Case # 280 Cutting Edge High Level CV Assessment

Recently I got an e-mail from a 71 year old physician who sent me a pretty exhaustive CV story (see below). It is a revealing story and basically shows you how poorly we might do if one religiously sticks to evidence based medicine to conventional guidelines as the "be all." Also keep in mind this patient's story covers decades and physicians did not know or have available to them what we now know and have. I will insert my comments in red font throughout the clinical story which is presented in the first person narrative from the doc.

This case will demonstrate if you are managing you CV patients with lipid panels you are not likely recognizing the entire pathological process and almost certainly not being aggressive enough with therapy. We are starting to get newer guidelines or expert position statements that are going beyond the standard lipid panel as per NCEP. The "change of thinking" was first expressed in the brand new AHA Women's Guidelines (Circulation. 2011;123:1243-1262**)** which noted: "*A major evolution from previous guidelines to the 2011update is that effectiveness (benefits and risks observed in clinical practice) of preventive therapies was strongly considered and recommendations were not limited to evidence that documents efficacy (benefits observed in clinical research); hence,* ***in the transformation from "evidence-based "to "effectiveness-based" guidelines*** *for the prevention of cardiovascular disease in women, the panel voted to update recommendations to those therapies that have been shown to have sufficient evidence of clinical benefit for CVD outcomes."* There are now 7 national and international guidelines or statements advising particle concentration testing using measured apoB or LDL-P via NMR.

After the physician sent me all of the info below he stated: *"I look forward to your comments and suggestions"*

Family history: Father had MI and CABG in early 60s and also T2DM diagnosed then; later an ischemic CVA and died age 83 with CHF. Maternal grandmother had DM. Mother died at age 88 of dementia. 60 year old brother had a sudden diffuse aortic dissection 2 years ago without aneurysmal dilation. He has some residual celiac axis stenosis but has not had any surgery and has remained stable.

Habits: no smoking, infrequent alcohol, 1-3 cups coffee

The doc states: I first became aware of having strikingly low HDL-C levels in my 30s, usually in the low 20s or even down to 16 mg/dL as I recall. The first lipids I can document are from 1994 at age 55:

TC = 176; TG = 335; HDL-C = 26; LDL-C = 83; VLDL-C = 67;
Apolipoprotein A1 = 109 (range listed as 85-157)
Apoprotein B = 89 mg/dL (range listed as 49-149)

TD in red font: I calculated: Non HDL-C = 150; TG/HDL-C = 12.8 as no one was using

those parameters in 1994. This looks like a typical TG/HDL lipoprotein axis disorder (the term originated with Szapary and Rader in 2004: Am Heart J 2004;148:211–21) which is indicative of insulin resistance. The only bizarre finding is the only slightly elevated apoB of 89 (would have expected much higher levels), but the apoB assays back then were fairly new and who knows how reliable. The perfect LDL-C is of little meaning in 2011 but almost certainly reassured all back then. That apoA-I value is very low. The very high TG/HDL ratio is associated with insulin resistance, increased total and CV mortality and the presence of small LDL particles. Of course using Framingham risk scoring he has a 6% 10 year risk of an event (low risk) and he was at NCEP ATP-II LDL-C goal. There was no non-HDL-C goal at that time. Even using ATP-III nothing changes except he might be a metabolic syndrome which would intensify his risk to moderate and thus he would still be at goals (non-HDL-C in play using ATP-III). If you apply the 2004 NCEP ATP-III addendum you could make the case there is an option to get the non-HDL-C to < 130 mg/dL. Using the Sniderman formula (Journal of Clinical Lipidology (2007) 1, 256–263) the Fredrickson lipoprotein phenotype in this man is IIB.

I had started at age 43 thru Harvard's Physician Health Study. I tried Niaspan (extended-release niacin) several times between ages 55-60 but couldn't hang in there due to flushing. At age 61 in 2000 showed TC = 194; TG = 305; HDL-C = 28; LDL-C = 105; non-HDL-C = 166

Non-HDL-C was actually a tad higher with this profile compared to the first one but they were still operating under ATP-II which had no non-HDL-C recommendations. Of course the proper first line drug (although it was no appreciated back then) would have been a statin.

I then went back to and stayed on Niaspan and transiently took Lopid (gemfibrozil).

