than they do apoB particles.

WOW: Despite the lower HDL-C the Provider has more HDL particles. Of course we know nothing about the functionality of either's HDL particles. Why does the provider have more?? One would think with his insulin resistance he would have had less HDL-C and LDL-P. ANSWER: The Provider is taking fenofibrate, a very effective drug at inducing hepatic production of apoA-I (a PPAR-alpha mediated process). The fenofibrate also induces upregulation of hepatic scavenger receptors B1, which delipidate larger, more mature HDLs causing them to shrink in size. This was seen in the VA-HIT trial with a fibrate and the author proposed that the resultant delipidated small alpha or pre-beta HDL would have more capacity to return to the artery wall and further delipidate the foam cells. Therefore with fibrates there will always be a disconnect between changes in HDL-C and HDL-P with the latter being affected more. If the particles are functional it is likely that HDL-P is a much more important parameter to follow than is HDL-C.

So I now come to the very real world question - Do I tell these gentlemen because their lipids are good and their apoB is perfect I do not believe the NMR diagnosed residual risk (high LDL-P) or do I take note that LDL-P out predicted apoB, LDL-C and Non HDL-C in several studies (like Framingham Offspring, Women's Health Study, VA-HIT) and advise both patients further therapeutic endeavors are needed. I choose the latter. I think the Professor should increase his dose of Crestor to 40 mg and I think the Provider should get more aggressive with therapeutic lifestyle or add Niaspan to the regimen. Niaspan through numerous mechanisms of action will increase his LDL size allowing them to traffic more cholesterol molecules per particle which should result in a dramatic drop in LDL-P.

I have a follow up: The Professor was indeed given the larger dose of Crestor (40 mg) and lo and behold:

TC = 121 HDL-C = 48 LDL-C = 68 TG= 27

Anyone surprised Crestor reduced the HDL-C (previously 56). Does that have any meaning? No: Anything that dramatically lowers total cholesterol (an apoB surrogate) can reduce HDL-C. Best example is the Ornish extreme low fat diet (which of course is associated with cardioprotection despite the dropping HDL-C). This is a great example of why there can never be a specific HDL-C target or goal of therapy.

Lets look at the lipoprotein concentrations on the bigger dose of Crestor

Total LDL-P (<1000 nmol/L)	983	(was 1428)
Small LDL-P (<600 nmol/L)	971	(was 1191)
LDL Size (<20.6 = small or Pattern B)	19.1	(was 20.3)
Large VLDL-P (<0.5 nmol/L)	0.0	(was 0.5)
Large HDL (> 9.0 umol/L)	8.6	(was 8.6)
Total HDL-P	37	(was 38.3)

So Crestor significantly improved the parameter that matters most: Total LDL-P ---- It is irrelevant that the small LDL-P is still 971 (still increased above desirable of 600). Not that Crestor 40 mg increase was associated with a shrinkage of LDL size - likely because it is significantly depleting the per particle cholesterol content -- however the additional LDL-receptor upregulation induced by the Crestor, reduced the all important total LDL-P. Also notice total HDL-P, as did the HDL-C, went down with the increased Crestor dose: This has been seen in rosuvastatin clinical trials as it has been seen with the 80 mg dose of atorvastatin (Lipitor). Likely the many upregulated LDL receptors (as seen with larger doses of statins) endocytose HDL particles.

Hope you all enjoyed the journey through particle land.

LIPID CASE 218

I Hi Lipidaholics: Always lots to discuss but I want to keep reminding everyone to visit www.lipidcenter.com which is rapidly becoming one of the best lipid sites on the web for cutting edge lipid/lipoprotein info (not the standard old time stuff). Dr. Michael Richman (a CV surgeon with a preventive mindset who actually understands lipoproteins) of the Center for Cholesterol Management in LA and I continue to add educational materials for professionals, It will take a few more weeks to get everything updated and on the site). However lots of the web site can be a very useful place for your patients to begin to understand their lipid/lipoprotein risk and especially lipoprotein testing. For those who have enjoyed my teachings, my writings and slides are there.

I have been consulted by a NP working at an adult cardiology practice about the 12 year old son of a man former smoker with heterozygous familial hypercholesterolemia (TC > 300 prior to Rx) who had his own CABG at age 29. The father takes Crestor 40 mg, Zetia 10 mg and Niaspan to control his lipoprotein risk. The son who is healthy and very active weighs 166 pounds and plays football. His father correctly wanted his son to have lipid evaluation

Son's Results:

TC = 159 mg/dL TG = 83, VLDL-C = TG/5 =17, HDL-C = 38 , LDL-C = 105
 NMR (nuclear magnetic resonance spectroscopy) LipoProfile (www.lipoprofile.com)
 Total LDL-P = 1428 nmo/L Small LDL-P = 1215 Large LDL-P = 213 LDLsize 20.3 (small or Pattern B)

The cardiology attending, in addition to lifestyle recommendations, started the boy on Crestor (rosuvastatin) 10 mg daily. The NP was uncomfortable with this decision to start a statin and the pediatrician wanted no treatment because of the very normal TC level.

8 weeks later

TC = 126 HDL-C = 46 TG = 75 VLDL-C = 15
 Total LDL-P = 844 Small LDL-P = 627 Large LDL-P = 217 LDL size = 20.7 (Pattern A)

I was asked to mediate and discuss the appropriateness of lipoprotein testing in this age group.

DAYSRING DISCUSSION:

If one looks at the 12 year old - he has a father with very premature CHD and he has a reduced HDL-C but no other obvious CV risk factors. There is no way any conventional guideline including the new Pediatric Guidelines would support drug therapy in this young boy. So I should end this discussion right now but that would make for a very short newsletter. Therefore all that follows are simply my feelings using 33 years of clinical experience and whatever I may know about atherosclerosis, lipids and lipoproteins. I totally agree with what the cardiologist did (initiated drug therapy: although see my discussion below). I would have no objections on referral to nutritional specialists but I have been around too long to know that the odds of that being successful in the long term are quite poor. The boy is big and likely wants to stay that way since he is a football player. His dad had horrible disease by the time he was 29. My bet is that if someone had started the father on statins when he was an adolescent and made him stop smoking, the father would not have had a bypass or have serious CAD.

Over the last year I have also noticed a paradigm shift in thinking: many articles and editorials are now starting to support recognition of lifetime risk and lifetime treatment beginning at much earlier ages than we ever considered appropriate (Disputation on the Use of Age in Determining the Need for Treatment of Hypercholesterolemia and Hypertension John B. Kostis, *J Clin Hypertens* (Greenwich). 2006;8(7): 519–520 and Evidence Mandating Earlier and More Aggressive Treatment of Hypercholesterolemia by Daniel Steinberg (*Circulation*. 2008;118:672-677). Steinberg states: "Is lowering LDL levels intrinsically dangerous? That possibility has been suggested in the past, but no hard evidence exists for such a concern, and a number of considerations make such an effect quite improbable." I (TD) believe, with the old mind set we let disease happen first before we got serious with drug therapies: hence the classification of Primary vs. Secondary." The sooner that old dogma disappears the better!

Now old time thinking would say the atherogenic cholesterol levels (TC, LDL-C, non-HDL-C) are fine. How many trials and new guidelines to we need before we all admit that it is atherogenic particle number (apoB or especially LDL-P) that drives atherosclerosis, not TC or LDL-C. Again let me refer to Bill Cromwell's analysis of the Framingham Offspring Trial (*Journal of Clinical Lipidology* 2007;1:583–592) 16 year follow up where LDL-P was twice as predictive as LDL-C with respect to long term risk. Dr. Alan Sniderman had a great analysis of this study in an article discussing the apoB/apoA-I ratio (*Future Lipidology* 2008;2:257-264) and he commented: "*When LDL-C and LDL-P are both high, risk is high and when they are both low, risk is low. The issue is what happens when the two indices are discordant. When LDL-P is low, even when LDL-C is high, risk is low. Similarly when LDL-P is high and LDL-C is low, risk is high. RISK FOLLOWS LDL-P, NOT LDL-C. THE OUTCOME COULD NOT BE CLEARER.*" In Cromwell's analysis of those patients in the lowest quartiles of LDL-C and LDL-P, there were 30% less clinical events (event rate per 1000 patient years) in the lucky ones with low LDL-P (<1252 men, < 1061 women), even though their LDL-C was in the lowest quartile (LDL-C < 111 women, < 102 men). Apply those numbers to this boy and you will see it is not unreasonable to presume he will develop an atherosclerotic event over the next 16 years -(at age 28 -- just like Dad).

So forget about the kid's LDL-C and TC. Does the low HDL-C concern you? It is clearly a strong risk factor in most people not on medication. The only way it concerns me is that low HDL-C is usually a surrogate of elevated apoB or LDL-P, as is the case here. So we are right back to the realization that the boy has too many potentially atherogenic particles. If one looks at the NMR report, a total LDL-P of 1215 is listed as near or above optimal. Now if the boy's dad did not have very premature disease we would encourage lifestyle and keep a yearly eye on the value. But Dad did development CHD in adolescence! LipoScience uses cut points from the Multi-Ethnic Trail of Atherosclerosis (MESA), but they are adult cut points, not pediatric. LDL-P cut points are also known for the Framingham Offspring Trial (FOS). An LDL-P of 1219 in an adult would be the 30th percentile for adults: i.e. 70% of adults would have a higher number, 30% a lower number. In

MESA the LDL-P would be closer to the 40th percentile. For a twelve year old I would have to guess that such an LDL-P would rank much higher in the population cut points table.

By the way the LDL-C of 105 is also much too high for a 12 year old and indicates like his father the boy is also an FH, just a young FH. Both his LDL-P and LDL-C will worsen with age. His dad's TC got as high as 300 prior to his event, and junior is likely on that path unless someone intervenes. Why such a high LDL-P with an LDL-C of 105? The LDL size is only slightly small at 20.3 nm. His TG are only 83. For likely genetic reasons he has increased CETP activity, or increased hepatic or endothelial lipase activity both of which would help generate LDLs and HDLs depleted of cholesterol. To traffic the cholesterol in his system, he needs more LDL particles. As the HDLs reduce in size, apoA-I breaks off and is excreted, reducing HDL-P, apoA-I and HDL-C.

Note that after taking a small dose of Crestor (much smaller than that used in the METEOR trial - where Crestor 40 was very effective as well as safe in preventing carotid atherosclerosis in "low risk patients), there was dramatic improvement in all parameters. Note that Crestor, a drug that has shown like other statins it can inhibit CETP, LDL size increased. As expected by the cardiologist, the Crestor upregulated Hepatic LDL receptors which are especially efficacious at recognizing and removing normal sized rather than smaller LDLs. Although I do not have the numbers, it is likely there was a shift on HDL size, explaining the robust increase (8 mg/dL) in HDL-C.

