LIPID CASE # 178

Hi Lipidaholics: Before we begin, a reminder: if you do not want to receive this newsletter please reply to this and put a "cancel" in the subject line. Now, let's start off 2007 with a GI disease, namely pancreatitis. Never forget the two major organs that regulate the body's cholesterol supply are the liver and small intestine, so should lipidology switch to a subspecialty of gastroenterology rather than endocrinology?

I was contacted about the following case: 41 year-old white male with a past history of gout and hypertension and abnormal lipids as shown below: Currently he is on allopurinol, ASA, and lisinopril. He does admit to 1-2 beers per day and claims his mother has high cholesterol but is still alive (in her late 70's) without CAD. Father also has hypertension.

October 2006 Lipid Profile

TC = 540 mg/dL, HDL-C = 57 mg/dL, TG = 3105 mg/dL LDL-C cannot be estimated

Glucose 114 mg/dL HgbA1c = 6.2 ALT = 87 (elevated) Renal function normal

The patient was started on TriCor 154, took it without any problems and took it for 2 months. He returned in December before his follow up appointment was due with severe abdominal pain and was diagnosed with pancreatitis, confirmed by lab testing. Repeat fasting lab during his appointment (was not eating for at least 24 hours due to the pain) revealed:

TC = 856 mg/dL TG = 2406 HDL-C = 42 LDL-C not reported Glucose 142 ALT 15

After recovery, Omacor 1000 mg (4 tabs daily) was prescribed to reduce his TG. The provider suggests he will need to probably be on a statin and/or niacin too? He inquired why did the cholesterol go up and should he order other tests ? He also desired to know what is the primary lipid goal in this patient triglycerides or cholesterol?

DAYSPRING ANALYSIS:

Patients like this have with familial combined hyperlipidemia (FCHL) with significant insulin resistance (in this case a T2DM) on top of alcohol abuse. Must rule out hypothyroidism and nephrotic syndrome as secondary causes of the dyslipidemia. His TG are certainly in the range capable of causing pancreatitis. These people have very delayed lipolysis (removal of lipids) of their TG-rich lipoproteins (chylomicrons and VLDLs). The elevated aminases likely signals alcoholic and/or steatohepatitis due to IR (a serious CV risk factor). Indeed, a recent article and editorial suggested that elevated GGT is an excellent marker of the metabolic syndrome and CV risk (Arterioscler Thromb Vasc Biol. 2007;27:127-133).

Lots of serious lipid and lipoprotein physiology and pathology follows. You have been warned!

After the intestine absorbs sterols and fatty acids (FA), they are incorporated into chylomicrons which after leaving the lymphatic system traffic to beds rich in lipoprotein lipase (LPL), namely muscles and adipocytes. LPL is a powerful triglyceridase that hydrolyzes the triacylglycerol (proper term for triglycerides) into FA and mono or diacylglycerol. As TG are hydrolyzed the chylomicron becomes smaller in size (called a remnant particle: an apoB particle carrying less TG along with its original cholesterol load). As the particle reduces in size surface

apolipoproteins (apoproteins) and phospholipids (PL) are released. The latter picked up by phospholipid transfer protein and the PL become available to tissues or maturing (enlarging) HDL particles. Of course the liver also takes any excess FA and converts them into TG and packages them into VLDL particles (the more TG made, the larger both the VLDL particle size and number becomes). The VLDLs have the same fate as do the chylomicra.

Intrahepatic synthesis of TG from FA is catalyzed by multiple enzymes, one of the more important of which is diacylglycerol transferase 2 (DGAT2). Anything that puts FA in the liver, like insulin resistance or diet will increase lipogenesis.

Chylomicra and VLDLs should undergo effective lipolysis in LPL-enriched beds as follows. TG-rich lipoproteins should have physiologic quantities of several apolipoproteins on their surface, including apoA-V, apoE, apoC-II all of which enhance lipolysis and apoC-I, apoC-III and apo-II which delay lipolysis. If one has the proper physiologic content of these apolipoproteins, lipolysis will occur at a proper physiologic rate. ApoA-V "parks" the TG-rich lipoprotein by binding to proteoglycans in the vicinity of endothelial cells that have LPL on their surface. VLDL receptors are also expressed in muscles and adipocytes and serve as a dock of apoE to attach to. Once "parked" the apoC-II on the particle surface can attach to LPL and TG lipolysis begins. Normal chylomicron half-life is 45 minutes and that of VLDL 4-6 hours. Why do chylos undergo more rapid lipolysis? They are incredibly large lipoproteins (much larger than VLDLs) and their surface carries more apolipoproteins and thus they are more likely grab the available binding sites. Of course, once the chylomicrons become remnants they with their sterols are internalized by the liver LDL receptors (LDLr) and LDL receptor related protein (LRP). The apolipoprotein E on the chylo surface is the ligand that binds to the LDLr and LRP. Thus chylomicrons deliver fat (energy) to muscles or adipocytes and sterols to the liver.

ApoC-II deficiency results in massive hypertriglyceridemia as the particles cannot attach to LPL and no lipolysis of TG occurs (Fredrickson's Type I Lipidemia). Excess apoC-I prevents VLDLs and remnants from attaching to VLDL receptors and can inhibit CETP (see below). Excess ApoC-III displaces apoE from the particle surface, making the particle less likely to attach to the VLDL receptor. It may also camouflage or displace apoC-II and apoA-V. Abnormal apoE (as seen in Fredrickson's Type III Lipidemia also interferes with VLDL as well as IDL binding to receptors. Excess apoA-II also camouflages other apolipoproteins and delays lipolysis. The characteristic of delayed lipolysis is postprandial lipemia (Triglycerides), a well know CV risk factor. So potential causes of hypertriglyceridemia and especially postprandial hypertriglyceridemia are abnormalities of apoC-II deficiency), apoA-V (deficiency), apoA-II (excess), apoE (defective) and apoC-III (excess). ApoA-IV is also involved with intestinal synthesis of chylomicrons, and HDL particle catabolism but its role in TG disorders is not fully understood. Of course a deficiency of lipoprotein lipase will result in defective TG-lipolysis and cause both fasting and PP triglyceridemia.

What are the consequences of the elevated TG levels? TG-rich lipoproteins associated with delayed lipolysis obviously have increased half-life's or residence time. This increases blood viscosity and worsens endothelial function. HDL and LDL are cholesterol-rich particles typically carry little TG. HDLs contain multiple apolipoproteins one of which is apolipoprotein D (over-expressed when TG are high). Of course apoD is better known by its other name, cholesteryl ester transfer protein or CETP. This protein facilitates a swap of neutral lipids (TG for cholesteryl ester or CE) between TG-rich particles and LDL and HDL. The latter become CE-deficient and TG-enriched. As the CE-poor LDL and HDL undergo further lipolysis by hepatic lipase (a triglyceridase and phospholipase) they become smaller HDL and LDL particles. Very small HDL are apt to be excreted by the kidney (contributing to low HDL-C) and if LDLs are small it will take a lot of them to traffic whatever cholesterol exists, thus driving up LDL-P (the major coronary risk factor).

The severe hypertriglyceridemia in the case at hand likely the result bad genes with a partial lipoprotein lipase deficiency (not uncommon in IR diabetics) combined with the alcohol use which

decreases the beta-oxidation (burning or catabolism) of fatty acids. If the liver cannot burn fat, those TG will be put in VLDLs. This man admits to 2 beers daily, so it is likely he is using more than that.

The likely explanation of the rising TC cholesterol in this FCHL patient is increased lipogenesis (synthesis of lipoproteins and their lipid content) but also contributed to by the sudden loss of appetite and food intake and associated weight loss. When one rapidly looses, weight adipocytes loose their lipids, including all of their substantial cholesterol (present in their cell walls). This will ultimately level out. Anorexics often have paradoxical hypercholesterolemia because of this phenomenon.

Treatment:

NCEP recommendations: First mission is to normalize the TG to < 500 mg/dL to remove the pancreatitis risk: Once that is achieved Non HDL-C (apoB-surrogate) becomes the goal of therapy.

There cannot be good success if he even touches another drop of alcohol
Lifestyle: DASH or South Beach type diet with daily exercise are critical
Aggressive BP control

Continue TriCor 145 mg daily: increases beta-oxidation of FA, inhibits DGAT2, increases LPL, increases apoA-V, decreases apoC-III, decrease microalbuminuria (see reference 3 below)
Continue Omacor (4-6 grams daily): increases beta-oxidation of FA, may inhibit DGAT2, increases LPL expression
Crestor 20 and then ultimately 40 mg daily (Zetia may ultimately be required): increase LDL-r, decrease hepatic lipogenesis: statins (not ezetimibe) increase LPL
Actos and metformin for glucose and treatment of insulin resistance and whatever beneficial TG effects occur.

If ultimately needed Niaspan (extended released niacin can be added): formerly thought to reduce lipolysis of TG in adipocytes (feeling on this is changing), DGAT2 inhibitor.

Why the Crestor? Persons with marked TG elevation has as discussed significant residence time of these particles. That makes them subject to upregulated LDLr. Statins or statin/ezetimibe are the best combos to cause increased expression of LDLr. In trials looking at patients with high TG Lipitor 80 and Crestor 40 are the best statins (equally efficacious) at reducing TG. Of course all statins can reduce TG to variable degrees. I'd choose Crestor because it has less drug-drug interactions, may have a more beneficial effect on HDL-C (if that is important) and because of Lipitor's propensity to aggravate hyperglycemia. I realize in the real world the formulary is likely to mandate your statin. With cost and compliance concern, Vytorin is certainly an option.

LIPID CASE # 179

Hi Lipidaholics: This week I want to discuss a getting to goal when HDL-C is low. I was asked about a 54 yo woman, with T2DM and hypertension, with a BMI of 20, who saw her provider for a second opinion on her exertional dyspnea. She had no typical chest tightness. Her family history is remarkably positive for premature atherosclerotic disease, beginning as early as 30's. Her glucose has been well controlled (A1c = 6.2) with Avandamet, Lantus and preprandial Humalog. Other medications are Diovan 320 mg and Coreg 12.5 mg BID with good control.

Her lipids 6 months ago while on Lipitor 40 mg daily showed:
TC = 159, TG =143, HDL-C = 34, LDL-C = 96.
.
She had a cardiolite stress test, which was dramatically positive, peripheral arterial dopplers which were in the claudication range, and carotid dopplers with 40-75% occlusion. Her coronary

angiogram showed multivessel disease and a "porcelain" aorta and she had a LIMA and RIMA bypass done off pump.

Post-operatively her cardiologist put her on Crestor 10 mg and Zetia 10 mg daily. Her lipids were:
TC = 140, TG = 212, HDL-C = 31, LDL-C = 67.
Her NMR LipoProfile showed: LDL-P 1098, (desirable < 1000)
Small LDL-P 758 (desirable < 600)
LDL particle size is large (Pattern A) at 20.7,
Large HDL-P = 7.0 Small HDL-P and total HDL-P not provided to me
Large VLDL-P 0.
Apo B 79 (desirable < 80)
APO A 93 (low).

The provider increased her Crestor to 20 mg daily in hope of improving her small LDL-P and perhaps improving her HDL parameters.He notes she will have her claudication addressed soon, since it limits her ability to walk very far and she is anxious to exercise more vigorously. He asks for any suggestions for further improving her care would be most welcome.

DAYSPRING ADVICE

As always, lets see what NCEP guidelines suggest and then start thinking "outside the box." She clearly qualifies for what is termed "Very High Risk" in that she has several beds with active atherosclerosis on top of diabetes and hypertension. Her "optional" goals of therapy are an LDL-C < 70 and because her TG are > 200 mg/dL to reduce Non HDL-C to < 100 mg/dL. This woman is at LDL-C goal (67) but her Non HDL-C is still a bit elevated at 109 (140 - 31). NCEP notes that when Non HDL-C is not normal on a statin (I think it would be safe to change that to statin/ezetimibe) one can 1) increase therapeutic lifestyle (her BMI is 20), 2) increase the statin dose (with the rule of 6, doubling the statin is not going to do very much), or add a fibrate or niacin. With the diabetes requiring multiple meds, gemfibrozil would be risky and with the HgbA1c not under control (still > 6.0) I would not use niacin (indeed in ARBITER 2, Niaspan did not significantly improve carotid IMT in diabetics). That leaves us with fenofibrate as an add on. There is new evidence that Omacor (N3 FA) can also help a statin get to non HDL-C goal, but there is no data with this drug in diabetics. The physician choose to double up on the Crestor and thus was within guideline recommendations. If the Crestor/Zetia drops the TC from 140 to 130 then the Non HDL-C would be < 100 and the patient would be at goal (even though the HDL-C is still low). I would have added fenofibrate. To find out why, lets look closely at what is elevating the Non HDL-C. Remember VLDL-C = TG/5.

Non HDL-C = LDL-C + VLDL-C = 67 + 212/5 = 67 + 43 = 110. Where is the problem in the lipids? The LDL-C is normal and the VLDL-C is elevated (n<30).

Why does VLDL-C go up in diabetics? Because of the extra fatty acids (FA) in the liver there is an overproduction of TG and increased numbers of larger TG-rich VLDL particles are secreted. These particles then swap their TG for cholesteryl ester (CE) with HDL and LDL particles using CETP (CE transfer protein, also known as apolipoprotein D). The CE that goes from LDL and HDL obviously increases VLDL-C while at the same time reduces LDL-C and HDL-C (LDL-TG and HDL-TG increases). These now TG-rich HDL and LDL particles as they pass through the liver are exposed to hepatic lipase: further lipolysis occurs and as they loose TG they become small and dense. The large VLDL now contains less TG and more CE: after lipolysis (hydrolysis or removal of TG by lipoprotein lipase) the VLDL reduces in size but packs a lot of cholesterol. These are called VLDL remnants and are considered atherogenic particles. They act as large LDL particles! On the NMR LipoProfile, remnants show up as small VLDL or IDL. The provider did not report these measurements to me. Unfortunately, very few clinicians even look for them (they are in the bar graph on the second page of the LipoProfile report).

So back to the Non HDL-C value: if elevated there are likely too many apoB particles. What type of apoB particles are elevated? In this case the LDL-C is normal and the VLDL-C is high. We thus should assume the patient has too many VLDL remnants and there have to be to many small LDL particles. Treatment should be directed against those particles. Notice that HDL treatment does not enter into the equation. There is no specific HDL-C goal of therapy in NCEP. NCEP states in this lady with low HDL-C and elevated TG, the goal of therapy is to achieve a Non HDL-C of < 130.

By far the best drug known to reduce VLDL-C are fibrates: In the SAFARI trial where simvastatin and fenofibrate were combined, there was a dramatic 49% reduction in VLDL-C. So the pearl you take from this is when you see elevated VLDL-C, think fenofibrate first (N3 FA and niacin as second and third choices). So adding fenofibrate instead of doubling the Crestor there might have been the better choice in this patient. Hopefully in a few years we will have a Crestor/TriCor combo tab (now in the works).

Of course if one really wants to get to the heart of the matter, it is wiser to quantitate lipoprotein particles (most available way of doing this is the NMR LipoProfile) instead of guessing their presence by looking at lipid concentrations. Lets face it: if you do not understand lipoproteins at a very high level it is easy to guess wrong when using lipid concentrations. Also, once you have normalized total LDL-P, the small LDL-P has little meaning. Likewise the meaning of low HDL-C in the face of a normal LDL-P is unknown but likely to be of little importance. Again HDL-C is not a target of therapy. There is emerging data the raising HDL-P might be important, but I think it would depend if those HDLs were functional or not. In the setting of diabetes and atherosclerosis, we probably need to improve HDL functionality. Of course we have no markers for this. Increasing total HDL-P (does not matter whether the particles are large or small) rather than HDL-C is probably wise.

In my opinion it was a correct decision to bail on Lipitor and use a more potent statin like Crestor with Zetia 10. You will reduce the LDL-P and to some extent VLDL-P even further. The Crestor plus Zetia should do that. Because of the severity of disease and very high risk in this patient, maybe we really should use Crestor 40 mg as the statin and go from there. The ASTEROID trial, where Crestor 40 induced plaque regression in the majority of patients, would make me be so inclined. The TriCor (fenofibrate) will further reduce the minimally elevated LDL-P (1098) and remove VLDL or IDL remnants. If extreme LDL-P reductions are not needed and the patient not as risky as in this case, Vytorin plus TriCor would be easier to use and save some money. So my advice: Crestor 40, Zetia 10 mg to blow away apoB and I'd add TriCor to improve macrophage RCT and HDL functionality and to reduce the need for peripheral amputation and avoid retinal photocoagulation surgery (as was seen in FIELD). The fenofibrate would also further improve lipoproteins in ways that statins ands ezetimibe cannot.

Of course, scrupulous BP and glycemic control (drive A1c < 6.0).

LIPID CASE # 180

This week we will discuss a very unusual case. I was asked about a 30 year old transgender patient (henceforth referred to as she) who is scheduled to have a male to female sex change operation in the spring. Past history includes depression/anxiety and gender dysmorphic disorder. She does not exercise regularly, does not smoke or drink alcohol and is HIV negative. There is no family history of cardiovascular disease or stroke. She has been on hormone therapy for 3 years and has been taking estradiol 2 mg orally twice a day and spironolactone 50 mg orally twice a day. Old records are not available.

Exam reveals a female-appearing individual with normal appearing breast development without any masses, nipple discharge or other irregularities. Vitals signs are BP 118/72, HR 61, R 12, H

5'9", W 158 lbs. Exam is normal without any signs of overt dyslipidemia or metabolic changes (no xanthomas, small waist circumference, no acanthosis nigricans).

Basic laboratory work is ordered as is below:

Total cholesterol = 205
TG = 1186
HDL-C = 35
LDL-C cannot be calculated
Chol/HDL ratio = 5.9
Non-HDL-C = 170

Fasting glucose =108
BUN =12 Creatinine = 0.8
AST = 20 ALT = 11
TSH = 2.4
Total testosterone = 39 (Males 241-827 ng/dL; Females 20-76ng/dl)
Estradiol = 68 (Males 13-54 pg/mL; Females 18-480 pg/mL midcycle)

Upon further questioning she admits to having been told before that her cholesterol was bad. Intermediate-acting niacin (Niaspan 500 mg daily) was begun. Labs are to be retested in 6-8 weeks and consideration of another or a different medication will entertained.

Her provider asks me:
1. Is there a better choice of a type of estrogen that could be used? Secondary sex characteristics for the desired gender must be maintained.
2. Is there any value in pairing the estrogen with a progestogen? Will a progestogen be too androgenic for this person?
3. Is there a better choice in medication to manage this persons dyslipidemia?
4. If lipids cannot be better controlled with medications or patient compliance, at what age should I consider doing more in-depth cardiovascular screening?

DAYSPRING DISCUSSION

This is a very complicated patient and a real lipid challenge with a very high risk triglyceride level. Is the severe TG/HDL axis disorder associated with insulin resistance (note the presence of the metabolic syndrome), despite the normal BMI? HIV has been ruled out so we are not dealing with a disease-related lipodystrophy or HIV drug related lipidosis. Likewise alcohol is not aggravating the situation. Does this person have Familial Combined Hyperlipidemia (high CV risk) or Familial Hypertriglyceridemia (not high for CV risk)? Read on!

Whatever the cause of the hypertriglyceridemia (HTG) one has to presume the extremely high oral estradiol dose is aggravating it. As most of my readers know, low HDL-C is very common when TG levels rise. This is because the TGs leave the VLDLs a (and chylomicrons if present) and invade the HDL particle via cholesteryl ester transfer protein (CETP) taking cholesterol out in and returning it to the TG-rich lipoprotein. Thus the HDLs are trafficking TG instead of cholesterol. The TGs also displace cholesteryl ester from LDLs via the same pathway. As they pass through the liver, the TG-rich, cholesterol poor LDLs and HDLs are hydrolyzed by hepatic lipase in the liver creating very small LDL and HDL particles. The latter, being quite small, are excreted by the kidney, reducing the patients HDL particle concentration.

Since stopping estrogen is not going to be an acceptable option for this person, treatment will depend on how many potentially atherogenic apoB particles are present (VLDLs, IDLs and LDLs). An apolipoprotein B level, or lipoprotein assessment using Nuclear Magnetic Resonance (NMR) spectroscopy (LipoProfile at www.lipoprofile.com) is needed to answer the question. If

apoB or LDL-P is elevated, CV risk is real. If this persons TG are driving apoB production it will be very high (familial Combined Hyperlipidemia). However, it is conceivable that TGs are all in very large TG-rich VLDL particles or chylomicron particles that, for a variety of reasons have absent or delayed catabolism (lipolysis) Thus TG will be high but there is no apoB elevation (this is termed familial hypertriglyceridemia). In such cases atherosclerotic risk will be low, but pancreatitis risk very high. The NMR analysis would have the advantage of quantifying LDL, IDL and VLDL particle numbers, whereas apoB is a collective measurement. Non HDL-C which is usually the marker we look at to predict elevated apoB is not helpful when TG are so grossly elevated as particle lipid-compositions (TG/cholesterol ratios) are impossible to predict or measure accurately in such patients.

So if apoB is normal, our mission is to prevent pancreatitis: we do this by trying to greatly diminish TG production to reduce VLDL-P or Chylomicron production. If chylomicrons are the problem, a low fat diet and orlistat can be beneficial. If VLDLs are the problem, we can reduce hepatic production of TG and VLDL particles with fibrates (fenofibrate preferred for safety and ease of use reasons), N-3 fatty acid (high dose) supplementation or niacin (Niaspan). The current 500 mg dose of niacin will have zero effect. Because of the impaired fasting glucose, One could make the case for Actos to prevent onset of T2DM and to perhaps help with the TG.

Estrogen cessation is going to have to be considered if those drugs fail. Here is an ethical question? Should a provider prescribe high dose estrogen to this patient (who clearly will be demanding it) if it is a contraindicated drug (as estrogen is when TG are this high)? What if she has a fatal episode of pancreatitis? Is the contraindicated use of estrogen defensible? If I could not control the TG with other meds, I would not given this person oral estrogen. With respect to the question of a progestogen (and androgenic ones like norethindrone can lower or negate estrogen induced hypertriglyceridemia in women), the only reason to prescribe it is uterine safety which is not an issue here. Transdermal estrogen would not aggravate the TGs as much but you could never achieve the high estrogen levels this patient wants to enhance secondary sex characteristics.

For those interested in knowing how estrogen aggravates triglycerides, it comes down to estrogens interaction with a nuclear transcription factor called the farnesoid X receptor (FXR). FXR regulates bile acid synthesis, among many other actions. It's major role is to prevent bile acid levels from becoming excessive as that would damage cells. So FXR agonism reduces the bile acid synthesis pathway and FXR antagonism stimulates bile acid production. However like all nuclear receptors FXR is involved with other metabolic functions including regulating lipogenesis (TG production) and glucose control. So estrogens antagonistic interaction with FXR is the reason why TG go up, bile becomes lithogenic and perhaps why insulin sensitivity improves. Bile acid sequestrant drugs, which reduce bile acid concentrations, of course affect FXR, explaining how they also can be associated with hypertriglyceridemia.

Back to the patient: If apoB is OK, she needs low fat diet, Orlistat, TriCor 145 mg, and minimum of 4 grams of omega-3 FA (Omacor) daily. If further control of TG is needed Niaspan (titrated up) and ultimately a statin or statin/ezetimibe should be tried. Statin/ezetimibe will upregulate LDL receptors which can increase hepatic removal (endocytosis) of TG-rich particles that have apoE on there surface. Under no circumstances should she consume any alcohol whatsoever.

If apoB or LDL-P is high (and because of the insulin resistance I suspect it is), then CV risk also enters the picture. She will for sure need a statin or statin/ezetimibe. Because of the polypharmacy likely necessary in this patient I would use Crestor 20-and ultimately 40 mg daily with ezetimibe.

As far as further screening: age does not necessarily enter into that. If a person has significant risk factors we should aggressively work them up so we have as good a risk estimate as possible regardless of age. I would do coronary calcium scoring or carotid studies in this patient. I would check the PLAC test (lipoprotein associated phospholipase A2) and hs-CRP.

LIPID CASE 181

I received the following case regarding a high risk patient who sees several physicians which results in different and sometimes conflicting treatment plans. The provider contacting me wants to achieve maximal reduction of atherogenic particles and perhaps induce plaque regression. He inquires as to what would be the apoB (a measure of VLDL, remnants, IDLs, LDLs) or LDL-P goal of therapy to accomplish regression.

Patient is a 65 year old male with hypertension, type 2 diabetes, metabolic syndrome and increased LDL-P. His family history is positive for diabetes and premature CVD. He denies symptoms of cardiac ischemia and has not had any evaluation for subclinical atherosclerosis, i.e. carotid IMT or coronary calcium scoring (CAC). A Cardiolite scan was negative in 2004. TSH is fine (0.86) and Creatinine is normal (at 1.0).

Current Meds: Vytorin 10/40, ASA 81, Metformin 500 bid, Byetta 5mcg bid, Lisinopril 20 bid, Norvasc 5mg, Terazosin 10 mg, Avodart .05 mg,

BP 120/82 ht 6'1" wt 258 BMI 33 waist > 40 in
Current Labs:
TC= 117 LDL-C = 62 HDL-C = 40 VLDL-C = 14 TG = 74 Non HDL-C = 77
ALT 15 A1c = 6.3 fasting glucose 120

NMR Profile (Nuclear Magnetic Resonance Spectroscopy doe at LipoScience)
www.lipoprofile.com
LDL-P = 1161 (desirable < 1000 umol/L)
small LDL P 1015 (desirable < 600)
LDL particle size = 19.9 nm (small) (Large is > 20.5)
Large HDL-P = 2.6 (low) There is no accepted HDL-P goal of therapy
Large VLDL-P = 0.4 (normal)

Apolipoprotein B = 55 mg/dl

I was not given any data for lipids prior to initiation of a statin. Treatment has varied in the past couple of years with most debate centered on the question of statin/ezetimibe vs statin + fenofibrate. He has made a lot of progress in controlling his diabetes over the past 2 years. The clinician is perplexed that the Apo B level is clearly in the lowest quintile, while NMR LDL P would suggest that there are still persistent atherogenic particles. He also asks is it better to increase the statin dose to achieve lower LDL P (and thereby reach non HDL C targets) or would the insulin resistant patient be better served with a lower dose of statin with the addition of fenofibrate which targets many of the problems encountered with insulin resistance?

DAYSPRING ANALYSIS

First some quick review: Lipids (cholesterol, triglycerides) are trafficked inside of protein wrapped particles called lipoproteins. The surface proteins are called apolipoproteins. The atherogenic lipoproteins (those capable of carrying cholesterol into the arterial wall) each contain a single molecule of apolipoprotein B (apoB) and thus apoB serves as a concentration of potentially atherogenic particles. Because LDLs have the longest half life, 90-95% of apoB particles are LDL particles (LDL-P). The determining factor on whether the particle stays in plasma or invades the artery is particle number or concentration. Lipid concentration surrogates of apoB are LDL-C or Non HDL-C (TC minus HDL-C). LDL size can be estimated by various ratios, but among the best is the apoB/LDL-C ratio. If there are more particles than cholesterol the ratio will be > 1.0 and the

particles are likely small. (This is based on the fact that average apoB is 100 as is LDL-C: the ratio should be 1:1).

A few quotes from the Expert Panel of 30 Lipidologists representing 10 countries published last year (Journal of Internal Medicine 2006; 259: 247–258): ":The lipid composition of the principal atherogenic lipoproteins differs substantially amongst individuals. Therefore, lipid levels do not automatically equal lipoprotein particle levels. ---- Atherogenic particle number has been shown to be superior to LDL cholesterol in judging the residual clinical risk on therapy in a number of the statin clinical trials such as AFCAPS/TexCAPS, the Leiden Heart Study and LIPID. ---- Because the amount of LDL cholesterol per LDL particle varies substantially both between and within individuals, LDL cholesterol does not necessarily equal the most critical variable, the total number of LDL particles. This is the key point."