They had Helsinki data as well as brand new data from VA HIT (N Engl J Med 1999;341:410-8). The latter showed Gemfibrozil would reduce events in men with CAD and low HDL-C and unremarkable HDL-C. The benefit at that time was thought to be due to raising HDL-C and lowering TG. However NCEP ATP-III dismissed the HDL-C rise as playing a role because although the 6% rise was statistically significant the absolute value rise of 1.8 mg/dL had no clinical meaning (within the realm of the assay error rate). Subsequent analysis showed the only patients helped by Gemfibrozil where those with HOMA calculated IR and in those patients the benefit of the drug indeed had no relationship to either baseline or on therapy HDL-C or TG (Arch Intern Med. 2002;162:2597-2604). Ultimately Otvos et al (Circulation. 2006;113:1556-1563) showed the benefit of gemfibrozil was related to a rise in total HDL-P (increased small HDL-P and reduced large HDL-P) and a decrease in total LDL-P (decrease in small LDLs and increase in large). Fenofibrate (namely TriCor) did not enter the US until 1998.

Another totally major paper was pretty much ignored in 2000. The AF-CAPS TexCAPS study (primary prevention trial of men and a few women with low HDL-C) showed that on-treatment apoB, especially when combined with apoA-I to form the apoB/AI ratio, may be a more accurate predictor than LDL-C of risk for first major event. (Circulation

2000;101:477-484). Very few in the real world were paying any attention to lipoprotein concentrations back then. It was an LDL-C world. Even fewer ever heard of a new company in North Carolina called LipoMed.

A routine treadmill in February 2001 showed 'borderline" ischemic ST changes and fatigue (no chest pain) as a symptom. A cardiac nuclear scan was considered essentially negative. The TC stayed in range of 190-205; TG were variable at 130-305; HDL-C ~ 33-39 mg/dL.

Again, non-HDL-C (~ 165) is nowhere near current goal. Note ATP-III (Executive Summary) was not published until May of 2002 (JAMA, May 16, 2002.Vol 285, No. 19 2486-2497) and thus almost no one was aware of non-HDL-C concept in early 2002.

Lescol was added and then I later switched to Zocor.

Finally a statin was added – For whatever reason Lescol was used first but no doubt the switch to simvastatin occurred when the Heart Protection Study was published in July 2002 (Lancet 2002; 360: 7–22) although its data was known a bit prior to that. The dose of simvastatin used in the HPS was 40 mg daily.

How many realize that in September 2001 (Circulation. 2001;104:1577-1579) the AHA issued an update on its secondary prevention guidelines and encouraged increased consumption of omega-3 fatty acids. Yet there is no mention that they are being used in this case. In 2002 there was an official AHA statement on Omega-3 which advised those with confirmed CHD to consume ~1 g of EPA + DHA per day, preferably from oily fish. EPA+DHA supplements could be considered in consultation with the physician (Penny M. Kris-Etherton, et al: Circulation. 2002;106:2747-2757). FYI, Penny is now the president of the NLA and one of the world's nicest persons.

Something else showed up in September of 2001: The HATS angiographic trial suggesting regression of plaque with statin + niacin (N Engl J Med 2001;345:1583-92). In retrospect this trial, based on unbelievably small numbers of people but used extensively in marketing unfortunately made people think of niacin as an HDL drug when in fact it is an apoB drug. No one paid the least bit of attention to the impressive apoB data which was in the original paper. Credit goes to Greg Brown for even measuring it.

Then in early 2003 at age 63 I had a coronary angiogram because of the onset of angina, showing right coronary dominance and 80-90% ostial and distal lesions and about 50% mid right lesion. On the left there was a 90% 1st diagonal. lesion and a couple of less severe areas. I then waited a week until the Cordis drug-eluting stents were officially released and had the 4 worst lesions stented. The precath lab showed TC = 183; TG= 194; HDL-C = 30; LDL-C = 114.

Lipid concentrations, now applied to an obviously no longer debatable high risk man, (2004 NCEP addendum not yet published and thus there was no very high risk category

in 2003) were now not at goal for a CHD patient (LDL-C < 100: technically because the TG were now < 200mg/dL, the non-HDL-C was not applicable). We now know that no matter what the TG level, non-HDL-C out performs LDL-C as a risk factor (Am J Cardiol 2006;98:1363–1368). However using today's knowledge or the 2004 NCEP addendum most would shoot for the optional LDL-C goal of 70 mg/dL and non-HDL-C goal of < 100 mg/dL. Looking at the above numbers the non-HDL-C is 153 (much too high). For anyone looking the TG/HDL-C is still grossly abnormal at 6.4 (although it should not be used as a goal of therapy). I hope my readers are thinking this guy is an atherogenic lipoprotein nightmare! But how many are really thinking outside the box and making a long list of potential other metabolic, genetic, coagulation, issues that should be evaluated and addressed.