Worried about lowering LDL-C too much? From the recent ACC/ADA consensus statement on lipoprotein management I quote: a plasma level of 25 mg/dl LDL cholesterol would be sufficient to supply peripheral cholesterol needs (Diabetes Care 2008;31:811-822 - specifically see page 813). There is abundant evidence including longevity in folks with hypobetalipoproteinemia that should alleviate concerns of lowering LDL-C.

Finally: If one decides on drug therapy is there another option other than a statin. Crestor has no approval for pediatric use but other statins do. If I wanted to use statin monotherapy I also would have given the boy Crestor (off-label) because a very small dose would likely get the job done. However, bile acid sequestrants have outcome data and one could clearly make the case for using a nonsystemic drug like Welchol (colesevelam). It might be especially useful if this boy is insulin resistant as his low HDL-C and weight suggest. As you know Welchol now has approval to lower glucose (via its actions on farnesoid receptors (FXR), short heterodimer partner (SHP), liver receptor homolog-1 (LRH-1) and liver X receptors (LXR) - a discussion for a future newsletter). Surely Welchol could get the LDL-P to goal (< 1000 nmol/L). Its problem is of course 6 large tabs daily are required. Welchol is much better tolerated than earlier sequestrants. Another issue to consider is this boy is going to play serious football for the next 10 years - the incidence of myalgias and rhabdomyolysis is increased in serious athletes on statins. That is another reason to consider Welchol.

I leave you all with one more classic quote from the particle master, Alan Sniderman of Montreal in a recent editorial entitled "We Must Prevent Disease, Not Predict Events" (JACC 2008;52:300-301). "Although the plasma lipoproteins are only risk factors for clinical events, they are prime causes of disease within the arteries. Second, transformation of a stable silent arterial lesion into an unstable one that produces a clinical event is a complex and unpredictable process. We know what causes disease within our arteries but can only guess at precisely what precipitates clinical events. It follows that prevention of coronary disease would be much simpler and much more effective if we focused on preventing disease developing within our arteries rather than trying to predict who is just about to become a victim and then trying frantically, at what might be just 1 min before their final midnight, to rescue them. The high-risk approach to prevention is often too high-risk for the patient and too late for his or her arteries. The bottom line is that, just as we need to revise how we measure the lipoprotein-related risk of vascular disease ----- **IF WE PREVENT THE DISEASE WE WILL PREVENT THE EVENTS.**

LIPID CASE 219

I get lots of questions from lots of folks, including both providers and those associated with pharmaceutical companies. I think the following inquiry from a company DM regarding a patient is worth a serious discussion. This will be very helpful for those preparing for the board examination in clinical lipidology.

The question posed was: "On field travel this week we spoke to a physician that has always been timid about using fenofibrate in combination with a statin. He was treating a patient on simvastatin (dose unknown) and 4 grams/day of Lovaza (N-3 fatty acids). The man had an on-treatment LDL-C around 100 mg/dl, with a TG = 1400 mg/dl and a history of pancreatitis. The provider was afraid of TriCor (fenofibrate) so he prescribed a bile acid sequestrant, namely WelChol (colesevelam) instead. This led to the discussion around why a fibrate and/or niacin might be appropriate for this patient. Neither I or my representative could answer the question of why bile acid sequestrants increase TG."

DAYSRING DISCUSSION:

One quick comment: With a TG of > 1000 mg/dL, I wonder how they know the on-treatment LDL-C is around 100 mg/dL. There is no way to calculate the LDL-C with that high a TG. I presume the provider measured LDL-C directly, which in general is a waste of money. It is not a standardized test and it has no correlation to apoB in a person with such a high TG level. Recognizing what risk is present with massive elevations of TG and then determining how to effectively treat them can be quite a challenge. Anyone with a TG > 1000 mg is certainly at risk for pancreatitis and some but not all are at risk for cardiovascular disease. The latter pretty much comes down to the question: is apolipoprotein B elevated or not -- If no, CHD is not a risk and if Yes - CHD is a big problem. The very high TG normal apoB patients have familial hypertriglyceridemia - basically they just have very large VLDLs not present in increased numbers (hence the normal apoB). The patients with very high TG and high apoB (combined familial hyperlipidemia), have high CV risk and they usually have very increased amounts of remnant VLDLs, chylomicrons, and cholesterol depleted LDL particles (very high LDL-P): the LDLs are usually small and can also be TG rich, further depleting how many cholesterol molecules they carry per particle. Regardless of which TG disorder is present treatment to reduce the TG below 500 is the first treatment priority. The best approach in addition to caloric restriction, glucose and fat restriction, alcohol avoidance, exercise are to prescribe the drugs that are the most powerful in reducing TG - namely fibrates (preferably fenofibrate or the soon to be available fenofibric acid) or high dose N-3 Fatty acids (Lovaza). Unless there is renal impairment the fenofibrate (TriCor) dose is 145 mg daily. The Lovaza has very little TG lowering effect at doses less than 4000 mg daily, so please dose this product appropriately. I am amazed at how many clinicians think they can treat TG with 1-3 grams of N-3 fatty acids - that is simply fiction. There is a threshold effect of 4000 mg for proper TG-lowering efficacy (see Jacobsen: Am J Clin Nutr 2008;87(suppl):1981S-90S).

Although there are certainly no outcome trials to tell us the best way to lower extreme TG elevations, a statin as a first line drug in such a patient is an inappropriate choice. Statins do nothing to reduce the synthesis of TG - they simply upregulate LDL receptors which clear TG-rich lipoproteins - in effect bringing the TG back to the liver (which is likely already loaded with TG). Fibrates, N-3 Fatty acids and to a slightly lesser degree high dose niacin have complex mechanisms of action to reduce TG synthesis and enhance catabolism of TG-rich lipoproteins. They do this by interacting with several nuclear transcription factors that regulate fatty acid synthesis, catabolism, TG assembly and TG hydrolysis especially PPAR alpha and in niacin's case PPAR gamma. Patients with extreme elevations of TG, often require in addition to lifestyle several drugs to reduce their levels. Most reach for fenofibrate and/or a minimum of 4000 mg of N-3 FA I prefer the FDA approved Lovaza in treating serious TG-rich lipoprotein pathology rather than OTC N-3s). I usually prescribe TriCor and N-3 FA together and go from there (J Acquir

Immune Defic Syndr 2008;47:459–466). If that dual therapy does not drop the TG to < 500 mg/dL, then it is time to add a high dose statin: rosuvastatin (Crestor) 40 mg or atorvastatin (Lipitor) 80 mg. The statin simply upregulates LDL receptors to help clear TG-rich lipoproteins. Ezetimibe by upregulating additional LDL receptors beyond what a statin can induce can also be used to achieve additional TG lowering. If still abnormal, Niaspan titrated to 2000 mg would be the logical next step. The one drug one would not use in this circumstance is exactly the one the provider was using - a bile acid sequestrant (BAS). Also no provider should have any hesitancy about using fenofibrate with any statin, because unlike gemfibrozil with statins (both hydrophilic and lipophilic), there are no known interactions. NCEP-ATP-III clearly lists fibrates as a good ad-on therapeutic option when non-HDL-C is not at goal in patients on statins and lifestyle. They also go on to state: Unlike gemfibrozil there are no known interactions with fenofibrate and no increase in myalgia/myositis when used with moderate doses of statins., I also point out there are no known interactions with larger doses of statin either. Lastly keep orlistat in mind when trying to reduce TG in obese patients. It works well with fenofibrate and I suspect N-3 FA. (Triglycerides and Risk for Coronary Artery Disease. Patrick McBride Current Atherosclerosis Reports 2008, 10:386–390).

But the real purpose of this newsletter is to explain why BAS can cause hypertriglyceridemia. This is an advanced discussion and is intended for those wanting to take their knowledge to the next level or lipidologists. This material is covered at the Master's Of Lipidology Course in the "Translational Lipid Biochemistry" lecture of which I have been privileged to do. Many of the slides that go along with this dissertation can be found on the Center for Cholesterol Management web site www.lipidcenter.com (Professional resource section).

TG production is regulated by lipogenic genes that create proteins which regulate (production and catabolism) enzymes necessary to change Fatty Acids (FA) into TG (three fatty acids on a glycerol backbone). Gene activity is regulated by nuclear transcription factors (NTF) that sense intracellular lipid excess or deficiency. The NTF that controls TG lipogenic genes is the sterol regulatory element binding protein 1C (SREBP 1C). However there are also NTFs that influence the SREBP 1C one of which is called the liver X receptor (LXR), which despite its name is found in multiple cells throughout the body. Basically the LXR is sterol toxicity NTF and it influences many proteins (enzymes) that reduce cellular sterol concentrations: thus one action of LXR is to induce bile acid synthesis, induce cellular cholesterol efflux transporters (ABC family) and induce TG synthesis. By upregulating foam cell ABCA1 transporters, LXR promotes macrophage reverse cholesterol transport (RCT) into HDL particles. If one stimulates (agonizes) LXR, both bile acid (BA) production and TG production also increases: both actions will reduce cellular cholesterol, the first by converting cholesterol to bile acids (by increasing the enzyme 7-alpha cholesterol hydroxylase) and the second by creating hepatic apoB lipoproteins (VLDL production) and exportation of cholesterol in the VLDLs. **In summary, LXR agonism therefore reduces cellular cholesterol, increases BA production, promotes macrophage RCT and increases TG production.** LXR agonists also under investigation to promote macrophage RCT are limited because they raise TG.

There is another nuclear transcription factor that regulates bile acid toxicity (increased bile acid levels, which are basically detergents, are toxic to cells). This NTF, called the Farnesoid or Farnesol X Receptor (FXR) prevents bile acid toxicity by reducing BA synthesis. If there is an excess of bile acids, FXRs become active and suppress the enzymes involved with converting cholesterol to BA (7-alpha cholesterol hydroxylase). This reduction in BA synthesis preserves hepatic cellular cholesterol levels. If you are following me, LXRs help cells get rid of cholesterol and FXRs helps cells keep it. The NTF have to work in harmony and they must communicate: they do so by using molecular messengers in a process called "crosstalk". FXRs also regulate BA by suppressing ileal reuptake of BA, leading to increased excretion of BA in the stool.

The FXR increases the production of another regulatory protein called short heterodimer partner (SHP) which takes part in "crosstalk" and suppresses LXR activity: SHP-induced LXR suppression will lead to inhibition of both TG synthesis (reduced SREBP 1C activity) and bile acid

synthesis. This gets even more complicated because there is another mediator of LXR at play -- something called liver receptor homolog-1 (LRH-1) which is influenced (inhibited) by the SHP. **In summary: FXRs induce SHP and LRH-1 crosstalk to inhibit LXR activity which will lead to less BA synthesis (reduced production of 7-alpha-cholesterol hydroxylase) and decreased TG (reduced SREB1c activity).** There are FXR agonists in development, which will reduce TG through LXR suppression of SREBP 1C and may be useful as a treatment for fatty livers.