There is no data that plaque regression improves survival any better than aggressive risk factor management. If we aggressively normalize atherogenic lipoproteins, control glycemia, prescribe anti-platelet drugs and control BP, we would maximize event reduction no matter what the arteries looked like. If we want to theorize outside of current evidence, perhaps if we reduced vascular wall inflammation and improved HDL functionality we could also improve outcome reduction. So I do not loose sleep if plaque regression is not occurring as long as inflammatory markers and lipoproteins are OK. Few of our patients are getting IVUS (intravascular ultrasound) studies so it is pretty hard to document regression in regular practice.

In the ASTEROID study (an IVUS study) patients taking Crestor 40 mg achieved a mean apoB of 85 and there was plaque regression in 2/3 and no plaque regression in 1/3. In REVERSAL Lipitor 80 mg achieved an apoB of 92 and there was no plaque progression (but no regression). In the same study Pravachol 40 mg achieved an apoB of 112 and there was plaque progression. These studies suggest the lower apoB is the better the arteries will look. However these trials were to small and too short to follow event reduction. Does what the statin do to HDL-C matter with respect to regression? In ASTEROID Crestor raised HDL-C by almost 14% yet that rise was not related statistically to regression. However, the study's author in a just published meta-analysis of several IVUS trials suggests that what a statin does to HDL-C is important. Her is the conclusion (please note the final sentence):

Statin therapy is associated with regression of coronary atherosclerosis when LDL-C is substantially reduced and HDL-C is increased by more than 7.5%. These findings suggest that statin benefits are derived from both reductions in atherogenic lipoprotein levels and increases in HDL-C, although **it remains to be determined whether the atherosclerotic regression associated with these changes in lipid levels will translate to meaningful reductions in clinical events and improved clinical outcomes.** JAMA. 2007;297:499-508

The case at hand involves a high risk patient (the T2DM qualifies him as a coronary heart disease equivalent). He does not qualify for the very high risk classification has he has no clinical atherosclerosis and has not had a CV event. I think an Lp-PLA2 and hs-CRP might help us. If they are high, there might be risk beyond that predicted by lipids and lipoproteins. However, his NCEP goals are an LDL-C of < 100 and a Non HDL-C < 130 mg/dL. NCEP would say for this patient: "Mission Accomplished." The apoB of 55 would seem to agree with the perfect LDL-C and the Non HDL-C. Thus how do we explain the still slightly elevated LDL-P?

Well, the particles are quite small so it might take a lot of particles to traffic the 62 mg of cholesterol within the LDLs that exist per dL. It is not uncommon to see discrepancies between apoB and LDL-P, especially when LDLs are small. Here is a provocative statement from a recent article on NMR technology that offers an explanation on how apoB and LDL-P might not always agree: "Preliminary data from the authors' investigations suggest that apo B, relative to LDL-P, ''undervalues'' small LDL particles compared with large LDL particles. A possible reason is that apo B adopts a substantially different conformation on small LDL than it does on large LDL, potentially causing differential exposure of the epitopes and differential antibody binding. Finally,

measured ratios of apo B:LDL cholesterol, which should always be greater for small versus large LDL particles, do not always show the expected consistency of association with LDL size." (Jeyarajah, Cromwell & Otvos Clin Lab Med (2006;26:847–870).

Note in the patient under discussion the apoB/LDL-C ratio is less than one (55/62) which should not be if small particles are present. So the actual apoB may be higher and closer to 80 which would correlate with the LDL-P of 1000. So in this case the LDL-P is more believable than the apoB.

If driving atherogenic particles down further is you mission, how can that be accomplished? Zetia is already on board. One option is to abandon the Vytorin 40 and go to Crestor 40 (the drug used in ASTEROID) and add Zetia. The about to be published EXPLORER trial (available on line in the American Journal of Cardiology) shows spectacular apoB lowering with Crestor/Zetia. There are other options: If however you want to drive apoB and improve macrophage RCT, impact microvascular disease, and improve many pleiotropic markers, one could also administer TriCor and add it to the statin/Zetia combo. This may be exactly the type of patient (a T2DM with multiple risk abnormalities) that deserves such aggressive therapy.

I like using fibrates in T2DM patients (to find out why I'd be happy to send anyone a pdf of my and Greg Pokrywka's recent review of fibrates from Current Atherosclerosis Reports 2006, 8:356–364). You get the pleiotropic benefits and additional apoB (Non HDL-C) control. However, adding any approved lipid drug to a statin will likely lower Non HDL-C by an additional 10-20%. You would have to double or triple a statin dose to achieve that. Also by increasing statin dose you increase intestinal absorption of cholesterol and noncholesterol sterols. Thus, I almost never use a statin without ezetimibe in high or very high risk (see reference 4 below).

Does it matter that the vast majority of the LDL particles are small. They are prone to oxidation by reactive oxygen species, adhere to intimal proteoglycans easily and are less likely top be cleared by LDL receptors. All of that is true but all of the recent studies that measured both LDL-P and LDL size, show that all LDLs are atherogenic if present in increased numbers and the risk disappears as LDL-P becomes normal. So once total LDL-P is at goal, I do not think one has to drive the LDL-P down any further. Using drugs that shift LDL size (fibrates, niacin, N-3 FA) may help LDL receptors more easily clear the particles.

Conclusions: On Vytorin, the high risk patient is at NCEP (and every other guideline) goal for lipids. ApoB looks good (although it is likely falsely low). The LDL-P is just about at target. As discussed adding fenofibrate may bring some benefits so if one wants to treat him very aggressively, TriCor makes sense. I'd push the metformin to try and drop the A1c further down.

LIPID CASE # 182

Hi Lipidaholics: It's nice to have a brother like this patient. I was contacted by someone a PhRMA (drug) rep about the following young man who just happens to be the reps brother. He is a 30 year old male who works out with weights frequently, eats normally and does not smoke or drink.

Vitals: 5"10 170 lbs
LDL-C = 127 HDL-C = 36 TG = 108 hs-CRP is elevated

The rep states and asks: The doctor believes that this is a Crestor patient because he wants to get his LDL-C below 100. Several other docs including cardiologists were asked about this profile and most said they did not see any risk worth treating with anything more than lifestyle. What is your opinion? If the patient doesn't go on the statin what risk is he at?

DAYSPRING ANSWER:

First: Is he high risk? His only major risk factor is the low HDL-C. Framingham scoring if done, rates him as low risk for an event over the next ten years. If he is low risk his LDL-C goal would be 130 mg/dL and Non HDL-C 1650 mg/dL and he would not qualify for drug therapy. He only has one criteria for metabolic syndrome (low HDL-C). However if the clinician believes the patient is high risk, using a statin to reduce LDL-C to < 100 mg/dL is going by the books!. NCEP states that in patients with low HDL-C, the goal of therapy is to first reduce LDL-C to goal and then normalize Non HDL-C, if TG are still high. Always keep in mind we must determine whether this patient has too many atherogenic apoB particles in his plasma. It is the number of atherogenic particles that determines risk. Can we figure it out particle number without advanced testing? The lipid surrogates of apoB or LDL-P are TC, LDL-C, Non HDL-C and the TC/HDL-C ratio

Let's do a little math:

TC = LDL-C + HDL-C + VLDL-C VLDL-C = TG/5 VLDL-C = 108/5 = 21
TC = 127 + 36 + 21 = 184
Non HDL-C = 184 - 36 = 148
TC/HDL-C = 184/46 = 5.11
TG/HDL-C = 108/36 = 3.0 If > 3.5 would be highly indicative of small LDL size

If we consider this man to be high risk, his LDL-C goal would be < 100 mg/dL and if TG are high, his non HDL-C should be < 130 mg/dL. Of course we now know from a study by Jian Liu et al including Scott Grundy using Framingham data that Non HDL-C is a better predictor of risk than is LDL-C no matter what the TG level is. (Am J Cardiol 2006;98:1363–1368). This study also shows VLDL-C is just as important as is LDL-C.

Let's look closely at the lipid profile: the LDL-C at 127, the non HDL-C at 149 and the TC/HDL-C ratio would suggest there is a mild apoB elevation. These lipid concentrations are lipid surrogates of apoB (atherogenic particles). If elevated The best strategy to attack apoB is to decrease apoB synthesis and upregulate LDL receptors to clear apoB particles. Statins or statin plus ezetimibe are the best ways to do that. If that therapy does not get the patient to goal then one would considering adding an adjunctive medication to normalize the Non HDL-C and in someone with low HDL-C (suggesting insulin resistance) TriCor or Niaspan would be the proper choice. Some use TG to determine wether to use TriCor or Niaspan in persons with low HDL-C. However if this man is low risk it would be hard to justify combination therapy.

The rep is making the same mistake that many providers make: when they see low HDL-C they think you have to raise it. You do not. There is no specific HDL-C goal of therapy in NCEP. This is likely an insulin resistant patient (do mostly to genetic forces) with high risk (note the CRP). If indeed he is insulin resistant and has inflammatory markers, he almost certainly has dysfunctional, proatherogenic HDL particles. Altering how much cholesterol is inside his HDL particles does not ensure you are improving his HDL functionality.

I was uncomfortable with the lab values. Until proven otherwise I assume almost all men with HDL-C between 25 and 40 or women between 25 and 50 are indeed high risk. I have little use for Framingham Risk scoring in such patients. I advised the rep to do lipoprotein concentration quantification. I stated to him: If you did an NMR LipoProfile (particle assessment using nuclear magnetic resonance spectroscopy) on this man you would likely see a very serious (high risk) increase in LDL (apoB-containing) particles. It was my opinion that this man needs urgent and aggressive therapy. He is what would call metabolically (not phenotypically) obese. I'd also like to know: What is his glucose and 2 hr post prandial glucose? What is his urine microalbumin? What about a PLAC test (lipoprotein associated phospholipase A2)?

I also went out on the limb and further stated: Although the statin or statin/ezetimibe might normalize Non HDL-C, his particle counts will likely remain abnormal and I believe he will then

need TriCor on top of those meds. The TriCor will help his insulin resistance and help wit HDL functionality.

If you want to follow the doc's advice, Crestor is a good choice. However if an NMR or apoB was done I think it would confirm my suspicion of very high LDL-P and Crestor/Zetia (or Vytorin depending on the level) would be a better choice. Then if particles not perfect add TriCor

Well shortly thereafter I received some follow up: the advanced particle testing was done.

NMR LipoProfile (www.lipoprofile.com)

Repeat Lipids showed a big jump in TC and LDL-C
Total-C = 202 LDL-C = 160 HDL-C = 27 Trigs = 73

Most docs would probably start a statin with an LDL-C > 160.
If you want to get it to 130 mg/dL. Start Pravachol 40 mg.
If you want 100 mg/dL start Crestor 20 or Vytorin 20 mg.

Or maybe you should look at the LDL-P before deciding on therapy.

LDL Particle Number = 1982 (desirable < 1000)
Small LDL-P = 1363 (desirable well under 1000
LDL particle size 20.6 (Pattern A: Large) However look at small LDL-P
Large HDL-P 6.9 umol/L (intermediate risk in a drug naive patient
Large VLDL-P 0.0 nmol/L

Hemoglobin A1c 5.1 Creatinine, Serum 1.0 Post prandial glucose 94
Not much supporting Insulin Resistance in the lipid, lipoprotein or glucose values. But I wonder!

I was right on the risk: Looking at his particles, the patient has very high risk: He has more LDL particles than almost 90% of humans. Hepatic LDL receptors are not great at removing small LDL (and this man has too many). If the liver is not clearing LDL particles, he has impaired indirect reverse cholesterol transport (LDLs can't return cholesterol to the liver which is their main job). So if they are not cleared by the liver, guess where the LDL's bring the cholesterol ---- right into an artery. We need to upregulate lots of LDL receptors.

LDL particle counts that high call for Crestor 10-20 mg plus Zetia 10 mg. Because of the risk I'd also add baby ASA plus 1000 mg Omega-3 FA. Repeat NMR in 8 weeks. I suspect he will need additional therapy: Since his TG are perfect, we would then probably add Niaspan to get to goal if needed.

Moral of the story from the rep: "Awful as it may be, I am learning a lot from this case and so many of my doctors that I work with were saying my brother was fine without any meds...nice right!!!

LIPID CASE #183

With Easter and all of its good gustatory treats coming up I thought it appropriate to look at a case where triglycerides (TG) are a problem. I received the following inquiry from a colleague and was asked to provide insight on a TG disorder.

The female patient is a healthy 33-year-old who six months ago delivered her second baby without complications. Her glucose screening was normal at 26 weeks in both of her pregnancies. She is a non-smoker with normal blood pressures and no family history of early-

onset cardiovascular disease. After her last physical her provider suggested a lipid screen. She complied and the fasting results were:

TC = 240; TG = 1078; HDL-C = 50; LDL-C = 76; VLDL = 216

The patient asked that we wait a week so that she could cut refined sugars out of her diet. She now volunteered that her mother and her grandmother both have a problem with their triglycerides and both can cut triglycerides significantly by restriction of refined sugars;The repeat study showed

TC = 211; TG = 501; HDL-C = 44; LDL-C = 97; VLDL = 100;

The provider then placed her on TriCor 145 mg daily and Omacor with the following results: TC =176; TG =131; HDL-C = 51; LDL-C = 97; VLDL = 26.

The clinician asked how does restriction of refined carbohydrates have such an impact on her triglycerides? Are these levels satisfactory or should I try to push the triglycerides lower with Zetia? Is the rise in the LDL-C a reflection of increasing particle size? The Omacor is expensive and she asked me if I could let her take other omega-3 fatty acids.

DAYSPRING ANALYSIS

My first comment is on the initial lipid profile: I was not informed how the lab determined the LDL-C (IDL-C plus LDL-C) and VLDL-C in face of an extreme TG level. There is no accurate way to calculate those values. Almost all labs report VLDL-C by dividing TG by 5 and LDL-C by subtracting the HDL-C and calculated VLDL-C from TC using the Friedewald formula:

TC = HDL-C + IDL-C + LDL-C + VLDL-C

Why does VLDL-C = TG/5? It does if the following assumptions are true:

Every TG molecule is in VLDL particles and the composition (TG/cholesterol make up) of the VLDL particle is 5 times more TG than cholesterol and there are no chylomicrons present. Of course the reality is that as TG levels increase, the composition of all particles change and the ratio is no longer 5 to 1. Also the excess TG found in TG-rich lipoproteins will find their way into other particles using the lipid transfer protein called cholesteryl ester triglyceride transfer protein (CETP). CEPT is also known as apolipoprotein D. It is produced in hepatocytes and adipocytes and that produced in the liver is trafficked on HDL particles.

Clinicians have been classically told that the Friedewald calculation is not accurate if the TG are > 400 mg/dL but we now know that the accuracy of the calculation deteriorates at values of 200 mg/dL or even lower depending on particle composition. This fact should make one realize that LDL-C values in patients with increased TG cannot accurately be used in risk assessment or goals of therapy. This is a big reason that NCEP adopted Non HDL-C as the secondary goal of therapy in patients with TG between 200 and 400.

Never forget that Non HDL-C = TC minus LDL-C minus IDL-C minus VLDL-C minus chylomicron-C minus VLDL-C remnant minus Lp(a) -C. Using Non HDL-C gives one a much better clue of potentially atherogenic cholesterol than LDL-C ever could. There is new news on this topic. Grundy and colleagues went back and re-analyzed data from several Framingham cohorts and last December published a paper that should be read by all: their conclusions based on > 5,700 patients is that Non HDL-C always out predicts LDL-C, no matter what the TG level and that VLDL-C is just as important a risk factor as is LDL-C. (Am J Cardiol 2006;98:1363–1368)

Of course I agree with the 30 Expert Panel, 10 Country consensus published last year (more must reading) that if we just quantitated atherogenic particle concentrations we would not have to worry about make decisions based on guesses using lipid concentrations as surrogates of particle concentrations. (J Int Med 2006;259:247-258). The reason they conclude this is that by far the most important variable that determines if an atherogenic particle (those wrapped with apolipoprotein B) is particle concentration (apoB or LDL-P) not how much cholesterol is in various particles and not LDL particle size. (MESA Study Doi:10.1016/j.atherosclerosis.2006.05.007 and EPIC-Norfolk (J Am Coll Cardiol 2007;49:547–53)

It is possible than the LDL-C was directly measured by the lab or that an advanced cholesterol test like VAP was done: that lab spins out the various particles and then reports how much cholesterol is in the particles. Unfortunately that lab does not report any particle quantification data. With regards to this case, since I was not told how LDL-C and VLDL-C was arrived at when TG were > 1000, I will dismiss their accuracy. However I can certainly conclude the following:

The woman has either way to many TG-rich lipoproteins (VLDLs and/or chylomicrons) or she simply has gigantic chylomicron and VLDL particles and thus may not have a high apoB level. There is a condition called Familial Hypertriglyceridemia (and obviously high TG run in her family) where patients indeed have very large TG-rich particles but do not have an excess of particles. TG are high but apoB (particle number) is OK. Even though the TG are very worrisome, these patients are not a very high CV risk. Of course anyone with TG > 1000 is at risk for pancreatitis.

Time for an academic taxonomy discussion that does not have a lot of clinical relavance.If we wanted to use the older Fredrickson, Levy, Lees classification of lipid disorders (Type I-V) only Type IIA is not associated with high TG. Type I and V: Very high: TG. Type IIB: high cholesterol and TG; Type III (very high TC and TG); Type IV High TG, cholesterol variable; and Type V very high TG cholesterol variable. It requires lipoprotein separation to accurately classify the disorders: Type I Chylomicrons, Type II LDLs, VLDLs, Type 3 IDLs, Type 4 VLDLs, LDLs, Type 5 Chylomicrons and VLDLs and LDLs. The Fredrickson types associated with CV risk are those that have too many IDLs and LDLs (II,III, IV, V). Types I and V are chylomicron disorders and thus if the serum tubes are allowed to stand overnight one would see the solid white band of fat on top of the tube. Disorders with too many VLDLs simply have turbid serum. Type V

(VLDLs and chylos) would have turbid serum topped off with a solid white (chylo) band. You may be shown such sera on the Lipid Board certification test.

If risk is determined primarily by particle number (apoB or LDL-P) what determines apoB number: over-synthesis of apoB or delayed proteolysis (catabolism) of apoB protein? In a 6 year old but still relevant discussion of diabetic dyslipidemia Ira Goldberg nicely discusses that is lipids that determines apoB level not the synthesis of the protein apoB. In diabetics (IR) increased lipolysis (release of fatty acids) from adipocytes increases FA deliver to the liver, stimulating TG synthesis. ApoB which normally would have been catabolized is now needed to increase VLDL production. Thus FA modulate hepatic apoB secretion. Of course realize the following: glucose, trans and saturated fat can dramatically alter FA synthesis or alcohol FA catabolism. The reason glucose raises TG is that it is rapidly absorbed and converted to pyruvate, which after further catabolism (Krebs cycle) becomes citric acid which can be a major substrate for TG production.

Now once the TG-rich lipoprotein is released (VLDL or chylo from enterocytes) the particle must deliver the TG (fuel) to muscles or adipocytes. How this is accomplished can get very complicated. Several other apolipoproteins and enzymes will determine how rapidly and efficiently these particle disappear. Delayed catabolism of such particles will obviously raise TG levels in fasting and postprandial states. Those apoproteins that enhance catabolism of TG-rich particles are apoA-V, apoC-II, apoD and apoE. Those that retard the catabolism of such particles are lack of AV, CII, or the presence of abnormal apoE as well as apoA-II, apoC-I, apoC-III. The main triglyceridase in plasma predominantly expressed in muscles and adipocytes is lipoprotein lipase, a deficiency of which will retard lipolysis of TG-rich particles. Knowledge of the above can be helpful when picking a drug to treat TG as various therapies cab alter the above apoproteins and enzymes in positive and negative ways.

In this patient without having an apoB level it is hard to know if this is familial hypertriglyceridemia without CV risk or Hypertriglyceridemia associated with both pancreatitis and CV risk. Almost all of the latter are insulin resistant. Interestingly this lady had two pregnancies one very recent with no glucose issues. She has no hypertension and is described as healthy so I presume that to mean non-obese. Thus other than the High TG, there are no other criteria for metabolic syndrome. However, the response to glucose restriction was pronounced. Notice that the original HDL-C was seemingly OK at the cutoff point of 50. We would expect with IR and atherogenic dyslipidemia for the HDLL-C to be lower due to CETP activity.

No matter whether she has CV risk or not, our mission is to get the TG levels out of pancreatitis ranges (fasting < 500). That is why TG treatment takes priority over apoB (LDL-C and Non HDL-C) in such patients. Obviously in this case lifestyle measures accomplished just that. Her profile became:

TC = 211; TG = 501; HDL-C = 44; LDL-C = 97; VLDL = 100 Non HDL-C = 167

Let's look carefully at the profile: I wish we could make it simple and just order an NMR lipoprotein analysis (www.lipoprofile.com) but in this case we have to guess what type of

lipoproteins are present. She is clearly at LDL-C goal (if you believe that LDL-C) but the non HDL-C is elevated. If we had to guess we must strongly suspect she has and elevated apoB (LDL-P) and most are small LDL particles as well as VLDL remnants. Although LDL-P would drastically outnumber VLDL-P, VLDLs convey risk through many mechanisms: even though there are not that many, they carry very large amounts of cholesterol and they increase blood viscosity, cause immediate endothelial dysfunction, likely set off several inflammatory actions and increase blood hypercoaguability. Using NCEP criteria the very high VLDL-C is indicative of cholesterol-rich VLDL, chylos and maybe IDL called remnants. Also notice now that the TD have been significantly reduced the remaining lipid profile looks like typical atherogenic dyslipidemia seen with insulin resistance.

After fibrates and Omacor the profile, became:

TC =176; TG =131; HDL-C = 51; LDL-C = 97; VLDL = 26.

The patient is at NCEP goal with normal LDL-C and Non HDL-C and the treatment has been very successful. She must be cautioned that bad lifestyle especially with alcohol or noncompliance with medication can cause a hypertriglyceridemic crisis including pancreatitis. Personally I would not be comfortable until I saw a normal apoB or better yet LDL-P, but unfortunately most clinicians base, for a variety of legitimate reasons, all treatment on lipid concentrations. What would one do if there LDL-P came back high with the above lipid profile? Simply add a statin (Crestor) or statin/ezetimbe (Vytorin) or sadly whatever a formulary mandates. Really would depend on the LDL-P. The provider asked about adding Zetia to the TriCor. This would certainly be FDA approved but I think because of the statin outcome data I would only add Zetia monotherapy if the patient was statin intolerant.

The LDL-C increase can be explained by the increase in LDL size that usually occurs when very high TG are reduced by drugs that inhibit TG synthesis (fibrates, N-3 FA). As you deplete the TG, there is less CETP activity and the TG are less likely to be transferred to LDLs and HDLs. If LDLs and HDLs do not carry much TG, they are not subjected to as much further particle lipolysis by hepatic lipase: the particle retain their size. LDL size does not really matter, only particle number. If you are a non HDL-C proponent, this lady is at particle number goal.

Can other N-3 products be substituted for Omacor: Yes if you trust the manufacturer on how much N-3 are in the tablets and you believe they have purified their product (removed heavy metals). Remember many OTC products carry only minimal amounts of N-3 so you need multiple tabs which drives the cost. You can always trust Carlson's Famous Fish oil products and their liquid has 2 gram/tsp.

LIPID CASE # 184

This weeks case: HDL is such a hot topic nowadays that almost all of the inaugural issue of the Journal of Clinical Lipidology was devoted to it. All NLA members should have received the journal by now. This is an unbelievable bonus for the meager $50 dues to belong to the organization (www.lipid,org). Anyone who enjoys this newsletter should certainly consider joining.

This issue I want to share a case sent to me regarding a physician patient who was perplexed with his response to lipid-modulating therapy.

He is in his late 50s and has a family history that reveals a father with CAD (? age of onset) with a CABG and stent x4. His Uncle died of CHF caused by MI (? age). His glucose is <100 and his BMI is 30. Blood pressure is reported as normal. Below are the baseline values: then the first set while taking TriCor, the second set off TriCor but on Crestor 10 mg daily.

	BASELINE	w/ Tricor	Crestor (10mg and no Tricor) after 6 weeks
Total-C	188	199	108
TG	196	202	136
HDL-C	37	37	32
LDL-C	112	120	49
Non Hdl-C	151	162	59

He questioned why did his HDL-C go down with Crestor therapy? Of course in most patients there is an increase in HDL-C and apoA-I with Crestor. He did NOT have any lipoprotein testing such as the NMR LipoProfile or apolipoprotein measurements done.

DAYSPRING DISCUSSION:

Because of his age, gender, ? family history of premature atherosclerosis, and low HDL-C I consider him a high risk patient. However if one did Framingham Risk Scoring, his calculated ten year risk of a CV event is 10% (moderate risk). The TG/HDL axis disorder (indeed he qualifies as a Metabolic Syndrome using NCEP criteria) adds to his risk. NCEP would advise lifestyle and if needed medication to achieve an LDL-C of < 130 mg/dL. NCEP would not suggest a Non HDL-C goal because his TG are < 200 mg/dL. Thus is you are an NCEP purist you would crack the whip and seek weight reduction.

Personally I have signed too many death certificates in people with normal or at goal LDL-C levels to be an NCEP purist. Even if you believe his 10 year risk is moderate, his lifetime risk for CHD is very high. In the recent METEOR trial, a significant number of seemingly low risk patients had subclinical disease using Carotid IMT testing. They benefited (disease did not progress) from statin therapy (Rosuvastatin 40 mg). I have to believe this man has IMT thickening or a positive coronary calcium score. (Please visit the BioCritique Website at http://www.biocritique.com/ if you would like to see my full review of the METEOR Trial). A great free website to stay on top of breaking knowledge in the CV and other fields. Please register and enjoy.

We all know what drives atherosclerosis is having too many atherogenic apoB particles (VLDL, remnants, and especially LDL) trafficking cholesterol into the arterial intima. Aggravating this is dysfunction al HDL particles that do not perform macrophage RCT and that lack many protective surface proteins. Anyone want to guess if this patient has too many such atherogenic "dump trucks?"

Published last year (Circulation 2006;113:20-29) was Framingham data in metabolic syndrome patients that revealed TG > 150 mg/dL and HDL-C < 40 mg/dL were significantly associated with increased LDL-P (in the high risk range). Want more evidence? This patient has a high TC/HDL-C ratio (>4.0) with an unremarkable LDL-C. That is a definite indicator of too many small LDLs. The TG/HDL-C ratio is > 3.5, another very predictive ratio of too many small LDL particles. Indeed at a TG of 196, about 80% of patients will have too many LDL particles (majority of which will be small). Thus I am fairly certain that a baseline. drug-naive NMR-LipoProfile testing would disclose increased numbers of VLDLs (remnants), way too many LDLs (majority small) and a decreased HDL-P (with a more pronounced reduction in the larger mature alpha HDL particles H4 and H5 (HDL2).

It does not look like the TriCor therapy did anything to the lipid profile. If one truly wants to respect fibrates, one needs to review all of the fibrate data (lots of clinical trials) published to date. I'll save

you the time: Fibrates work best in those who are insulin resistant (with or without T2DM) and the benefit of the fibrate does not correlate with the baseline lipid values or what the fibrate does to the lipid profile. Many fibrate experts have written that performing a lipid profile after prescribing a fibrate is a waste. Lipoprotein testing however usually demonstrates reductions in apoB or LDL-P, reductions in VLDL-P, upward shifting of LDL size, increases in HDL-P but reductions is HDL size (as the fibrates make the liver delipidate mature HDL particles of their cholesterol). Of course much of the fibrate benefit is likely pleiotropic and will never been seen in a lipid or lipoprotein panel. That being said, I do not believe that TriCor was a wise initial choice in this patient. The problem is too many atherogenic apoB (especially LDL) particles: we will rewuire a more potent first line apoB med than a fibrate.