Rehab went smoothly but the progress and post-rehab treadmills both showed ischemic changes but no symptoms. Because I was determined to become very active with exercise, I had a follow up coronary angiography in August 2003 and that fortunately was unchanged from post-stenting and showed good hemodynamics. I then continued Zocor at 40 mgs, progressively increased Niaspan to 1500 mg, took food supplement fish oil as well as Lovaza in varying amounts, Toprol and Altace, and continued aspirin. The lipids ranged: TC = 120-130; TG = 75-95; HDL-C = 33-43 mg/dL

The LDL-C and non-HDL-C would be at goal with those numbers. Look closely: What happened when Niaspan was added to the statin: there was a dramatic drop in TG, a significant rise in HDL-C, dramatic drop in TC and a big improvement in non-HDL-C which for the first time is at goal (now in the 90 range). Of course back then no doubt all were celebrating niacin's ability to raise HDL-C. Back then no one would have cared much that it lowered TG so dramatically and few knew the importance of apoB, LDL-P or even non-HDL-C. Please never fail to remember non-HDL-C is simply a surrogate of apoB which is simply another way of assessing LDL-P. Yet few ever gave credit to niacin on anything but what a great HDL-C rising drug it was! Amazing how misunderstood this drug has been.

Unfortunately I became less diligent about exercise and did the male thing of weight/belly building. In late 2009, I was alarmed with onset of recurrent angina, started more serious weight loss, and finally gave up my denial and had coronary angiography in early 2010. I stayed awake enough to be aware of results and to watch my desired easy fix of more stents but was quite dismayed to see the prominent multiple lesions, especially at bifurcations and appearing "soft"-fragile. My cardiologist felt it was unwise to do these bifurcation stents but I was stubborn and went to the Mayo Clinic. They initially thought they could do the stenting but during their preliminary study came to the same conclusion. I then had CABG with internal mammary to LAD and 2 vein grafts. I have mostly suppressed the post-op course. Rehab went well, and metformin was started for the TGs and HDL-C and a borderline HgbA1C. Labs at that time in 2010: TC = 108; TG = 64; HDL-C 44; LDL-C 51.

That lipid panel is certainly at NCEP ATP-III lipid goals. Finally the glycemic path to diabetes which could have been predicted with the very (very high TG/HDL-C ratio) first

profile is emerging. The lipid benefits of metformin have been exaggerated for a long time. There is no serious data that it seriously improves TG or affects HDL-C (which is not an NCEP specific goal of therapy anyway). To me the real reason for metformin use was to delay the onset of T2DM.

I've had variable TSH levels for 10+ years, usually in the 4s, occasionally down to 2.6, but then 7.1 with free T4 of 0.72 (0.71-1.85) in August 2010. Replacement started then and gradually increased. I've been checked twice for sleep apnea and seem to have improved with weight loss. Follow up echocardiogram was totally normal at the end of 2010. Labs at that time were: TC = 121; TG = 52; HDL-C = 49; LDL-C = 62. Other labs: creatinine 1.4 (0.8-1.3); TSH 1.7; HgbA1c = 5.7 (4.0-6.0).

The doc concludes with a listing of his current medications
AM: metformin 1000 mg. PM: metformin 1000 mg
Levothyroxine 75 mcg
Zocor 20 mg daily and Niaspan 2000 mg
Vitamin D3 2000 IU
Altace 1 mg daily and Toprol 2.5 mg
Folic acid 600 mcg
Fish oil 1400 mg and Fish Oil 2800 mg and Lovaza 1000 mg
B12 2500 mcg sublingual 3 times/week
Centrum Silver daily
Aspirin 365 mg

The physician then concluded: "*I am entirely open to any evaluations you feel are appropriate thru your preferred lab. I have been concerned that my therapy in some fashion has possibly been causing increased atherogenicity--such as abnormal type or particle number of HDLs, increased insulin resistance, etc.*"