Let's return to the question of how BAS raise TG. If one prescribes WelChol (colesevelam), it will bind bile acids in the gut and force their excretion in the stool. Less bile acids are reabsorbed at the ileum which is what normally happens to them. Bile acid levels in the serum go down. Less bile acid return to the liver. Because the primary FXR function is to prevent BA, toxicity, less BA returning to the liver will cause a down regulation (reduction) of FXR activity. Likewise as FXRs downregulate, there will be less production of SHP, LRH-1 and ultimately (because SHP and LRH-1 inhibit LXR), increased LXR activity occurs which will then stimulate SREBP-1C and TG production. Hence BAS can raise TG. However since LXRs also suppress via many actions glucose production, BAS can also improve glycemic control (for which colesevelam now has a FDA indication).

Do not lose sight of the big picture -- BAS work: Sequestrants (cholestyramine) have CV outcome data going back to the 1980s in the Lipid research Clinic Primary Prevention Trial (LRC-PPT). Through the same genes they also reduce glucose. Although they raise TG, because they upregulate LDL receptors they lower apoB. Therefore their TG elevation likely has no clinical significance for most patients. Also they are almost always written with a statin which enhances their apoB activity and helps to offset the TG. However in someone with serious (above 200 mg/dL) and especially massive TG elevations (well above 500 mg/dL) their use is not advised.

LIPID CASE 220 What else can be offered?

This week I received an inquiry from a provider very concerned about his friend who is a 54 year old white male who had an MI in 2004 after which 3 stents were performed. He gave up smoking, lost 60 lbs. and is now 155 @ 6' in height. About 1-11/2 years ago went to a very dedicated low fat vegan lifestyle. Unfortunately he was left with an ejection fraction of 32% but exercises 2-3 hrs per day to his capability usually without symptoms. He has been on Zocor (simvastatin) 20 mg, Plavix 75 every other day alternating with ASA and Coreg 10 mg. In January 08 he had a stress test and was told he failed it and another stent was performed. Recently he has had some mild but infrequent symptoms and was told that he failed another stress test and is scheduled for another angiogram and perhaps a stent. Last week he had an NMR LipoProfile and his values are listed below:

Lipids: TC = 119, LDL-C = 38, TG = 103 HDL-C = 61 (all in mg/dL)
Total LDL-P = 881 nmol/L (desirable for a very high risk patient < 750)
Small LDL-P = 423 (desirable < 600)
LDL Particle size 21.6
Large HDL-P 13.4 (excellent)
Large VDLP-P 0.0
Lp-PLA2 91 (normal)
CRP 0.4 (normal)

The provider states: I am reluctant to advise but doesn't he seem under medicated for his risk level? What about increasing statin and adding niacin or Zetia before another stent?

DAYSRING ANALYSIS

Who in their right mind would get more aggressive with lipid management in a patient with an LDL-C of 38. Well, I do not consider it unreasonable: after all despite the seemingly perfect and almost perfect lipoproteins, the man is still having recurrent ischemia requiring interventions. I believe there are a few issues to consider. What does one have to lose as this man is clearly on the downside of a survival curve! Where are the areas that we might do better?

1): This man is a serious vegan and has lost lots of weight. There is no evidence of metabolic syndrome at this time and inflammatory markers including the atheroma specific Lp-PLA2 are fine. However, pure vegans eat nothing but noncholesterol sterols, primarily sitosterol and campesterol. Those of you who studied for the lipid boards are aware of a condition called phytosterolemia (sitosterolemia): these patients, unlike most of us absorb noncholesterol sterols, which find their way into chylomicrons and ultimately VLDLs and LDLs and the artery wall. Since humans have no enzymes capable of esterifying noncholesterol sterols, sitosterol is easily converted into oxysterols, which are the cause of atherosclerosis. Human cells and human lipoproteins esterify cholesterol into cholesteryl ester (CE) using ACAT (in cells) and LCAT in lipoproteins. CE is less vulnerable to reactive oxygen species and is not as prone to become oxysterols. The chapter in Therapeutic Lipidology which I authored deals with this very topic: Phytosterolemia. Briefly, because unlike cholesterol, noncholesterol sterols serve no physiologic functions. Thus the intestine has a sterol efflux protein called ATP Binding Cassette Transporter G5 and G8 (often called sterolin). This enterocyte heterodimer immediately re-excretes the absorbed noncholesterol sterols back into the lumen of the gut. Thus when chylomicrons are constructed by the enterocytes, they fill with TG, CE and phospholipids but not noncholesterol sterols. However if a patient has a variant or polymorphism of ABCG5,G8 they may not be able to thoroughly re-excrete noncholesterol sterols into the gut lumen and these molecules are thus absorbed. So if this strict vegan has a defect of his ABCG5,G8 his LDLs may be trafficking sitosterol and campesterol rather than cholesterol. I believe this man should have a sitosterol, campesterol level checked. If it is high, we then have a potential answer of why his plaque has been so aggressive. Of course ezetimibe (Zetia) has an FDA approval to prevent noncholesterol sterol absorption and thus could be of considerable help to this man. Ezetimibe prevents the NPC1L1 protein from absorbing sterols. The sitosterol level should be well under 5 mg/dL. For those who would like to read about new info on exactly how both the NPC1L1 protein and ezetimibe works at the membrane level please see Cell Metabolism 7, 508–519, June 2008.

Interestingly patients who take statins upregulate the intestinal and hepatic Niemann Pick C1 Like 1 protein (NPC1L1) and downregulate the ABCG5,G8 in the intestine and hepatobiliary interface. Therefore statins inadvertently increase noncholesterol levels, which is clearly not desirable. Indeed, in a study published 4 years ago, patients who were on statins who underwent carotid endarterectomies, has noncholesterol sterols in their artery deposits, whereas folks not on statins did not.

If the sitosterol levels are OK, what might be the next approach? I'd try and drop his LDL-P a bit further and get it below 700 nmol/L. Should we just switch to a more powerful statin than simvastatin - i.e. Crestor (rosuvastatin) 40 mg? I think not. Although the HDL-C is fine and there large HDL-P is excellent, we really have no idea if this man has functional HDL particles. By that I mean do his HDLs perform foam cell delipidation (macrophage reverse cholesterol transport) and do his HDLs carry all of the cardioprotective proteins that HDLs should? Who knows? Do we have therapies that increase HDL functionality and increase macrophage RCT? Yes: the best studied are fibrates, niacin and most recently ezetimibe. Since his TG are not very abnormal I would not choose a fibrate, but would give niacin a chance. Indeed instead of adding Niaspan to his simvastatin one could easily transfer him to Simcor. Although (compared to statins and fibrates) niacin is the least studied drug with respect to outcome evidence, niacin has always been associated with positive outcomes in its multiple small outcome and angiographic trials. It is important to note that in all of these trials, the dose of niacin was maxed out. There is almost no data that niacin improves outcomes or angiographic parameters unless large doses are used. Fortunately the extended release formulation (Niaspan) is pretty well tolerated if one escalates the titration slowly and instruct persons how to properly take it. I'd add Niaspan at 500 mg and

over several weeks titrate it up to 2000 mg (even if the lipoprotein (LDL-P) goals were achieved. He would wind up on two Simcor 20/1000 tablets daily. If you are one who believes that larger dose statins have other beneficial properties other than lowering apoB, then use Crestor/Niaspan. Although there is no level 1 evidence on any combination therapy with respect to outcomes, the two small trials that suggest two drugs are better than one are Statin/high dose niacin or bile acid sequestrant (cholestyramine)/niacin.

Lastly aggressive endothelial therapy might help. Why is not this patient on an ACE inhibitor if his ejection fraction is poor? Why is he taking the Plavix every other day - unless there have been bleeding complications I am unaware of. Of course according to the AHA Secondary Prevention Guidelines of 2006, all such patients belong on 1000 mg of N3-FA daily (Lovaza) If a nuclear stress demonstrated ischemia he likely needs another angiogram and instead of a stent, perhaps a bypass is possible.

LIPID CASE 221 Lipid Goals and Statin Intolerance

The patient for discussion is a 73 year old male who is ideal body weight and exercises. He is s/p CABG x 2, and has a history of intermittent atrial fibrillation, hypertension (controlled) and a spastic colon. His meds are simvastatin (Zocor) 10 mg (cannot tolerate any higher dose or other statin), cholestyramine (Questran) BID and Coumadin.

Lipid Panel: LDL-C = 80 HDL-C = 42 TG = 172 Non-HDL-C = 114

NMR LipoProfile:

Total LDL-P = 1280 nmol/L Small LDL-P = 973 (physiologic < 600)

LDL particle size of 20.4 (Pattern B or small)

Large VLDL-P of 5.4. (normal < 0.5)

I was asked about my thoughts of how do further decrease his risks??

DAYSRING DISCUSSION:

Clearly a 73 year old man with known CHD is a high risk patient and one should strive as hard as possible to aggressively control all treatable risk factors. BP is controlled and he is anticoagulated. Following a strict interpretation of NCEP ATP-III goals the LDL-C should be < 100 with an option for 70. Since the TG are not > 200, non-HDL-C is not applicable. Well with an LDL-C of 80 he is technically at standard but not the optional LDL-C goal. Data published subsequent to the 2004 NCEP addendum has shown that non-HDL-C always out predicts LDL-C as a risk factor regardless of whether TG are < or > 200 mg/dL (Am J Cardiol 2006;98:1363–1368). However for a high risk man, the non-HDL-C would be 130 mg/dL. If one considers this patient as very high risk (and that is a stretch) he is not at the non-HDL-C goal of 100. How about LDL-P goal: well there are no existing guidelines that provide an LDL-P goal. The recent ADA/AHA guidelines suggest an apoB of 80 for very high risk and 90 mg/dL for high risk patients. Let's look at the lipid, apoB goals and see if we can set an equivalent LDL-P goal.

If we measure lipids in large populations, which is done in epidemiological trials, we know the frequency of various concentrations throughout the population: these are called cut points. For decades LDL-C has been the primary goal of therapy in every guideline. Here are the Framingham Offspring cut points:

LDL-C of 100 mg/dL is the 20th percentile (goal for high risk patient)

LDL-C of 70 is the 2nd percentile (goal for very high risk patient)

Translation: If you have an LDL-C of 100, 80% of people have a higher value and 20% have a lower value. With an LDL-C of 70, 98% of folks have a higher and 2% a lower value. How about non-HDL-C?

Non-HDL-C of 119 is the 20th percentile
Non-HDL-C of 83 is the 2nd percentile

Thus if we follow guidelines, and shoot for a non-HDL-C of 130, that would be the 30th, not the 20th percentile. A non-HDL-C of 100 (the very high risk goal) is the 9th, not the second percentile. Perhaps we need more aggressive non-HDL-C goals. Well if one realizes that the non-HDL-C goal is simply the desired LDL-C goal plus 30 (which was considered a normal VLDL-C by NCEP seven years ago - and $VLDL-C = TG/5$), we have to wonder if a more desirable VLDL-C is 15 or 20 which would translate to a desirable TG of 75-100 mg/dL. Those levels would be much more in line with newer epidemiological studies than the value of 150 mg/dL put forth by NCEP 7 years ago.

