

Hi Lipidaholics: I recently received a very succinct and brief e-mail about a patient: The clinician, asking for my opinion writes: "Below are lipid values and anything else that showed too high or low:" No clinical information other than the age of 38 was provided.

Uric acid - 8.3 (2.0-8.0)

Albumin - 5.2 (3.2-5.0)

GGTP - 56 (5-50)

TC = 364 Triglycerides = 219 HDL-C = 39

VLDL -C (calculated) =44 LDL-C (calculated) = 281

Non HDL-C = 364 - 39 = 325

ApoA1 = 116 ApoB - 211

## **DAYSRING ANALYSIS**

First I must point out there is far more to Lipidology than just analyzing a bunch of lipid values. These concentrations come out of very living and often very different people. No preventive cardiologist or lipidologist can make accurate assessments of RISK without clinical details, including history and physical examination. Docs too often loose tract of the essential fact that every bit of advice we offer patients will depend on the risk of that patient.

Example: Would you recommend to a patient with an LDL-C of 85. Is the answer nothing? Well if you knew the patient was a type 2 diabetic age 49 that would change things: Both new ADA and NCEP update suggest a statin is appropriate for such a patient. If it were a 49 year old in perfect health, no therapy is necessary. If he is an ACS survivor serious therapy is needed.

Most physicians cannot name the five major risk factors listed by NCEP that will influence at what LDL-C level treatment is advised To be considered as high risk you have to have two of them. Interestingly only one lipid concentration is listed among these top 5 risk factors!

1) Age, 2) Family History of premature CHD, 3) Hypertension, 4) Smoking and 5) Low HDL-C

So if we all want to do our jobs properly and prescribe drugs when indicated never, ever dictate lipid therapy without remembering the art of practicing medicine involves non-laboratory issues. As bad as all of the lipid measures listed above are in this patient, the goals of therapy will depend on the overall risk of the patient. There is little doubt the above man needs serious therapy, but the goals of that therapy absolutely depend on his risk! The Non HDL-C that I WILL ATTEMPT TO ACHIEVE WILL BE DIFFERENT if he is otherwise health, a diabetic or an ACS survivor.

So for the sake of this discussion, let's assume he has not had an MI, is not a type 2 diabetic and has no evidence of atherosclerosis on examination. The patient should be examined carefully for cutaneous signs of lipidoses: palms, tendons, integument, eyelids. Of course a BMI and blood pressure are essential.

Would any other lab tests be helpful before determining risk and planning treatment. I would obtain:

Renal function, urine microalbumin, TSH, glucose, homocysteine, CK and hs-CRP. Some might check an Lp(a) value on the believe it would factor into therapeutic decisions if elevated. I would not if there was no premature family history of CHD or if the patient was an African-American (they often have elevated Lp(a) and it may not be related to CV risk).

Why the CK? I am anticipating combination therapy and NCEP advises baseline CK in such patients. In the future if myopathic symptoms occur, you have a baseline CK to follow up on. Why

a homocysteine? It is an emerging risk factor and it can be elevated with niacin or fibrate therapy, so again a baseline level is very useful.

If available, an EBCT (coronary calcium score) would be very wise. You can get a nice idea of existing plaque and use it as a motivator and it can be followed over time.

With the information at hand and presumed this man has familial combined hyperlipidemia. He is very likely insulin resistant and has the metabolic syndrome (MS). This lipodosis and MS is associated with fatty liver and hyperuricemia.

The lab value most predictive of CV risk is the incredibly high apoB level (a marker of atherogenic lipoproteins). Outside of measuring individual lipoprotein concentrations, in study after study apoB is the best lipid (lipoprotein) surrogate predictor of risk. However with such a high Non HDL-C, spending money on an apoB was probably not worth it. An apoB of >200 puts this patient in the top 1-2% of patients. In AFCAPS-TexCAPS the apoB/apoAI ratio was the best predictor of risk at baseline and one year into the trial. TC and LDL-C had no statistically significant predictive abilities in this study. If apoB is elevated the person has too many remnants, IDL and LDL particles (all atherogenic if present in increased concentrations) and if apoA is low, the patient will not likely have perfect reverse cholesterol transport and will lack HDL particles to perform their anti-atherogenic functions.

The VLDL-C and LDL-C are calculated values using the Friedewald formula: They are both erroneous. In a patient with elevated TG, the direct LDL-C determination would be higher than calculated value of 281. The cholesterol in VLDLs is not really 44. VLDL-C is calculated by dividing TG/5, on the assumption that the composition of TG and cholesterol in VLDL exists in a 5/1 ratio. Therefore  $VLDL-C = 219/5 = 44$ . Well when a patient has a TG of 219 some TG exists in other particles (not only VLDL) and the composition of the particles is likely to be a 10/1 or greater ratio of TG to cholesterol. So VLDL-C is probably closer to  $219/10$  or 22. So if the VLDL-C is really 22, where is the extra 22 mg of cholesterol that the calculated value reported? Surprise: the cholesterol is in the LDL particles. The LDL-C is thus going to be > 300 mg/dL.