I immediately advised the doc that no truly sensible recommendations could be made unless he pursued modern CV testing and I advised him obtain the full CV profile at my preferred lab, namely Health Diagnostic Labs (HDL) in Richmond, VA. It is where I and my associate (a non-lipidologist internist) now send 100% all our testing. As many of you know I became part of their advisory board in mid-2010. Until then I was pretty much a lipoprotein guy, but after more than a year of performing comprehensive testing (which of course includes the full NMR analysis) I am amazed by what I have been missing. So back then I would look at the lipid numbers in this man and guess was risk likely eliminated but I for sure would demand NMR-determined lipoprotein concentrations to verify that they are also at desirable levels. Does anyone reading this case think we are going to find much more, especially treatable risk with a lipid profile showing a TC of 121, a TG of 52, an HDL-C of 49 and an LDL-C = 62?

WHAT WAS FOUND: all of the subsequent discussion is me (TD) so it is back to black font. This 71 year old man has significant and seemingly at this time stable CAD and is status post CABG, angioplasties. He is on BP treatment, combination lipid therapy,

omega-3 therapy, insulin resistance therapy, aspirin, thyroid-replacement therapy and vitamins.

So what dis major-league testing bring to the case? The HDL CV profile revealed an apoE3/E4 genotype with a normal lipid profile (with everything well at goal) and much more importantly spectacular levels of LDL-P and apoB: well below the 5th percentile population cut points. This is not surprising as the patient is taking two very potent apoB (LDL-P) lowering drugs: statin plus high dose extended release niacin. Keep in mind that seemingly successful therapies may have downsides: so keep reading. But wait a minute: do statins or niacin have any downsides?

TC = 113 HDL-C = 46 LDL-C = 42 TG = 66 Non HDL-C = 67
ApoB = 40 mg/dL
LDL-P = 683 nmol/L

Despite the excellent lipid and apoB containing lipoprotein concentrations, the total HDL-P and apoA-I both are pretty low at 28 umol/L and 125 mg/dL respectively. Looking at the full NMR report the HDL size is large (10.0 nm) and the large HDL-P is high (10.3 umol/L): my guess is way back when, at baseline prior to therapy because of the high TG, the total HDL-P was even lower and the HDL size was small and the large HDL-P would have been very low. Obviously all that changed with statin and especially niacin therapy. Here is the dilemma of niacin: via several mechanisms niacin increases HDL size and large HDL-P concentration (inhibits hepatic lipase, reduces CETP activity) but does nothing to increase total HDL-P. So niacin paradoxically increases HDL-C but does nothing to the far more important parameter HDL-P. If one has "X" number of HDL particles and a drug enlarges those particles, but does not increase particle number, HDL-C goes up – but if CV benefit is related to HDL-P but not HDL-C, then the drug will not benefit persons with low HDL-C. It is crucial for all to know what how various drugs remodel HDL particles: do they affect size, core composition, and most importantly particle number.

The sdLDL value is normal. There is a slight increase in % sdLDL. However who cares? Those measurements really have no meaning in the face of low total LDL-P. Despite their name, those tests are not particle or particle size measurements, but rather indicate the amount of cholesterol trafficked within small LDLs or the % of LDL-cholesterol that is in the small particles. A more accurate label would be sdLDL-C and % sdLDL-C. Based on several trials we now know once you have total LDL-P, such subparticle measurements have no real statistically significant clinical significance. On the full NMR report (that comes with the HDL report) the LDL size is actually quite large at 21.2 nm and small LDL-P, is extremely low at < 90 nmol/L. The perfect total LDL-P is due to statin/Niaspan. The niacin has also shifted the LDL and HDL size upwards, thus the very low small LDL-P. All of the LDLs are large but the key parameter is the very low LDL-P concentration.

The LP(a) and Lp(a)-C [which indicate apo(a) mass and the amount of cholesterol carried in Lp(a) particles] is a bit high and that adds to CV risk, but the goal of therapy in such

patients is to aggressively lower total LDL-P which has been accomplished. There is no doubt that these numbers were worse prior to statin/niacin therapy. There is little evidence that reducing apo(a) mass per se is or is not beneficial. But reducing the number of LDL particles carrying apo(a) meaning of Lp(a)-P surely is. Right now the only surrogate we have of Lp(a)-P is not apo(a) mass but rather Lp(a)-C. No doubt an elevated Lp(a)-P was a major contributor to the CAD in this man, but it is well controlled at this time. HDL is one of the few labs offering Lp(a)-C.