If we translate LDL-C goals to apoB and LDL-P: it seems reasonable to reduce both apoB and LDL-P to the 20th and 2nd percentiles. Here are the Framingham cut points for those parameters:

apoB of 80 and LDL-P of 1100 is the 20th percentile
apoB of 54 and LDL-P of 720 is the 2nd percentile

One should then argue that the apoB goals suggested in the ADA/ACC 2008 guidelines are very debatable. An apoB of 90 which is suggested as the goal for high risk patients is actually the 40th percentile cut point. Plain and simple we have to do better than that. If we must drive LDL-C to the 20th and 2nd percentile for the high and very high risk patient then we have to drive the apoB to 80 and < 60 and the LDL-P to < 1100 and 720 nmol/L respectively. For those very familiar with the NMR LipoProfile offered by LipoScience, they do not use the Framingham Offspring population as their reference, but rather the Multi-Ethnic Study of Atherosclerosis (MESA) instead. In that database the 20th percentile of LDL-P is 1000 not 1100. If we translate this to the patient under the discussion his LDL-P is not at the 20th percentile and is far from the second percentile.

Therefore and LDL-P of 1280 is not bad for most but with his history and higher risk it would be preferable to reduce it further. Obviously, because of tolerance issues, one cannot use a more powerful statin or a larger dose of simvastatin. Doubling the simvastatin would only add 6% further LDL-C lowering and even less with apoB or LDL-P (see Journal of Clinical Lipidology 2008;2:36-42 for a great discussion of how weak statins are in normalizing apoB). Many do not realize that the vast majority of LDL receptor (LDLr) upregulation (and hence apoB lowering) induced by statins occurs with the lower doses and that each doubling of the statin dose upregulates far fewer LDLr (than did the original dose), but increasing statin doses certainly increases the incidence of muscular side effects. This is why statin titration is a thing of the past and one should predict from the baseline non-HDL-C, apoB or LDL-P how much particle lowering is needed and then day one prescribe that dose of the statin. It is silly to start baby (weaker) statins when they have no prayer of achieving goal. This was discussed in detail in the 2004 NCEP ATP-III addendum (Circulation 2004;110:227-239). In that paper they also offered a second treatment option: instead of prescribing the larger statin dose needed to get to goal one could (with the full blessing of NCEP) instead use a smaller statin dose combined with ezetimibe, niacin or colesvelam. The combo of the smaller statin dose with any of those drugs would be as good as or actually outperform the larger statin dose monotherapy in achieving goal and likely with less myopathic symptoms. We actually have two combination products that would be in line with these guidelines: Vytorin, i.e., simvastatin and ezetimibe (Zetia) or Simcor, i.e., simvastatin and extended release niacin (Niaspan).

Therefore in this patient it makes sense to simply switch to Vytorin 10 mg (simvastatin and ezetimibe at 10 mg dose) and that alone might do it. However closer examination of the

lipoprotein analysis reveals a significant elevation of large VLDL-P (a TG-rich lipoprotein) as well as a small LDL size. Ezetimibe, by further depleting the liver of other sources of cholesterol (intestinal and biliary) upregulate further LDLr. However, LDLr are much better at recognizing and removing normal sized, rather than the smaller LDLs. The apoB conformation of a small LDL is not as identifiable by LDLr as is the apoB conformation of a larger LDL. Therapies that reduce TG synthesis such as lifestyle, fibrates (fenofibrate or fenofibric acid), high dose niacin and 4000 mg of N-3 Fatty acids (Lovaza) have the potential to shift LDL size from small to large. The COMBOS trial did demonstrate that high dose N-3 fatty acids plus simvastatin perform better together than individually to reduce non-HDL-C in patients with TG between 200-500). Welchol might be a better sequestrant than Questran to use in this patient as it is better tolerated and does not raise TG as much. But it also means that there is a good likelihood that TriCor or Niaspan could also improve the particles if necessary and you might be able to stop the sequestrant. In the Farnier study TriCor/Zetia got 2/3 of patients to non-HDL-C goal (European Heart Journal (2005) 26, 897–905). There would be Coumadin/fenofibrate issues in this patient which would necessitate a reduced dose of Coumadin.

LIPID CASE 222 Unhappy with HDL-C

I was asked about the following case: A male age 46 who is slightly obese (no additional history) is on 2000 mg of extended-release niacin (Niaspan), 10 mg of rosuvastatin (Crestor), 10 mg of ezetimibe (Zetia) and his conventional lipid panel reveals:

TC = 126 mg/dL HDL-C = 38 mg/dL LDL-C = 80 mg/dL TG = 110 mg/dL Non-HDL-C = 88

Apolipoprotein testing: ApoA-I = 174 mg (excellent- above the 80th percentile) and apoB = 74 (80 is the 20th percentile of the population)
ApoB/apoA-I ratio = 0.42 (desirable <.7)

I was asked if I thought the patient needed more niacin or should fenofibrate be added for optimal benefit or did I think the apoB/apoA-I ratio was doing great?

DAYSRING ANALYSIS:

Of course the goals of lipid-modulating therapy depend on both the ten year and lifetime CV risk of the patient. I have limited clinical information other than age, obesity and on-treatment lipid values. It would not be a stretch to assume this man has the metabolic syndrome and at least is in the moderate risk or moderately high risk category. I was not advised of any diabetes or of known atherosclerosis so he would not qualify as ten year high risk using NCEP ATP-III criteria. I think we'd all agree his lifetime risk for a CHD event is high and his risk of developing T2DM is also high.

If for purposes of discussion we assume he is moderately high risk then the case is closed as far as both NCEP ATP-III and the new ADA/ACC Consensus Guidelines of 2008 are concerned. The patient has achieved the LDL-C, non-HDL-C and apoB goals of therapy for a **very high risk person** (which he most certainly is not based on the info provided). So why did the clinician want to treat more aggressively? The answer is that he is unhappy with an HDL-C of 38 mg/dL. It is amazing how many providers do not realize there is no specific HDL-C goal of therapy in NCEP ATP-III nor in the new ADA/AHA consensus. Outside of the VA-HIT Trial, in which gemfibrozil barely raised HDL-C (6% or 1.8 mg/dL) there is no level one evidence demonstrating that one can predict CV outcomes related to the degree of drug induced HDL-C rising. There are drugs that dramatically raise HDL-C and provide no cardioprotection (torcetrapib, oral estrogen, phenytoin), therapies that lower HDL-C and provide cardioprotection (Ornish low fat diet and probucol) and of course the fact that statins, fibrates and niacin all improve CV outcomes as monotherapies to extremely similar degrees, yet they vary widely in their effect on HDL-C.

People like to quote the data that in many of the statin trials, the on-treatment HDL-C level can still predict residual risk on a statin: i.e. people on statins who still have low HDL-C do not so as well as people on statins who do not have a low HDL-C. Although as a generalized statement I can accept that, in all honesty it is not entirely a true statement. If one looks at TNT study, where atorvastatin (Lipitor) 80 mg was compared to atorvastatin 10 mg aggressive lowering of LDL-C was superior to benefit compared to less aggressive LDL-C lowering. At many lectures you are likely to be shown the slide where in those patients with very low LDL-C (under 70 mg/dL) who were in the lowest quintile of HDL-C had more events than did those in the higher HDL-C quintiles. However close examination of the data reveals that the above statement is true in the patients taking Lipitor 10 mg but it is not true in those taking 80 mg of Lipitor. In those patients (on 80 mg) there was no statistically significant residual risk identified by any value of HDL-C (low or high). To me the obvious explanation is that persons on Lipitor 80 will have significantly better levels of apoB or LDL-P than those on Lipitor 10 mg (no matter what the LDL-C level is) and once apoB or LDL-P is OK, HDL-C is not much of a risk factor. As Cromwell so nicely showed in the Framingham Offspring Study, people with excellent LDL-C levels still have serious residual risk if the LDL-P is still elevated.

There is more interesting data when one more deeply examines the TNT data with respect to residual risk and the need to raise HDL-C. Unfortunately not only to most physicians erroneously believe there is a specific HDL-C goal of therapy in NCEP (as mentioned there is not), they also believe that with respect to HDL-C, higher is better and thus why stop. I have heard some say (without a shred of clinical trial support to support their belief) that why not try and make the HDL-C 70 mg/dL! Interesting that in the HERs trial of >2000 women with CHD, 20% had baseline HDL-C values between 60 and 80 mg/dL. If HDL-C is so predictive of benefit, one wonders how these women got their CHD. Back to TNT: Looking at everyone in the study (those on both atorvastatin 10 and 80 mg), as mentioned there was residual risk in the two lower quintiles (< 37 mg/dL and 37-42 mg/dL) of HDL-C even with low LDL-C concentrations. Yet if one looks at that curve, the residual risk disappears in the third quintile (HDL-C of 42 - 47). It appears that risk starts to increase again (not statistically significantly) as the HDL-C rises above 55 mg/dL. There is not any lower risk in those in the upper HDL-C quintile (> 55 mg/dL) as there is in those in quintile 3 (47-54)

One of the best articles written on understanding is also by Cromwell (Journal of Clinical Lipidology 2007;1: 57-64) in which he notes that as HDL-C rises from low levels (20s) to about 40-45 mg/dL, there is a tremendous increase in the number of HDL particles (HDL-P), the vast majority of which are small. As HDL-C rises above 45, there is almost no further increase in the HDL-P, but rather the rise in HDL-C is explained by the maturation (increasing size and cholesterol lipidation) of the HDL particles. This would also suggest that once HDL-P has been normalized, further increases of HDL-C are unlikely to be of benefit (as also suggested in the TNT study described above). More support of this theory comes from the VA HIT trial mentioned above (Circulation. 2006;113:1556-1563). Although the HDL-C rise induced by gemfibrozil was quite small, the HDL-P rise was quite significant. However the vast majority of the HDL particles (as expected on a fibrate) were small. So although HDL-P skyrocketed, and the particles were small, the HDL-C rise was trivial, but benefit occurred. Fibrates by inducing (upregulating) hepatic scavenger receptors B1 delipidate mature HDLs, converting them into small HDL species. This also refutes the premise that only large HDLs are cardioprotective.

With respect to ratios: The apoB/apoA-I or the TC/HDL-C or LDL-C/HDL-C is an attempt to divide a marker of atherogenic particles by a marker of antiatherogenic particles. The apoB/apoA-I ratio was highly predictive of events in the INTERHEART and AFCAPS/TexCAPS studies as well as others. I highly recommend the following article written by Alan Sniderman (Future Lipidology 2008;3:257-264) which discusses the usefulness or lack of usefulness of ratios in general including the apoB/apoA-I ratio. Ratios may have little value unless both the numerator and the denominator have equal weight in their predictive abilities. Well, apoB is a proven risk factor and a proven goal of therapy. ApoA-I is not. Drugs like estrogen or torcetrapib which do not reduce

the all important apoB, but do raise apoA-I would beneficially improve the ratio but these drugs are not associated with CV benefit.