Therefore the first therapy, backed by substantial clinical trial data is to upregulate LDL receptors (apoB/apoE receptors) which will help clear the plasma of the apoB load. The best way to upregulate LDL receptors is to deplete the liver of its cholesterol stores: inhibit hepatic cholesterol synthesis with a statin and block chylomicron delivery of cholesterol to the liver with a sterol absorption inhibitor (ezetimibe). The dual mechanism will upregulate the maximal numbers of LDL receptors. **In high risk patients,** we want to maximally upregulate LDL receptors. That is why I am such a fan of ezetimibe added to lower and presumably safer doses of statins or higher doses if needed. If the apoB load is really high then Crestor and Zetia makes for the most powerful combination (see EXPLORER Trial: Am J Card 2007;99:673-680) but if the load is not very high Vytorin makes better economic sense. For anyone who wants to use a statin over statin/ezetimibe combo to lower apoB or LDL-P (non HDL-C) ask you Merck SP reps for their many trials showing superiority of the combo to any statin monotherapy to achieve goals.

The doc at hand, dumped the TriCor and went to Crestor 10 mg monotherapy. All of the lipid parameters moved dramatically in the desired direction except the HDL-C which many would have predicted should have elevated with Crestor therapy. Dos the reduction in HDL-C worry anyone? Should the Crestor be immediately stopped? I hope none of my readers answered yes to that question. Let's review what our lipid concentration parameters tell us about cholesterol homeostasis?

TC is the cholesterol trafficked in all of the lipoproteins that exist in a deciliter of plasma. HDL-C is the cholesterol trafficked by HDL particles, LDL-C that in the LDLs and VLDL-C in the VLDLs. Labs report a total TG concentration (the TG trafficked in all of the lipoproteins) but never report individual particle TG values like they do with cholesterol. Have you ever seen an LDL-TG or HDL-TG level reported. Of course not, but that could be useful info in some persons. When one prescribes lipid drugs that affect cholesterol and TG, one will surely affect the lipid composition within the various lipoproteins.

It should be pretty obvious that if with lifestyle or with potent drugs, one drastically reduces TG and total cholesterol levels it no be a surprise that it is possible to reduce TG and cholesterol concentrations in many if not all of the lipoproteins. In this case Crestor blew away the TC level and that resulted in significant reductions in LDL-C, VLDL-C and even HDL-C. Why did Crestor do such a good job on lowering TC? Statins by inhibiting HMG CoA reductase, slow the synthesis of mevalonic acid, a cholesterol precursor. If the liver synthesis of cholesterol is reduced the liver must obtain cholesterol elsewhere (as cholesterol is needed to make bile acids and lipidate HDL particles). When cholesterol is depleted in hepatocytes the sterol regulatory element binding proteins through genomic actions causes increased transcription of mRNA which will increase synthesis of the protein called LDL receptors. The LDLr translocates to the hepatocyte surface and internalizes lipoproteins with apoB and apoE on their surface (VLDLs, IDLs and LDLs as well as HDLs that contain apoE). So in this case the Crestor seems to have upregulated an extraordinary amount of LDL receptors.

My guess is that this person is a hypoabsorber of cholesterol. He does not have many Niemann Pick C1 Like 1 proteins (a sterol absorption protein) in the microvilli of his jejunal enterocytes. If there is decreased sterol absorption the chylomicrons that form do not traffic much cholesterol to

the liver. In effect, the liver is short-changed with respect to cholesterol delivery. Genetic forces go into play to upregulate HMG CoA reductase and cholesterol synthesis becomes excessive. Obviously if you give a statin to a person with excess HMGCoA reductase activity, you will get a great response (hyper-response) to the statin. Crestor is already the statin that most perfectly binds to and inhibits HMG so it should not be a shock that it is the most efficacious statin in upregulating LDLr and it will be even more potent in persons who hypoabsorb cholesterol. The wrong dug to use in a hypoabsorber would of course be ezetimibe which has little efficacy in such patients. Never forget that once you write for a statin and slow cholesterol synthesis, the intestine will start to increase sterol absorption NPC1L1 upregulates).

Never forget that the only NCEP ATPIII goals are to normalize LDL-C and Non HDL-C, both of which have been achieved in this person. There is no medical-legal reason to attempt and raise his HDL-C as there would be no trial data to suggest that this man (at Non HDL-C goal) would be further benefited by such rise.
However is this man really at apoB or LDL-P goal? I think you really have to measure either if you really want to reassure him he has no atherogenic particles. What would you do if he still had a high LDL-P despite the perfect apo-B lipid surrogates? The answer is a fibrate or niacin. Your reason for using them is not to raise HDL-C (fenofibrate did not although niacin probably would). You add them because: both would shift LDL size, making the LDL particles more amenable to LDLr removal and help drop LDL-P even more. Both would likely enhance macrophage RCT (very desirable).

Bottom Line: if apoB is at goal you probably do not have to loose sleep because you have not normalized or even lowered HDL-C.

LIPID CASE # 185

Time to solve another case. I was asked for input on a 35 year old woman who is 5'9" with a weight of 146 and a BP of 130/80. She does not have a family history of premature cardiac disease. Her mother has some elevation in her LDL and is on Lipitor. She does not smoke or drink. Her original lipid profile done two years ago while she was using OrthoNovum 7/7/7 are as follows:

TC = 208 TG = 281 HDL-C = 55 LDL-C = 97 TC/HDL = 3.8
Non HDL-C = 153

Her provider thought a change to OrthoEvra might help the TG since it was transdermal. She was also advised to decrease simple carbs and increase exercise.

A few months later. on OrthoEvra her lipids were:

TC = 230 TG = 381 HDL-C = 39 LDL-C = 115 TC/HDL = 5.9
Non HDL-C = 191 hs-CRP = 4.79 (desirable < 2.0)

She was then changed to from OrthoEvra to Micronor with the lipids repeated one month later:

TC = 209 TG = 178 HDL-C = 35 LDL-C = 138 TC/HDL = 6.0
Non HDL-C = 174 hs-CRP = 2.28

The clinician notes, "the TG looked better but the HDL and LDL looked worse." She was advised to further lower saturated fats and increase her exercise. Her next lipids were done at Berkeley HeartLab. The LDL fractionation showed a mix of large and small particles -- an indeterminate pattern.

TC = 209 TG = 148 HDL-C = 41 LDL-C = 138 TC/HDL = 5.10
Non HDL-C = 168

On follow up: Her weight was down to 140 with a BMI of 21 and BP of 112/70. She was on no hormonal contraception. Her lipids were:

TC = 248 TG = 197 HDL-C = 50 LDL-C = 159 TC/HDL = 5.0
Non HDL-C = 198 hs- CRP 2.62

She was doing pretty well with diet and exercise but had not absolutely optimized it. She spent the next 4 months exercising 5 days/wk, eliminating saturated fats and trans fatty acids, adding nuts and soy and fiber (though she didn't add fish oil or flaxseed) and eliminating processed carbs. Her next lipids were done with an NMR (nuclear magnetic resonance) LipoProfile:

TC = 239 TG = 189 HDL-C = 34 LDL-C = 167 TC/HDL = 7.03
Total LDL-P 2151 (very high risk) Small LDL-P 1654 (high)
LDL particle size 20.2 (small) Large HDL-P 4.1 (decreased
Large VLDL-P 0.3 (normal)

Her FBS has always been normal.

Her provider was confused that an improvement in life style seems to have made the lipids worse and since she is only 35, guidelines would not recommend meds.
I was asked what would I recommend at her age to help optimize these lipids?

DAYSPRING ANALYSIS

This is a case involving a young woman with elevated LDL-C and seemingly variable HDL-C levels. The Non HDL-C has been consistently high. The CRP is bouncing all over the place which is a major limitation to its use.

The original profile: TC = 208 TG = 281 HDL-C = 55 LDL-C = 97 TC/HDL = 3.8 Non HDL-C = 153
Uusing NCEP ATP III guidelines, at best this case calls for lifestyle management which was advised. Both the Ortho 7/7/7 and the Ortho-Evra (fairly high dose estrogen even though given transdermally) significantly raised the TG). One can see how difficult it can be to truly estimate which lipoproteins are present by using lipid concentrations as lipoprotein proxies. Never forget, it is apoB particles (VLDL, IDL and mostly LDL) that drive disease and risk. Our lipid concentration surrogates of apoB are TC, low HDL-C, elevated TG, LDL-C, TC/HDL-C ratio and Non HDL-C (TC minus HDL-C).

Note about estrogen and lipids: oral estrogen (dose dependent) usually lowers LDL-C, raises HDL-C and raises TG as well as improving insulin sensitivity and delaying T2DM onset. This is exactly what the bile acid sequestrant colesevelam (WelChol) does. Do WelChol and estrogen have anything in common as to their mechanism of affecting lipids? Yes: they both downregulate farnesoid X-receptor which is involved with metabolic regulation of bile acids, TG, HDL-C and glucose..

The follow up on Micronor (norethindrone) and increased lifestyle resulted in the following lipids:

TC = 209 TG = 178 HDL-C = 35 LDL-C = 138 TC/HDL = 6.0
Non HDL-C = 174

There was improvement in the Non-HDL-C and TG with a reduction in HDL-C and little change in the ratio. The Norethindrone is a very androgenic progestin: It reduces apoA-I production (HDL precursor protein) and induces hepatic lipase (which by hydrolyzing the TG and surface phospholipids in and on the HDL particle remodels HDL from large to small). However, androgens by upregulating lipases, usually help reduce TG.

Next profile on no contraception

TC = 248 TG = 197 HDL-C = 50 LDL-C = 159 TC/HDL = 5.0
Non HDL-C = 198

A bit worse than where she started

After extensive lifestyle:

TC = 239 TG = 189 HDL-C = 34 LDL-C = 167 TC/HDL = 7.03
Total LDL-P 2151 (very high) Small LDL-P 1654 (high)
LDL particle size 20.2 (small) Large HDL-P 4.1
Large VLDL-P 0.3

Her LDL particles are slightly small but not that tiny. Why does she require so many LDLs to traffic her cholesterol? First of all she has a lot of cholesterol within her LDL particles (167 mg per deciliter). Is there anything else competing with cholesterol for space inside her LDL and HDL particles. YES! Her TG are high at 189 and they have to be trafficked within lipoproteins including LDLs. Not she has very few large VLDL particles (the particle that usually traffics most of the TG). Thus not only are her LDLs somewhat small, but they are full of TG. Therefore she needs lots and lots of small, TG-rich LDLs to also carry her 167 mg of cholesterol. Unfortunately elevated LDL-P is a major risk factor and her LDL-P level of 2151 is extremely high which puts her in a risk category which we likely would not have suspected if we made judgements based solely on lipids. Certainly her Non HDL-C and LDL-C are not in the very high risk levels.

How do we explain the lack of any response to lifestyle. This woman is probably insulin resistant and almost all of it is explained by her genes, not her lifestyle or waist size. There are many reasons how this is possible and I refer you to a current discussion of the metabolic syndrome : AHA/NHLBI Scientific Statement (Diagnosis and Management of the Metabolic Syndrome Circulation. 2005;112:2735-2752.)
which I encourage all to read in its entirety. It explains that MS has many phenotypes and visual obesity does not have to be present. The folks where genetics, not lifestyle cause the IR, of course will not respond to lifestyle. Had this woman not done lifestyle her numbers would be even worse. One might want to do a 2 hr PP glucose to check on impaired glucose tolerance which has a higher incidence than IFG.

The new AHA Women's guidelines discuss the dilemma clinicians now face. We have a woman with fairly low 10-year risk of having a clinical CV event, but a high lifetime risk of CVD. When do you intervene? This is where the art of practicing medicine comes in. You must think outside of the box (guidelines) using current evidence. If she consulted me, because of the extreme LDL-P elevation and the variable but high CRP, I would start something like Vytorin 20 mg to upregulate hepatic LDL receptors and see what happens to LDL-P. On follow up testing one must repeat the NMR: the lipids have let us down in this case. Fertile women, must be instructed as to the Category X of statins and other types of contraception likely have to be addressed. One might advocate N-3 fatty acid supplements to help reduce the TG rather than a fibrate because of the pregnancy issues. Even though it appears it is not helping, lifestyle remains an essential part of therapy.

LIPID CASE 186

I was asked for an opinion by a provider working in a lipid clinic on the use of Crestor in diabetics. The patient with known CAD s/p CABG, with an LDL-C of 185 (on lovastatin 80 mg used because of insurance preference), HDL-C of 37, Triglycerides of 254, and a VLDL-C of 51. She has normal creatinine (0.9 w/ GFR >60) and has no history of renal insufficiency. Her

diabetes is uncontrolled - she is type II, insulin dependant. Her last A1c was ugly at 11.3 - but she has not had one since January (this is managed by her PCP.) They have been working on adjusting her insulin dose. She already does a pretty good job of following a low chol/low carb diet.

The clinician asks whether or not to use Crestor in this patient, noting she has no history of proteinuria, although. The patient was given various options including Lipitor, Vytorin, and Crestor as well as the role of Zetia. She preferred Crestor as she has been doing research about this medication and has a number of friends on it as well. The clinician gave her Crestor 10 mg. and stated, "I never use a 40 mg dose because of the risk for proteinuria, but am wondering if it is appropriate to use the 10 mg dose (and potentially the 20 mg dose if necessary) in this poorly controlled diabetic. If so, should I obtain regular UA's and follow her creatinine more closely than usual?"

DAYSPRING ANALYSIS

How is this for a blunt statement: **Statins do not cause proteinuria** (the quote comes directly from the NLA Statin Safety report published last year (Am J Cardiol 2006;97[suppl]:82C–85C) The FDA has cleared all statins including Crestor as being associated in and significant way with proteinuria. **All statins** can cause minor non-pathologic proteinuria by inhibiting HMGCoA reductase and cholesterol synthesis in renal tubules. This affects receptors used in the re-uptake of normally filtered protein. The microalbuminuria that sometimes occurs has never been associated with renal worsening: indeed in most the GFR improves even though there is some protein loss. There is no FDA mandate to monitor albuminuria when prescribing any statin! As long as there is no creatinine problem, all doses of Crestor are fine to use. Of course hydrophilic statins (Pravachol and Crestor), since they are excreted in the urine must be used at low doses if renal insufficiency is present.

Lets look more carefully at the case and see if a high dose statin is the way to go.

On Lovastatin 80 mg: LDL-C = 185 HDL-C = 37, VLDL-C = 51. Triglycerides = 254
TG/HDL-C ratio = 6.8 (very suggestive increased small LDL)
Non HDL-C = 236 (apoB must be very high)
Anyone with an LDL-C of 185 who has small LDLs, will have an incredibly high total LDL-P

apoB (LDL-P plus VLDL-P) is estimated by Non HDL-C (LDL-C + VLDL-C) VLDL-C is the lipid surrogate of remnant lipoproteins. Remnants are TG-rich particles (VLDL, chylomicrons and IDLs) that exchange their TG for cholesteryl ester (CE) with LDL and HDL particles. The TG-rich particles thus become CE-enriched. Thus remnants are carry extra CE (which they obtained when they dumped their TG) and that is why NCEP considers elevated VLDL-C as a surrogate of remnants.mThe LDLs and HDLs become CE poor and TG-rich. Upon exposure to hepatic lipase their TG and surface phospholipids are hydrolyzed creating small LDL and HDL: The HDL-C and HDL-P decreases as the small HDLs are excreted by the kidney, and LDL-P increases. The apoB/apoA-I ratio (TC/HDL-C) ratio, a very important risk predictor, will be high.

This is familial combined hyperlipidemia (hyperbetalipoproteinemia) with associated uncontrolled diabetes. This case will be solved if we can get the TG under control. Of course, better glucose control is a high priority, because the apoB nightmare will be tough to correct without getting the glucose driven hypertriglyceridemia under control. Our options to lower apoB (non HDL-C) are 1) upregulating LDL receptors, 2) slowing production of apoB particles, 3) enhancing lipolysis (TG & phospholipid hydrolysis) and 4) enhancing the clearing of apoB particles.

1) Upregulate LDL receptors: If we deplete the liver cells of cholesterol by inhibiting synthesis or delivery in chylomicrons (block cholesterol absorption) the liver will upregulate LDL receptors.

The starter dose of the statin (not second and third titrations) upregulates most of the LDLr that a statin can upregulate. Ezetimibe (Zetia) can upregulate as many LDLr as tripling the statin dose. Normally one would start Vytorin, but in this case the apoB is so high, Crestor plus Zetia might be a better choice. There is very new and preliminary data that fenofibrate can inhibit a protease (via PPAR alpha agonism) involved with catabolism of LDL receptors, thus explaining how feno can reduce LDL-C. The protease is called proprotein convertase subtilisin kexin type9 (PSCKS). You will be hearing a lot about this protein in the future. It is a great target to help lower LDL-C. (Endocrinology 147: 4985–4995, 2006)

2) Stop apoB production: This is done by depleting the liver of lipids (cholesterol and TG). So statin/Zetia will slow apoB particle production, but in this case we really need to reduce TG synthesis: Fibrates, N-3 FA (high dose) and Niacin (Niaspan).

3) Enhance lipolysis of TG-rich particles: Fibrates are the best: They increase apoAV (helps bind VLDLs to areas of LPL expression), decrease apoCIII (blocks LPL), increase lipoprotein lipase all of which will shorten the half life of TG-rich particles. N-3 FA can help with LPL expression as can some statins.

4) Enhance apoB particle clearing: Since most of the apoB are LDL-P, the best way to enhance clearance after upregulating LDLr is to shift LDL size. replace the small LDL which to not bind well to LDLr with larger LDLs. Fibrates, niacin, N-3 FA can help with this. By reducing TG, they are associated with less CETP activity (the protein that swaps TG for CE between VLDL and LDL and HDL).

Thus it is easy to see this patient will need statin/ezetimibe, fibrate or niacin (or both) and N-3 FA (4 grams). Since the patient has diabetes, fenofibrate (TriCor) should be used over Niaspan as it has microvascular benefits (including preventing microalbuminuria) and improves insulin sensitivity, neither of which will likely occur with Niaspan. In FIELD, TriCor achieved its primary endpoint in diabetics without know heart disease (like the case at hand).

LIPID CASE # 187

The patient is a 56 year old woman with a history of Gestational Diabetes Mellitus, who has been on Lamictal, Klonapin, Prozac, Seroquel for a long time. She had the following metabolic parameters:

TC = 306, HDL-C = 42 TG = 270 Non HDL-C = 264 TG/HDL-C > 6 TC/HDL-C > 7
LDL-P = 2214 nmol/L (desirable < 1300, perfect < 1000)
Glucose & HgbA1c are normal.

She was started on Lipitor and titrated to 40 mg and eventually TriCor 145 mg was added and Her lipid profile improved significantly:

TC = 142, TG = 60, HDL-C = 54
LDL-P was 1163.

However, over time her homocystine went from 10.3 to 16.2 with normal MMA (methylmalonic acid), negative anti-parietal abs. She was started on Metanx. Next her LFTs began to increase and her most astonishingly her HDL-C dropped to 13 and homocysteine ultimately went to 28.

Current Lipids: TC = 144, TG = 165, HDL-C = 13, Non HDL-C = 131
AST 159, ALT 112, GGT 112, Alkaline Phosphatase 44.

The provider would like to know: "What now?"

DAYSPRING ANALYSIS

This seems to be a straight forward case of a woman with previous gestational diabetes (suggesting a propensity to insulin resistance) who has what looks to be familial combined hyperlipidemia with the metabolic syndrome. The very high TC, Non HDL-C, TC/HDL-C ratio all suggest very high levels of atherogenic apoB particles (LDLs, IDL and VLDL remnants). The very high TG/HDL-C ratio is a strong indicator that the LDL particles will be small and dense. Indeed, the NMR LipoProfile (www.lipoprofile.com) revealed a very high LDL-P of 2214 (> 90th percentile). Although I was not provided with vital statistics, we would suspect some degree of central adiposity, enlarged waist size and BMI, and possibly hypertension. A study published a few years ago (Circulation.2005;111:1883-1890) and always worth re-reading is the EWET trial (Enlarged Waist, Elevated TG). In this epidemiological trial the women with the most CV events had EWET (with a TG > 128 and waist > 35 inches). Thus the [patient at hand is certainly at CV risk.

Framingham risk scoring (FRS) puts the patient at low risk (even if she has hypertension). That is a big reason why the recent AHA women's guidelines suggests not using FRS in women over 50 unless it rates a woman as high risk (>20% chance of event over ten years). The AHA concludes that a woman > age 50 with a single CV risk factor is at a 50% chance of a lifetime CVD event. Our woman has multiple CV risk factors, several severe. Thus I think we all agree that the clinician was correct to initiate statin therapy ultimately combined with a fibrate (TriCor is the appropriate choice as it is safer with statins than gemfibrozil) to achieve Non HDL-C and LDL-P goal.

The response was textbook (LDL-C, Non HDL-C and LDL-P were satisfactorily controlled). I could argue that initially using a statin/ezetimibe instead of statin monotherapy) and then adding a fibrate would have achieved goal more rapidly as one would not have to waist time titrating the statin. With numbers as severe as this woman's, it is extremely unlikely that any type of lipid monotherapy would get to goal. We need to upregulate as many hepatic LDL receptors (LDLr) as possible (statin or statin/ezetimibe) as well as shift the size of the LDLs from small to large (fibrates, niacin) as the latter are more efficaciously grasped and internalized by LDLr. LDLr recognize specific apoB conformations and obviously the apoB shape on a small LDL will be very different than that on a normal sized LDL particle.

The something happened: the HDL-C plummeted homocysteine elevated and aminases became abnormal. What's going on? I assume the profile was repeated to rule out lab variation or error. If you want to take NCEP ATP III literally:

Current Lipids: TC = 144, TG = 165, HDL-C = 13, Non HDL-C = 131 LDL-C = 100

The patient is actually at LDL-C and Non HDL-C goal, so must we worry? Maybe if the liver was not injured we could observe, but something is going on here!

Of course the first thing to rule out is some liver injury (toxic or infectious) or pathology. Acute liver inflammation would be associated with rising aminases (usually higher) and low HDL-C. Presuming no binge occurred and no obvious explanation is seen, it is likely we are dealing with an unusual reaction to fenofibrate.

Statin/fenofibrate theoretically can raise aminase levels but is rare. In the 10,000 FIELD trial using fenofibrate with significant statin contamination, only folks in the placebo group had aminase elevations. However in a given individual anything is possible. Fibrates have long been know to reduce alkaline phosphatase (Atherosclerosis 165 (2002) 187-188) and indeed can be used by the clinician as a sign of fibrate compliance. Fibrates, especially fenofibrate can elevate homocysteine although the response in this patient is extreme. The NLA paper on fibrate safety ((Am J Cardiol 2007;99[suppl]:3C–18C) states: In the DAIS trial (a trial of diabetics in which fenofibrate demonstrated angiographic benefits) the rise in homocysteine (55%) had no

correlation with what happened to the artery wall. In a post-hoc analysis of the FIELD trial, in patients with the highest tertile increase in homocysteine (>4 umol/L), there was proportionately less reduction in CVD events. They conclude further study is needed. Folic acid therapy has been reported to reduce homocysteine in patients taking fibrates (Nutrition 2001;17:721-723), however several trials (in which patients were not on fibrates) have not related lowering homocysteine to CV benefit.

How about the drop in HDL-C? In the inaugural issue of the Journal of Clinical Lipidology a paper by Goldberg (Journal of Clinical Lipidology (2007) 1, 41–56 e) entitled acquired HDL-C deficiency he describes "The Disappearing HDL Syndrome." This is most frequently seen with PPAR therapy (gamma or alpha) including rosiglitazone therapy, fenofibrate therapy or the combination thereof. HDL literally disappears to levels as low as 0-15. Several mechanisms are postulated to explain this phenomenon (see the paper). Statins have not been implicated in acquired HDL-C deficiency. Lipitor is well know for not raising HDL-C as one escalates the dose, but it usually does no reduce HDL-C. The patient is also on several psychotropic drugs and in actuality any number of bizarre drug-drug interactions might be going on, although temporally the fibrate is the most obvious explanation.

So assuming fenofibrate is the explanation for the homocysteine elevation and HDL-C reduction, the aminase elevation does not seem that critical (borderline threefold elevation) and could be explained by statins or fibrates or the combination. I think I'd simple stop the TriCor and see what happens. Some, for purely medicolegal reasons might want to stop statin and fibrate and I would not argue. If all parameters returned to pretreatment levels, I'd resume therapy with a hydrophilic statin, specifically rosuvastatin or Crestor (with or without ezetimibe). If LDL-P goal or Non HDL-C goal is not achieved then Niaspan would be better in this patient rather than a fibrate.

By the way, the FDA has approved a film-coated formulation for niacin extended-release capsule-shaped tablets (caplets; *Niaspan*; Abbott Pharmaceuticals Inc) in 500-, 750-, and 1000-mg strengths that are bioequivalent to the previously approved uncoated 500-, 750-, and 1000-mg caplets, respectively. Reduced flushing may enable patients to better tolerate the 1000-mg caplets, thereby improving dosing convenience relative to 2 caplets of the 500-mg strength.

LIPID CASE # 188

I want to discuss the following case sent to me by a gynecologist. He saw a 25 year old asymptomatic, married white female who has a father and paternal grandfather and grandmother as well as paternal aunt who require statins. Apparently none have had cardiovascular events. The patient weighs 114 pounds and has little to no body fat. Her lipid profile is as follows:

Initial: TC = 279 mg/dL HDL-C = 83 mg/dL LDL-C = 174 mg/dL TG = 110 mg/dL

4 months later: TC =246 HDL-C = 70 LDL-C = 157 TG = 96
NMR LipoProfile: LDL-P (LDL particle concentration) = 1691 (high risk or > 80th percentile)
Desirable total LDL-P is < 1300 and perfect is < 1000 nmol/L
Small LDL-P = 244 (fairly low)
LDL Particle size is 22.5 (quite large) Cutoff between large and small is 20.5 nm
Large HDL-P = 12 (low risk) She has lots of large HDLs

Her CRP was 3.6 (normal <3) and her homocysteine is 10.5 (normal <10.4)

She has had significant menstrual cycle trouble which has finally been corrected with the Orthro Evra patch. She is aware of higher basal E2 levels and risk of stroke. I was asked, considering her age, what would I suggest as to management.

DAYSPRING DISCUSSION:

Her elevated TC and LDL-C suggests she is beginning to manifest the phenotype of familial hyperlipidemia and indeed the NMR LipoProfile confirms hyperbetalipoproteinemia. If one uses the older Fredrickson's Classification she would be classified as Type IIa (cholesterol elevations with normal TG). Her abnormal particle numbers as well as her cholesterol concentrations will likely continue to worsen with time. As all my readers should know, it is apoB or LDL particle concentration (90% or more of aboB particles are LDLs) that determines atherogenesis. Recall that the recent METEOR trial showed that even younger patients with borderline lipid abnormalities had significant subclinical atheroclerosis (on carotid ultrasound) and its progression was halted by use of rosuvastatin 40 mg daily! Should we just start her on Crestor 40 or think about it a bit more? Using NCEP ATP-III she would not qualify for drug treatment as her ten year risk of an event is low and her LDL-C is not 190 mg/dL. She does not even qualify for Framingham risk scoring as she does not have two major risk factors for CHD.