HDL measures several inflammatory markers including hs-CRP, fibrinogen, lipoprotein phospholipase A2 (Lp-PLA2) and myeloperoxidase (MPO). Of great importance in this patient is that all of the inflammatory markers are normal: this is especially important in folks with Lp(a) issues [as apo(a) is a sink for trafficking oxidized lipids]. These normal values suggests that any plaque present in this patient is stable.

The NT-proBNP (N-terminal prohormone of brain natriuretic peptide) is a bit elevated at 375 pg/mL and that is always a worry. It is a myocardial protein which unless there is stretching of cardiomyocytes it is not present. It is a predictor of CV mortality, sudden death and ultimate CHF. A recent echo was normal but if this value persists there has likely been some myocardial damage from the long standing atherosclerosis: I'd repeat it but also order a Galectin-3 level (used to diagnose myocardial fibrosis). If both are abnormal, be sure the BP and all other treatable risk is well controlled. Fortunately the patient is on the ACEi and Toprol. NT-proBNP is a marker to be taken very seriously and should be part of the work up and periodic follow up of all CHD patients. Ordering a high sensitivity troponin-I might shed some insight on underlying ischemia. I get that test through Singulex labs (http://www.singulex.com/news.html).

Coagulation markers: The Factor V Leiden mutation is present (a once per lifetime test) and thus there is risk for VTEs. Precautions must be taken prior to surgery, long flights, immobility, fractures with a cast, etc. Should Coumadin ever be required, the patient will will respond well as he has normal warfarin metabolism enzymes. However the VKORC1 3673 genotype (vitamin K epoxide reductase complex subunit 1 polymorphism) is a G/A genotype: carriers of the A allele respond to a lower initial dose of warfarin than do carriers of the G allele. It should be noted that this effect is also additive, and that heterozygotes (like this patient) respond to an intermediate warfarin dose, and homozygous carriers of the A allele respond to the lowest dose of warfarin, and are at the highest risk for warfarin-related adverse events. Recent clinical studies showed that individuals with the A allele require a 28% decrease in the therapeutic warfarin dose per allele and this SNP is used as an important predictor of initiation dose for warfarin. http://www.pharmgkb.org/search/annotatedGene/vkorc1/variant.jsp

The AspirinWorks (urinary 11 dehydrothromboxane B2) test is pending. This metabolite of platelet over activity if abnormal is associated with a 4-fold risk of CVD events. One would expect it to be normal in a person on full dose aspirin. However if it is not one would conclude aspirin resistance is present. Should the need for Plavix ever arrive, this man has a gene abnormality (CYP2C19 *1/*2 genotype) which indicates his body would have difficulty converting the prodrug clopidogrel to its active metabolite and other anti-

platelet drugs should be considered. The Plavix package insert now advises this test be done on those about to receive Plavix. Think of all of this incredibly useful coagulation info that is now known about this man that will surely be useful in anticipating coagulation therapies --hardly useless information.

Several markers of insulin resistance were present: despite the 2 grams of metformin. There are abnormal glycemic issues including a HgbA1c of 6.0 as well as a fairly high insulin level (24 mu/ml where < 10 is normal) and an abnormal free fatty acid concentration (which is associated with HTN, elevated glucose and beta-cell death). Looking at the full NMR lipoprotein analysis which provides the Lipoprotein Insulin Resistance (LP-IR) Score we do not see any TG-rich lipoproteins (large VLDL), or small LDL size, or small HDL size all of which are consequences of insulin resistance. Indeed the Lp-IR score is quite low suggesting no IR. However this score is not validated to be of use in persons on medication especially niacin. Niacin is known to potentially aggravate insulin resistance, yet because it increases LDL and HDL size and decreases large VLDL-P all of which paradoxically reduces the Lp-IR score. The score was indeed very low at 13, but is not useable because of the niacin.

Vitamin D, a CV risk factor, is normal on the current regimen. Both homocysteine and uric acid are elevated and no doubt part of the explanation is the high dose niacin use. However the patient has a fairly high homocysteine level of 17 umol/L and an abnormal methylenetetrahydrofolate reductase (MTHFR) C/T genotype and methylfolate (FolaPro or Metanx) rather than folic acid might be a better therapeutic choice, to reduce the homocysteine.