In the case at hand, the patient as described is at apoB goal from the ADA/ACC 2008 guidelines (suggesting atherogenic particles have been eliminated). Although at first glance, one might be alarmed by the low HDL-C, the HDL particle number (as measured by apoA-I) is OK. Thus the patient has more than adequate numbers of HDL particles. Complicating analysis of any HDL parameter (HDL-C or HDL-P) is the fact that we have no way of knowing if his HDLs are functional where functionality is described as the ability to traffic multiple cardioprotective proteins to the arterial wall and the ability to delipidate arterial wall foam cells (macrophage reverse cholesterol transport). A drug's ability to improve HDL functionality has little to do with what it does to HDL-C. Both niacin (and fibrates) increase HDL functionality yet both have very different abilities to raise HDL-C. Ezetimibe can increase macrophage RCT but does little to HDL-C.

Moral of the story: For now, there is one and only one goal of therapy: apoB (LDL-P) or their lipid surrogates (LDL-C and especially non-HDL-C). There is no HDL-C or apoA-I goal of therapy. There is no evidence that therapeutically raising HDL-C once apoB is perfect has any clinical benefit, so why attempt it? Pfizer just lost a billion dollars trying to prove it. Therefore using apoB or Non-HDL-C, there is no need for further lipid medication in the above patient. My only concern: In many patients with metabolic syndrome with low LDL-C, especially if LDLs are small, there is a disconnect between apoB (false negative low values) and LDL-P. It seems like the configuration of the apoB on a small LDL may not be recognized by the protein immunoassay. So it is possible that a patient with an apoB of 74 could still have increased numbers of atherogenic LDL particles as measured by nuclear magnetic resonance (NMR LipoProfile). I'd suggest confirming the normal apoB with an LDL-P. If the LDL-P is indeed still high I would then add Niaspan. Fibrate efficacy is best seen in insulin resistant patients with high TG and low HDL-C.

LIPID CASE 223 VeryHigh LDL-C Is treatment needed?

The patient is a 65 year old female with a markedly elevated LDL-C (off meds), but an LDL-P that is well below goal which again brings up the question does the LDL-C (very high in this case, as opposed to very low in JUPITER trial) have any value in evaluating this patient? The patient has a past medical history significant for hypercholesterolemia and osteoporosis. She has no personal history of smoking or hypertension. Her ethnic background is Russian-Jewish. Her family history is significant for her father dying at age 70 from multi-infarct dementia and mother passing away at age 80 of breast cancer. She has three sisters, one with breast cancer. There is no family history of coronary disease. Her current medications include Forteo, Citrical, Vitamin D and a multivitamin. For approximately three years, she took Lipitor 40 mg daily.

Her last lipid panel (on treatment) revealed:

TC = 224 mg/dL, LDL-C = 50 mg/dL, HDL-C = 164 mg/dL, VLDL-C = 10 mg/dL, and TG = 53 mg/dL. Afterwards, Lipitor was discontinued in an attempt to reassess whether she truly needs lipid lowering therapy.

Three months later, here are the labs:

TC = 362 mg/dL, LDL-C = 223 mg/dL, HDL-C = 129 mg/dL, VLDL-C = 10, TG = 51 mg/dL.

NMR LipoProfile (done at LabCorp) revealed the following results:

Total LDL-P = 1117 nmol/L (20th percentile of Framingham Population) Small
LDL-P = 90 nmol/L
LDL size = 22.4 (gigantic)
Large HDL-P = 90 umol/L
Large VLDL-P = 0.3

According to her risk factors, here goal LDL-C should be under 130 mg/dL which she is severely over. Yet the LDL-P goal is < 1300 nmol/L which she achieves without meds. I was asked which of the two tests is a more reliable measure of CV risk, or do we need to consider both?

DAYSRING DISCUSSION:

The LDL size in this woman is extremely large: as you know large LDLs are defined as having a diameter > 20.5 nm. The volume of a sphere is $\frac{4}{3}(\pi)$ radius cubed. Thus even tiny diameter (radius) changes translate into very large volume differences. With lipoproteins, the particle's volume is dedicated to trafficking lipids - primarily cholesterol, cholesteryl ester and triglycerides. The phospholipids are on the surface not in the core of the particle (Journal of Internal Medicine 2006; 259: 247–258).

Her most recent results revealed a very decent LDL-P of 1117 nmol/L, virtually no small LDL-P (90 nmol/L), large HDL-P 30.2 μ mol/L (extremely high), and large VLDL-P 0.3 μ mol/L (perfect). Meanwhile, the total cholesterol was 362 mg/dL, LDL-C was 223 mg/dL, HDL-C was 129 mg/dL and the triglycerides were 51 mg/dL. So do we resume the Lipitor or respect the data that particle number not particle cholesterol concentration is what drives atherogenesis.

She has physiologic amounts of TG (< 70 mg/dL), which means that the major component of all of most of her lipoproteins is cholesterol. Her TG are primarily where they belong, in her VLDL particles. The large VLDL-P concentration is physiologic. Little if any TG is competing for space in any lipoprotein especially her IDLs, LDLs and HDLs: this means they can traffic more cholesterol. Using the formula developed by Bill Cromwell and Jim Otvos (Journal of Clinical Lipidology 2007;1:583–592), we can calculate the number of molecules of cholesterol that are carried in each LDL particle: Divide LDL-C (in mols/L) by LDL-P (mol/L). In the case at hand, that calculation is 6793 cholesterol molecules per LDL particle: very big dump trucks carry an awful lot of cholesterol! For comparison sakes: in a person with an LDL-C of 100 mg/dL and a TG < 100, LDL particles each typically carry 2000 molecules if their LDL size is 20.8 nm. If the size were 21.2 it is 2500 molecules. Again in the case at hand where the patient has gigantic LDL particles, those particles have almost three times the cholesterol carrying capacity of more normal sized LDL particles.

Back to the case: The TC is alarmingly high at 362! But that by itself cannot tell the story. Which specific lipoproteins are trafficking the majority of cholesterol? The HDL-C is 129 mg/dL. Theoretically that is cholesterol the preventive cardiologist does not worry about. Yet recent data has shown that many patients with high HDL-C do get events. We got a little smarter recently when we received data from the IDEAL and EPIC Norfolk studies (J Am Coll Cardiol 2008;51:634–42) showing that as long as one had lots of HDL particles (which can be measured by apoA-I or HDL-P by NMR) the high HDL-C was not a risk factor. It was a risk factor if one had too few HDL particles: if one has a high HDL-C and a low HDL-P (apoA-I) the HDL size would have to be very large potentially making the particle dysfunctional. The authors even concluded such HDL particles might at the foam cell interface be cholesterol donors rather than as usual, cholesterol acceptors. In this case the large HDL-P is extremely high. Although we do not have the medium and small HDL-P values, which contribute to total HDL-P (not reported in the LabCorp NMR), I suspect this patient has very large amounts of non-gigantic, non-dysfunctional HDL particles. The large HDL-P of > 30 μ mol/L is very high and by itself puts the patient in the upper percentiles of total HDL-P (in the MESA study).

If we calculate the non-HDL-C (293 - 128) we get 233. If this is a low risk person, the NCEP-ATP-III goal for non-HDL-C is either 160 + 30 or 190, or 130 + 30 = 160. Thus, despite the high HDL-C, using non-HDL-C we are still suspicious that the person has too many apoB (or LDL) particles. With a TG of 51 mg/dL, the calculated VLDL-C = 51/5 or 10 (Friedewald formula: VLDL-C = TG/5), so remnant particles (diagnosed by high VLDL-C) are not a concern. Most providers would say: the high TC, high LDL-C, and high non-HDL-C mandates drug therapy. NCEP ATP-III states that an LDL-C > 190 mg/dL virtually always requires LDL-C lowering

therapy. But they said that several years ago and we are smarter now and we have newer and better ways of estimating LDL particles and their association with atherogenicity. Never forget that the risk associated with a given level of LDL-C comes from observational and clinical trials: but because of the heterogeneity of LDL particle lipid composition there are always exceptions to the rule: i.e not every person with high LDL-C gets disease and not all folks with low LDL-C are protected. This lady is one of the exceptions: her high LDL-C is not associated with risk. The LDL-P (a much better marker of risk than LDL-C) confirms that.

We now have numerous studies and an official ADA/ACC guideline (Diabetes Care 2008;31:811-822) revealing that the major determining force that drives apoB (LDL) particles into the arterial wall is particle number - not particle size. Big LDLs enter the arterial wall as easy as do the small ones. The NMR analysis in this patient shows a very low risk number of LDL particles and very few VLDL particles. I know we are not dealing with a type III hyperlipidemia (too many IDL particles) because of the perfect TG level. Using the Cromwell/Otvos formula, I realize that because of the very large LDL size and the large volume capacity and # of cholesterol molecules per particle, it is perfectly possible to have severely abnormal LDL-C values with relatively healthy LDL particle numbers. Since it is particle number not particle cholesterol content that drives the particle into the arterial wall, no treatment is indicated in the case at hand.

The Lipitor therapy significantly inhibited cholesterol production in this patient. Such hyperresponsiveness to statins is indicative of overproduction of cholesterol and under absorption of intestinal cholesterol from the gut and bile (low activity or down regulation of Niemann Pick C1 Like 1 or NPC1L1 protein). Such patients over manufacture cholesterol in all tissues including the liver: they have lots of HMG-CoA reductase and the statins are obviously very potent in inhibiting HMG CoA reductase and dramatically reducing cholesterol synthesis in such patients. In this case because her TG are so low, her liver produces few VLDLs but instead produces cholesterol-loaded IDLs or in the case at hand, very large LDLs. A different patient would over produce and secrete smaller LDLs and the LDL-P would be much higher. For whatever reason this woman is able to produce gigantic LDLs.

Also: in patients with tremendous over production of cholesterol, liver and other tissue ATP Binding cassette transporters A1 (ABCA1) are upregulated via the liver X receptor (LXR) trying to export cholesterol in an attempt to export the overproduced cellular cholesterol: there is overfilling the HDLs and a dramatic rise in HDL-C. The LXR is a sterol toxicity nuclear transcription factor that attempts to make the body export cholesterol to restore cholesterol homeostasis. The main determinant of serum HDL-C is hepatic (and intestinal) ABCA1 expression.

Can we speculate other reasons why the LDL particles and the HDLs are so large? Hepatic lipase deficiency would keep both LDLs and HDLs large - but TG would be quite high so this is ruled out. Endothelial or other lipase deficiency or dysfunction? Phospholipid transfer protein problem? One can only speculate. I suspect this might be a combination of a patient with a naturally low TG and some polymorphism or variant of CETP deficiency: The apoB-containing VLDLs have no TG to swap with the LDLs and the HDLs particles cannot swap neutral lipids so readily and thus the LDLs and HDLs stay cholesterol-rich. These types of cases are more examples of why particle quantification tests can prevent both under and over-treatment. Bottom line is that because of her gigantic LDL particle size and particle composition (all cholesteryl ester - no TG), this woman does not need very many LDLs to traffic her LDL-C and thus the LDL-P has no correlation with the LDL-C.