LDLs are simply the by-product of lipolysis (removal of lipids: mostly TG and phospholipids induced by various lipases) of VLDL and IDL particles. The LDL half-life is 2-3 days during which time it traffics tocopherol (vitamin E) to various tissues. In its journey it accumulates more cholesteryl ester from HDL particles by swapping its triglycerides using the lipid transfer protein called cholesteryl ester transfer protein (CETP). So if one asks: Where does the cholesterol in LDLs originate, the answer is from VLDLs and HDLs. Very few clinicians have ever been taught that a significant part of LDL-C (that they manage every day) originates in HDL particles. After three days most of the LDLs have been internalized into tissues by LDL receptors (LDLr). Since the liver has by far the ability to upregulate LDLr, most LDL particles (>80%) are cleared by the liver, in a process that is now termed indirect reverse cholesterol transport. Classically none of were ever taught that the primary function of LDL particles is to perform reverse cholesterol transport. Under physiologic conditions LDLs do not traffic cholesterol or cholesteryl ester to any other tissue. If there are too many LDL particles in plasma, they have another option other than the liver and unfortunately that is the arterial intima, where they are prone to oxidation and ingestion by macrophages creating foam cells (the histologic hallmark of atherosclerosis).

What determines LDL-C (there amount of cholesterol trafficked within all of the LDLs that exist in a deciliter or 100 cc of plasma)? Obviously it will be a product of the number of LDL particles and the volume of the LDL particles. The volume of a round particle (sphere) is 4/3 pi R cubed (where R is the radius of the particle). Since the volume of all lipoproteins is related to the third power of the radius and trivial size shifts can dramatically influence the volume. The volume of a ping pong ball which is maybe 3-4 times the size of a marble is 17 times greater. Thus one's LDL-C is related to LDL-P and LDL size. The patient at hand has very large LDL particles (22.5 nanometers or nm). She also has an LDL particle count of almost 1700 nmol/L, thus explaining why she has very high LDL-C concentrations. Imagine what her LDL particle count would be if she was a diabetic with very small LDL particles. It might approach 3000 depending on how small her particles were. This illustration should make it obvious why it is almost impossible to estimate LDL-P (apoB) in patients who have small LDL particles even if there LDL-C is normal.

People with familial hypercholesterolemia typically have increased numbers of very large LDL particles, thus explaining their horrific LDL-P (apoB levels). So although we have classically been taught that LDL-C explains their risk, it is really LDL-P that is the true risk factor. Do not forget that it is LDL-P that drives the particle into the arterial wall, not LDL-C.

This same principal relates to HDL particles also. If one very high HDL-P concentrations, yet the HDLs were very small, the HDL-C might even be low, but if the HDL particles are functional, the patient would not have the risk typically expected in patients with low HDL-C. This clearly explains one of the many reasons why fibrates work so very well in insulin resistant patients with low HDL-C. Fibrates increase the HDL-P (number of HDL particles) but because fibrate upregulate hepatic HDL delipidation proteins (Scavenger receptors B1 or SR B1), and thus enhance HDL particle delipidation the rise in HDL-C may not be terribly dramatic. On the other

hand niacin which downregulates a hepatic HDL preceptor that internalizes HDL and inhibits hepatic lipase (preventing large HDLs from effective lipolysis, increases HDL-P and HDL size, leading to much more dramatic rises in HDL-C. Yet if we look at what fibrates and niacin do to HDL-P it is very similar but on HDL-C niacin is better. Yet recent trial data implicates HDL-P and not HDL-C as a better therapeutic goal. So even though fibrates and niacin have different abilities to raise HDL-C, they both raise HDL-P very similarly. Wish we had a test that enlightened us as to which would increase HDL functionality more. We sure want high levels of HDL-P, but you better pray the HDLs are functional (defined as ability to delipidate arterial wall macrophages or macrophage reverse cholesterol transport, and as to the ability to traffic anti-atherogenic proteins on their surface).

Why do the patients with familial hypercholesterolemia have such high LDL-P levels. You would think that the hepatic LDLr would simply clear the particles from plasma. First a little education on how LDL particles are upregulated, stay upregulated and how do they and which lipoproteins do they internalize. Liver cells upregulate LDLr to when they need to replenish their cholesterol storage pools (the liver needs cholesterol for its cell membranes, to lipidate HDL particles and to make bile acids. There is a nuclear transcription factor called sterol regulatory element binding protein (SREBP) that is activated when cellular cholesterol levels are low. One of its actions is to affect response elements on genes to initiate LDL receptor protein synthesis. The LDLr translocates to the hepatocyte surface and attaches to either apoB or apoE on lipoproteins causing their endocytosis. With respect to apoB, the LDLr is a protein with specific surface charges (such charges depends on the LDLr configuration). The charges on LDLr recognize opposing charges on the apoB on the surface of the lipoprotein. However those charges and their specific locations depends on the configuration of the apoB on the lipoprotein. Clearly very large and very small LDL particles will have very different apoB configurations than normal sized LDL particles. Upregulated LDLr would be inefficient in recognizing and effectively clearing very large or very small LDL particles. Thus impaired clearance, better termed ineffective indirect reverse cholesterol transport would increase the plasma residence time (half life) of either very large or very small LDL particles. The familial patient with too many very large LDLs will have high levels of LDL-C, the diabetic with too many small LDL particles may or may not have a high LDL-C.

Both defective LDL receptors or defective apoB are well know causes of familial hypercholesterolemia. There are many other potential defects beyond the scope of this newsletter. One emerging area of great interest is understanding proteases (peptidases) that catabolize LDL receptors. If one had to much of such an enzyme one would have very short lives of LDLr which clearly would be associated with high LDL-C and LDL-P. On the other hand if one had low levels of such a protease, LDLr half life would increase and such betas would have low levels of LDL-C and LDL-P (hypobetalipoproteinemia). Such a protease has been discovered and functions as stated. The gene that controls this enzyme is undergoing intensive research as inhibition of such enzyme would help clinicians further lower LDL-C and LDL-P by extending the life of ones LDLr. The gene is called PCSk9 or proprotein convertase subtilisin Kexin Type 9). Pay attention to this topic. The first drug identified to modulate this enzyme's activity is fenofibrate and this may an explanation as to why this fibrate is somewhat better on lowering LDL-C than other fibrates (Endocrinology 147: 4985–4995, 2006).

One other aspect to discuss in this patient. What about her high HDL-C level? Does it provide cardioprotection? Without knowing whether her HDL particles are functional with respect to antiatherogenesis I cannot answer the question. In general patients with high HDL-C have functional HDL particles and cardioprotection, but there are numerous contradictory examples especially in women. Her large HDL-P is elevated (other HDL particle concentrations were not forwarded to me so I do not know if she has a high HDL-P or not). Remember using NMR HDL particle data:

Total HDL-P = prebeta HDL-P plus large HDL-P plus medium HDL-P plus small HDL-P. NMR spectroscopy technology is not capable of measuring prebeta HDLs. The more mature alpha

HDLs (small, medium and large) are quantified. However prebeta HDLs are among the most cardioprotective HDL species.

So I do not know what her total HDL-P is , but she has lots of large ones and that explains the high HDL-C. Probably 80% or more of a total HDL-C concentration is trafficked within the larger mature alpha HDLs (H4 and H5 on NMR or HDL2s on gel fractionation). Thus one who lacks large, mature HDLs (mostly insulin resistant persons) will almost always have reduced HDL-C, and epidemiological trials have shown that a lack of large HDL-P is a serious risk factor. It is a topic for another day but almost all of these folks have high LDL-P (mostly small particles). Where are the HDLs being lipidated (acquiring cholesterol) in this lady? Where do HDLs always lipidate: mostly the liver and small intestine but also any cell that has extra cholesterol and is looking to get rid of it. So in a patient with FH, there are many tissues where HDL "fill up." Always keep in mind that in patients who over-absorb cholesterol in the proximal small intestine, their HDLs are usually lipidated and they have both high LDL-C and high HDL-C. If we knew hyperabsorption is present, then ezetimibe (Zetia) has to be one of the therapeutic weapons.

The CRP of 3.6 is also of some concern. It should be repeated but because of her risk of stoke (including estrogen levels) I would run a PLAC test (lipoprotein associated phosholipase A2) which is a more atheroma specific marker of inflammation and one of our best predictors of stroke..

Since she is on a contraceptive (and we all know it is associated with venous thrombosis even though it is a patch) so there should be no reluctance to prescribe systemic lipid modulating drugs. Our mission is to upregulate LDLr as much and as safely as possible: this is best accomplished by the use of drugs that deplete the liver of its cholesterol stores, thereby forcing upregulation of as many LDLr as necessary to control LDL-P or its lipid surrogates (LDL-C, Non HDL-C). So we are looking at statins, ezetimibe (Zetia), bile acid sequestrant (colesevelam or WelChol) and plant stanol (Benecol) or combination thereof. If hyperabsorption of cholesterol is a part of her problem we might be able to get away with low dose statin and ezetimibe. If not, we will need higher dose of more potent statins.

I think I'd give her Vytorin 20 mg daily (less costly and also helpful with compliance), Benecol and a baby ASA to start and see what happens. if that does not cut it then it will have to be Crestor 20 plus Zetia 10 mg and if that does not get to goal add the WelChol. Of course, if she ever wants to get pregnant stop them both and prescribe WelChol for the length of the pregnancy or just cease lipid therapy for 9 months. Before starting the lipid meds, do a pregnancy test and certainly educate and document that education informing her that she cannot get pregnant on a statin. Also before proceeding with a pregnancy she would be well to have her husband screened because if he also has heterozygous familial hypercholesterolemia, their child has the risk of being a homozygote.

I see no reason a gynecologist could not mange this patient unless she was refractory to the above approach.

LIPID CASE # 189

This issue's case deals with the fairly common problem of dealing with rising CK levels on lipid meds, especially statins. I was asked to comment on the following case. The patient is a 49-year-old gentleman who is mildly overweight and who smoked. He has no history of diabetes. He presented to the hospital with a myocardial infarction and found to have occlusion of his right coronary artery. He had a successful angioplasty and stent. He quit smoking and has been good with his diet and exercise. At that time his lipid panel was:

TC = 214, TG = 155, HDL-C = 39 and LDL-C = 167. He was then treated with Crestor 10 mg a day.

A few months later he had some vague muscle complaints but not typical for a statin myopathy. His insurance company had switched his lipid medication to generic simvastatin 40 mg daily. A lipid profile afterwards was:

TC = 189, TG = 136, HDL-C = 47, LDL-C = 115

A creatine kinase 915 (normal less than 204) A. prior TSH has been normal. The simvastatin was discontinued and he was started on Zetia 10 mg. There was no real change in his minimal symptoms. Otherwise he was feeling well and was restarted on Crestor 5 mg a day along with Zetia 10 mg.

He then had a lipid profile and an NMR performed on the next follow up. The lipid profile report from LabCorp showed TC = 125, TG = 69, HDL-C = 49 and LDL-C
= 62.

Creatine kinase was elevated at 579 and TSH remained normal at 1.73. NMR LipoProfile was as follows:

LDL particle number (LDL-P) = 1396, (goal for this patient < 1000)

Small LDL-P = 323 (normal),

LDL particle size 22.1 (quite large). They lipid concentrations reported by LipoScience were: TC =190, LDL-C = 120, HDL-C = 52 and TG = 88.

I was asked to comment on the following: (1) What is you comfort level with an elevated creatine kinase and a very high risk patient? At this point the patient is having no muscle aches or pains. Would you feel comfortable with the current dose of Crestor? Do you think it would be safe to try increasing the dose? (2) The other interesting question is his current lipid profile. There appears to be a significant discrepancy between the reported total cholesterol and LDL cholesterol as measured by LabCorp and that measured by NMR LipoProfile. Do you know if the NMR LipoProfile report measures total cholesterol and LDL different than a standard lab would? If one is to believe the report from LabCorp than his cholesterol numbers look exceptionally good with the TC 125 and an LDL of only 62. This would make it very hard to imagine how his LDL particle number can still be as high as 1396. Your guidance and insight would be extremely helpful.

DAYSPRING ANALYSIS

The NLA published a report of statins and myopathy last year (Am J Cardiol 2006;97[suppl]:69C–76C). The statement notes that in an asymptomatic patient one need not stop lipid medication unless there is a ten fold elevation of CK. Hypothyroidism has been ruled out. It does not appear there are other obvious causes of myopathy. I think one can feel very comfortable treating this patient despite the CK level. The NLA statement also acts as a "standard of care statement" which is important medicolegally. The position paper also notes that if the myopathic symptoms are tolerable and the CK elevation is not ten fold, it is also fine to continue the statin (keeping an eye on the CK with aborting therapy at a ten fold elevation). We must always consider benefit vs risk: this MI survivor, who just stopped smoking is a very high risk patient. So I would continue the statin and ezetimibe and follow the CK: abandoning the CK approaches a ten fold elevation. The patient should be warned to avoid extreme exercise or states of dehydration and he should drink plenty of fluids.

Recently there have been two articles looking at statins and myopathy: The first is an excellent review (J Am Coll Cardiol 2007;49:2231–7) and the other a miniscule trial where ubiquinone 100 mg daily (Coenzyme CoQ10) and Vitamin E (400 IU) therapy seemed to alleviate muscle symptoms ((Am J Cardiol 2007;99:1409 –1412).

With respect to the lipid profile discrepancies: LipoScience determines TC via the same chemical methodology as LabCorp. However HDL-C and TG are determined via NMR technology (well standardized and authenticated). The LDL-C is determined the same as most labs: It is calculated using the Friedewald formula where:

LDL-C = TC minus (VLDL-C plus HDL-C) VLDL-C is calculated by dividing TG by 5

I notice in this patient, it was the TC that varied between the two profiles: It was 125 at LabCorp and 190 at LipoScience. One is clearly in error. I have to believe that it is most likely LabCorp. The NMR particle numbers are rarely wrong as that technique is subject to little potential error. As one should expect if a patient has an LDL-P of 1396 nmol/L and the particles size is large, the LDL-C (the amount of cholesterol trafficked in all of the LDL particles that exist in a dL of plasma) has to be elevated which it is on the NMR report. You cannot have an LDL-C of 62 if you have > 1300 nmol/L of LDL particles the majority of which are large. Indeed with a size of 22.5 the LDL-C has to be abnormally high unless they are trafficking excess TG.

Keep in mind: LDL-C is a variable related to the number of LDL particles, the volume of the LDL particle and the TG/cholesterol composition of the particle . Remember the volume of a circular particle is 4/3(pi)(radius cubed). Thus subtle diameter changes can translate into very different levels of cholesterol that a given particle can traffic. How much bigger is a ping-pong ball than a marble: 3-4 times bigger?? Does a ping-pong ball have 4 times the volume of a marble. No, a ping-pong ball has > 15 times the volume of a marble!

Also do not forget that LDL particle lipid composition also determines LDL-C. You would expect that if one had too many large LDL particles, LDL-C would be high. However if the LDLs were carrying lots of TG, they might not be trafficking a lot of cholesterol. This is seen in patients with hepatic lipase deficiency. Such patients have large LDL particles which are TG-rich and cholesterol-poor (usually the serum TG levels are elevated). They can have an elevated LDL-P, large particles and LDL-C values that are not very high. Of course we all dealing everyday with insulin resistant patients who have very high LDL-P levels and normal LDL-C. It takes a lot of small LDL particles to traffic a given level (load) of cholesterol.

In general, always resist the temptation to look at lipid concentrations when you have lipoprotein concentration data. It is the particles that drive the disease (deliver sterols to the arterial wall). Lipid concentrations are just "guesses" (estimations, surrogates, proxies, etc.) of lipoprotein particle concentrations. It is only fairly recently that lipoprotein testing became readily available. Lipid profiles have been widely available for decades.

Obviously this is a high risk patient and you need to get the LDL-P lower than 1000 nmol/L if possible even with myopathic symptoms. There is no reason not to titrate the Crestor now that Zetia is on board. Each doubling of the statin dose will cause the typical 6% drop. Thus it is likely Crestor 40 mg would be needed. One would have to watch for symptoms and follow the CK as the titration is made. However it might be more prudent to continue the Crestor 10 / Zetia 10 and add the bile acid polymer colesevelam (WelChol) 6-7 tabs a day as well as a plant stanol (Benecol).

LIPID CASE # 190

Anyone following my newsletter certainly knows that almost everything we were taught about High Density Lipoproteins was pretty much wrong, other than the fact that most (but not all) persons with low HDL-C are at risk for atherosclerosis. Whether it is necessary to therapeutically raise HDL-C to reduce risk is still an open question and indeed there is no specific HDL-C goal of therapy in NCEP ATP-III due to the fact that there is no Level I evidence that therapeutic raising of HDL-C will result in predictable benefit. Drugs that may benefit or aggravate CHD are all over the map with what they do to HDL-C. Look at the following:

Torcetrapib (a CETP inhibitor) raises HDL-C > 50% and does nothing to plaque and increases mortality

Niacin raises HDL-C 15-20% and is cardioprotective

Estrogen raises HDL-C 10-15% and may be beneficial in women with healthy arteries and injurious in women with plaque

Dilantin raises HDL-C 20% and does nothing to cardioprotection

Fibrates raises HDL-C 10% and reduce events to the same extent as niacin

Statin monotherapy raise HDL-C 5-8% and are slightly more cardioprotective than fibrates or niacin

Bile acid sequestrants raise HDL-C 3-4% and are as cardioprotective as some of the above agents

Probucol (a CETP inducer) lowers HDL-C 20-30% and has nice angiographic data in preventing restenosis in a post-angioplasty trial.

It is obvious that drugs which raise HDL-C may or may not be cardioprotective and certainly the HDL-C rise does not correlate with the cardioprotection. As Dan Rader remarked in one of his many papers on HDL, treating at-risk persons with low HDL-C does not necessarily require that a drug raise HDL-C per se. This is an immensely complicated topic but it is becoming rapidly apparent that the cardioprotective abilities of HDL particles have little to do with how much cholesterol they traffic. HDL-C is simply the amount of cholesterol carried by all of the HDLs that exist in a dL of plasma. That value tells us nothing about where the HDLs lipidated (received the sterols) or to where it will delipidate (loose the sterols). Indeed probably the most cardioprotective thing an HDL does is to delipidate sterol-laden foam cells (macrophages) in plaque. Yet the process of macrophage reverse cholesterol transport as it has be named by Dan Rader does not contribute to the total HDL-C values. We know that fibrates and niacin likely induce macrophage RCT, yet none of the HDL-C rise induced by those drugs can be explained by macrophage RCT. Thus two drugs that equally reduce CHD events and that induce macrophage RCT affect HDL-C levels differently. Seems to me it is therefore may be of little value to follow therapeutic changes in HDL-C. We have to learn to trust the outcome and apoB (or apoB lipid surrogate like non HDL-C) lowering ability (the only proven way to reduce CHD events) and angiographic data of drugs rather than what they do to HDL-C. HDLs can also deliver several cardioprotective proteins (anti-oxidative, anticoagulant, profibrinolytic, etc.) to plaque and again that ability of an HDL has little to do with its cholesterol content or size. Macrophage RCT and HDL proteinomics are now referred to has "HDL functionality." Patients whose HDLs are not functional (most often seen in those diseases in which chronic inflammation is prevalent) are now said to have "proinflammatory" or "proatherogenic HDLs." In choosing event reducing therapies we need to lower apoB and we need to increase HDL functionality. Which drugs do that best or do not do it at all remain to be determined, but the two that almost certainly do are fibrates and niacin. Both of those drugs have been around for decades and it is only very recently that we are beginning to understand their very complex MOAs.

I go into this as a prelude to the case to be discussed below. I want to bring you all up to date on the current understanding of niacin's MOA. I was asked about the following case: A 30 year old Caucasian male who does not smoke and eats normally. He lifts weights but does no aerobics. His grandfather had two strokes before dying at 77. His father takes Zocor but has no CHD. Mother's lipids are OK. The patient's lipids are:

TC = 185 TG = 108 HDL-C = 36 (was 40 a few years ago), VLDL-C = 22 LDL-C = 127
TC/HDL-C ratio = 5.1 Non HDL-C = 149 hs-CRP = 8.5 (abnormal > 3.0)

The clinician suggested starting Crestor to drop the LDL-C to < 100 mg/dL but wanted my opinion on the risk of not using a statin.

DAYSPRING ANALYSIS

NCEP states that a low HDL-C is associated with a high risk of heart disease and indeed is the most predictive lipid in the lipid profile in ascertaining risk. Thus I believe the doc's approach is correct. Many folks with low HDL-C also have high TG and are clearly insulin resistant: these are termed TG/HDL axis disorders.They typically have TG/HDL-C ratios greater than 3.0. Advanced lipoprotein testing usually reveals increased numbers of LDL particles (predominantly small), VLDL remnants a reduction in HDL-P. Since virtually all of these people have high apoB (too many LDLs, VLDLs and IDLs) NCEP states that in patients with low HDL-C the goal of therapy is to first reduce LDL-C to goal and then normalize Non HDL-C especially if the TG are elevated. Since the publication of NCEP we now know that non HDL-C out predicts LDL-C regardless of the TG level: thus TG no longer factor into the decision as to whether LDL-C or Non HDL-C is the target: Non HDL-C is the better target (apoB or LDL-P would be even better).

Many providers are making the following mistake: when you see low HDL-C they think you have to raise it. You do not. As noted this is likely an insulin resistant patient with high risk (note the CRP). He is what we would call "metabolically (not phenotypically) obese." Because of the inflammation, he almost certainly has dysfunctional, proatherogenic HDL particles. As discussed above, altering how much cholesterol is inside his HDL particles does not ensure you are improving his HDL functionality.
It would also be helpful to know, what is his glucose and 2 hr post prandial glucose and what is his urine microalbumin?

If you look closely at the lipid profile, the LDL-C at 127 and non HDL-C at 149 are both elevated. These are lipid surrogates of apoB (atherogenic particles). The best strategy to attack apoB is to upregulate LDL receptors and using statins or statin plus ezetimibe are the best ways to do that. If that therapy does not get the patient to goal then one would considering (as instructed in NCEP) adding a fibrate or niacin to normalize the Non HDL-C. Which one would be better? There are no empowered outcome data which clearly answers the question. As far as monotherapy trials, fibrates have vastly more data than niacin. Fibrates are more tolerable, but the new coated Niaspan tablets are significantly better tolerated that the older Niacin tabs. Fibrates improve insulin resistance in diabetics reduce macro and microvascular disease and niacin does not. If one looks carefully at the fibrate outcome data, they work best when insulin resistance is present and when both TG are high (>150-200) and HDL-C is low. In the patient at hand, TG are not a problem. The lipid abnormality is high apoB (LDL-C and Non HDL-C) and low HDL-P (low HDL-C, high TC/HDL-C ratio). Thus in this case I think niacin (Niaspan) would be the a good addition to the statin.

If I add Niaspan I expect the HDL-C to rise, and if I added fenofibrate I would not expect a tremendous HDL-C increase. As my newsletter title suggests: who cares? Both drugs would help the statin further lower apoB. Both would help reduce the CRP (if that is important to do). I have discussed fibrate MOA in previous newsletters so lets look at how niacin works.

1) By attaching to the niacin receptor (called HM74A) in adipocytes, hormone sensitive lipase is inhibited. This reduces lipolysis (hydrolysis of TG). Less fatty acids (FA) are secreted into plasma and the liver is denied a substrate of TGV production. By the way, no one knows what is the natural ligand for HM74A. Lancet 2004; 363: 1892–94

2) In hepatocytes niacin inhibits both FA synthesis and incorporation of FA to glycerol both of which will reduce TG production. Arterioscler Thromb Vasc Biol. 1999;19:1051-1059

3) Inhibits diacyl-glycerol acyl transferase 2 which esterifies monoglycerol and diglycerol into triacylglycerols (TG). J. Lipid Res. 45 (2004) 1835–1845, Arterioscler Thromb Vasc Biol. 1999;19:1051-1059

4) The reduction in TG synthesis causes a posttranslational degradation of apoB and thus less VLDL particles are produced. Ultimately this leads to less IDL and LDL. Arterioscler Thromb Vasc Biol. 1999;19:1051-1059

5) The VLDLs are less likely to be TG-rich: this reduces CETP activity and there will be less swapping of TG for cholesteryl ester between VLDL and LDL and HDLs. This will increase LDL and HDL size. Larger LDLs are more amenable to endocytosis by LDL-receptors (indirect reverse cholesterol transport).

6) Niacin's main ,metabolite is prostaglandin D2. In turn its metabolite is prostaglandin J2 which is a potent PPAR-gamma agonist. Thus Niacin will have PPAR gamma activity. This likely is associated with some cardioprotection as follows:

In the liver PPAR gamma cross communicates with the Liver X receptor (LXR). LXRs main function is to prevent intracellular sterol toxicity. LXRs accomplish this through many functions including the upregulation of several sterol efflux transporters. ATP Biding Cassette Transporter A1 (ABCA1) effluxes cholesterol from within cells to apoA-I (the HDL precursor protein). Thus on niacin the liver rapidly fills the nascent HDL (prebeta) and it develops into a large, more mature HDL particle (this will raise HDL-C, but obviously would not be cardioprotective). Fortunately ABCA1 can also be expressed in arterial wall foam cells. Thus niacin through its metabolite having PPAR gamma activity would enhance macrophage RCT. However as mentioned above even though macrophage RCT is cardioprotective, it does not affect the total HDL-C level. The PPAR gamma activity of niacin also causes an increase in expression of a scavenger receptor located in arterial wall macrophages called CD 36. This receptor internalizes oxidized LDL particles. The cholesterol within the LDLs can then be excreted into HDLs via the upregulated ABCA1. Thus niacin in effect makes the macrophages clear or internalize atherogenic LDLs, but immediately gets the cholesterol transferred to an HDL. Biochemical Pharmacology 67 (2004) 411–419

7) Niacin inhibits hepatic lipase (HL). This is a major enzyme in the HDL remodeling process. By removing (hydrolyzing) TG and surface phospholipids HL remodels large HDLs into small. Because niacin inhibits HDL lipolysis patients on niacin will typically have lots of large HDL particles (which carry more cholesterol). This is certainly another way Niacin raises HDL-C. Circulation. 1999;99:1959-1964.)

8) The liver has three receptors which play a role in the direct RCT pathway (HDLs returning cholesterol to the liver). The hepatic scavenger receptor which attaches to and delipidates large HDL and then returns the empty smaller HDL to plasma is not affected by niacin. LDL receptors (LDLr) can internalize HDLs that are rich in apoE. Niacin does not affect LDLr. There is also a holoparticle or catabolism receptor which attaches to and internalizes large HDL particles. This receptor is down-regulated by niacin enabling large HDLs to have a longer half life (clearly that would raise HDL-C and apoA-I). Seems like it is likely beneficial for HDLs to have increased half lifes as they would have more time if functional to be cardioprotective. NATURE |VOL 421 p 75 | 2 JANUARY 2003

9) Because niacin (and fibrates) is so good at reducing TG (as explained above) there will be less CETP activity. That would keep cholesterol within HDLs, again leading to larger HDLs and again raising HDL-C. Of course if the "natural" RCT is HDLs giving cholesterol to LDLs to return to the liver, the fact that niacin decreases CETP activity may not be cardioprotective even though it helps raise HDL-C. Pfizer found that out the hard way with their blockbuster CETP-inhibitor,

torcetrapib. Of course niacin (and fibrates) to not reduce CETP activity anywhere near the level that torcetrapib did.

So if we had to sum up: here is niacin's lipid MOA and how it may or may not relate to cardioprotection.