The Cystatin C (a very sensitive marker of renal disease) level is slightly abnormal and confirms that the slightly elevated creatinine is associated with reduced eGFR: but the clearance is still fine at 72. This should be followed closely. Attack any hypertension aggressively and fight the IR. Cystatin C is especially useful in those with decreased muscle mass, liver disease. However apart from what it tells one about renal dysfunction it is also a predictor of CHD and CHF in older folks. Cystatin C is produced throughout the body at a constant rate and removed and broken down by the kidneys, it should remain at a steady level in the blood if the kidneys are working efficiently and the GFR is normal. Concentrations of Cystatin C are not affected by gender, age, or race and Cystatin C is not affected by most drugs (see below), infections, diet, or inflammation. See http://labtestsonline.org/understanding/analytes/cystatin-c/tab/test

Fatty acid analysis: The omega-3 index is excellent at 10.1% and clearly the patient is taking proper amounts of omega-3 fatty acids. The trans-fat index is on the high side at 1% (n <0.7%), so obviously the nutrition is not perfect. Fatty acids are trafficked for the most part in TG and in phospholipids. So by separating out red blood cells and analyzing the fatty acid content of their surface phospholipids one gets fatty acid indices: If 8 of 100 fatty acids are Omega 3, then the Omega-3 index is 8% (desirable). Most Americans run 6%and those not making an effort to eat properly or eating fatty fish run at 4%. A low Omega-3 index is associated with significant CVD risk.

With respect to the markers of cholesterol absorption and synthesis: There is a clear indication of hyperabsorption and decreased synthesis with elevations of sitosterol/cholesterol, campesterol/cholesterol and cholestanol/cholesterol ratios. Elevated absorption markers have significant associations with CV risk in many studies including Framingham and PROCAM. It may be associated with the apoE4 allele as well as being induced by both the statin and niacin. Persons with strong family history of premature CHD also have increased absorptive markers. There are studies that show both drugs can through a variety of complex mechanisms increase sterol absorption (J. Lipid Res. 2003; 44:800–806). Since hyperabsorption of sterols is an additional risk factor and will therefore have to be addressed therapeutically.

The low desmosterol and desmosterol/cholesterol ratio (a cholesterol synthesis marker) indicates the statin is doing exactly what it should be doing (inhibiting cholesterol synthesis). There are numerous studies that show one of the consequences of statin use is that the body, as compensation for the statin-induced reduced cholesterol synthesis increases intestinal sterol absorption. Little known to many is that statin-induced depletion of hepatic cholesterol pools also induces a backward flux of cholesterol from the bale back into the liver. For lipidologists interested in understanding how this is so, hepatic and enterocyte cellular cholesterol depletion upregulates the sterol influx protein (Neiman Pick C1 L1) and down regulates the sterol efflux protein the ATP Binding Cassette Transporters ABCG5 and ABCG8. This action diminishes the ability of a statin to more effectively reduce cholesterol. For a more thorough discussion of this please see http://www.lipidcenter.com/pdf/Understanding_Sterols_Stanols.pdf

Finally what about the apoE3/E4 genotype? The E4 genotype puts one at increased CHD risk and is often a signal that significant therapy including lifestyle and medication will be required to achieve goals. This patient has already proven that as he has required powerful combo therapy and yet still has some abnormal lipoproteins (low HDL-P) and lipid issues (hyperabsorption of sterols). Of long term concern is the association of the E4 allele with Alzheimer's disease (AD). This is more worrisome if there is a family history (as in the patient's mother) and the risk would be higher if he had E4 homozygous genotype. Here is likely what we can do in 2011 to forestall AD manifestations: 1) eliminate insulin resistance preferably with lifestyle (very low carb diet) but also meds if needed. 2) Continue to push Omega 3 fatty acids (a crucial CNS FA) and keep the Omega-3 index well above the 8% value (the current 10% is superb). Personally I'd prefer the prescription OM3-FA or Lovaza (off label use) as the FDA guarantees its purity (important when one is taking very large doses). Finally after age 50 have someone competent in performing careful short term memory testing on a yearly basis. At the first sign of slippage, consultation with a neurologist is indicated to see if some of the early therapies that delay AD onset should be used. Right now this patient need to sit down with a nutritionist familiar with the issues discussed throughout this newsletter (they are few and far between). HD Lab provides at no cost a competent Healthcare Coach team where a patient can get serious on-going nutritional and exercise advice on how to better tackle IR and CV risk.