Think of another patient with an LDL-C that was perfect (68 mg/dL): yet who passed with an LAD occlusion - Tim Russert. Because his TG were very high his LDLs were TG-rich and cholesterol-poor, necessitating large numbers of LDLs to traffic his trivial LDL-C. In his case the LDL-P would be extremely high, and require aggressive Rx, despite his spectacular LDL-C.

Because of medicolegal issues, when one ignores the NCEP ATP-III guidelines (and does not treat an LDL-C > 200) one should explain this condition in depth to the patient and see if they

agree. If the patient demanded treatment, I'd reluctantly do it. I'd also screen for subclinical heart disease with a coronary calcium score and I would treat if that was positive. I do not trust CIMT unless done by those with impeccable credentials in doing the test, so in my practice I do not use CIMT. But if you had someone you trust that is another way of looking for subclinical disease. I close by again reminding you that the JUPITER trial has demonstrated once and for all how inferior LDL-C is as a test to adjudicate risk and as a goal of therapy. Can we all move on to non-HDL-C or better yet LDL-P?

LIPID CASE # 224 VeryHigh HDL-C Is Treatment Needed?

Last issue we talked about an unusual case where an LDL-C of 223 required no lipid therapy. This issue deals with an equally unusual scenario. What to do with someone who has serious CAD yet an HDL-C > 100 mg/dL. I was asked about a 70 year old white woman with a history of hypertension, coronary disease with a myocardial infarction and a CVA (1990), peripheral vascular disease (with a left above the knee amputation), metabolic syndrome and hypovitaminosis D. She stopped smoking in 2002. Her current medication is Advicor (extended release niacin and lovastatin) at a dose of 20/1000, two tabs each day, TriCor 145 mg and aspirin 81 mg daily, high dose vitamin D supplementation, Plavix, Effexor, and Tegretol.

Current labs:

TC = 217 LDL-C = 66 TG = 205 HDL-C = 110 TC/HDL-C = 2.5 (Previous HDL-C was 130)
Glucose = 105

Berkeley Heart Lab Testing was done using gradient gel electrophoresis:

ApoB = 35 (Less than 54 mg/dL is the second percentile in the Framingham Population)
ApoB ultra (apoB after removing VLDL) = 30 (desirable < 60)
LDL distribution - mostly larger LDLs. Has low levels of the smaller LDLs (IIIa&b and IVb)
HDL distribution mostly large
ApoE genotype is 2/2
Lipoprotein associated phospholipase A2 (Lp-PLA2) or PLAC test = 350 (desirable < 180)
hs-CRP = 13,5 (n < 2.0)
Fibrinogen elevated
Insulin 57 (should be < 10)
Lipoprotein (a) = 8

The provider is seeking additional advice:

DAYSRING DISCUSSION

This is about as very high risk a person as one will ever see and yet NCEP ATP-III tells us a high HDL-C (>60 mg/dL) is cardioprotective. That is one of those generalized statements that is often true but has many exceptions to the rule. In the Heart and Estrogen/progestin Replacement Study (HERS) which enrolled > 2000 women with significant CHD: 20% had HDL-C values between 60 and 80 (Amer Heart J 2000;139:288-96). The authors suggested NCEP redefine HDL-C values for women. A more recent publication ((Am J Cardiol 2007;99:1- 4) discussed men and women getting CHD with HDL-C values > 70 in men, >80 in women). Interestingly they found no other traditional CHD risk factor abnormalities in the lab to explain the CHD. Their conclusions were: "patients with high HDL and CAD had a similar or lower prevalence of traditional CAD risk factors compared with patients with normal HDL levels and CAD." For all of you who believe that a high HDL-C has much meaning or what a drug does to HDL-C has much meaning, please go to our web site www.lipidcenter.com, click on professionals and scroll down to Power Point Presentations and look at the program entitled: HDLs - Do we have a clue? In it I quote numerous top HDL experts. In essence HDL-C is about as useful as LDL-C -- Good predictors when looking at populations but with LOTS OF SHORTCOMINGS IN INDIVIDUAL PATIENTS.

Of course when people get CHD with high HDL-C levels we now use the term dysfunctional or proatherogenic HDLs. What the heck is that? Briefly, HDLs have two functions in humans: 1) cholesterol trafficking and 2) protein trafficking. If they do not do either of those they are dysfunctional. Neither 1 nor 2 has any relationship to a plasma HDL-C level.

First some HDL nomenclature basics: HDLs consist of a cholesteryl ester (CE) core surrounded by a phospholipid surface (with some unesterified cholesterol molecules also on the surface) wrapped by numerous surface proteins (apolipoproteins). The main structural HDL apoprotein is apoA-I and each HDL has 2 to 4 molecules. There are very few TG molecules within HDL particles (typically 5%). An HDL's life begins with hepatic or jejunal production and secretion into plasma of apolipoprotein A-I and A-II (a PPAR, mostly PPAR-alpha, mediated process). The apoA-I attaches to cells wishing to export phospholipids and cholesterol and willingly accepts those lipids. Cells that need to export cholesterol upregulate a sterol export protein termed ATP binding cassette transporter A1 (ABCA1). As the HDL lipidates it changes into a prebeta HDL species - the smallest contain apoA-I and phospholipids but ultimately a few molecules of cholesterol join. Soon apoA-II attaches and the free cholesterol is esterified (a fatty acid replaces the OH group at the # 3 position on the first sterol ring) via an enzyme called lecithin acyl cholesterol acyltransferase (LCAT). The HDLs are now called alpha species (alpha 4 is very tiny). As they mature (gather more cholesterol and esterify it) they become large: alpha 3, alpha 2 and ultimately large alpha 1 HDL particles. Alpha HDLs have other nomenclature more familiar to many of you: In the NMR report from LipoScience H1 is the small alpha 4 particles and alpha 1 are the large H5 particle. In gel fractionation (Berkeley) or ultracentrifuge labs (VAP), tiny alpha 4s are the HDL3 species and large alpha 1 are the HDL2 species. Apo A-II dissociates from and is not found on the larger HDL species. ApoA-II is needed for proper HDL maturation and modern data reveals both high apoA-I and apoA-II levels are associated with cardioprotection.

1) HDL CHOLESTEROL TRAFFICKING: The vast majority of the cholesterol within the HDLs is acquired by export via ABCA1 located in hepatocytes or enterocytes (jejunal). Of course any other cell with excess cholesterol (including arterial wall foam cells or sterol-laden macrophages) can also export sterols to an HDL. However the contribution of cholesterol to an HDL from peripheral cells or arteries is very, very tiny compared to the contribution of the liver and small intestine. The very small unlipidated A-I protein, or tiny prebeta HDLs are the HDL species with maximum ability to delipidate (accept cholesterol) from these cells. As it acquires and esterifies the cholesterol the HDL matures or enlarges from prebeta, to alpha HDL 4 and 3 and ultimately to alpha 2 and 1 (H4 and 5 on NMR or HDL2 on Berkeley or VAP). Clearly as the majority of HDL species enlarge (fill with cholesterol) one would expect HDL-C to rise. Once full the HDLs must traffic their cholesterol load: there are several options:

A) Forward cholesterol transport: take the hepatic and GI cholesterol to cells which consume a lot of cholesterol: namely steroidogenic tissues (adrenal cortex and gonads) or adipocytes (which have high cholesterol needs due to their extensive surface cell membrane area). At these tissues the HDLs are delipidated by a cell membrane protein called the Scavenger receptor B1 (SRB1). The HDLs now become very small again (alpha 4 or even prebeta). The alpha 4 are available to return to tissues to acquire more cholesterol or proteins (i.e. they live for another day!). Some of the prebeta or unlipidated apoA-I species can be excreted by the kidney.

B) Reverse cholesterol transport: if the cholesterol within the HDLs is not needed by steroidogenic or adipocyte tissues then the HDL ultimately has to get rid of it. It does this via many avenues:

a) Direct Reverse Cholesterol Transport: return to the jejunum or liver and be delipidated by upregulated SRB1 receptors. The HDLs will become small alpha 4 or prebeta and return to plasma for reuse or excretion. The liver can also endocytose the entire HDL particle via the

holoparticle (catabolism) receptor which is officially called the apoA-I beta chain synthase protein. Once endocytosed the HDL is destroyed.

b) Indirect RCT (at least 50% of the RCT pathway): The HDL using cholesteryl ester transfer protein (CETP) swaps its cholesteryl ester (CE) in a one for one exchange of TG molecules present in chylomicrons, VLDLs, IDLs and LDLs. In essence the HDL acquires TG and gives up its CE to the aforementioned apoB particles. The apoB particles (the vast majority of which are LDLs) then are endocytosed by hepatic LDL receptors (LDLr). Amazingly the LDLs complete the RCT process, explaining why this pathway is called indirect RCT. Unfortunately few physicians have been taught that the cholesterol in LDLs comes from the both VLDL/IDL precursors as well as HDLs. The major function of LDLs in plasma is to return unwanted cholesterol to the liver via the LDLr pathway.

If you can try and envision the whole dynamic, remodeling, flux process performed by HDLs - little ones fill up and then empty, hundreds of thousands of times over their six day half life. One can easily understand because of the rapidly changing volume of HDL particles, a serum HDL-C has no relationship whatsoever to the RCT process. When you look at an HDL-C level, you have no clue whether the HDLs are filling and emptying properly: if HDL-C is very high, maybe they are not delipidating properly! That might not be so desirable!

2) HDL protein trafficking: The reasons HDLs are found at the bottom of the centrifuge tube is that they are much denser (heavier) than the other lipoproteins and that is because they contain very little lipids, but a lot of proteins. Indeed over 50 proteins have been indentified on the surface of HDL particles. We have no idea about the function of many of these particles. Many are involved with lipid and lipoprotein metabolism (apoA, and apoC families, apoD, apoM, apoE, and others). The rest of them are immunomodulatory proteins involved with fighting infections or reducing inflammation. Thus HDLs are an innate part of the immune system with a mission of trafficking these immunomodulatory proteins to areas of infection and inflammation. Interestingly many of these proteins may be cardioprotective by reducing arterial inflammation, inhibiting coagulation, inducing fibrinolysis, upregulating nitric oxide, etc. The cholesterol content of the HDL particle (HDL-C) has no relationship to which proteins are present or not. So again HDL-C has nothing to do with HDL functionality. Many believe the small HDL carries more of the beneficial proteins than do the large HDLs.