1) Lower apoB, LDL-C and Non HDL-C through its TG lowering abilities (GOOD)
2) Improves HDL functionality by increasing macrophage RCT (Good) (does nothing to HDL-C)
3) Lipidates HDLs by upregulating hepatic ABCA1 and then keeps them mature by inhibiting HL: this raises HDL-C considerably but is not necessarily cardioprotective.
4) Prevents hepatic delipidation of HDLs which increases the half life of circulating large HDL: this of course helps raise HDL-C and is likely cardioprotective if and only if those HDLs are functional (we have no way of assaying that).

Since we cannot measure HDL functionality, I believe the most important test to follow that should ensure cardioprotection is apoB or LDL-P. Since the rise in HDL-C is expected (I'd be alarmed if there was no HDL-C increase) but has no correlation with HDL functionality, I am not sure that following HDL-C on niacin tells you anything and thus following Non HDL-C or the TC/HDL-C ratio would not be as good as apoB or LDL-P.

Although we still await serious, well empowered outcome data with niacin, we certainly have good data from very small trials that niacin added to a statin improves angiographic findings, lessens carotid intimal thickening and reduces clinical events and is well tolerated. We await confirmation of this in the much larger AIM HIGH trial not slated to finish for a few more years. I'll leave the discussion of niacin and glucose and insulin resistance for another newsletter, but I think that will ultimately be crucial now that we know fenofibrate improves insulin sensitivity and beneficially impacts microvascular disease. Again, AIM HIGH should begin to help answer that question.

My conclusion on raising HDL-C therapeutically. Does it matter? The answer is perhaps a qualified yes: If you use Niacin, the drug works and almost always there will be a significant rise in HDL-C. However if you use a statin or fenofibrate the HDL-C rise although expected will be much less and both drugs clearly improve outcomes in persons with reduced HDL-C at baseline. Bile acid sequestrants work and you should expect a rise it HDL-C but it will be small. I'd stay away from Dilantin for CV purposes even though it will give you a nice rise in HDL-C. I believe the real answer to my question is we need to improve HDL functionality. Raising HDL-C is no absolute guarantee that is occurring.

LIPID CASE #191

I was contacted for comments on a I have a 58 yo Caucasian male, hypertensive (on Altace), non-smoker whose father had angina and then died suddenly at age 63. A 55 year old brother is well. He is 68" with a weight of 153. His management is complicated by the fact he cannot swallow pills so his medication is compounded by a pharmacist specializing in compounding. His compounded Altace controls the BP well.

Original lipid profile:
TC = 245 HDL-C = 46 TG = 98 Direct LDL-C = 180
Repeat direct LDL-C = 186
Non HDL-C = TC minus HDL-C = 245 - 45 = 199 (desirable < 130)
TC/HDL-C >5
TG/HDL-C = 2.1

The patient was started on Lipitor and titrated to 80 mg daily, and then Zetia 10 mg was added. Surprisingly his LDL-C dropped only to 168 mg/dL on the dual therapy.

His provider was concerned that the compounding was somehow effecting the potency of the meds, and then convinced the patient to actually swallow the meds for 6 weeks.

The follow up profile was:

TC = 239 Direct LDL-C = 165 (no change) TG = 68 HDL-C = 51

An NMR LipoProfile was done at LipoScience (www.Lipoprofile.com)

LDL particle concentration (LDL-P) = 2104 ((top 10th percentile of humans)
Perfect is < 1000 nmol/L
Small LDL-P 1523
LDL particle size 20.6 (Pattern A)
Large HDL-P = 9.9 (normal)
Large VLDL-P = 0.2 (normal)

The clinician asks me, other than his not actually taking his medication or the possibility of counterfeit medication (obtained from a local pharmacy, not the Internet), what other plausible explanation could there be for the lack of effectiveness in this patient?

Here is the additional info requested on my difficult case.

DAYSPRING DISCUSSION

Let's discuss the lipid profile all by itself before we judge the efficacy of the treatment. When presented with a patient who has high TC, high LDL-C, high non HDL-C but no abnormalities of the TG/HDL axis really tells us that there are too many atherogenic lipoproteins present. Of course atherogenic lipoproteins are those containing a single molecule of apolipoprotein B (chylomicrons, VLDLs, IDLs, and of course LDLs). In most patients 90-95% of apoB particles are actually LDL particles because of their 3 day half-life. Thus it is no shock that the LDL-P on NMR (nuclear magnetic resonance spectroscopy) testing was so high. However I am not so sure many of us would have predicted his LDL-P would be in the top 10th percentile.

The normal TG/HDL-C ratio predicts his LDL particle size is Pattern A, but with a diameter of 20,6, it is just minimally above the cutoff point of 20.5 separating large from small LDLs. Indeed he has elevations of his small LDL-P even though the peak particle size is 20.6.

With respectable (likely normal TG levels how do we explain his abnormal numbers of small LDL-P? Depending on multiple factors such as hepatic lipase, endothelial lipase, LCAT (cholesterol esterifying enzyme), CETP, phospholipid transfer protein, other lipases, LDLs can be small. In patients with such abnormalities even a TG of 98 might be enough to generate small LDL. All we know is he has too many LDL particles both large and especially small.

Treatment of too many LDL particles (if normal sized) is usually straight forward. One can reduce their synthesis by lifestyle which can reduce cholesterol synthesis substrate in the liver (saturated and trans fats). Of course we can inhibit cholesterol synthesis in the liver with an HMG CoA reductase inhibitor (statin). If that is one's inclination (statin monotherapy) I am not sure, other than formulary why anyone would use anything but the best HMG CoA reductase inhibitor (rosuvastatin or Crestor). We can also reduce cholesterol delivery to the liver by blocking the absorption of sterols in the small intestine using ezetimibe or we can block the reabsorption of bile acids using a sequestrant like colesevelam (WelChol), forcing the liver to use up its endogenous cholesterol to make new bile acids. All of there above would by depleting hepatic cholesterol pools activate the sterol regulatory element binding proteins which are nuclear transcription factors that upregulate the synthesis of LDL receptors (this explains why statin/ezetimibe or statin/sequestrant is a better apoB reducing therapy than statin monotherapy).

The more that cholesterol is depleted, the more LDL receptors will be upregulated and of course they recognize and attach to apoB on normal size LDLs facilitating their internalization or removal from plasma (indirect reverse cholesterol transport). This should reduce apoB, LDL-P, LDL-C, and non HDL-C. So why did that not happen?

Lab error unlikely as the profile has been done at least twice. Here are other possible pathophysiologic explanations:

1) Defective LDL receptors (which are dysfunctional and cannot attach to apoB on the beta-lipoproteins) or defective apoB, which is also dysfunctional and does not bind effectively to LDL receptors (LDLr). Statins and ezetimibe upregulate LDL receptors facilitating removal of apoB containing lipoproteins from plasma. Thus defective LDLr or apoB would explain the dilemma. Usually patients have much higher LDL-C values, but perhaps this patient only has mild dysfunction.

2) There is also another rapidly area of lipidology interest. There is a cellular peptidase that degrades LDL receptors, lessening their half life. It is called proprotein convertase subtilisin kexin type 9 (PCSK9). Persons who have too much of this enzyme rapidly catabolize their LDL receptors and thus they tend to have high TC and LDL-C levels as they do not effectively clear LDL particles from plasma. Might this patient have some PCSK9 polymorphism. Severe defects are associated with severe familial hypercholesterolemia. On the othe hand people who have reduced PCSK9 activity have extended LDLr activity and have very, low LDL-C and apoB levels.

3) This man does have significant numbers of very small LDL particles. Small particles are not well recognized by LDLr and even though statins and ezetimibe upregulates lots of LDLr, those receptors may not be able to remove the smaller particles, thus explaining the non drop in LDL-C. As in this case, because he has lots of small LDLs and his LDL-C is 168, his LDL-P (LDL particle number) or apoB is extremely high. If such cases adding a fibrate (TriCor) or Niaspan might shift LDL size making the LDLs more amenable to LDL receptor removal from plasma. Then the LDL-C would drop. Because the TG are so very good, I think I would recommend Niaspan instead of the fibrate ion this case to see if replacing small LDLs with larger species would facilitate their removal (keeping the patient on statin/ezetimibe to maximally upregulate the LDLr). Likewise N-3 fatty acids are unlikely to be of value with LDL size in view of the normotriglyceridemia.

4) If you give statins to people whose main problem is over-absorption of cholesterol rather than over[production, typically there is a "hypo" or diminished effect on lowering LDL-C. Usually however the stain will lower LDL-C about 15% in such folks. However, they usually have a dramatic response to ezetimibe and the patient did not (if he is taking the Zetia), making this scenario unlikely.

I do not see how compounding the tabs would diminish there efficacy unless they are being added to a vehicle that binds them and prevents absorption.

Thus before I'd believe problems 1 or 2 exist I'd add Niaspan to the statin/ezetimibe regimen anticipating problem 3 is present. Personally I'd switch the Lipitor to Crestor 40 mg since rosuvastatin is a more efficacious apoB drug than atorvastatin. Had there been a response at a lower Lipitor dose, Vytorin would be the drug of choice instead of Lipitor/Zetia (2 co pays) but not if Lipitor 80/Zetia is not working.

LIPID CASE # 192

I have been asked about a female patient who is 56 years with HTN, and T2DM. She is also taking Amaryl 4 mg bid and Metformin 2000 mg daily. Her last hemoglobin the A1C was 9.5 and she is reluctant to start insulin, so as a last ditch effort, I added Januvia last month and blood sugar dropped 25 points less than before.

Her last lipid numbers are:

TC =259, TG = 700, HDL-C = 38, LDL-C = 81
Calculated VLDL-C = 140 (N<30)
Non HDL-C = 221 (goal < 130) TC/HDL-C > 6 TG/HDL-C extremely elevated

For her lipid management, she is taking lovastatin 80 mg, TriCor 145 mg daily, Zetia 10 mg daily and fish oil. Her provider attempted to change her to Vytorin last visit and her insurance wouldn't cover it.

DAYSPRING DISCUSSION:

LDL-C cannot be calculated when TG are elevated as in this case, so I presume the LDL-C reported above (81 mg/dL) is a direct measurement. The patient certainly qualifies as a TG/HDL axis abnormality, a term coined by Philippe O. Szapary and Dan Rader in 2004 (Am Heart J 2004;148:211–21.) used to describe patients whose lipid abnormality is elevated TG, low HDL-C and normal LDL-C. It is most often seen in insulin resistant (IR) patients with T2DM and/or metabolic syndrome. Obviously these patients usually have significant CV risk, despite their at goal LDL-C. What explains the CV risk?

Of course Framingham risk scoring is not indicated as the T2DM puts her in the CHD equivalent high risk category. She deserves aggressive treatment to lower her risk. How should she be approached? If she had been drug naive with this lipid profile her TG deserve primary attention. Attacking such a high fasting TG requires ruling out hypothyroidism and other secondary causes, and then radically altering her lifestyle, (to include alcohol avoidance) and getting more aggressive with glycemic control. Insulin is almost certainly required to lower the A1C and also to help the TG by increasing lipolysis of TG-rich lipoproteins. We have not been provided with her weight but Byetta also might be considered. Despite her reluctance to use injectables, such a patient must be seriously informed (with chart documentation) that her future morbidity and mortality depends on glucose and TG control.

Before we decide on lipid therapy it is always wise to figure out what atherogenic lipoproteins are present and they we can more intelligently direct therapy. Anyone with TG > 500 mg/dL has a problem with TG-rich lipoproteins which are either chylomicrons (intestinally produced apoB48 particles), VLDLs (hepatic produced apoB100 particles) or IDLs (apoB100 particles either produced and secreted by the liver or the result of VLDL lipolysis). Lipolysis is a term that implies lysis of lipids. This is accomplished by various lipase enzymes that hydrolyze triacylglycerol (TG) or phospholipids). The main triglyceridase is Lipoprotein Lipase (LPL) expressed mostly in the endothelium of muscle and adipocyte vasculature. Hepatic lipase (HL) is both a triglyceridase and phospholipase (hydrolyzes phospholipids) and endothelial lipase (EL) is primarily a phospholipase. EL primarily acts on the phospholipids of HDLs thus aiding remodeling by reducing HDL size. Obviously exposure of a lipoprotein to lipases results in the loss of lipids (the particles are delipidated) and their particle size becomes smaller.

How can you know if chylomicrons are present to any appreciable degree? Let the serum stand overnight and a dense white band will appear on top of the tube. If it is just VLDLs that are present the serum will be turbid or milky without the dense white band on top. If a patient has very severe triglyceridemia due to too many chylomicrons, eruptive xanthomas may be on the skin (especially trunk) and lipemia retinalis might be present. Pancreatitis is a major concern.

A word about apolipoprotein B which is a nontransferable apolipoprotein found on each chylo and VLDL (as well as IDL and LDL and Lp(a) particle). ApoB provides the particle with structure, stability and solubility in plasma and can serve as a ligand for the LDL receptor (LDLr) of LDL receptor related protein (LRP): receptors used by the liver to internalize apoB or apoE containing lipoproteins. ApoB48, produced by enterocytes, is a truncated version of apoB100 which is

produced by the liver. Simply put apoB48 has 48% of the molecular weight of apoB100. ApoB48 is obviously found on intestinal produced chylomicrons and apoB100 on hepatic produced VLDL. ApoB48 is not recognized by LDL receptors: therefore the only way chylomicrons can be internalized by the liver is through chylo apoE attachment to the LDLr. All apoB particles (48 or 100) have atherogenic potential in that they can enter the arterial intima, and be exposed to oxidative forces and then be ingested by CD36 or scavenger receptors on macrophages leading to the formation of foam cells. Large VLDLs and most secreted chylomicrons are too large to enter the vascular endothelium, but after lipolysis they reduce in size and can easily enter the artery wall.

After secretion chylomicrons and VLDLs (already containing some apoproteins attached like apoA-IV, apoA-I) rapidly acquire several other apolipoproteins, mostly transferred from HDL: apoA-V, apoC-I, C-II, C-III, apoE, apoD (better know as cholesteryl ester transfer protein or CETP), and others. All of these serve crucial functions in regulating (speeding up or reducing) lipolysis of VLDL and chylomicrons. ApoA-V parks the particles in muscle and adipocyte endothelial cells in the vicinity of expressed LPL. ApoE binds to VLDL receptors also primarily expressed in those tissues. ApoC-II binds to the LPL and TG-hydrolysis is initiated. As the TG is removed, the VLDL starts to collapse and chunks of phospholipids (PL) break off, as do surface apolipoproteins like apoA-I. The released PL attach to phospholipid transfer protein and are trafficked elsewhere (to cells or to remodeling, enlarging HDLs). The VLDL and chylomicron reduces in size (contain less TG) and are now called remnant lipoproteins. They have two fates: they can continue the lipolytic process and become much smaller and transform into IDLs or they can be removed (internalized) by the liver LDLr and LDL receptor related proteins (these lipoproteins contain apoB and lots of apoE which binds to the LDLr). IDLs can likewise be removed by the liver or undergo further lipolysis and become LDL particles. Thus under normal conditions, an LDL has lost all apolipoproteins but apoB and most of the TG. LDL composition is about 80% cholesteryl ester and 10-20% TG. Ultimately the LDL is internalized by hepatic LDLr. The process of the ;liver clearing apoB particles like VLDLs and chylos and IDLs is now termed indirect reverse cholesterol transport. Please remember that the vast majority of VLDLs and IDLs are removed by the liver before they ever form into LDLs. However the LDLs that are formed have a half life of three days so they accumulate and ultimately vastly outnumber VLDLs, chylos and IDLs in plasma. Thus the vast majority of apoB particles in plasma (>90-95%) are LDLs (LDL-P).

In IR states there is often variable degrees of LPL deficiency or dysfunction leading to impaired lipolysis of TG-rich LP. Also if an excess of apoC-III is present there will be delayed lipolysis. ApoC-III interferes with the binding of apoC-II with LPL or actually displaces apoC-II and apoE from VLDLs and chylomicrons. ApoC-III can also block the attachment of TG-rich LP and even LDLs to LDLr or LRP. Anything that delays lipolysis of or prevents hepatic internalization of apoB particles will elevate apoB (big risk factor). If TG-rich LP have delayed lipolysis or decreased clearance patients will obviously have both fasting and postprandial hypertriglyceridemia. Recent data are showing the postprandial TG elevations convey even more risk that does fasting TG.

Do TG-rich LP with delayed clearance contribute to CV risk in other ways? You betcha! The longer they exists the more time they have to transfer their extra TG to LDLs and HDLs (particles that should not have much TG). The swapping of 1 molecule of TG for 1 molecule of cholesteryl ester (CE) is mediated by CETP. This results in VLDLs acquiring CE (becoming cholesterol enriched) and the HDLs and LDLs loosing CE but acquiring TG (becoming TG enriched). VLDL-C (a major independent CV risk factor) rises but HDL-C and LDL-C drop (thus creating the TG/HDL axis). The now CE-poor, TG-rich LDL and HDL loose their TG as they pass through the liver (via lipolysis by HL), creating small LDL and HDL. The latter can become so small (7 nm) that it filters through the glomerulus and is excreted by the kidneys explaining why diabetic with elevated TG lave so few HDL particles. Of course if VLDL-C goes up and HDL-C goes down, the Non HDL-C will rise. For those who calculate and look at Non HDL-C you would realize that apoB is high even if LDL-C is at goal. Also when you see high VLDL-C you will realize you need not a statin but rather a drug that inhibits TG synthesis and enhances lipolysis of TG-rich LP. That of course

includes fibrates niacin and N-3 fatty acids (as well as lifestyle and glucose control). ApoC-I also helps regulate lipolysis of TG-rich LP. As C-I jumps from HDL (where it was inhibiting CETP activity) to VLDL it prevents apoE from attaching to the VLDL receptor and which would further delay clearance. Once it is off the HDL, CETP (on the HDL) activity increases, enhancing remnant creation and small LDL formation.

There are even more consequences to increased residence time (half life) of TG-rich LP. They (I like to refer to them as fat balls) injure the endothelium, decrease nitric oxide production, increase markers of coagulation (fibrinogen and PAI-1) as well as increasing multiple inflammatory cytokines. ApoC-III (prominent on these particles) through induction of nuclear factor kappa B can also induce many abnormal cytokines aggravating inflammation.

So what have you learned? Patients with high TG, low HDL-C and norm al LDL-C are likely extremely high CV risk patients because they have increased chylomicron and VLDL remnants (due to increased production and decreased clearance), way too many small LDLs (high LDL-P and apoB) and decreased numbers of HDLs as well as hypercoaguability of plasma and significantly increased inflammatory markers. Tragically there are clinicians who when they see the normal LDL-C, they think there is no lipid-related risk. TG are often routinely ignored in this country.

Treatment: You must decide how to reduce TG-rich LP, reduce the greatly increased numbers of small LDL and improve the adverse rheological forces.

1) Control glucose: insulin an excellent choice. 2) Stop TG synthesis and therefore reduce creation of TG-rich LP: Best choices are Fibrates, N-3 FA (start at 4 grams and escalate the dose) and niacin (2 grams Niaspan). 3) Orlistat can be very helpful. 4) Express LDLr with high dose statin (clearly a job for rosuvastatin 40 mg, although atorvastatin has good data with TG). Lovastatin should be abandoned in a polypharmacy situation where fibrates are going to be used. 5) Add Zetia to further express LDLr. There is a nice study showing Zetia can increase the remnant removal seen with statins.

This patient's clinician has him on lovastatin 80, TriCor, and N3-FA (dose not provided) and the lipids are still horrific. Much of that is driven by the very abnormal A1C which is why insulin is going to be crucial. I can only suggest maximizing the N-3 FA dose, the switch to Crestor 40 mg, addition of Zetia and orlistat and Niaspan (titrated to 2 grams). Alcohol must be avoided like the plague (alcohol reduces beta-oxidation of fatty acids).

Once the TG are reduced to < 500 mg/dL, non HDL-C of < 130 (apoB surrogate) becomes the goal of therapy.

LIPID CASE # 193

I received a fax from a NJ physician who wanted my opinion on his recently performed lipid profile. I have no info other that he is around 40 years old and looks very physically fit. I do not have a BP and do not think he smokes. Here are the labs sent to me:

TC = 179 mg/dL HDL-C = 29 mg/dL LDL-C = 97 mg/dL TG = 262 mg/dL
Chol/HDL-C Ratio = 6.2 Non HDL-C = 150 mg/dL TG/HDL-C ratio > 8
Glucose = 100 mg/dL

Even with a normal BMI and BP, he is a full blown metabolic syndrome (IFG+, TG+. HDL-C low). Using NCEP scoring he is low risk, however the MS elevates his risk. Lifestyle would be advised and the lipids should then be followed. However, his lifestyle with respect to weight is good. Maybe he can be advised switch to the South Beach or Mediterranean type of diet supplemented with daily exercise. However does he require lipid-modulating therapy? I am going to try and stop

using the term lipid-lowering therapy, as there are lipids that may or not have to be lowered or raised for CV protection, so I consider lipid-lowering a meaningless term.

Long time readers of my newsletter and all lipidologists certainly know the patients risk is related to the concentration of atherogenic lipoproteins, anti-atherogenic lipoproteins, endothelial integrity and function, inflammatory and rheological forces that may be present or absent. What would your guess be as to how lipids are trafficked in this man? Keep in mind that atherosclerosis is a disease of abnormal sterol trafficking. We do not want sterols delivered (trafficked) to the intimal layer of any artery. Hydrophobic lipids are trafficked inside of protein-wrapped vehicles called lipoproteins. The enwrapping proteins are termed apoproteins or apolipoproteins. Anyone want to guess, using the above metabolic parameters, as to what type of lipid-transportation vehicles (lipoproteins) are present in this patient?

Anyone with a high TG, low HDL-C and normal LDL-C has is called a TG/HDL axis disorder (a term coined by Szapary and Rader: Am Heart J 2004;148:211–21). They state: "This lipid abnormality is a fundamental characteristic of patients with the metabolic syndrome, a condition strongly associated with the development of both type 2 diabetes and CHD. Patients with high TG and low HDL-C should be aggressively treated with therapeutic lifestyle changes. For high-risk patients, lipid-modifying therapy that specifically addresses the TG-HDL axis should also be considered. Current pharmacologic treatment options for such patients include statins, fibrates, niacin, fish oils, and combinations thereof."

So a little pathophysiology will make it easy to predict the lipoprotein abnormalities likely present in this man. Anyone with a TG level > 250 clearly has a problem with overproduction or decreased catabolism of TG-rich lipoproteins (VLDLs and chylomicrons & IDLs). Note these are all apo-B containing particles. Thus most people with TG > 130-150 have high apoB levels (lipid coronary risk factor #1). The elevated glucose is a clue that he is insulin resistant and that the glucose will ultimately become citrate which is a substrate for TG synthesis. If I see this man as a patient I will want to know what his 2 hr PP glucose is as impaired glucose tolerance (IGT) or T2DM would further elevate his risk beyond what IFG predicts.

What is the fate of the large TG-rich LP? As soon as TG-rich LP enter plasma they acquire many other apoproteins transferred from HDL particles: apoC-III, apoA-V, Apo CI, apoE to name a few. The particles often have decreased catabolism due to inability to attached to endothelial surfaces where lipoprotein lipase (LPL) is expressed. If there was a deficiency of apoC-II (the ligand for LPL), the TG would be in the thousands (obviously not so in this patient). Decreased catabolism can be due to too much apoC-III (blocks or displaces apoC-II) or too little apoA-V (which helps dock them particle near LPL). Lipidologists: For a just published review of the how apoA-V binds to endothelial surfaces see the current issue of Current Opinions in Lipidology. The receptor is GPIHBP1 short for glycosylphposphatidylinositil-anchored HDL Binding Protein 1 (perhaps a new target of therapy). (WHO THINKS UP THESE NAMES?)

If TG-rich particles have increased half life there will be more time form CETP to transfer from HDL to VLDL and facilitate the swapping of TG for cholesteryl ester (CE) between apoB particles and HDLs. This enriches the apoB particles with CE and depletes the HDLs of CE (helping to explain the TG/HDL axis lipid abnormalities). TG-rich, CE-poor LDLs and HDLs loose the TG as the are exposed to hepatic lipase in the liver and become smaller LDLs and HDLs. That will increase LDL-P as small LDLs are not efficiently cleared by hepatic LDL receptors (LDLr) and diminish HDL-P as small HDLs are subject to renal excretion. This explains why folks with TG/HDL axis abnormalities have high apoB/A-I ratios (or TC/HDL-C rations or elevated Non HDL-C). Of course the VLDLs will now be carrying the extra CE that came over from HDLs: VLDL-C is as important a predictor of risk as is LDL-C. Please note that anyone with increases in VLDL-C, LDL-C or reductions in HDL-C will obviously have elevated Non HDL-C. Even if the LDL-C is normal, the Non HDL-C will still be high because of the elevated VLDL-C and low HDL-C. If one focused only on LDL-C, the risk would be missed!

ApoC-I blocks or prevents HDLs from shedding CETP. Unfortunately in situations of high TG, the HDLs are remodeled by hepatic lipase, and the apoC-I is lost from the HDL and transfers to the VLDL, where it now delays the clearance of the CE-enriched VLDLs (remnants). Remnants are very atherogenic particles for a variety of reasons including their ability to worsen the vascular inflammatory process (Fat Fuels the Flame: Triglyceride-Rich Lipoproteins and Arterial Inflammation by Peter Libby Circ Res. 2007;100:299-301).

So to answer the question I posed: What type of particles are present in this patient? If we did NMR-spectroscopy (LipoProfile from LipoScience) we would see: too many LDL particles (primarily small), took many large VLDL-P (a great predictor of risk), too many smaller VLDLs (remnants), perhaps too many IDLs, and significantly decreased Total HDL-P with an absence of large HDLs. In other works there would be way too many apoB particles (the bad guys) and too few HDLs.

So how would we treat beyond lifestyle?

1) Reduce apoB particle production in the liver: Primarily done by reducing hepatic TG synthesis. Best accomplished by fibrates or niacin or N-3 fatty acids.

2) Reduced FA delivery to the liver: (Orlistat or niacin)

3) Reducing hepatic cholesterol stores can slightly diminish apoB particle production (statins, ezetimibe, sequestrants)

4) Enhance lipolysis (hydrolysis of TG) of TG-rich LP: (fibrates, N-3 FA)

5) Restore CETP activity (exchange of TG for CE) to normal (DO NOT WANT AGGRESSIVE INHIBITION): fibrates, niacin and statins to variable degrees (rosuvastatin the most potent). This will result in large HDL and LDL particles (which are easier for LDLr to internalize). Statins will increase HDL size more than LDL size. Fibrates and niacin work on HDLs and LDLs.

6) Induce HDL functionality: By this I mean induce macrophage reverse cholesterol transport or the process of delipidating arterial wall foam cells (fibrates, niacin, sequestrants). This will have no effect on HDL-C but will reduce or stabilize plaque.

7) Reduce systemic inflammation: Diet, exercise, statins, fibrates, N-3 FA and niacin and ezetimibe if added to statins. Stop any smoking.

8) ASA: anti-platelet

Here is my algorithm on how to choose what drug, with the given being that first mission is always to upregulate LDL receptors to lower apoB. The best way to do that is statin/ezetimibe. So we should all be starting statin monotherapy or statin/ezetimibe. If on return visit, Non HDL-C (or apoB or LDL-P) remains high combination therapy as well as more aggressive lifestyle is indicated. Indeed in NCEP ATP-III we were told if there Non HDL-C is high on a statin then the benefit of adding a fibrate or niacin would outweigh any perceived risk of combo therapy. Since that statement was published statin/ezetimibe has received an FDA indication to lower Non HDL-C. Interestingly Lovaza (formerly called Omacor) does not have an indication to lower Non HDL-C but looking at data within the package insert (COMBOS trial from Michael Davidson), N-3 FA at 4 grams daily can reduce Non HDL-C if TG are > 200.

