LIPID CASE 268 Niaspan or statin for 1st line Rx?

This case at comes from a military base. I heard from a lipid clinic provider who said he had a patient referred to the lipid clinic from primary care for lipid management. The patient is a 38 y/o physician who has multiple sclerosis but no known cardiac disease. Family history reveals CHD in his father who had triple vessel CABG at age 67. He is normotensive, does not have metabolic syndrome and does daily exercise. He does not consume alcohol, denies active and passive smoking exposure. His only medication includes copaxone for his MS.

Here are the initial labs:

TC = 182 HDL-C = 28 TG = 74 LDL-C = 139 VLDL-C = 15 Non-HDL-C = 154

TC/HDL-C = 6.5 TG/HDL-C = 2.6 hs-CRP = 2.59 (elevated)

Based on these results, prior to the referral the primary care provider started extended-release niacin (Niaspan) 500 mg daily. The lipidologist ordered a follow up panel which included lipoprotein testing:

TC = 179 HDL-C = 32 TG = 87 LDL-C = 130 VLDL-C = 17 Non-HDL-C = 147

TC/HDL-C = 5.6 TG/HDL-C = 2.7

Total LDL-P = 1402 nmol/L Small LDL-P = 808 nmol/L LDL size is small at 20.3 (Pattern B)

Total HDL-P = 26.3 umol/L (quite low) Large HDL-P = 1.4 (quite low) HDL size < 8.3 (quite small)

Lipoprotein Insulin resistance score is reported as elevated (meaning > 50 - the scale is 0-100 with > 50 indicative of IR)

Lp-PLA2 = 222 (elevated) hs-CRP = 2.71 (elevated)

The treating lipidologist asked: "Should I start this 38 y/o man on statin therapy?" He also stated: "I feel that his LDL-P and Lp-PLA2 is a more pressing issue than treating his low HDL."

DAYSPRING DISCUSSION:

As always our first mission is to ascertain the degree of risk present. He is a male but is young. The father's problem would not be considered as premature heart disease but as a baby boomer hitting 65 next year I sort of look at CABG at age 67 as premature! A low HDL-C is considered a major independent risk factor for CHD. Since he does not have two major risk factors, he does not qualify for the archaic (no longer viable)Framingham

Risk Scoring (which I hope will disappear in ATP-IV). The LDL-C might raise some concern at 139 mg/dL. Certainly a TC/HDL-C ratio > 6 is alarming. So despite his very low HDL-C and his paternal genes, NCEP would consider him low risk: his LDL-C does not qualify for initiation of drug therapy and lifestyle would be advised. However, the patient has maxed out lifestyle. So NCEP would rather have you wait until he develops much more serious risk and/or disease and then treat. Certainly, the panel who authored the new AACF Primary Care guidelines mentioned above would see absolutely no reason to perform lipoprotein testing in this man.

Because of the low HDL-C, The first thing we must specifically ask before we go any further: is this man using anabolic steroids? Check for any sign of acne, especially on the posterior thorax. Anytime you seem a physically fit person with low HDL-C, eliminate androgen use ASAP. Despite having no guideline support to do so, the primary care clinician decided to prescribe Niaspan at the 500 mg starter dose. I presume it would be titrated to an effective dose over time. For most people 500 mg would be a lipid placebo, but to minimize flushing you must start low dose and slowly titrate. If you look at the follow up lipid panel the HDL-C did go up 4 mg/dL, which most would credit to the niacin effect, but the reality is that amount of change is within the realm of error of HDL-C testing. But more importantly let's discuss if Niaspan was an appropriate first line choice of therapy in this "low risk" primary prevention patient. My guess is the primary care doc thought his therapeutic mission was to raise HDL-C and what better than Niaspan? However, even though NCEP encourages increasing HDL-C via lifestyle and FDA approved medications, it provides no specific HDL-C goal of therapy (for the simple reason that there is no clinical trial evidence that would support a specific HDL-C goal of therapy). Now there is one small buried caveat in ATP-III that in HIGH RISK patients with isolated low HDL-C, fibrates or niacin can be used to raise HDL-C. However this patient is not high risk, is he?

The ADA/ACCF2008 consensus statement on management of lipoproteins in patients with cardiometabolic risk state that the proper treatment of low HDL-C is to prescribe an apoB (LDL-P) lowering drug - namely a statin. They state that because in the overwhelming majority of patients who have CV risk with low HDL-C, the number of atherogenic lipoproteins (measured by apoB or LDL-P) is always elevated. ATP-III even suggested that low HDL-C was simply an epiphenomenon indicative of elevated apoB. So if one wanted to start a drug in this patient, a statin would have been a more appropriate choice. Statins are the best apoB lowering monotherapy (way better than niacin) and they unlike niacin have primary prevention outcome data. Yet why commit someone to lifelong statin therapy if he did not need it. This is a case where you absolutely have to order apoB or better yet LDL-P. If it is high, start the statin, if it is low the patient may well have a low HDL-C (hypoalphalipoproteinemia) disorder not associated with atherosclerosis.

How about the somewhat elevated hs-CRP - According to JUPITER, this man might benefit from statin therapy? Well JUPITER studied older folks who did not have LDL-C values of 139 mg/dL. But nonetheless I would advise that whenever you see elevated hs-

CRP, strongly suspect insulin resistance and until proven otherwise assume LDL-P (apoB) is elevated. That (apoB elevation) certainly was the case with the JUPITER study.