What if one had HDL particles that lacked all of the potentially cardioprotective proteins (paraoxanase, etc). It would be likely that these are the dysfunctional or proatherogenic HDLs that folks are now talking about. What would displace the protective proteins? Here is one possibility: under conditions of inflammation not only does CRP rise but so does amyloid. Amyloid has a significant affinity for apoA-I and by binding to HDLs can displace the beneficial proteins, rendering the HDL dysfunctional. In the patient under discussion, the two inflammatory markers Lp-PLA2 and CRP are both quite high. I'll bet she might have serious amyloid elevations which are likely rendering her HDLs as useless (not able to deliver protective proteins and not able to perform macrophage RCT).

Now comes the crucial part to understanding the relationship between HDL-C and HDL-P. Must reading is Bill Cromwell's phenomenal paper entitled High-density lipoprotein associations with coronary heart

disease: Does measurement of cholesterol content give the best result?: Journal of Clinical Lipidology (2007) 1, 57-64. Promise me you will all read this paper before the new year! He concludes: "Although HDL-C is

thought to indicate the quantity of circulating HDL particles, it is under appreciated that the amount of cholesterol carried inside lipoprotein particles is highly variable among individuals with the same HDL-C."

What is the relationship between HDL-C and HDL-P? HDL-C is the cholesterol content within all of the HDLs that exist in a deciliter of plasma whereas HDL-P is the number of alpha HDLs that exist in a liter of plasma. If you use the NMR assay: add small, medium and large HDL-P to get the total HDL-P. Of the total HDL-C the vast majority of the cholesterol exists within the large, mature alpha 1 and 2 particles (HDL2 or H4 and H5). Bill demonstrates in his paper that as HDL-C rises from 20 to 40 mg/dL there is a tremendous increase in the total HDL-P, yet almost all of them are small particles. As HDL-C rises above 40 mg/dL the small and medium HDLs disappear and are replaced by large HDLs (the little particles are being lipidated or filled up). Of most interest is that once the HDL-C is at the 40-45 mg/dL range there is virtually no increase in the number of HDL particles (total HDL-P) present per liter. Thus one would predict that if it is the HDL-P itself that is cardioprotective, then once you have maxed out the number of HDL particles, continued raising of HDL-C would be an exercise in futility. If you insist of raising HDL-C beyond 40-45 you are simply making HDLs larger and what we need to know is at what size does the ever enlarging HDL become dysfunctional?

Supporting this data is a recent analysis from TNT where atorvastatin lowered LDL-C to below 70 mg/dL in many patients. Residual risk on a statin seemed to be present in patients with such low LDL-C if their HDL-C was below 43, but no longer present once the HDL-C was 43 or above -- of most interest is there was no further lessening of the residual risk beyond an HDL-C of 43 -- indeed there was a suggestion that risk began to elevate at HDL-C > 55 (almost sound like some of the women in HERS). The final nail in the coffin for the very large HDL comes from data from IDEAL (a statin trial) and EPIC Norfolk (an epidemiological trial) J Am Coll Cardiol 2008;51:634-42. They looked at people having CV events despite high HDL-C (like the patient under discussion)

In patients with high HDL-C they either have to have a lot of normally sized HDLs or they could have a few extremely large HDLs. In the first patient subset both HDL-C and HDL-P (apoA-I) would be high. In the latter subset HDL-C is high but HDL-P (apoA-I) is low. Guess what: the persons with the low HDL-P (apoA-I) had the clinical events despite their great HDL-C. I wonder - does the lady under discussion have a low HDL-P and if so can we increase it? Maybe she lacks apoA-II - can we increase it? Read on!

An even more interesting study is THROMBO Study where the best predictors of clinical events were a very high CRP (inflammation) and the presence of large HDL particles (obviously dysfunctional) and high HDL-C (Corsetti et al Atherosclerosis 2006;187:191-197 Sounds like this woman!

So the Advicor has beautifully reduced the LDL-C to normal and the apoB also is superb. That could be misleading. Under conditions of high inflammation, the multiple inflammatory molecules can alter apoB in a way that the epitopes (to which the antibody in the assay attach) are damaged and it is not uncommon to see false negative apoB levels in such patients. I do not believe the normal apoB level in this patient and would much prefer to see an NMR LDL-P level (NMR not affected by inflammatory states).

The TG are still high which means the VLDL-C (TG/5) is also elevated. NCEP reminds all that a high VLDL-C is diagnostic of remnants (VLDLs and chylomicrons and IDLs that have lost TG and gathered cholesterol from CETP swapping of TG for CE). Remnants are considered highly atherogenic as they have the ability to increase endothelial inflammation and reduce nitric oxide in the endothelium. Remnants also often carry apoC-III an injurious apoprotein which delays the catabolism of TG-rich lipoproteins. I'll bet an NMR analysis in this patient would show increased VLDL remnants (high VLDL-P) and also high LDL-P. Her LDL-C is fine because her LDLs are carrying TG instead of cholesterol. It takes an awful lot of TG-rich, cholesterol poor LDLs to traffic even 66 mg of cholesterol. Remember Tim Russert died with an LDL-C of 68, but he also had similar LDL composition abnormalities because of a very high TG (~400) - The lady under discussion is in the same scenario, except in her case it only took a TG of 205 to change the composition of her LDL particles. The odds are great is that she has serious abnormal

compositional abnormalities in all of her lipoproteins. If the LDL is carrying excess TG it will have to carry less cholesterol. Thus even large LDL particles can be cholesterol depleted: it always takes more cholesterol depleted LDLs to traffic a given level of LDL-C. Again I really suspect this woman has a high LDL-P despite the normal apoB.

I'd continue statin/niacin, except that if the LDL-P is indeed quite high I'd move to more potent therapies like Simcor or ultimately Crestor/Niaspan. If the LDL-P is good, Advicor is fine. Because of the remaining TG elevation despite the TriCor (fenofibrate), I would add Lovaza at 4000 mg daily. That would lessen the number of remnants and drive LDL-P down further. As seen in FIELD fenofibrate reduced several microvascular endpoints (retinopathy, glomerulopathy and of great interest to this woman, reduced neuropathic amputations of the lower extremities. Fenofibrate will also increase apoA-I and apoA-II production. and enhance macrophage RCT (as does the niacin she is already taking. All follow up in this patient will require NMR lipoprotein analysis. Guessing everything from a lipid profile is really very tough.

I'll close with a way out thought: What if this high HDL-C is due to CETP deficiency? The treatment then would be to reduce the HDL-C and that can be done by using a CETP inducer - namely probucol (available in Europe but no longer in the US). *Atherosclerosis* 186 (2006) 225–227 C Sirtori et al. This is a question that stumps almost all lipidologists? When would you ever recommend lowering HDL-C? Read Dr Sirtori's comments.

LIPID CASE # 225 “Nobody Dies of High Triglycerides”

While visiting a town recently I had lunch with a provider who shared the following with me. A 48 year old premenopausal woman was in for a visit for some abdominal complaints and had lab tests which included a lipid profile. There is no history of atherosclerotic cardiovascular disease but she is hypertensive and she is slightly overweight. She does not use alcohol.

TC = 354 HDL-C = 32 TG = 1650 Neither VLDL-C or LDL-C can be calculated with such a high TG

TSH = 1.74 Amylase and Lipase normal

AST 44 (N< 40) A:T = 66 (N<55) Bilirubin and alkaline phosphatase normal Total protein normal

Glucose 117 Renal functions normal CBC normal

The provider had never seen such a high TG and was quite concerned so she consulted (via phone) a cardiology colleague. I kid you not: his response was "Nobody ever dies of high TG" and no treatment was advised. Fortunately, the provider ignored the cardiologist and started atorvastatin (Lipitor) 10 mg daily. She knew I was coming to town and asked my opinion.

DAYSRING ANALYSIS:

If you need me to tell you what a MISINFORMED, pathetic statement on TG that was, please delete this e-mail immediately and then retire from practice. In the Paris Prospective Study looking at diabetic men as well as those with impaired fasting glucose over an 11 year period, CV death was statistically significantly associated with a TG > 133 mg/dL (*Diabetologia* 1989;32:300-304). In data from Framingham, 2/3 of women who had a CV event had an LDL-C < 140, but all had either a high TG (>200 mg/dL) or a high TG with a reduced HDL-C (*Arch Intern Med.* 2001;161:949-954). In obese women (waist size > 35 inches), CV risk is associated with TG > 128 mg/dL (*Circulation* 2005;111:1883-1890). If you would like to see dozens of other studies linking CV morbidity to TG at very low levels (low 100s) visit www.lipidcenter.com and click on Professionals and scroll down to the PP slide deck on Atherothrombosis and TG.

NCEP ATP-III in 2001 stated a TG of 200 mg/dL is associated with high CV risk and a TG of > 500 mg/dL with very high risk. NCEP went on to say that if a person was not overweight,

exercised, did not have an endocrine problem, was not using certain drugs, did not smoke the TG should never be above 100 mg/dL. If some of those were present the levels would rise to 150-199 (with the most common reason being obesity and lack of exercise). For those with genetic problems, the TG can rise to > 200 mg/dL. Is everyone listening: A TG > 100 mg/dL is potentially ABNORMAL. Noninsulin resistant populations have fasting TG of 10-70 with a mean of 30 mg/dL. Normal postprandial excursions are 30-100 mg/dL: thus anyone with a PP TG of > 170 has a pathological TG condition (The TG Tolerance test: Diabetes Care 27:89-94, 2004). If you see a TG of 200 mg/dL do not waste your time asking if the patient was fasting or not: that level is abnormal in either case. Never bring the patient back fasting to repeat the TG. It might drop to below 150 and you would erroneously believe that is normal.

A key concept related to TG is the Friedewald formula where VLDL-C = TG/5. Thus with a TG of 150, the VLDL-C is 30. The formula makes certain assumptions. All TG are in VLDLs and VLDL composition is 5/1, i.e. a VLDL has five times more TG in its core than cholesteryl ester. With physiologic levels of TG (10-70), the vast majority of the TG are in VLDLs. However as TG levels rise, other lipoproteins, specifically IDLs, LDLs and HDLs also become overloaded with TG and the VLDL composition changes from the 5:1 ratio. That is why the Friedewald formula cannot be used to calculate either VLDL-C or LDL-C as TG rise. Many labs state the formula is accurate with TG up to 400, but few lipidologists agree with that. Note that $LDL-C = TC - [VLDL-C + HDL-C]$.

The following is obvious and explains so much of what you all see every day. Above I stated that as TG levels raise IDLs, LDLs and HDLs become TG-rich. How does that happen? If the liver overproduces and secretes increased numbers of TG-rich VLDLs (or the jejunum does the same with chylomicrons) serum TG levels will obviously increase. If these particles do not undergo rapid lipolysis (fat breakdown) they will have increased half life's or plasma residence times and postprandial hypertriglyceridemia occurs. Lipolysis is the hydrolysis of lipids like TG (triacylglycerol), cholesteryl ester, or phospholipids. Hydrolysis is the chemical reaction where water (or H or OH groups) is formed by separating molecules: the hydrolysis of triacylglycerol or TG results in the release of one or two fatty acids (acyl groups) resulting in diacylglycerol, monoacylglycerol and FA. A TG-rich lipoprotein with increased plasma residence time can create a lot of havoc.