Here is a simple, but easily understood algorithm of getting Non HDL-C to goal if a statin has not done so:

Note: First line therapy (if TG<500) is upregulating LDL receptors (best way to maximize apoB reduction): When starting a statin as first line therapy in your patients do not be shy; Predict how many LDL receptors you have to upregulate and how much apoB (Non HDL-C) lowering will be required to get to goal and then start with the correct dose. The sooner apoB is eliminated the better the CV health provided. Thus most have to use much larger doses of statins than in the past or better yet, use smaller doses combined with ezetimibe (Zetia) as the starter therapy. I only use two possible therapies in my high risk patients depending on apoB (non HDL-C): Vytorin or Crestor/Zetia. I see no need for any other starter therapy (formulary issues aside).

Non HDL-C = TC minus HDL-C = TC plus VLDL-C plus LDL-C
VLDL-C is determined by dividing TG by 5 Thus the higher the TG, the higher the VLDL-C. Anyone with a TG > 150 has high VLDL-C (> 30 mg/dL)

So if on a statin, Non HDL-C is elevated we need to know is the Non HDL-C increase being driven by 1) LDL-C, 2 VLDL-C, 3 predominantly low HDL-C or 4) a combination of all.

Scenario 1) High LDL-C normal TG and HDL-C
Advanced testing: High apoB Elevated Total and large LDL-P: VLDL-P and HDL-P OK

Therapy add Zetia or WelChol or both top statin: Use clinical judgement as to whether Vytorin will
get to goal or if Crestor/Zetia will be required.
If statin intolerant: Zetia plus WelChol plus Plant Stanol (Benecol) plus aggressive low fat diet

Scenario 2) High VLDL-C (TG elevated) LDL-C normal HDL-C usually low but may be normal
Advanced testing: High apoB Elevated Total and small LDL-P Increased VLDL-P and decreased Total HDL-P and large HDL-P, increased small HDL-P Glucose intolerance often present: hypertension and hyperuricemia as well

Therapy: Add fenofibrate (TriCor) and omega-3 Fatty (N-3-FA) acids if necessary (4 grams or higher). Fibrate must go first but I often use both depending on TG elevation. Fenofibrate unlike
gemfibrozil is safe with all statins. If Non HDL-C goal not achieved add ezetimibe (Zetia) or Niaspan.

Scenario 3) Low HDL-C, TG not very high (<200) LDL-C OK (so called isolated HDL-C)
Advanced testing: Elevated apoB Decreased apoA-I Elevated Total and usually small LDL-P VLDL-P may be slightly up. IDL-P may be up Total HDL-P and Large HDL-P quite low.
If apoB or LDL-P is OK, this is likely a genetic hypoalphalipoproteinemia not associated with significant CHD risk and thus therapy not needed

Therapy: Add Niaspan and titrate to effective dose to get to goal. Adding ezetimibe (Zetia) can help normalize apoB (LDL-P)

Scenario 4) High LDL-C and VLDL-C (combined hyperlipidemia) HDL-C often low:
Advanced testing: Elevated apoB & decreased apoA-I Elevated Total LDL-P (large and/or small)
Elevated VLDL-P (especially large), Decreased Total and large HDL-P

Therapy: Statin/ezetimibe (Crestor/ezetimibe or Vytorin depending on how elevated apoB or LDL-C is) plus fenofibrate (TriCor) for the attack on TG and/or Niaspan if low HDL-C is the major
problem. N-3 FA at 4 grams often very useful. In some severe cases you need aggressive triple or
quadruple therapy: statin/ezetimibe/fenofibrate/niacin/N-3 FA will also help.

STATIN Intolerance:

Scenario 1) Ezetimibe (Zetia) plus WelChol plus Plant stanol (Benecol) plus very low saturated/trans fat diet
Scenario 2) Fenofibrate (TriCor) plus Ezetimibe plus N-3 FA plus Niaspan
Scenario 3) Ezetimibe plus Niaspan
Scenario 4) Fenofibrate (TriCor), plus Niaspan plus Ezetimibe (Zetia) plus N-3 FA plus Stanol

LIPID CASE # 194

A practitioner writes me: I have a patient (who happens to be my husband) who is 34 year old, non-smoker, with normal BP. He is physically active, but he does not have a good exercise regimen. He has no family history of premature cardiovascular disease. Mother and father are both alive and well; grandparents on both sides lived into 80's. He does have 2 maternal aunts with DM, and I think that his mother has pre-DM. He has the following lipid panel:
TC =103 TG = 102 HDL-C = 28 VLDL-C = 28 LDL-C = 55 Glucose = 93
TC/HDL-C = 3.8 Non HDL-C = 75 TG/HDL-C = 3.7

The clinician states I know that the real question with HDL is functionality, but do you think that it would help to do a Lipoprotein testing on him? Other than looking at his LDL-P, what would I be looking for in his HDL-P?

DAYSPRING DISCUSSION:

This is a real brain teaser. And of course making the correct assessment of cardiovascular risk is critical, as we surely want to treat if risk exists and not waste money or subject the patient to side effects if there is no risk. First never forget if an apoB particle does not traffic sterols into the artery there can be no atherosclerosis or lipid related CV risk. Thus risk assessment and treatment goals always comes down to particle concentrations (apoB or LDL-P) or lipid surrogates of apoB (TC, LDL-C, Non HDL-C). Does anyone think the above patient has too many apoB particles or do we really have to measure those parameters?

Let's start by discussing why the body both synthesizes and absorbs cholesterol. Simple, it is a crucial molecule for human existence. Without cholesterol: no steroids, no vitamin D, no bile acids and no functional cell membranes. Evolution has granted virtually every cell in the body the power to de novo synthesize cholesterol and the proximal intestine the power to absorb it. Clearly evolution gave us the genes to have enough cholesterol. However we really only need a small amount and unfortunately too much cholesterol in any cell will crystallize and kill the cell. Thus for us to have perfect cholesterol homeostasis, evolution also had to give us genes to diminish cholesterol when excess exists. The primary dietary substrate feeding cholesterol synthesis is saturated fat of which no shortage seems to exist in today's diets. Although cholesterol can be absorbed it is mostly free or unesterified cholesterol (OH group at the # 3 position) that is pulled in by the intestine via the Niemann Pick C1 Like 1 protein. It is rapidly re-esterified in the enterocytes via the enzyme ACAT or with lipoproteins by LCAT (a fatty acid replaces the -OH group, creating cholesteryl ester or CE).

Any cell that has too much cholesteryl ester (the storage and transportation form of cholesterol) is at risk of death. There is a nuclear transcription factor called the Liver X Receptor (LXR) that senses the excess and by transcription of DNA results in protein synthesis (proteins that regulate sterols). These ATP binding cassette transporters are translocated to the surface of cells and these pump out cholesterol to cholesterol-acceptor proteins (mostly apolipoprotein A-I but also E). It is through this mechanism that apoA-I or pre-beta HDL attaches to ABCA1 and lipidates (fills

with cholesterol) creating more mature HDL species (first small and ultimately large). LXR also upregulates ACAT forcing the synthesis of cellular CE which can be incorporated into apoB particles (VLDLs, chylomicrons). The LXR also upregulates ABCG5 and ABCG8 which are sterol efflux pumps forcing cholesterol from hepatocytes to bile and enterocytes to intestinal lumen. The LXR in an attempt to reduce sterol levels also downregulates the NPC1L1 protein, and thus at times of cholesterol excess there will be less absorption of cholesterol via enterocytes.

From the discussion so far one can see that underproduction of ABCA1 will cause hypobetalipoproteinemia as will a deficiency of LCAT. Obviously if one does not make apoA-I or rapidly catabolizes it, HDL-C will be low. If there is a homozygous absence of ABCA1 we have Tangiers Disease (HDL-C of zero) and if a heterozygote (HDL-C 20s-30s), a Tangier's carrier. ApoB levels dictates their heart disease. If there is an LCAT deficiency we have a heterozygote form termed Fish Eye Disease. The latter do not get a lot of heart disease despite HDL-C in the 10 mg/dL range.

Diabetics do not have HDL-C that low but they sure have high CV risk with their moderate HDL-C reductions (25-40 male, 35-50 woman). The answer is virtually all diabetics have serious apoB concentration elevations and it is usually TG driving the apoB. Insulin resistance with TG > 130 are associated with hepatic overproduction of or delayed catabolism of TG-rich VLDLs. Some of these go on to form LDLs which because of their 3 day half life accumulate (driving LDL-P). The TG also activate CETP (cholesteryl ester transfer protein) mediated exchange of TG for CE between VLDLs and both LDLs and HDLs, creating cholesterol poor, TG-rich LDL and HDL particles. Such particles as they pass through the liver are exposed to hepatic lipase, loose the TG and become small LDL and HDL species (the latter more easily pass through the glomerulus and are excreted). No matter what is your LDL-C, it will always take considerably more small compared to large LDL particles to transport or traffic that cholesterol. **If you did not understand this paragraph, re-read it as it is crucial to this case.** Thus diabetics or met syndromes with low HDL-C virtually always have high LDL-P (apoB) an that is primarily what drives their disease and it (apoB) becomes the most important risk factor or goal of therapy. After one lowers apoB to normal then we can try and improve HDL functionality, reduce inflammatory markers, reduce noncholesterol sterols or do whatever else you believe must be done with lipids, but if you want to be evidence based, **YOU ALWAYS CHASE APOB (LDL-P) FIRST.**

So solving this case comes down to measuring atherogenic particle number: apolipoprotein B or LDL-P (NMR LipoProfile). LDL-P is also available by a company called Spectracell: their technique is separation of particles via the ultracentrifuge and then particle stating and quantification. I am unaware of this method of LDL-P be used in any trials correlating it with risk unlike NMR LDL-P.

The practitioner also asks will HDL particle, measurements be of value? A quick review of HDL particle biology: **ALL THAT FOLLOWS PRESUME THE PATIENT IS DRUG NAIVE.** Hepatic or enterocyte produced apoA-I acquires some phospholipids and becomes prebeta-1 or prebeta-2 HDL (discoidal). They attach to ABCA1 and start to acquire unesterified cholesterol from cells (mostly hepatocytes and enterocytes) and mature into alpha HDLs (4,3,2 smallest to largest) also called HDL3 on electrophoresis or H1 and H2 on NMR. Often these particles have apoA-II and LCAT and the cholesterol is esterified into CE. The particles mature (enlarge and become spherical) and are now classified as alpha-1 or HDL2 or H4 and H5 species depending on the methodology used. Over 80 percent of the total HDL-C is trafficked in the alpha 4 (very mature particles) species (HDL2 or H4 and H5). Clearly any person with low serum HDL-C levels will not have very many large HDL particles. This is most often (but never always) associated with CV risk. Folks with LCAT deficiency or apoA-I Milano have no large, mature HDL particles yet get no CHD. The major risk of too few large HDLs occurs when it is in association with too many apoB particles.

There are 1-4 apoA-I molecules on each HDL particle, thus apoA-I measurements estimate how many HDL particles are in plasma. HDL-P (NMR) cannot quantitate prebeta HDL-P particles

which are by far the most important HDL species. So if an NMR HDL analysis was performed in this patient there would be a reduced total HDL-P and there would be a marked reduction of large HDL-P. Who cares, because if LDL-P is OK, there is not a need to treat.

So again this case comes down to apoB or LDL-P. What would NCEP say? NCEP would want us to do risk scoring and then get his LDL-C to the appropriate LDL-C goal. Using Framingham Risk equation, this man has is low risk and his LDL-C goal is 160 mg/dL. NCEP also state if his TG is > 200 mg/dL, then we should get him to Non HDL-C goal (130). Newer data tells us Non HDL-C always out-performs LDL-C as a risk factor regardless of the TG. NCEP does state if the patient is at high risk and the low HDL-C is isolated (normal LDL-C and normal TG) then a fibrate or niacin can be prescribed. This may be NCEP's opinion but there are no clinical trials that have tested that hypothesis. Since this man is low risk, he is not a niacin or fibrate candidate according to NCEP.

So of course I advised the practitioner to get an NMR or apoB and make risk and treatment decisions based on that value. What's my guess? I stopped guessing in lipids a long time ago as patients lives depend on us being correct. His TC of 102, TG of 103, Non HDL-C of 75 all suggest he does not have an apoB problem. However his TG/HDL-C ratio gives him an 80% chance of small LDL particles. If they are very small it would not be impossible for him top have too many LDLs. It is unlikely, but not impossible. So NMR testing is mandatory here. If indeed he has too many LDLs, then out comes the statin or statin/ezetimibe scrip depending on the actual number.

LIPID CASE # 195

Summer is just about gone, fall is around the corner, kids are back at school, and our soldiers are still courageously and bravely defending us at home and away and we as always must proceed with "lipiding." Those of us seriously involved with lipid management often get the "most dreaded" patients and by that I mean physicians or their immediate relatives. No room for mistakes! (Just kidding). With that in mind let's examine this weeks dilemma.

I was asked for guidance on a 74 year old woman, who was the wife of a physician colleague of the provider writing to me. She leads a very active lifestyle without limitations but has a family history of CAD and prior dyslipidemia. This is her first visit to the new provider. She has some atypical nocturnal symptoms (not specified). A stress perfusion study did not reproduce symptoms and showed no ECG abnormalities and the scans were normal, 90% of predicted HR was achieved. She is taking Lipitor 40 mg plus Zetia 10 mg daily.

Current lipid profile:

TC = 142 LDL-C = 69 HDL-C = 63 TG = 49 Non HDL-C = 79 Glucose = 92 HgbA1c = 6.1

Yea!!!! NCEP gives the treating physician an A+. So, send her home, wish her well and wonder why the heck she was referred --- RIGHT?

Anyone want to do coronary calcium scoring? Well it was performed and the Calcium Score was 569 with left main of 292, LAD of 292 and RCA of 176. Please see reference 2 below. Should we follow it in the future? See reference 5 below

DAYSPRING DISCUSSION: Clearly we are dealing with a high risk patient with fairly extensive CAD which at least according to the stress test is nonocclusive. She is on combination lipid therapy and is at NCEP goal of therapy. so should we be content. Obviously anything I am going to say would be opinion. Number one, we do not have the pretreatment lipid panel, which might help us ascertain the exact lipoprotein disorder. Readers of my newsletter know my approach to correctly diagnosing lipid-related disorders, estimate risk and prescribe appropriate therapy is

lipoprotein or particle based. Yes it is the sterols that wreck havoc, but sterols go nowhere unless they are trafficked with other lipids inside of our lipid-transportation vehicles, more appropriately and scientifically named lipoproteins. Since lipoprotein concentrations may or may not be entirely predicted by looking at lipid concentrations (numbers in a lipid profile). In our insulin resistant patients, more often than not the lipid concentrations, especially LDL-C is misleading or downright fraudulent!. So I prefer not to tell high or very high risk patients that there is no lip[id-associated risk without a thorough examination of the lipoproteins.

However, as I proceed with additional lab studies, I certainly want one of my invasive colleagues to maybe inject some dye into those arteries or at least get one of those spectacular CT images. That left main score is a bit too intimidating for me. Maybe it is epicardial, but we can't miss Left Main lesions. So why that decision is being made, of course I want lipoprotein concentrations. The number one risk factor in the lipid world influencing atherogenesis is atherogenic particle number (how many remnants, IDLs, LDLs are present). If those particles are numerous, it matters little how much the sterol load is within each particle. If one has a few quadrillion extra apoB-containing particles (the vast majority of which would be LDLs, due to its 3 day half-life), they are going to invade the endothelium. Their lipid composition or size is not a major determinant as far as whether they do or do not enter the artery. Those who like to guess or estimate particle numbers by looking at lipid concentrations would certainly say with the TG and HDL-C being so good, it is unlikely there are any remnants or small LDLs in this lady and it is very likely her LDL particles are normal sized. Therefore with an LDL-C of 69, she would not have too many normal sized LDL particles: if she did the LDL-C would be considerably elevated. Although probably true, I am not betting her life on it. Other factors beyond TG can influence particle size: multiple lipase activities, and lipid transfer protein abnormalities, none of which we assay. Could she have a problem of too many noncholesterol sterols? How about plaque vulnerability? I'd like to see the PLAC test (lipoprotein associated phospholipase A2), as well as hs-CRP, and even a microalbumin level (see the A1c). If any were up, even though there is no level one evidence to support it, I might try and reduce those markers (see PROVE IT trial where those with the best outcomes had aggressive reduction of both LDL-C and CRP). I would not order homocysteine because even if elevated I have no therapeutic options.

What if lipoprotein testing and inflammatory markers were OK? Based on ASTEROID data I'd switch to a more potent statin than atorvastatin and obviously that is rosuvastatin. In reversal atorvastatin certainly arrested plaque, but it ASTEROID, rosuva demonstrated an ability to regress. I know I have no evidence that regression would provide anymore clinical benefit than stopping progression (but see reference 5 below). However as a lipidologist I hate excess apoB and LDL-P and since LDLs are not delivering any necessary cholesterol to any of her cells. I want them gone. I want to turn her into a newborn baby or into a hypobetalipoproteinemic patient as they do not get atherosclerosis and they have no harm from their physiologic LDL-C levels under 40-50. NOTE: I do not see a need to lower apoB or LDL-C that much in the lower or moderate risk patients, but our patient is high risk.

Even though I would switch to the rosuvastatin (Crestor) I am not abandoning the Zetia. The EXPLORER Trial (Am J Cardiol 2007;99:673– 680) looking at rosuvastatin 40 mg / ezetimibe 10 mg combination therapy showed the most potent LDL-C (70%) and apoB (56%) reductions ever seen. CRP was also reduced by 46% (way beyond what Crestor could do by itself which was 29%). It would also reduce any noncholesterol sterols if they are a contributing factor in this case. If one went with potent statin monotherapy, it is likely noncholesterol sterols would rise and even wind up in the artery wall (PLEASE see Plant Sterols in Serum and in Atherosclerotic Plaques of Patients Undergoing Carotid Endarterectomy Tatu A. Miettinen, et al. (J Am Coll Cardiol 2005;45:1794–801). While your at it, see Physiological and therapeutic factors affecting cholesterol metabolism: Does a reciprocal relationship between cholesterol absorption and synthesis really exist? Sylvia Santosa et al. Life Sciences 80 (2007) 505–514. It is my personal opinion that all those writing lipid therapies needs to read this article. The days of treating lipid disorders by attacking only the liver are DONE. The small intestine is also a key player in lipid

homeostasis. Those of you planning to attend the NLA's Master Summit on lipids and the gut at AHA this year will certainly get a great update on this complex topic.

Would the Crestor/Zetia raise the HDL-C and apoA-I more than did the Lipitor/Zetia: for sure, but who cares. We have no prospective evidence from any trial that what statins do to HDL-C is related to their benefit. In ASTEROID the rosuvastatin induced 15% rise in HDL-C was not correlated with the regression, whereas the LDL-C and apoB lowering capabilities of rosuva was. My hope is that the reduction of inflammatory markers would help the HDL functionality which is probably more important than what a drug does to HDL-C.)High-Density Lipoprotein as a Therapeutic Target A Systematic Review Inder M. Singh, et al. JAMA. 2007;298(7):786-798. I really beg you to read this very recent article).

LIPID CASE # 196

I was asked about a 45 year old female that presented for a routine physical. She is a smoker, but had no specific complaints. The patient denied any chest pain or shortness of breath on exertion. She is adopted and has no knowledge of the health of her natural parents. On exam, her blood pressure was 170/100, and a right carotid bruit was auscultated. To follow this up, a carotid ultrasound was obtained. This showed a 50-70% stenosis on the right. The rest of her exam was within normal limits. Due to the patient's high risk, the provider placed her on Benicar HCT 20/12.5. The following lipid results were obtained:

Total Cholesterol = 185 mg/dL Triglycerides = 114 HDL-C = 44 LDL-C (Direct) = 114 The TC/HDL Ratio is 4.20

NMR LipoProfile reported:

Total LDL-P = 1502 (borderline high risk) Desirable < 1000 nmol/L Small LDL-P = 952 LDL Particle Size = 20.9 (Pattern A) **Lipoprotein (a) = 90.7 nmol/L**

Lipoprotein associated phospholipase A2 (PLAC test) Lp-PLA2 = 147 (normal) hs-CRP elevated at 14.0

The provider stated his lipid plan was to focus on treating the Lp(a) with Niaspan, as this was the predominant form of LDL. Her repeat lipids on 500 mg show

Lp(a) still greater than 95 TC = 178
LDL-C of 109, HDL-C = 40
LDL-P of 1257, Small LDL-P 622, LDL Particle Size of 21.4,

The Niaspan was increased to 1000mg with a follow up visit next month. Meanwhile, her blood pressure is 122/78 on Benicar HCT, but she continues to smoke despite aggressive counseling. On her repeat exam, the carotid bruit was gone. Serial ultrasounds are planned. The provider questioned how to manage a high risk patient's

LDL with such a high Lp(a)? It was his understanding that statins are ineffective for these patients and he wondered if that is true?

DAYSPRING ANALYSIS

In the final report of 2002, NCEP-ATP III guidelines listed Lp(a) as an emerging risk factor and that is pretty much what it still is. It is still debated exactly how apo(a) may in some patients aggravate CV risk and likely it is multifactorial.

First a little review: Lipoprotein (a), pronounced lipoprotein "little a" is simply an LDL particle (an apolipoprotein B wrapped collection of phospholipids, free and esterified cholesterol and TG), to which a protein called apolipoprotein (a) is attached to the apoB (via a disulfide bond). Apoprotein (a) is a glycosylated heterogenous protein that has a variable number of repeats of a protein domain, kringle 4, which are genetically determined. There are different apo(a) isoforms that account for a range of Lp(a) molecular weights from 280 to 800 kDa, and are inversely associated with circulating Lp(a) concentrations.

Apo(a) can also be attached to TG-rich VLDL particles. The Fractional Catabolic Rate of apo(a) is approximately half that of Lp(a) B-100. Apolipoprotein (a), attached to triglyceride-rich lipoprotein apoB-100, is released from the hepatocyte surface. This newly formed Lp(a) particle releases apo(a) as the triglyceride-rich lipoprotein portion is catabolized via receptor-mediated clearance. The free apo(a) then recombines with another apoB-100 particle, most likely of triglyceride-rich lipoprotein origin. Because about 50% of triglyceride-rich lipoprotein is converted to LDL in the fed state, the second Lp(a) particle may survive catabolism (The metabolism of apolipoproteins (a) and B-100 within plasma lipoprotein (a) in human beings. Jennifer L. Jenner et al. Metabolism Clinical and Experimental 2005;54:361– 369)

It is very important to know how the Lp(a) is measured. Labs report Lp(a) as mg/dL or nmol/L (number of Lp(a) particles).The NHLBI issued a position paper which advised: The expression of Lp(a) values in terms of total Lp(a) mass **<u>should be abandoned</u>** because what is measured is the protein component of Lp(a) and not its lipid and carbohydrate content. In addition, to correctly reflect the number of Lp(a) particles and to compare data from different studies, the values should be expressed in terms of nmol/L of Lp(a) protein.(see Report of the National Heart, Lung, and Blood Institute Workshop on Lipoprotein(a) and Cardiovascular Disease: Recent Advances and Future Directions Santica M. Marcovina, et al. Clinical Chemistry 2003;49:11:1785–1796). LipoScience reports Lp(a) in molar concentrations but Berkeley does not. VAP reports how much cholesterol is within the Lp(a) particles and thus provides Lp(a)-C concentrations. Since the risk of apo(a) seems to be related to LDL-C (see below) some find the Lp(a)-C measurement helpful. Be sure you know how your lab reports the data and insist on molar concentrations.

The NHLBI report goes on to state: On the basis of currently available data, individuals with Lp(a) values exceeding the 75th percentile are at increased risk for CVD. For Caucasians, based on the Framingham data, this percentile corresponds to an Lp(a) value of 75 nmol/L. So this patient under discussion certainly has an elevated Lp(a). However, we now have new epidemiological data in bith men and women that was not available to NCEP-ATP III.

1) Men: High Lp(a) predicts risk of angina, and the risk is substantially increased with high concomitant

LDL-cholesterol (reported as > 160 mg/dL). The study found that Lp(a) concentration strongly contributed to CHD risk when LDL-C was concomitantly increased, consistent with several other studies. In other words the risk of Lp(a) is not there if LDL-C is OK (< 160 mg/dL). The men with the highest risk had Lp(a) concentrations > than the 80th percentile and LDL-C > 160 mg/dL. The reference is: Apolipoprotein(a) Size and Lipoprotein(a) Concentration and Future Risk of Angina Pectoris with Evidence of Severe Coronary Atherosclerosis in Men: The Physicians' Health Study Nader Rifai et al. Clinical Chemistry 2004;50:1364–1371.

2) Women: In this cohort of initially healthy women, extremely high levels of lipoprotein(a) (90th percentile), measured with an assay independent of apolipoprotein(a) isoform size, were associated with increased cardiovascular risk, particularly in women with high levels of LDL-C. However, the threshold and interaction effects observed do not support routine measurement of lipoprotein(a) for cardiovascular stratification in women. Lipoprotein(a), Measured With an Assay Independent of Apolipoprotein(a) Isoform Size, and Risk of Future Cardiovascular Events Among Initially Healthy Women Jacqueline Suk Danik, et al. JAMA. 2006;296:1363-1370

Ok so it seems like we only need to consider Lp(a) a risk factor when it is extremely high (>80th or 90th percentile) and when LDL-C (apoB or LDL-P) is elevated. How about treatment in those with the very, very high levels? Since there has never been a trial that gives us evidence on how to treat folks with Lp(a) abnormalities, anything one says is conjecture. There are zero trials showing that partially reducing apo(a) with niacin or any other drug conveys CV protection. Indeed, the following is an exact quote from NCEP ATP-III: "At present no clinical trial evidence supports a benefit from lowering Lp(a) levels with particular agents."

Since the newer studies show there is little or less risk associated with less than extreme Lp(a) levels or if LDL-C (LDL-P) is at goal, the proper way to treat patients with severe apo(a) elevations is to treat them like we do everyone else: that is to normalize LDL-C, and non HDL-C (apoB or LDL-P). Of course the best way of doing that is to upregulate LDL receptors with a statin or statin ezetimibe. Here is what NCEP ATP-III states: "if a person has a high LDL cholesterol and only one other risk factor, the finding of a high Lp(a) could count as a second risk factor to justify a lower goal for LDL cholesterol. ATP III did not find strong evidence to support this approach, but accepts it as an option for selected persons."

Dr Greg Brown has reported: "In an analysis by Maher et al. of the Lp(a) data in the FATS trial, lowering LDL levels in those with high LDL and high Lp(a) levels dramatically reduced risk. Without treatment, these patients had a 42% risk of a major clinical event, including MI, the need for revascularization, or CV death over the 2.5 year study. When LDL levels were lowered aggressively, even though the Lp(a) levels remained high, the risk of this group was reduced to less than 10%, for a roughly 75% reduction in the risk of a major cardiovascular event. While Lp(a) (and probably risk) may be modestly lowered with niacin therapy, and with estrogens in women, aggressive lowering of LDL levels appears to be the most reliable way to treat patients at high risk due to elevated Lp(a)."

Of course the best proven way to reduce atherosclerosis is to reduce apoB or LDL-P (or their lipid surrogates like LDL-C and Non HDL-C). Any LDL particle with an apoprotein (a) attached in effect has a camouflaged apoB on its surface. Such particles are far less susceptible to removal via the LDL receptor LDLr) mechanism (upregulated by statins and ezetimibe), as the apoB is not visible to the LDL receptor. Of course LDL particles that do not have the apoprotein (a) attached to their apoB are cleared normally by statin or statin/ezetimibe upregulated LDLr. This scenario of removal of normal LDL particles, but no removal of Lp(a) particles would result in little change of Lp (a) levels with statin therapy even though LDL-C, apoB and LDL-P and clinical risk would be reduced. Thus the most potent therapy to most significantly upregulate LDL receptors and lower LDL-P is combination therapy with a statin and ezetimibe or bile acid sequestrant.
Thus one can normalize LDL-C, LDL-P, apoB and lower CV risk without doing anything to apo(a) levels.