The high TG, reduced HDL-C, the increased TC/HDL-C ratio, the abnormal TG/HDL-C ratio (well above 4.0) are all surrogates for small dense LDL particle phenotype. So the physical chemistry question is how many LDL particles does it take to carry 300 mg of cholesterol in deciliter of plasma? The volume of a sphere or circular particle is a third power of the radius. So it will take far more small LDL particles than it would large to transport the 300 mg of cholesterol. Indeed depending on the "smallness" of the particles it will take 40-70% more small LDL particles than large to transport any given concentration of cholesterol. So at any given LDL-C value the LDL-P or apoB will be much, much higher in a person with small particles. That is why the apoB is so high in this case.

Our therapy in this patient has to be directed at the increased numbers of apoB particles, most of which are small LDLs. We have to decrease the synthesis of such lipoproteins, increase their catabolism and/or increase their removal.

1) Reducing synthesis: Drugs that decrease TG synthesis (fibrates and niacin) will reduce VLDL production. If you make less VLDLs, you will ultimately have less LDLs.

2) Increasing catabolism: By increasing lipoprotein lipase and decreasing apoCIII, fibrates will enhance more efficient lipolysis of TG-rich lipoproteins. Statins through a PPAR alpha effect can also increase LPL to varying degrees and reduce apoCIII (Pravachol did this nicely in the CARE study).

3) Enhancing removal of apoB/E particles: Statins, ezetimibe and bile acid sequestrants all increase or upregulate LDL receptors which will enhance removal of apoB particles. Indeed in just

published data from the STELLAR trial, rosuvastatin (Crestor) blew away all the other statins in its ability to reduce the atherogenic lipoproteins so prevalent in metabolic syndrome patients. (Am J Cardiol 2005;95:360–366)

If we have to do everything in steps 1, 2 and 3, it should be very obvious that combination therapy is frequently necessary to achieve just that. NCEP states that when Non HDL-C is not achieved on lifestyle and a statin, that is when the benefit outweighs any risk of adding a fibrate or niacin of the statin. Combinations of statins, ezetimibe and fibrates will do all of the above without raising glucose, uric acid, and statins (Pravachol in WOSCOPS) and fibrates (bezafibrate in BIP) delay the onset of IFG and type 2 diabetes. Fenofibrate (TriCor) increases insulin sensitivity.

So my advice for the above patient is to: .

- 1) Mediterranean or South Beach diet and > 30 - 60 minutes aerobics daily. Take a treadmill exercise test before starting serious exercise.
- 2) Crestor 20 mg daily along with Zetia 10 mg daily
- 3) Wait two weeks, recheck lipids and if Non HDL-C still abnormal start TriCor 160 mg daily
- 3) Daily ASA
- 4) Daily omega-3 FA supplement (Coromega, etc): Also have option to push omega-3 FA to higher doses (3-6 gm) to help with the TG
- 5) Must have a BP < 130/85 If up use an ACEI or ARB
- 6) If obese and will not exercise, start metformin and titrate to 2 gms daily

#### **REFERENCES OF THE WEEK**

- 1) Effects of Rosuvastatin, Atorvastatin, Simvastatin, and Pravastatin on Atherogenic Dyslipidemia in Patients With Characteristics of the Metabolic Syndrome. with MS. Rosuvastatin had the most favorable effect on the atherogenic lipid profile of MS overall. Am J Cardiol 2005;95:360–366
- 2) Should Age and Time Be Eliminated From Cardiovascular Risk Prediction Models? Rationale for the Creation of a New National Risk Detection Program Paul M Ridker, MD, MPH; Nancy Cook, ScD This is a fabulous discussion of why it is not in the best interests of our patients to make age such a major determinant of risk. Many young people, especially women are being denied treatment as they fail to be identified as high risk using Framingham risk scoring advocated by NCEP. Circulation. 2005;111:657-658.)
- 3) Efficacy and safety of ezetimibe co-administered with simvastatin in thiazolidinedione-treated type 2 diabetic patients Diabetes, Obesity and Metabolism, 7, 2005, 88–97 Conclusions: Co-administration of ezetimibe with simvastatin, a dual inhibition treatment strategy targeting both cholesterol synthesis and absorption, is well tolerated and provides greater LDL-C-lowering efficacy than increasing the dose of simvastatin in T2DM patients taking TZDs.

#### **DAYSRING TRAVELS:**

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Atlanta, GA, Snellville, GA  
Phoenix, AZ  
Louisville and Lexington, KY  
Providence, RI  
Gary, IN  
Chicago, IL  
San Diego, CA

For my GYN friends: I will be doing a series of CME programs in person and through webcasts throughout the US discussing estrogens, progestins, CHD in women, etc. Look for me in March in San Diego, Minneapolis, Chicago, Philadelphia, Detroit

Reminder: My previous cases vcan be reviewed and downloaded in PDF form at <http://www.nypcvs.org/pages/1/index.htm>

National Lipid Association [www.lipid.org](http://www.lipid.org) Join: The new syllabus on Metabolic syndrome is just about ready for release.

North American Menopause Society [www.menopause.org](http://www.menopause.org)

Last but never least: Have you tipped your hat to a soldier yet. I do it often in airports. We just can never let a day go by without respecting and admiring those who give so much of themselves to provide you and me with freedom and all of the rights we enjoy and take as granted as Americans. Never take your freedom for granted. A high and dear price is always paid and it is paid by our special soldiers.

Happy Lipiding,

Tom

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