- They increase blood viscosity
- They create endothelial dysfunction by down regulating NO production
- They are associated with abnormal coagulation markers (PAI-1, fibrinogen)
- They are associated with elevated apoC-III an independent risk factor for CHD (see ref 2 below)
- They are associated with insulin resistance
- They traffic Lp-PLA2
- They are associated with increased numbers of atherogenic remnants
- They are associated with increased cholesteryl ester transfer protein (CETP) activity
- Since FA can become soaps (detergents), they destroy cell membranes (especially in pancreatic cells)

The increased CETP activity is crucial to TG's ability to create lipoprotein havoc. This protein swaps one molecule of TG for one molecule of cholesteryl ester (CE) between lipoproteins. The VLDLs and chylos (TG-rich particles) send their TG to LDLs and HDLs -- to make room for the arriving TG, the HDLs and LDLs send CE back to the VLDL or chylo. In effect, the LDLs and HDLs become TG-rich and CE-depleted whereas the VLDL (and chylo) becomes CE-rich. The particle sizes remain the same: the only thing that has happened is a transfer of core neutral lipids. If you take a moment to think of these compositional changes in terms of the lipid profile the following axiom develops:

As TG levels rise, VLDL-C rises and LDL-C and HDL-C falls. Analyzed in a different way as TG levels rise there will be a fall in VLDL (and chylo) TG content and a rise in LDL-TG and HDL-TG.

Well, an LDL and HDL carrying TG is a pathological lipoprotein. Their physiologic function is to traffic CE, not TG. If you have a lot of LDLs and HDLs carrying TG they contribute to the endothelial dysfunction, coagulation and blood viscosity conditions described above. TG-rich HDLs are usually quite dysfunctional and are less likely to perform cardioprotective actions - i.e. TG-rich, CE poor HDLs are dysfunctional. Let's take this one step further:

If LDL-C and HDL-C goes down, and VLDL-C goes up -- what happens to non-HDL-C? The obvious answer is it goes up and remember non-HDL-C is simply a surrogate of apoB or LDL-P (atherogenic particles if present in increased numbers). Non-HDL-C is the secondary goal of therapy on NCEP. You have just learned what you probably already knew but never verbalized. Elevations of TG in the vast majority of cases is a surrogate increased apoB (too many LDLs and remnants). Also when using non-HDL-C remember it is influenced by VLDL-C (TG/5). Anyone with a high TG, has a high VLDL-C. If LDL-C is fine and VLDL-C is high, non-HDL-C will also be high. This is an easy way to spot someone at risk despite an at goal LDL-C.

Thus do not be fooled by dropping LDL-C levels as TG rise: the LDLs are simply carrying TG instead of CE. Do not be dumb enough to tell a patient with high TG but normal LDL-C (like menopausal women or metabolic syndrome patients) that they are fine and are at goal. If you would simply stop being one of the 80-90% of providers who do not calculate non-HDL-C you would see the risk. Anyone with a normal LDL-C but a high non-HDL-C is at risk as they still have too many apoB particles in their plasma. The CE that used to be in their LDLs and HDLs are now in the VLDLs (chylols) and you would know that if you took the time to calculate and use VLDL-C.

The process is not over with: If you are still with me you realize that CETP simply swaps TG for CE and the LDLs and HDLs are afterwards carrying TG instead of CE. This lipid swap did nothing to the size of the HDL, LDL or VLDL particles. However, as the VLDLs (chylols) enter vascular beds in myocytes and adipocytes they are exposed to lipoprotein lipase (LPL) and undergo further hydrolysis of the remaining TG. LPL does not hydrolyze CE. Thus the VLDLs lose their TG but not their CE. As they lose TG they shrink and chunks of the surface phospholipids break off and are picked up by phospholipid transfer protein for use elsewhere. The resultant (post lipolytic) VLDL (or chylo) is smaller and now carrying predominantly CE: these are termed remnant lipoproteins and numerous studies have shown they are associated with increased CV risk (through a variety of mechanisms). NCEP stated that anyone with a TG > 200 has increased remnants which convey CV risk CV risk not explained by their LDL-C levels. Thus VLDL-C is the poor man's remnant lipoprotein assay! Those doing NMRs can simply look at VLDL-P subparticle concentrations. What about the TG-rich, CE poor HDLs and LDLs. They are not substrates for LPL but as they pass through the liver they are substrates for hepatic lipase which is capable of hydrolyzing both TG and surface phospholipids. The LDLs and HDLs lose the TG but not their CE: they shrink and turn into small particles. Sometimes the HDLs are made very small or they release surface apoA-I which is vulnerable to renal excretion (ultimately causing low HDL-P or apoA-I and further contributing to the drop in HDL-C). The small LDLs are too large for renal excretion. However they are not readily recognized by hepatic LDL receptors and small LDLs have longer half life's than larger ones, explaining why most folks with small LDLs have such high LDL-P (apoB) levels. This was first described by apoB guru Alan Sniderman way back in olden times (in *Atherosclerosis* 1991;89:109-116). SO IT IS NOT REALLY THE SIZE OF THE LDL THAT CREATES HAVOC BUT RATHER IT IS THE PARTICLE CONCENTRATION, AND THE VAST MAJORITY OF FOLKS WITH SMALL LDL HAVE VERY HIGH LDL-P (APOB) LEVELS. There are other attributes of the small LDL that contribute to its atherogenicity, but particle # is the most critical.

I want to expound further: As mentioned, NCEP states, that high TG (and its association with remnants) convey CV risk way above that predicted by LDL-C. But the vast majority of folks with remnants also have tremendous elevations of LDL-P (apoB). So is the risk due to the VLDL remnants or LDL particles or both? I believe it is both as remnants aggravate disease through mechanisms other than entering the arterial wall. With respect to what particle is dumping

cholesterol in the artery it is the LDLs. In Bill Cromwell's analysis of Framingham (a year ago in J Clin Lipidol 2007;1:583-592) he demonstrated:

" Not only was non-HDL-C more weakly related to incident CVD than LDL-P, the risk prediction given by LDL-P was improved only slightly by taking into account the contribution of VLDL-P. This latter finding is perhaps not surprising, given that VLDL-P constitute only a small fraction (about 5%) of the total number of atherogenic VLDL + LDL-P. Even when triglycerides are significantly elevated, VLDL-P numbers are only modestly higher because the excess triglyceride is carried predominantly by large VLDL-P, which are relatively few in number. Furthermore, in terms of the percentage of total atherogenic particles, VLDL-P levels are not very different in persons with high triglycerides because these same individuals also typically have elevated numbers of LDL-P that are smaller than average."

OK, OK - back to the case. Very high TC and Very High TG -- Familial Combined Hyperlipidemia. This is a Fredrickson Type IV if the TG are explained by VLDLs and Type V if chylomicrons are also contributing. Both of these are highly associated with T2DM. This woman might have T2DM and we would need a 2 hr PP glucose to make the diagnosis as the fasting glucose is only 117. Presuming the aminase elevations are diagnostic of fatty liver (NASH or nonalcoholic steatohepatitis), she is in big trouble for development of T2DM and for the presence of atherosclerosis. Many believe fatty liver is a CHD risk equivalent (The American Journal of Medicine 2008;21:72-78). She qualifies as a 5 for 5 metabolic syndrome patient (IFG, weight, HTN, low HDL-C and high TG). The hyperinsulinemia sets off lipogenic genes (SREBP) explaining the dramatic rise in both cholesterol and TG. Often these patients have eruptive xanthomas and can develop lipemic retinalis. Pancreatitis is clearly a risk.

Despite the cardiologist's admonition that nobody dies of high TG, I and 99% of the remaining lipid world would treat and treat aggressively. First mission to eliminate the risk of pancreatitis. If HgbA1C is high - normalize that or get it below 7. A statin is an inappropriate first line therapy for TG > 500 mg/dL. We need to inhibit TG synthesis in a big way: reduced caloric diet, exercise, no alcohol of course: Then drugs that inhibit TG synthesis: First line therapy is 4000 mg of N-3 (previously called omega) fatty acids (Lovaza) plus fenofibrate (TriCor). Each can lower this level of TG by 50%, but with monotherapy it will still be too high so I use both. That should get the TG under 500 and then non-HDL-C becomes the goal of therapy. One must add a statin (high dose) or statin/ezetimibe combo. The two most efficacious statins on lowering TG are high dose Crestor or Lipitor. However TG is not our goal; Non-HDL-C, apoB or LDL-P is the goal. Crestor is superior to Lipitor on Non-HDL and apoB parameters. Statin/ezetimibe would also be as powerful. How do drugs like statins or ezetimibe lower TG? They upregulate hepatic LDL receptors which endocytose all apoB particles including VLDLs carrying TG. One note of caution: the patient had some abdominal pain: cholelithiasis has to be ruled out because the package insert warns against using a fibrate if gallstones are present. However in the FIELD trial they recruited several patients with gallstones and the fenofibrate did not aggravate their condition or cause new gallstones in the remaining patients. Thus if fenofibrate by increasing biliary cholesterol causes gallstones, the incidence is very, very small and in this patient the benefit would outweigh the risk. There is also a very tiny risk of pancreatitis with fibrate. Again in this case the benefit of a fibrate would outweigh any risk.

A word about using Lovaza: to lower TG, a threshold dose of 4000 mg is required. I find it so sad that some providers only, prescribe 1-3 grams of N-3 FA to lower TG. Also if one had ordered a direct LDL-C measurement in this woman, after Lovaza, TriCor or both are prescribed it is very likely LDL-C will go up. WHO CARES? As the TG fall the LDLs go back to carrying CE instead of TG - of course LDL-C rises. However at the same time there is a drastic fall in VLDL-C and a rise in HDL-C (as the HDLs go back to trafficking CE instead of TG). Even with LDL-C rising, Non-HDL-C drops, indicating a reduction in apoB particles. Any rise in LDL-C in the face of a dropping apoB is explained by particle composition changes. Despite the rising LDL-C, LDL-P drops. **Anyone** who stops Lovaza (N-3 FA) or TriCor (or fenofibrate) or the newly approved Trilipix

(fenofibric acid) because of a rising LDL-C or an attenuation of the statin induced LDL-C reduction (despite a falling non-HDL-C) DEMONSTRATES THEY HAVE LITTLE LIPOPROTEIN KNOWLEDGE and they are brainwashed with the meaning LDL-C. If you want to see what a fibrate or N-3 FA is doing in a patient with high TG, follow VLDL-C and non-HDL-C: following LDL-C by itself is a useless waste of time. If you want to make life really easy, simply follow non-HDL-C (the NCEP goal of therapy).

Thus, in my opinion, this lady requires serious lifestyle adjustments and aggressive meds (TriCor and Lovaza) day one. Then to get non-HDL-C (LDL-P or apoB) to goal a statin or statin/ezetimibe combo. Of course you can forget everything I just wrote and if you believe the cardiologist that TGs kill no one.