The drugs that inhibit hepatic apo (a) synthesis (Niacin, fenofibrate, estrogen, raloxifene) will cause less apoprotein (a) to be attached to LDL particles. These drugs reduce Lp(a) levels but none as monotherapy are particularly efficacious in reducing LDL-P or LDL-C. For years many have advocated niacin as the mandatory treatment for elevated Lp(a). Yet there is no clinical trial evidence that clinical events would be affected. Many people have extremely high Lp(a) levels. Niacin can only lower it 25-30% which would never get the Lp(a) concentration close to a normal level. However Niacin could help a statin further lower apoB.

So: The patient has: Total LDL-P = 1272 (borderline high risk) Desirable < 1000 nmol/L Small LDL-P = 952 and an LDL Particle Size = 20.9 (Pattern A) with an Lipoprotein (a) = 90.7 nmol/L (obviously greater than the 75th percentile. Last LDL-C was 107.

For such an LDL-P, some would just prescribe a statin, but statin/ezetimibe (Vytorin in this case to save a co-pay) would very likely get the person to LDL-P and LDL-C and Non HDL-C goal and stop the Niaspan. However, since it is already being taken (and tolerated) one could continue the Niaspan 1000 mg and simply add a statin (rosuvastatin 5-10 mg). I'd also advise aspirin therapy.

LIPID CASE #197

I was asked about a T2DM female, aged 71 who is obese and hypertensive with treated hypothyroidism (TSH normal now). She does not exercise and obviously is not great with calories. She takes glyburide for the diabetes (no HgbA1c data forwarded). Her lipids and lipoproteins, while she was on Crestor 10 mg daily, Zetia 10 mg daily and TriCor 145 mg daily are:

TC = 131 LDL-C = 51 HDL-C = 29 and TG 254 Non HDL-C = 102
LDL-P = 1122 (perfect < 1000), Small LDL-P-661
LDL particle size = 21.0 nm (Pattern A phenotype: large)
VLDL particle and HDL particle information not forwarded to me

The clinician wonders if adding Niaspan is appropriate?

DAYSPRING DISCUSSION

Lots of interesting lipid issues going on in this woman: How did she make it to 71 with all of those risk factors? Is she being treated too aggressively? Is her current regimen wise? Do we have to get even more aggressive? Well, her risk status determines how aggressive we need to be. She qualifies as high risk by Framingham risk scoring, by her T2DM on top of which is her 5/5 criteria metabolic syndrome (diabetes, Obese, HTN, low HDL-C and high TG). For the rest of this discussion I am presuming kidney and liver functions have been done and are normal. Since she is coming to the office I presume she desires aggressive treatment. We clearly have clinical trial evidence that treating T2DM patients, even in her age group can reduce CV events. NCEP ATP III would encourage us to get to goal in this woman if we want to minimize risk related to lipids.

For a high risk patient, NCEP suggests an LDL-C of 100 mg/dL with an option for taking it to 70 mg/dL. That certainly has been accomplished. NCEP would also state, that because of the still elevated TG, the Non HDL-C should also be brought to goal. The goal for a high risk patient is 130 with an option for 100. Note that the non HDL-C goal is 30 mg/dL higher than the LDL-C goal. Since Non HDL-C is simply LDL-C plus VLDL-C, the 30 mg represents VLDL-C. Of course labs usually calculate that by dividing TG by 5, on the assumption all TG are in VLDLs and the VLDL particle has 5 times more TG than cholesterol (since both of those assumptions are almost never present in diabetics with elevated TG, the calculated VLDL-C is often erroneous. Of course if VLDL-C calculation is incorrect, then LDL-C is also going to be wrong as labs report LDL-C from using the Friedewald formula: LDL-C = TC minus (HDL-C plus VLDL-C). However, if one calculates Non HDL-C by using TC and HDL-C (lab assays: not calculations), then the Non HDL-

C is accurate. One can argue if you know the Non HDL-C, and that is your NCEP designated target, who cares what the individual LDL-C and VLDL-C are: normalizing Non HDL-C corrects both. This woman has a normal Non HDL-C.

NCEP would thus state that since both LDL-C and Non HDL-C are at goal no further treatment is needed that would be supported using clinical trial outcome evidence. Since it is a high risk patient they do give an option to add either niacin or a fibrate to raise HDL-C, but clearly state there is no specific HDL-C goal to shoot for. Although epidemiological and clinical trial evidence clearly indicate that patients with higher HDL-C levels have less events than those with lower (even if on statins), we have no level one trial evidence that proves the hypothesis that raising HDL-C is required once apoB or its surrogates are at goal.

But wait a minute: why am I even discussing the lipid concentrations when we have NMR determined lipoprotein concentrations? We use lipid concentrations as surrogates, or proxies or guesses as to what type of lipoproteins are present. We do know that the only way cholesterol gets into the arterial wall is if a lipoprotein containing apoB (VLDL, IDL and LDL) traffics it there (and of course the vast majority of apoB particles are LDLs). Thus, since we have lipoprotein concentrations, do the lipid concentrations provide any useful information?

In this case the lipoproteins and LDL-C and Non HDL-C are in synch. Although VLDL-P may be somewhat up, her LDL-P is really quite good and that is primarily what drives atherosclerosis. In this case it is likely that the Crestor/Zetia by depleting the liver of its cholesterol stores (by inhibiting synthesis and absorption) has upegulated significant numbers of LDL receptors which are effectively internalizing the apoB lipoproteins (primarily LDL particles): in effect promoting what is called indirect reverse cholesterol transport (apoB particles returning cholesterol to the liver). It is also likely that the TriCor administration by reducing TG synthesis and enhancing lipolysis (hydrolysis of lipids like TG and surface phospholipids) of TG-rich VLDL enhances a shifting of LDL size from smaller species to large. LDL receptors are more effective at recognizing, attaching to and endocytosing larger rather than smaller LDLs. So the triple combination of statin/ezetimibe and fenofibrate have practically eliminated the apoB risk in this woman.

What more need we do? How about promoting macrophage reverse cholesterol transport, a term coined by Dr Dan Rader in describing HDL particles delipidating cholesterol from arterial wall foam cells. Macrophage RCT when induced in rodents erases plaque but has no effect on plasma HDL-C (simply because the cholesterol removed from arteries is miniscule compared to the cholesterol extracted from the liver and gut by HDLs and thus cannot influence total HDL-C). The ability of an HDL to delipidate sterols from plaque is part of what is termed "HDL functionality." Functional HDLs thus are likely cardioprotective. Unfortunately we have no lab test for HDL fucntionality? Also HDL functionality does not correlate with what a drug may or may bot be doing to HDL-C levels. We have rodent data that both fibrates (via PPAR alpha agomism) and niacin through the action of one of its metabolites having PPAR gamma agonism). Since we know both fibrates and niacin reduce events in patients with low HDL-C why not use them to not only help the statin lower apoB but maybe to enhance HDL functionality.

In a recent article entitled "Different cellular traffic of LDL-cholesterol and acetylated LDL-C leads to distinct reverse cholesterol transport pathways" by MD Wang et al., it is stated " the existence of dual pathways for macrophage cholesterol transport implies that effective intervention against atherosclerosis may require LDL cholesterol-lowering therapy with statins in combination with specific agonists to increase the expression and function of both ABCA1 and ABCG1." In other words: Statins and ezetimibe for all: then increase macrophage RCT: only drugs that we have evidence on doing that: fibrates and niacin! Name the three drugs that have trials showing they improve outcomes in patients with low HDL-C: Surprise --- Statins, fibrates and Niacin. PS: Zetia (ezetimibe makes all of them better lipid-modulating drugs).

Well this women has been given fenofibrate so I think we are done and I do not think I can make the case for additional therapy. If you think the still high TGs might be causing rheological or coagulation or inflammatory disturbances, maybe adding a high dose N-3 fatty acid (like Lovaza) makes sense. However, be sure glklucose is well controlled before adding other TG therapies. With apoB (LDL-P) OK and a fibrate already on board in a 71 y/o likely uncontrolled diabetic who is at NCEP goal, I cannot see adding Niaspan. I'd be loathe to stop the fibrate (since the lady is at goal) and replace it with Niaspan, because you might be loosing some microvascular benefits recently seen in trials using fibrates.

LIPID CASE # 198

This weeks case deals with an everyday problem that is so often misunderstood and mismanaged in "everyday" lipid management. I was contacted about a case where supposedly Crestor (the most efficacious lipid-modulating statin) worsened the lipid profile. The case is that of a 40 year old male, with abnormal lipids who had been seen for the first time on 6/19/07. At that time he was on Tricor 145 qd, Simvastatin 20 qd, fish oil (? dose), vitamin C and a multivitamin. On that regiment the lipid profile revealed:

TC = 153, HDL-C = 34, LDL-C = 75 and Triglycerides = 221
TC/HDL-C >4.0 Non HDL-C = 119

The provider was unhappy with that profile primarily because the HDL-C was still low, but also because the TG were still high. So he switched from simvastatin to Crestor 10 hoping to at least improve
his HDL. Three months later a repeat lipid profile revealed:

TC = 127, HDL-C = 31, LDL-C = 54 and Triglycerides = 210.
TC/HDL-C = 4 Non HDL-C = 96

The clinician asked if I had any thoughts as to the next therapeutic step or should he leave well enough alone. I was asked about adding Niacin?

DAYSPRING DISCUSSION:

I'll bet among those reading this case there are niacin, fibrate, ezetimibe and N-3 FA advocates all ready to co-prescribe their favorite add on medication. Well as always lets discuss the case using standard of care (NCEP ATP-III) and then lets do what we have to do to eliminate this man's CV risk. We do not have his original drug naive profile nor do we have a smoking history, family history, BP, waist size or glucose level. Odds are high that he is insulin resistant (almost all TG/HDL-C axis disorders are) and he meets at least three of the five criteria to diagnose the metabolic syndrome (ICD-9 code 277.7). Using Framingham risk scoring his risk status could be moderate, moderately high or high. Aggressiveness of treatment depends on the perceived risk, with the goals of therapy being stricter in those with the highest risk. For sure therapeutic lifestyle (TLC) is key in this man's management and from the results of the last profile he should get even more strict.

Once treatment is initiated NCEP provides only two goals of therapy. No matter how much I lecture or distribute these cases I am amazed at how few clinicians seem to know that there is no specific HDL-C or TG goal of therapy, due solely to the fact that no clinical trial evidence that exists would support advising what an HDL-C level or indeed a TG has to be reduced to improve CV risk. NCEP certainly advocates increasing HDL-C and lowering TG, but provide no specific goals to attain. I cannot repeat often enough: if you are evidence based, there are no level one evidence trials that have shown that therapeutic raising of HDL-C will reduce CHD. It is a theory that has never been proven. THERE ARE TWO AND ONLY TWO GOALS OF THERAPY in

NCEP: LDL-C and if the TG are > 200 mg/dL, Non HDL-C. Note: Of course we now know from Framingham data that TG are no longer relevant as far as when to use non HDL-C and that at TG either above or below 200 mg/dL, Non HDL-C always out performs LDL-C as a risk factor. (Please see Non–High-Density Lipoprotein and Very-Low-Density Lipoprotein Cholesterol and Their Risk Predictive Values in Coronary Heart Disease. Jian Liu, Christopher T. Sempos, Richard P. Donahue, Joan Dorn, Maurizio Trevisan,and **Scott M. Grundy** Am J Cardiol 2006;98:1363–1368). Of course readers of my newsletter who truly understand that sterols are trafficked within lipoproteins know that only the apoB containing particles (90-95% of which are LDLs) can deliver sterols to the arterial intima. LDL-C and Non HDL-C (the only two goals of therapy are simply lipid concentration surrogates or proxies of apoB or LDL-P where LDL-P signifies LDL particle number or concentration. Thus, NCEP is in fact an apoB or LDL-P based-guideline.

If we go back and analyze this case there is a big surprise: Let's presume this patient is in a high risk category. His NCEP goals of therapy would be an LDL-C < 100 and a Non HDL-C < 130. On the combination of simvastatin and TriCor (fenofibrate) the LDL-C was 75 and the Non HDL-C was 119: In other words LIPID GOAL HAD BEEN ACHIEVED. NCEP advises that when on a statin and lifestyle, that a fibrate or niacin be added if the Non HDL-C is still abnormal. So, despite the still low HDL-C and elevated TG, using the two apoB surrogates advised by NCEP (LDL-C and Non HDL-C) this man needs no further treatment other than more aggressive TLC. By the way the SAFARI trial, authored by Scott Grundy showed that simvastatin plus fenofibrate was actually quite good at improving all lipid parameters (Am J Cardiol 2005;95:462–468). Fortunately there are no drug interactions between feno (unlike gemfibrozil) and simva or any other statin.

Ironically, the physician was quite wrong by saying things got worse on Crestor: things actually got much, much better, NOT WORSE, on the Crestor (as one would expect). Please note that there was a very significant response to Crestor: The TC dropped 26 mg/dL. Since the majority of cholesterol is carried in apoB, not HDL particles, TC is an apoB surrogate. The LDL-C also dropped 21 mg/dL and of course since > 90% of apoB particles are LDLs, LDL-C is an apoB surrogate. Most importantly of all non HDL-C (the cholesterol within all of the apoB particles) dropped from 119 to 96 (a fantastic level). Also note that this tremendous improvement was with the same dose of simvastatin and rosuvastatin. If you ever needed more prove that rosuva inhibits far more HMGCoA reductase inhibition and therefore upregulates far more hepatic LDL receptors (which internalize apoB particles) this case is a good example. Think about this when using weaker generic statins in cases where apoB is quite high. Thus, the reality is in this patient Crestor blew away apoB much more so than did simvastatin.

Yet why did Crestor result in a lower HDL-C? Isn't it supposed to be the best statin at raising HDL-C? This is another good reason that it makes no sense to have an HDL-C goal of therapy.If we had one, you like the clinician involved might suspect Crestor is not helping. Remember the old Dean Ornish, extreme low fat diets that showed dramatic improvements on follow up angiograms. The weight loss and reduced saturated fat intake lowered HDL-C in those trials even though the arteries improved. Is that a shock? Remember the following Formula:

HDL-C = TC - (LDL-C + VLDL-C). Thus if one dramatically lowers both TC and LDL-C and does not raise VLDL-C, is it really a shock that in some cases the HDL-C will also reduce. There are several genetic hypoalphalipoproteinemias in which patients do not get CHD despite there very low HDL-C levels. If the last phase of the reverse cholesterol transport system is for the HDLs to return its cholesterol content to the liver, gut or LDLs (using CETP mediated transfer) why would one expect HDL-C to rise? Would not one suspect that of a drug dramatically raises HDL-C, perhaps either direct or indirect RCT might be impaired?

May I quote noted lipid researchers Sergio Fazio and MacRae Linton of Vanderbilt in their recent brilliant paper entitled "A new age of discovery for plasma lipoproteins." They state: "Somehow, the unstoppable progression of the LDL concept dragged along the notion that its perceived counterpart and nemesis, HDL, would carry equally large opportunities for therapeutic maneuvers

in atherosclerosis. Indeed, armed solely with the power of epidemiological observations, the idea that raising one's plasma HDL cholesterol levels will reduce the risk of a heart attack has become so entrenched in clinical thinking that many doctors switch to target an unproven HDL goal before 'finishing off' the LDL villain. Therefore, a current was created for an expectation that any rise in plasma HDL cholesterol would always indicate improved reverse cholesterol transport and enhanced vascular protection. Here, too, we got our share of shocking surprises in the last few months, ----- The most devastating blow, however, was taken by all of us lipidologista, who are now forced to rethink reverse cholesterol transport as a therapeutic target and cannot expect any longer for HDL to follow LDL's easy street. This means that any target leading to HDL increases must be tested for cardiovascular
benefits, and, most importantly, that there may be interventions on HDL that may be beneficial without raising HDL cholesterol **or even by decreasing it**." **AMEN! In this case the more powerful Crestor lowered HDL-C by blowing away TC and LDL-C.** If one takes a lot of cholesterol out of the system sometimes not only TC and LDL-C but HDL-C may also drop. Get over it! Check out reference 4 below for some new data on Rosuva and HDLs. Note the authors seem surprised rosuvastatin helped HDL function despite (their word) raising HDL-C.

ADVANCED TOPIC PARAGRAPH (Lipidologists only): Actually there is another potential cause of the reduced HDL-C. One of a fibrates MOA via PPAR alpha agonism is to upregulate hepatic scavenger receptors B1 (SRB1). These attach to and delipidate larger, mature alpha HDLs (HDL2). The HDL becomes smaller (HDL3 and 4 and thus potentially a better plaque delipidators). Of course in some cases if a drug is increasing delipidation of larger HDLs, it might reduce HDL-C. Thus, fibrates shift the predominant HDL species from large to small. Usually the fibrate also increases hepatic production of apoA-I and apo A-II in effect increasing the number of HDL particles in plasma (which is often but not always associated with increased HDL-C). Each patient likely has somewhat differences in response to PPAR alpha agonism: if one really gets a tremendous increase in SRB1 upregulation (stimulating efflux of sterols from HDLs), then the expected HDL-C rise will not be dramatic and it may even fall. In this case the drop seemed to be Crestor related and my previous explanations probably suffice. But be aware that statins can have powerful effects on sensitizing PPAR alpha nuclear transcription factors to better respond to their endogenous ligands (Circ Res. 2006;98:361-369). Thus introducing an efficacious statin like Crestor may have given this mans PPARs extra reason to respond to fenofibrate and increase SRB1 delipidation of HDLs.

BACK TO REALITY: Now let's finish up the case with the real DAYSPRING OPINION: No further therapy is necessary according to the NCEP guidelines. That may turn out to be the case. However, if you (like I) are uncomfortable betting patient's lives on lipid concentrations and suspect there is still residual risk despite the normal non HDL-C, you must order an apolipoprotein B or LDL-P level (using NMR LipoProfile). Severnts. al trials have taught us that the residual risk may still be high in patients at statin induced LDL-C goal, especially if HDL-C is low or TG remains abnormal. The only way to assay this is to measure apoB or LDL-P. That is of course exactly why I use NMRs and/or apoBs on all my patients.

Whatever Non HDL-C is (and it is better than LDL-C) it is not a laboratory assay of atherogenic particles: it is an educated guess of their presence. If apoB or LDL-P is indeed elevated, despite the at goal lipid profile, then Niaspan (titrated to 1000 mg and higher if needed or 4000 mg of N-3 FA should be added to the above regimen. One might say ezetimibe might also help and it may. However if LDL-P is elevated, it is because the LDLs are small or TG-rich and cholesterol poor (that is why LDL-P would be high in the face of normal LDL-C). Fibrates or high dose N-3 FA would shift LDL size making it more likely to be "grabbed" and removed by upregulated LDL receptors. All ezetimibe would do is further upregulate the LDLr beyond what the statin has done. If I had seen this man originally I'd have used a statin/ezetimibe combination first line and then added the additional drugs in stepwise fashion.

MORAL OF THE STORY: Ultimately, you must concentrate on LDL-P or apoB and if you cannot get them, then concentrate on their predictors: LDL-C and Non HDL-C. They are the only goals of therapy in NCEP. Never think you can accurately judge what you have done to someone's CV risk but the response to HDL-C. In general we'd rather have sterols, trafficked in HDLs than the apoB particles, but we really would have to know if those HDLs are functional (have antiatherogenic properties) or not. No such available test currently exists. I'll end by quoting from a nice review just published in the Cleveland Clinic Journal (available free on line: google it), where HDL expert Ben Ansell states: "Although a low level of high-density lipoprotein (HDL) cholesterol is a useful clinical predictor of coronary heart disease, raising the HDL cholesterol level does not necessarily lower this risk. Part of the explanation for this paradox may be that, under certain conditions, HDL either can be less functional as an antioxidant or can even enhance the oxidation and inflammation associated with atherosclerotic plaque. Thus, the functional properties of HDL—not simply the level—may need to be considered and optimized." Once again: **AMEN!**

LIPID CASE # 199

Hi Lipidaholics:
Sorry for the delay in the newsletter release but I have been at the AHA meetings in Orlando and was just too darn busy. Lots of new information became available at AHA and it is always great to see so many friends and colleagues. This weeks case does not require a lot of thought, but when practitioners see it for the first time the often do not know what to do.

I received the following e-mail from a well respected cardiologist stating he just got a call from a primary care doc about a lipid profile on a seemingly healthy person with the following lipid concentrations checked twice.

Total cholesterol = 56 mg/dL
calculated LDL-C = 10,
HDL-C = 36,
Triglycerides = 25.
VLDL-C would be calculated as 25/5 or 5, but this calculation is likely erroneous in this patient

The referring clinician and the patients family are worried about the lipid values being "too low." I was asked about my thoughts.

DAYSPRING DISCUSSION:
My goodness: isn't cholesterol required for human life? Can a person survive long with an LDL-C of 10 mg/dL? Since the patient is described as healthy, obviously one can exist with such values. Does this disorder have a name? From reading my previous cases you know extreme reductions of HDL-C (< 20 mg/dL) are referred to as hypoalphalipoproteinemia. HDLs separate with alpha proteins in electrophoretic gels and classically HDLs were referred to as alpha-lipoproteins. All other lipoproteins separate with beta-proteins and thus were called beta-lipoproteins: they include VLDLs, IDLs, and LDLs. Thus persons with very, very low LDL-C and VLDL-C are classified to have hypobetalipoproteinemia. It is not only fully compatable with human life but most of the patients have longevity since it is impossible for them to have atheroscerosis. Their apoB levels are extremely low and since particle concentration is what drives apoB into the vessel wall atherogenesis is not a worry. But what about LDLs delivering choelsterol to tissues? That really is not needed and not a major function of LDLs.

Every cell in our body has the de novo power to synthesize cholesterol from fatty acid (FA) breakdown molecules (Acetyl CoA). So most cells can make all of the cholesterol they need as long as they have a supply of FA. FA are abundant in plasma as they are released as TG and phospholipids undergo hydrolysis by various lipases. The FA enter the cells or bind to albumin and are transported to cells. A physiologic TG level is 10-70 mg/dL with a mean of 30, so this young man has normal amounts of TG to supply fatty acids for cellular cholesterol synthesis.

Hydrophobic lipids are delivered to cells inside of protein wrapped, water soluble particles called lipoproteins. The jejunal enterocytes and our hepatocytes release chylomicrons and VLDLs respectively. These particles carry more TG than cholesterol and traffic the TG to muscles or fat cells where they undergo lipolysis (hydrolysis of phospholipids and TG to fatty acids). When the TG are removed we are left with smaller (TG-depleted) chylomicron or VLDL remnants which still have their cholesterol content. The chylos take their sterols to the liver and the VLDLs either return to the liver (most of them) or undergo further lipolysis and become smaller IDLs and LDLs. The LDLs have a much longer half life (2-3 days) as their mission is to hang around to see if HDLs want to share their cholesterol. If HDLs want to rid themselves of cholesterol (so they can survive longer to perform other functions) they can send their cholesterol to LDLs (or VLDLs) using cholesteryl ester transfer protein or CETP. The LDLs thus get their cholesterol from both VLDLs and HDLs and sooner or later are removed from plasma by hepatic LDL receptors. Thus the main job of LDLs is not to deliver cholesterol to cells, but rather transport unneeded cholesterol back to the liver. This process is now termed indirect reverse cholesterol transport.

Of course steroidogenic tissues need more cholesterol than they can synthesize, but under physiologic conditions that is delivered by HDLs not LDLs. An HDL-C of 36 mg/dL is more than enough cholesterol for the needs of the adrenals and gonads. In an adrenal crisis LDLs can help with extra sterol delivery. Steroidogenic tissues upregulate scavenger receptor B1, which delipidates large HDLs, converting them to small species.

This patient obviously has very few apoB VLDL and LDL particles in circulation. Why? Either he is not making them or his liver is rapidly removing them by over-rexpressing LDL receptors (LDLr). The latter can occur with statin or statin/ezetimibe use, but this man is on no drugs. Recently a new cause of hypobetalipoproteinemia was described. There is an enzyme called PCSK9 or proprotein convertase subtilisin kexin type 9 which increases degradation of LDLr. If one lacks this enzyme LDLr have significantly decreased catabolism and apoB particles are rapidly cleared and as expected these patients have very low LDL-C levels and significantly reduced risk of atherosclerosis. Even more amazing is one has an excess of PCSK9, one will lack LDLr and this is associated witrh familial hyperbetalipoproteinemia (very high levels of apoB and LDL-C) and high risk of CHD.

This patients LDL-C is really, really low so it is likely he is not producing much apoB and therefore not producing very many VLDLs and their by-product LDLs. This is a heterozygous condition fully compatable with life and longevity. My bet is the patient under discussion has this disorder. Are there any consequences of this? Well, since they undersecrete VLDLs (the TG carriers) there is a potential for FA to accumulate in the liver and cause fatty liver, which fortunately in most patients is not a problem. ApoB particles also deliver tocopherol to tissues and one must watch for vitamin E deficiency but again this does not seem to be a major problem for most. Howeve,r if two hetrozygotes mate, one could produce a fetus with abetalipoproteinemia: this is associated with severe in utero vitamin E deficiency and the babies have severe neurologic and hematologic sequelae.

So the best advice I have to the family of this patient is to have him cloned. Neither his cells or yours depend on LDLs to deliver cholesterol. The HDLs have more than enough to keep the adrenals happy and he has more than enough TG to supply his muscles with energy. Other family members should be screened. Since these patients are asymptomatic they are usually discovered on routine screening. Si should you see one, do not panic. Let them know they will never need a cardiologist!

References on Hypobetalipoproteinemia are: 1) JCI; 1979:64:292-301, 2) Nice review: J. Lipid Res. 2003;44:878–883 and 3) Molecular diagnosis of hypobetalipoproteinemia: An ENID review: available prepublication on-line in the journal Atherosclerosis

By the way, since such extremely low levels of LDL-C are fully compatable with healthy lives and since new born babies seem very healthy with their LDL-C of 30-40, I doubt if anyone has to worry much about lowering LDL-C too low with a statin or statin/ezetimibe (Zetia) or statin/colesevelam (WelChol). There are now several publications from large clinical trials showing no adversity in people on statins with very low LDL-C.
1) Safety and Efficacy of Atorvastatin-Induced Very Low-Density Lipoprotein Cholesterol Levels in Patients With Coronary Heart Disease (a Post Hoc Analysis of the Treating to New Targets [TNT] Study)†
John C. LaRosa, (Am J Cardiol 2007;100:747–752) and 2) Can Low-Density Lipoprotein Be Too Low?
The Safety and Efficacy of Achieving Very Low Low-Density Lipoprotein With Intensive Statin Therapy. Stephen D. Wiviott, et al. (J Am Coll Cardiol 2005;46:1411– 6)

LIPID CASE # 200
Happy Thanksgiving Lipidaholics: There are always many to bestow thanks upon this time of year, but our first thoughts and THANKS must go to our armed services personal who have given up their family Thanksgiving Holiday so as to protect our rights to be thankful at this time of year. Before gobbling down our scrumptious meals Thursday, a quiet moment of contemplation seems appropriate.