Moral of the story: **Unless TG are > 500 mg/dL, statins, unless they cannot be used (allergy, intolerance) are always without question the first line lipid drug. The reason is the cause of atherosclerosis is hyperbetalipoproteinemia and by far the best apoB lowering monotherapies are statins. Order of statin efficacy (looking at max dose) with apoB: rosuvastatin (Crestor 40), atorvastatin (Lipitor 80), simvastatin (Zocor -but who uses 80 mg), pitavastatin (Livalo 4), lovastatin (Mevacor 80), fluvastatin (Lescol 80), and pravastatin (Pravachol 80). Yet adding ezetimibe or colesevelam to any statin dose (especially high dose statin) also maximizes apoB lowering**

The treating doc ordered lipoprotein testing, specifically the NMR LipoProfile (www.liposcience.com or www.myhdl.com) as well as lipoprotein associated phospholipase A2 (Lp-PLA2). The measurement of atherogenic lipoproteins using LDL-P was an absolutely essential test if you really wanted to truly understand this man's real risk. When I first read the case **the red flag in this man is the vast majority of folks with low HDL-C have hyperbetalipoproteinemia.** But to effectively plan treatment we have to know the extent of the elevation of LDL-P.

So we saw that not only was the LDL-P is elevated at > 1400 nmol/L but the Lp-PLA2 is worrisome. . Using Framingham Offspring (FOS) Study lipid/lipoprotein data, both the LDL-C and the LDL-P are at the 50th percentile cutpoint. However using the more contemporary MESA data both are at the 70th percentile cutpoint. This is a case where the LDL-C and LDL-P are concordant. This also shows the patient's risk is much higher than one could have ever ascertained using either the NCEP ATP-III guidelines or the silly AACF Primary Prevention statement. **Whether his Lp-PLA2 is high or normal, because of the hyperbetalipoproteinemia he needs a statin.** The high Lp-PLA2 simply means he is at higher risk than originally thought and his LDL-P should be aggressively lowered. I would shoot for a value < 1000 nmol/L, which means a 40% drop in LDL-P (never forget that statins are far less effective reducing apoB or LDL-P than they are in reducing LDL-C). If you want to go with statin monotherapy, I'd start rosuvastatin 20 mg daily. Many who are practice under the influence of a formulary might be forced to initially go with generic simvastatin (titrated to 80 mg) which is unlikely to get the LDL-P to < 1000 but you can give it a try. Again I almost never use simvastatin 80 mg as the myopathy risk is way too high (see in major trials - most recently SEARCH).

Many of the patients with hyperbetalipoproteinemia and low HDL parameters (even with the normal TG) are insulin resistant. The elevated LP-IR score supports that. Both the HDL-C and the total HDL-P are significantly low. As expected, a person with an HDL-C < 30 mg/dL will have very few large HDL particles and indeed his large HDL-P is very low. A little know fact, seen in the VA-HIT trial was that the absolute best baseline predictor of risk was not any lipid concentration, not the TC/HDL-C ratio, not the apoB/apoA-I ratio but the LDL-P/HDL-P ratio. In this case 1402/26.3 = 53.3. Using

the data from VA-HIT, 53.3 puts this man in the 3rd quartile of risk: for your future information, if you want to use the LDL-P/HDL-P (see Circulation. 2006;113:1556-1563)

Quartile 1 (low risk): 13.9 - 40.5
Quartile 2 (moderate risk) 40.5 - 51.2)
Quartile 3 (high risk) 51.3 - 61.2
Quartile 4 (very high risk) > 61.3 Highest value seen in VA-HIT was 127.7

Again: The proper, evidence-based treatment for patients with low HDL-C and high apoB (LDL-P) especially in the face of insulin resistance and elevated hs-CRP and Lp-PLA2 is to normalize their LDL-P, is a statin. If the statin does not normalize the LDL-P and the patient is high risk, then one must consider combination therapy. So if the LDL-P of < 1000 nmol/L is not achieved - should we add ezetimibe (Zetia), Niaspan or Welchol. A fibrate is not a consideration with a TG well under 200 mg/dL. Most would say the HDL-P is extremely low, and although it is not a goal of therapy, in the VA-HIT study, increasing HDL-P (but not HDL-C) with a fibrate was associated with outcome benefit. So Niaspan, which can lower apoB (LDL-P) as well as raise HDL parameters, would be a logical add on. I would even consider starting him on a combination product like Simcor (simvastatin/extended-release niacin) titrated over time. For those with extremely high LDL-P (not this patient), one might ultimately need statin/Niaspan/Zetia. If his glucose was high Welchol would be a potential add on as it can lower LDL-P beyond what a statin does, raise HDL parameters and of course reduce glucose.

Do you want your lipids and lipoproteins to be at the 50th population percentile cutpoint, the 20th or the 5th percentile. I think those at risk for CHD should ideally all be under the 20th percentile for sure. However guidelines think only high risk folks need to be below the 20th percentile cutpoint (1000 nmol/L or LDL-C < 100 mg/dL). Clearly an insulin resistant man with a family history of CHD with a high LDL-P (70th percentile cutpoint) and very low HDL-P needs to get his LDL-P below 1000 nmol/L. I consider this patient high risk - even though 2001 ATP-III would not.

Another moral to the story: Any person seen in a lipid clinic should have as a minimum work up, lipoprotein concentration data. Indeed they should have a lot more than lipoprotein assessment which is why my patients get the Health Diagnostic Labs (www.myhdl.com) advanced CV panel (custom designed for my practice -as could you if you use their services).