I hope this case demonstrates how much CV ugliness (residual risk) was still going on in an aggressively treated person with severe CHD. Much of the newly discovered risk is treatable (using either evidence-based or effectiveness-based medicine). The reality is most of that "residual risk" will be missed without the sophisticated testing the HDL offers. So with the new information at hand, how should the treatment regimen be altered? There is a lot to consider.

The LDL-P is fine but the HDL-P is too low. There is hyperabsorption of sterols and there are insulin resistance issues despite the metformin. The statin/niacin combination has corrected then LDL-P issue nicely [crucial in view of the high Lp(a)]. The statin also may have helped the total HDL-P a bit but the level is still too low. Fibrates are the best available drug to raise total HDL-P (although no one should be using gemfibrozil anymore). Fenofibrate in addition to significantly raising total HDL-P (beyond what a statin can do) also significantly reduces cholesterol (and noncholesterol sterol) absorption. So one possible adjustment is to switch from statin/niacin to statin/fenofibrate or statin/fenofibric acid (FDA approved) and repeat the NMR analysis and plasma sterols in 8-12 weeks. Since fibrates do not help a statin reduce total LDL-P, it is likely (depending on how well the patient does lifestyle) that the LDL-P may start to rise (off of the Niaspan). Off the niacin I hope the hyperuricemia will return to normal and the homocysteinemia might lessen. A little know attribute of fenofibrate is its ability to significantly reduce uric acids levels but like niacin fenofibrate can aggravate homocysteinemia. If the hyperhomocysteinemia persists Metanx (methyl folate) and not folic acids should be prescribed. Although there are multiple trials that seem to indicate lowering homocysteine with B-complex and folic acid does not reduce clinical events, there has never been a trial of high risk folks <u>all of whom</u> have hyperhomocysteinemia are randomized to homocysteine-lowering therapy vs. a placebo.

If the LDL-P does worsen off the Niaspan, one could simply add ezetimibe (Zetia) and the LDL-P will rapidly return to the current level. Ezetimibe/Fenofibrate combo is incredibly effective at reducing hyperabsorption. Since this patient has such high risk and controlling insulin resistance is desirable, one could stop the statin/Niaspan combination and instead use statin/ezetimibe plus fenofibrate or fenofibric acid triple combination therapy. LDL-P should remain excellently controlled and remember that is the goal of therapy in treating patients with high Lp(a) and high Lp(a)-C. So although apo(a) mass levels may go up off niacin, Lp(a)-P or LP(a)-C likely should not on statin/ezetimibe.

There is also some consideration to switching the statin. I'd pick the statin that has the least propensity to aggravate insulin resistance if it has noninferiority to the 20 mg of the simvastatin being used. That statin is pitavastatin (Livalo) - I'd start 2 mg daily. To my knowledge it is the only statin not associated with glycemic issues or diabetes onset. It also has a cleaner pharmacokinetic profile than do other equally potent statins and this is important in a polypharmacy patient like one under discussion. It is also the best statin on raising HDL-P (as likely evidenced by its apoA-I data). It can be safely used with a fibrate with no clinically significant AUC increase.

If this physician commits to proper low-carb lifestyle, continues the metformin and follows the IR markers (perhaps checking adiponectin during future testing) the hope is to see additional improvement. If lifestyle does not happen or is not totally successful, additional therapies need to be considered: GLP agonists, pioglitazone (despite its many downside issues).

Other antiplatelet therapy (not Plavix because of the abnormal CYP2C19 genotype may be indicated depending on if the AspirinWorks test shows aspirin resistance. We do need to get a urine microalbumin and if it is abnormal, that is more justification to be on a fibrate (in addition to the ACE). In the future, because of the presence of Factor V Leiden precautions against VTEs are a must.

So what would I do- I'd simply try adding fenofibrate (fenofibric acid) to the current regimen id the hopes it would reduce the hyperabsorption of sterols, lower the uric acid, and significantly increase the total HDL-P (it reduces large HDL-P and increases small HDL-P). It might further aggravate the homocysteine and that would have to be watched. The feno might also offer significant protection against future microvascular disease. I do realize that current CV outcome data would not support adding feno to a statin where high TG (>200 mg/dL) is not present.

TAKE HOME POINTS: Please do not think there are no treatable risk factors remain when lipid concentrations and even apoB are at goal. Seek and ye might find!