You are now reading Lipid Case # 200. This newsletter started as a lark several years ago for me to chat lipids with a handful of lipid loving colleagues. It has grown tremendously and now is distributed to several thousand "lipidaholics" around the globe. Considering this is a work of love, with me discussing real patient lipid cases, off the top of my head using my knowledge (evidenced based if possible, educated guess if not) I am amazed as to the popularity of the rantings. My aim is to approach each case as do you when you are confronted with a patient's history and lab profile and I write as I hope you think when solving these disorders. I have been involved with aggressive lipid treatment for 32 years and have lived through the evolving "cholesterol hypothesis." When I started out we had diet, cholestyramine, immediate release niacin, clofibrate, neomycin and ileal bypass as our lipid therapies. Thank goodness we have progressed. **I thank all of you** for your comments and for allowing me to share these cases with you. As always if you have had your fill of lipids, shoot me an e-mail with Discontinue Newsletter in the subject line. Now to the case:

I was asked about a 57 year old Caucasian male with "combined dyslipidemia," hypertension and a family history of CAD (no mention of who or at what age). He has been on significant combination lipid modulating therapy: Crestor (rosuvastatin) 20 mg, Zetia (ezetimibe) 10 mg, TriCor (fenofibrate) 145 mg for 18 months. A recent stress test revealed ischemia and a coronary angiogram demonstrated 2 vessel disease requiring stents. Follow up labs were:

TC = 137 TG = 65 LDL-C = 84 HDL-C = 40
NMR (nuclear magnetic resonance spectroscopy) LipoProfile (www.lipoprofile.com)
LDL-P = 1399 (desirable in high risk patient < 1000 nmol/L)
Small LDL-P = 1210 nmol/L
Large HDL-P (very low)
Lipoprotein associated phospholipaase A2 (Lp-PLA2 or the PLAC test) = 264 (desirable < 180)

Based on these findings the clinician increased the Crestor to 40 mg daily and added Lovaza (N3 FA esters) at 1000 mg daily. He questioned whether Niaspan (extended release niacin) should also be added, because of the small LDL and lack of large HDL or whether that would be overkill.

DAYSPRING DISCUSSION:

Clearly this is a high or very high risk person, depending on what is your definition of those entities. I believe a person with stents, history of ischemia, with several lipid abnormalities on

aggressive therapy and especially with a high Lp-PLA2 is a very high risk individual. So if I am to follow NCEP ATP-III guidelines I would attempt to get the LDL-C < 70 mg/dL. Technically there is no Non HDL-C goal as the TG are well under 200 mg/dL. If it were, the Non HDL-C goal would be 100 mg/dL. Please note that Liu, Grundy (of NCEP fame) et al reported, using data from Framingham, that TG have no bearing on Non HDL-C value and whether the TG are > or < 200 mg/dL, non HDL-C always out predicts LDL-C as a risk factor (Am J Cardiol 2006;98:1363–1368). Thus using NCEP criteria the LDL-C is slightly elevated at 84 mg/dL but the non HDL-C is at goal. NCEP would suggest dropping the LDL-C to < 70 mg/dL.

Of course we have lipoprotein concentration data showing that despite the decent lipid concentrations there are still too many LDL particles, the vast majority of which are small, in the patient's plasma. It is particle concentration, not LDL size or composition, that is the main determinant as to whether the LDL enters the arterial wall or stays in plasma, ultimately to be cleared by the hepatic LDL receptors (indirect reverse cholesterol transport). I direct your attention to a paper authored by Bill Cromwell about to be published, but available on-line at the Journal of Clinical Lipidology: using data from the Framingham Heart Study -- CONCLUSIONS: In a large community-based sample, LDL-P was a more sensitive indicator of low CVD risk than either LDL-C or non–HDL-C, suggesting a potential clinical role for LDL-P as a goal of LDL management. The data showing that LDL-P, not LDL size is the meaningful risk factor comes from analysis of the large MESA trial (Mora et al. Atherosclerosis 192 (2007) 211–217) and the EPIC Norfolk trial (J Am Coll Cardiol 2007;49:547–53).

On top of the abnormal LDL-P, the elevated PLAC test is a real concern. The data is now overwhelming on this risk factor as a predictor of CVD (including stroke) events. We have to presume this man not only has extensive atherosclerotic plaque, but some of it may be unstable. Most of the lipid drugs we use have benefit on reducing Lp-PLA2, but like CRP we lack prospective outcome data that this is required or should be a goal of our therapy. However it is hard to imagine that improving Lp-PLA2 levels is not desirable. For a nice review: see Prev Cardiol. 2006;9:138–143. It is also interesting to note that Lp-PLA2 has a predilection to be associated with the smaller, dense LDL particles, so prevalent in this case (J. Lipid Res.2007. 48: 348–357).

ADVANCED DISCUSSION: Nuclear transcription factors tightly regulate lipid homeostasis and we as clinicians with our therapies modulate their activity. Several such factors exist and here I discuss a few:

1) Sterol regulatory element binding proteins (SREBP) ensure adequate amounts of cellular cholesterol by inducing lipogenic genes (such as that regulating HMG CoA reductase) and regulate expression of LDL receptors (LDLr) to internalize apo B particles carrying supplies of cholesterol and cholesteryl ester. Drugs that deplete hepatic cholesterol stores (like statins and ezetimibe) activate SREBP and upregulate increased numbers of LDLr, leading to apoB reductions. Clearing using statins and ezetimibe together will upregulate more LDLr than either drug alone. Using ezetimibe monotherapy will induce LDLr formation (desirable) but also will upregulate HMGCoA reductase (undesirable)

2) Liver X Receptor (LXR) - found in many tissues, not only the liver: This prevents sterol toxicity. In the presence of increased cellular oxysterols, LXR influence several cellular processes to eliminate sterols: upregulate the ATP binding cassette transporters which efflux sterols from cells: ABCA1 transfers cholesterol from hepatocytes and enterocytes to small HDL particles. ABCG5, ABCG8 transfers cholesterol from enterocytes and hepatocytes to the gut lumen and biliary system respectively. LXR downregulates the Niemann Pick C1 Like 1 (NPC1L1) which reduces the ability of enterocytes to absorb sterols and for the liver to extract sterols from the bile back to the hepatocytes. Anything that decreases cellular cholesterol (statins) will downregulate LXRs and thus increase absorption of cholesterol (undesirable) by the enterocyte (from gut) and liver (from bile). Not only will cholesterol absorption be induced but so witll that of the more toxic noncholesterol sterols (sitosterol, campesterol etc).

I believe the clinician made an appropriate decision in increasing the statin dose. That will further inhibit (slightly) cellular cholesterol synthesis: this will increase levels of sterol regulatory element binding protein (SREBP) which through genomic actions increases production of additional LDL receptors (LDLr), leading to additional hepatic endocytosis of LDL-P. You all know to expect 6% further reduction in LDL-C when one doubles the dose of a statin. Further inhibition of cholesterol synthesis of course will down regulate the Liver C Receptors (LXR) which leads to increased expression of the Niemann Pick C1 Like 1 Protein which facilitates both intestinal and hepatic internalization of cholesterol: however that will not matter in this case as the patient is on Zetia which will black the NPC1L1 protein function.

Do we need to be concerned about the lack of large HDL-P. In drug naive patients, the lack of large HDL-P is a major predictor of risk. Since the large HDLs carry most of the cholesterol within HDLs, most people with a lack of large HDL particles have low HDL-C. In drug naive patients the lack of large HDL is usually due to abnormal TG levels (>100 mg/dL). The TG leave the TG-rich particles via action of CETP and enter the HDLs and LDLs where they exchange for cholesteryl ester molecules. The result ids TG-rich, cholesterol poor HDLs and LDLs which upon exposure to hepatic lipase in liver sinusoids, loose the TG and become smaller HDLs and LDLs: Thus the majority of patients who do not have large HDLs have very high levels of atherogenic LDL (apoB particles). However this patient is not drug naive and different drugs remodel HDL particles in very different ways. Specifically the TriCor (fenofibrate) induces liver scavenger receptors B1 (SRB1) to delipidate the large HDLs, changing them into small HDLs which can return to the arterial wall and extract more sterols from the foam cells (macrophage reverse cholesterol transport). Thus when one prescribes fibrates one will notice a reduction in large HDL-P but an increase in total HDL-P and small HDL-P. This HDL remodeling (from large to small) is associated with benefit in fibrate trials. The fibrate-SRB1 induced cholesterol that enters the liver is excreted in the bile and instead of being reabsorbed at the enterocytes by NPC1L1 protein (which are blocked by ezetimibe in this man) is excreted in the stool. Fenofibrate and ezetimibe have the potential to cause significant stool excretion of cholesterol (desirable).

Will adding N-3 FA at 1000 mg help. YES: AHA recommends, in high risk, secondary prevention patients, N-3 FA supplementation at 1000 mg (by tablet or food) to reduce sudden death and improve mortality. The 1000 mg of N-3 FA (Lovaza is the new name of Omacor) provides no lipid benefit. The TG benefits of N-3 FA require 4000 mg daily. The recently published COMBOS trial did reveal that 4000 mg of Lovaza added to simvastatin will further help reduce Non HDL-C and apoB (Davidson M et al: Clin Therapeut 2007;29:1354-1367)

Finally how about Niaspan? It may not be overkill. As mentioned this is a very high risk patient who still has too many LDL particles. Small particles are difficult to remove by LDLr as the receptor does not readily recognize the distorted apoB conformation on small LDL particles. Shifting LDL size (something niacin is good at) would likely make it easier for the statin/ezetimibe upregulated LDLr to attach to and internalize the abnormal concentrations of LDL-P. I'd probably wait and see what the increased Crestor dose did to LDL-P before adding Niaspan. Like fibrates and statins, niacin also reduces Lp-PLA2.

Last but not least: how about WelChol (colesevelam)? We are all going to be hearing lots more about this "old drug" as we are realizing that it can improve glycemic control (this patient is likely insulin resistant) and induce macrophage RCT as well as lower apoB (by binding to and reducing bile acid return to the liver, hepatic cholesterol stores will be used to make new bile salts, leading to SREBP upregulation of LDLr). It will enhance the ability of ezetimibe and statins to reduce LDL-P.

LIPID CASE #201

Good Day Lipidaholics: As I fly into a very cold and snowy Milwaukee from a slightly less cold NJ, I'd like to present an interesting case I was asked about. A 53 year old man who is asymptomatic and presents for his annual exam. He jogs regularly and has no personal history of of

hyperglycemia or DM. Currently he uses no medications although in the past he had taken ASA 81 mg daily and 3000 mg daily of N-3 fatty acids (previously called omega-3). His past history includes gout and a minimally elevated homocysteine of 11.6 in 2002. Family history reveals a sister and a brother with premature CHD as well as others with hypertension and T2DM. Height 5'11" with a weight of 217 and a BMI of 30. His BP is 120/80.

Lipoprotein analysis from 2002 including NMR LipoProfile (nuclear magnetic resonance spectroscopy)

LDL-P (LDL particle concentration) = 2225 (very high risk) Desirable < 1300 Perfect < 1000 nmol/L
LDL size quite small at 19.6 nm
Large HDL-P = 4 (very low and considered high risk in a drug naive patient)
Large VLDL-P = 148 (extremely high) This is also an independent risk factor for CHD
Uric acid 8.8

Current 2007 Lipid Profile

TC = 189 mg/dL HDL-C = 35 LDL-C = 121 TG =165 Non HDL-C = 154

Patient has a coronary calcium score (ultrafast CT analysis) of zero

The clinician is perplexed as to what advice be given to the patient.

DAYSPRING ANALYSIS:

The old Dutch proverb tells us the apple never falls far from the tree. Although there is no detectable calcium in his coronary arteries, can this man be dismissed with that family history, past lipoprotein abnormalities and obesity? He certainly has three (BMI, low HDL-C and high TG) of the five risk factors enabling us to make a diagnosis of metabolic syndrome (ICD9 code 277.7).

Let's get the NCEP-ATP III "What to do" out of the way. He does qualify for Framingham risk scoring (FRS) because he has a major risk factor for CHD (the low HDL-C which is a powerful independent predictor of risk). But his FRS puts him in the low risk category. Because of the Met Synd, NCEP would advised therapeutic lifestyle advice to reduce weight. His NCEP lipid goal of therapy would be to reduce LDL-C to < 130 with an option for 100 mg/dL). His current LDL-C of course is 121. Since his TG is < 200 mg/dL there is no non HDL-C goal for this man. NCEP (in the full 365 page pamphlet) does discuss the use of coronary calcium scoring and implies it can be of benefit in better estimating risk in patients with subtle risk factors. Well this man has a zero score making his short term risk nil. So if this man were you or your patient are you content to go with lifestyle alone? Do you want additional testing before making a decision?

To the surprise of none of you, I am not content to prescribe TLC and see what happens. I am glad his arteries show no calcium, but can they stay that way for long? The insulin resistance, obesity. Met Syn, FH of T2DM and the very strong FH of premature CHD and his previous nightmarish lipoprotein analysis simply cannot be ignored.Do not forget the gout, high UA and homocysteine levels. If possible, I personally no longer bet people's lives on lipid concentrations and clearly think the NMR LipoProfile must be repeated in this patient along with some current inflammatory markers like hs-CRP, lipoprotein associated phospholipase A2 (PLAC test), urinary microalbumin and perhaps a 2 hour postprandial glucose.

More and more data is revealing that even the most experienced lipidologist cannot accurately guess or estimate atherogenic lipoprotein concentrations (apoB or LDL-P) by examining the lipid profile. The data is now unimpeachable that it is atherogenic particle concentration (not their lipid

content) that determines if the particle will penetrate the arterial intima and initiate atherogenesis. And because of its long half life, about 95% of apoB particles are LDLs. Especially in insulin resistant persons with unphysiologic TG levels (>100 mg/dL) it is next to impossible to estimate how many LDLs are needed to traffic (transport) a given level of LDL-C.

The volume of a sphere is 4/3 Pi Radius cubed. Thus subtle diameter changes in spherical lipoproteins are associated with very significant volume differences. Depending on how small the LDL is, it takes 40-70% more small than big LDLs to carry a given level of LDL-C. But LDL size is only one parameter causing major disconnects between LDL-P and LDL-C. What if I have two people with the same size LDL particles (either normal sized or small) and the same exact LDL-C value: Would they have to have the same LDL particle number (LDL-P)? The answer is not necessarily. LDL particles have a variable cholesterol to TG composition. Normal LDL particle lipid composition is a cholesterol to TG ratio of 4.0. In other words there is usually 4 times more cholesteryl ester (CE) and cholesterol inside the LDL than there is TG (thus a normal LDL particle has a composition of 80% cholesterol and 20% TG). Yet one fifth (20%) of a healthy population will have a lower CE/TG ratio than usual meaning they have more TG and less CE (reduced CE/TG ratio) inside their LDLs. How would this affect or translate into LDL-P?

LDL-C is the amount of cholesterol trafficked within all of the LDLs that exist in a deciliter (dL) of plasma. If there are two people with the exact same LDL size, the patient with LDLs containing a low CE/TG ratio (<4.0) or composition will obviously require more LDL particles to traffic their load of cholesterol. Thus the patient with increased TG inside their LDLs will almost always have more LDL particles than another patient with the same sized LDLs who has less TG within their LDL particles. So again we have the paradox of the futility of trying to estimate LDL-P by looking at LDL-C. There is no way we can estimate the CE/TG composition within a patient's LDLs.

This situation has just gotten even more complicated. In an about to be published analysis of LDL particle data from the Framingham Offspring trial (authored by lipid guru Bill Cromwell and others) and available on line at the Journal of Clinical Lipidology (the journal of the National Lipid Association) there is amazing new data. Is it possible to have CV risk even with really excellent LDL-C levels? Which is more important to have: normal LDL-C or normal LDL-P? The data shows that in patients with normal sized particles with very low (at goal) LDL-C there can be a significant LDL-P vs LDL-C disconnect irrespective of either TG or LDL size. When LDL-C is low (often driven low by a statin), the LDL particles become cholesterol depleted: in the past we have always believed that the only way for an LDL particle to be depleted of cholesterol was for it to carry too much TG (at the expense of cholesterol) or for the particle to be small and thus have size limits on how much cholesterol it could carry. Now we know that some people excellent at goal LDL-C levels who have LDL particles that irrespective of size or TG content are just cholesterol deficient. Thus it is possible to have perfect LDL-C, wonderful TG levels, and normal size LDLs and still have too many LDL particles (the determining factor on whether the particle enters the arterial intima). How scary is this? This clearly helps us understand why statins can dramatically lower LDL-C and TG but fail to normalize LDL-P in every patient. These PATIENTS WITH WONDERFUL LDL-C VALUES, INDUCED BY STATINS, are still at risk: that will need additional treatment to normalize LDL-P.

By now my readers know that when statins and whatever lifestyle the patient is willing to do have not normalized LDL-P, we need to add ezetimibe (Zetia). Bile acid sequestrants (BAS) like WelChol are suddenly re-emerging as an exciting therapy. Fibrates like the safer fenofibrate (TriCor) or niacin (extended release: Niaspan) are options. These latter two drugs make more sense if the HDL-C is low or TG are high.

In the case at hand, the metabolic syndrome, abnormal Non HDL-C and still high TG as well as low HDL-C, almost certainly means he still has a very high LDL-P despite a mildly elevated or even at goal LDL-C. His LDLs will be small (as they were previously) or TG-rich and cholesterol poor. Either scenario will be associated with very high LDL-P levels and risk. If his LDL-P is still in the 95th percentile (>2000 nmol/L) he will need:

With so many LDLs likely still present we need a potent HMG CoA reductase inhibitor to upregulate as many LDL receptors as possible: Formulary issues aside I'd start with Crestor 20 mg daily. There is little likelihood any generic statin could normalize LDL-P levels in the > 2000 nmol/L range. The statin alone (even the mighty Crestor) is unlikely to upregulate enough LDL receptors: thus we need to add Zetia 10 mg or 6 WelChol tabs a day. Because the CAC is zero and we have time to play, for compliance sakes I'd go with Zetia. The BAS could bring glycemic control (if needed) and likely help delipidate foam cells by inducing macrophage RCT (but this is not needed yet as the CAC is zero). Of course fenofibrate (TriCor, etc) or Niaspan cld help address the TG-rich lipoproteins (remember the very high large VLDL-P level) as well as help shift LDL size, making the apoB on the LDLs more amenable to LDL receptor induced removal. Either niacin or fibrate would also help HDL functionality. With the TG in the 165 range, and no T2DM, I'd be inclined in this man to go with Niaspan added to the Crestor or Crestor/Zetia rather than the fibrate (or WelChol). I see no lipid indication for N-3 fatty acids in this patient. Of course because of his risk and Met Syn he should resume the ASA unless there is some reason not to do so.

So is it time for LDL-P or apoB measurement for everyone. In my mind, yes. We would save a lot of time and money by simplifying risk assessment. We could abandon lipid profiles and stop making inaccurate risk-assessment guesses using lipid concentrations. The Thirty Person - Ten Country consensus published last year (Journal of Internal Medicine 2006; 259: 247–258) clearly favors that approach (By the way the thirty people were among thirty of the worlds top lipidologists). The time is NOW to realize the illegal dumping of cholesterol into our arteries is a particle (lipoprotein) driven disease. We must be able to readily and accurately diagnose those illegal dumpers (using particle, not lipid, concentration tests) and eradicate them with aggressive TLC and lipid-modulating medication. The sooner our third party payers recognize this, the better.

LIPID CASE # 202

Merry Christmas Lipidaholics: I was asked about the following case about a women with a family history of heart disease, who is a"naturalist" with a love of herbal medication. She uses 4000 mg of pure natural fish oils/day. Her past history includes a cholecystectomy. She has a normal BMI. Two months ago she had the following lipid panel:

TC = 221 LDL-C = 155 HDL-C = 42 TG = 121 and Non HDL-C = 179

After some coaxing her provider got the patient to agree to trying ezetimibe (Zetia) 10 mg daily. The patient was 100% compliant for three months and had a repeat panel:

TC = 225 LDL-C = 164 HDL-C = 48 TG = 63 Non HDL-C = 177

The patient and clinician were disappointed with this response, as Zetia's package inserts would have one expect a 15-20% drop in LDL-C. I was asked if the absence of the gall bladder might affect Zetia's action.

DAYSPRING ANALYSIS: No the gall bladder (GB) is irrelevant to the patient's lipids: it is simply a storage organ for bile acids, phospholipids and cholesterol: Without the GB, the bile and cholesterol simply flows to the intestinal lumen without being stored. So having or not having a GB plays has no effect on the amount of biliary sterols or bile acids that reach the intestine in a

24 hour period. With an intact GB, those molecules are delivered postprandially: without a GB they are constantly delivered.

Before we figure out what Zetia did or did not do, we need to review how the intestine and liver handles sterols (this happens to be what my chapter in Therapeutic Lipidology covers). Cholesterol exists in an esterified or unesterified (free) state. The free cholesterol (FC) is an alcohol (sterol) with a hydroxy (-OH) group at the # 3 position and the ester (cholesteryl ester or CE) has a fatty acid replacing the -OH. The most common FA that esterifies cholesterol is oleic acid, forming cholesteryl oleate. Every cell in the body can synthesize cholesterol in a series of over 37 steps with the rate limiting step being catalyzed by HMG CoA reductase. Another crucial step is that catalyzed by squalene synthase. For FC to be stored for future use or to be transported by lipoproteins, esterification occurs: within the endoplasmic reticulum of cells using an enzyme called acylcholesterol acyl transferase 2 (ACAT-2) or within lipoproteins using an enzyme called lecithin cholesterol acyltransferase (LCAT). If a cell wants to export CE, it must de-esterify it to FC (the form that can pass through a cell membrane).

The cholesterol consumed in the diet (300-600 mg daily) consists of both FC and CE (20% CE and 80% FC), whereas all of the cholesterol in the bile is FC (1200 mg/day). The same amount of noncholesterol sterols are also usually ingested. As cholesterol is eaten the CE component is acted upon by esterolases in the GI tract which transform some of the eaten CE to FC. The CE that is not converted to FC cannot be absorbed by the intestine (see below). So if one eats 500 mg of cholesterol, maybe 100-200 mg is CE only some of which is converted to FC. This joins with the 1200 mg of bile FC. It is obvious the vast amount of FC in the intestine is of biliary origin, not dietary origin. It should be obvious why restricting cholesterol in the diet is unlikely to play a major role in lipid control. In cells the majority of FC synthesis is from FA, and that should be the major dietary advice to lower cholesterol: restrict saturated fat.

As soon as FC (CE cannot be transferred from hepatocyte to bile) is secreted from the liver to the bile, through the hepatobiliary canalicular membrane via an ATP binding cassette transporter G5 and G8 (ABCG5, ABCG8), it mixes with biliary bile acids and phospholipids forming biliary micelles. Since the bile acids and phospholipids are amphipathic molecules (has a polar and nonpolar surface: i.e. water soluble and non water soluble) they are soluble in aqueous intestinal juices. Once in the intestine dietary noncholesterol (plant and shellfish) sterols and fatty acids also enter the micelles. Micelles, once loaded up with lipids enter to the microvilli of the intestinal brush border (they are like a little ferry boat transporting lipids). Fatty acids pass via diffusion and fatty acid transport proteins into the enterocyte. The sterols are pulled in by what used to be called a sterol permease (a protein that permits sterols to enter) but has now been identified as the Niemann-Pick C1 Like 1 (NPC1L1) protein. There are other proteins and processes involved with sterol entry (but get the book and read my chapter for more advanced discussion). Only FC enters the micelle and only FC or unesterified noncholesterol sterols can gain entry into the enterocyte: CE is not absorbed.

So at any given moment, small intestinal sterols come from 1) eating, and 2) noncholesterol sterols and FC (and occ noncholesterol sterol) of hepatic origin in the bile: (bile enters the intestine as constant diffusion in those lacking a gall bladder or in those with a GB, postprandially after GB contraction. Over a 24 hour period the same amount of biliary FC enters the gut: gal bladder plays no role.

Although the average person absorbs about 50% of the FC in the proximal small intestine, the cholesterol absorption varies tremendously between individual patients. Some are hyper (70-90%) and some are hypoabsorbers (20-30%). If someone is a hypoabsorber they have very little expression of NPC1L1 the protein required for sterol delipidation of micelles and entry into the enterocyte. It is very likely that the patient under discussion is a hypoabsorber of cholesterol and thus has very little intestinal expression of NPC1L1 protein. Ezetimibe's (Zetia) main mechanism

of action is to block the NPC1L1 protein from working. A person who has little expression of NPC1L1 protein obviously will have very little response to Zetia.

There are ways to prove this: 1) measure plasma noncholesterol sterol levels: they will be extremely low in hypoabsorbers. This is only practical in research settings. 2) Observe the response to a statin. This patient has a high LDL-C level. If it is not coming from over absorption of cholesterol, it hast to be due to over production. Any person who is over producing cholesterol will have lots of HMG CoA reductase. The more of that enzyme that is present the more efficacious will be a statin. If one prescribes what NCEP calls the standard dose of a statin (Crestor 5-10, or Zocor 20-40, or Lipitor 20) there should be a reduction of LDL-C by 35% in the average person. However if the same dose is given to someone with lots of HMG CoA reductase, the LDL-C reduction will be significantly greater. This patient would likely respond very ell to even small doses of a statin.

Conversely if a statin is given to a hyperabsorber of cholesterol there will be a very poor response to the statin ("hyporesponder"). If some one is over absorbing cholesterol there will be a marked reduction of cellular expression of HMG CoA Reductase and hence less cholesterol synthesis. Persons with little HMG Co A reductase expression obviously cannot respond to statins. This it is why when one prescribes a statin and sees little response, it is silly to increase the dose of the statin. The problem is not hypersynthesis but rather hyperabsorption and the clear therapeutic response is to prescribe Zetia. Since in most of our patients we have no clue who is a hyper or hypoabsorber or synthesizer, it certainly makes sense to combine statin and ezetimibe therapy to achieve goal. Please see: Life Sciences 80 (2007) 505–514

This also makes sense for another reason: Remember the concept of statin tachyphylaxis. This was first described with Lipitor but has been seen with all statins. The statin works well but over time the LDL-C starts to rise somewhat again. The reason behind this was not understood for some time. We now realize the following: When one reduces cholesterol synthesis with a statin, the live must obtain cholesterol elsewhere: it does that upregulating LDL receptors (clear apoB LDL particles from plasma). This clearly and rapidly reduces apoB and LDL-C. However, there is also a response to the decreased cholesterol synthesis by nuclear transcription factors which reduce excretion of cholesterol into the bile (down regulation of hepatobiliary ABCG5, G8), reduce bile acid synthesis, and increase biliary cholesterol to return to the liver through upregulation of NPC1L1 protein in hepatobiliary canaliculi. In the intestine there is an upregulaltion of NPC1L1 and downregulation of G5 and G8 with an overall effect of increasing intestinal absorption of FC.

An interesting study was published this year showing the effect of Zetia when given to pure vegans (eat zero cholesterol). Why do not they die of cholesterol deficiency? Indeed they are often very healthy. Humans synthesize about. Guess what? Zetia reduces cholesterol absorption the exact same in Vegans or in beef eaters which clearly proves the main action of ezetimibe is to block the absorption of biliary cholesterol, not dietary cholesterol. (J. Lipid Res. 2006. 47: 2820–2824.)

Lastly, this naturalist may bot want a chemical like a statin! Well lovastatin, simvastatin, and pravastatin are all distillates of their yeast precursors. Formerly they were called the "natural statins." So the easiest way to control the LDL-C long term in this patient is to use one of the natural statins with ezetimibe (to prevent statin tachyphylaxis). So one could go with one of those statins and make her formulary happy, but if not at long-term goal with that, it seems like Vytorin would be an obvious choice to save a co-pay.

For excellent reviews of cholesterol absorption please see: GASTROENTEROLOGY 2005;129:718–734 and Annu. Rev. Physiol. 2007. 69:221–48. If studying for the,lipid board exam, these are a must.