

Hello Lipidaholics: I have been asked to give a quick opinion about the following case:

54yo Caucasian female. Menopausal. Not on EPT. Family history of elevated Triglycerides. Mother and Father BOTH with elevated TG, but no heart disease or stroke. One Uncle died of a heart attack at age 53. Was given Lipitor 2 years ago by another MD...didn't change her TG much. Medication was stopped.

Lipid panel TG = 1105, HDL-C = 38, TC = 219 Fasting serum glucose 113,
SGPT slightly elevated at 54. Non HDL-C = 181 (perfect < 130)
TC/HDL-C = 5.7 (risk if > 4.0) TG/HDL-C = 29 (should be < 3)

The physician recommended 6 weeks of modified Atkin's diet with white meat, fish, etc...30 gram Carbohydrate diet, Multivitamins and Omega 3 fatty acids.

6 weeks later repeat labs: TG 239, HDL 42, TC 198, LDL 108 Non HDL-C = 156
Fasting Glucose 96, Liver all WNL. No NMR LipoProfile data yet.

What's your next recommendation?

DAYSRING ANALYSIS

This woman has a familial lipidemia, probably Fredrickson type IV. Type V can be ruled out by letting the red-top tube stand overnight looking for a chylomicron layer. One can also do lipoprotein electrophoresis (looking for a pre-beta band) or check Apo E genotype to R/O a Type III, but her cholesterol is not high enough to suggest that phenotype. Fredrickson Typing is in reality academic as the treatment is not going to be dependent on the lipid phenotype.

Presuming she does not smoke or have hypertension, using the NCEP (National Cholesterol Education Program) Guidelines, this 54 y/o woman would not be considered at much risk for CHD. This is the type of person that the Framingham risk assessment will really underestimate risk (since it does not factor in BMI or waist-hip ratio or impaired fasting glucose. TG are also not part of that risk equation, but HDL-C and the total HDL-C are. However, because of the risk of pancreatitis, a TG that high calls for immediate pharmacotherapy with therapeutic lifestyle changes.

To further assess risk we would want to know her thyroid status, her estrogen status (since a statement was made that she is not on EPT we should assume she is menopausal) and her dietary history (including alcohol use). Her weight, BMI and waist/hip ratio would likely reveal obesity with an apple shape. Her glucose is way above 100 (the ADA level indicative of impaired fasting glucose). It is very possible a glucose tolerance test may show Type 2 diabetes is present which would immediately place her in a CHD Equivalent risk category. She clearly has several of the criteria to establish the metabolic syndrome (likely overweight, impaired fasting glucose, elevated TG and low HDL-C). A hs-CRP test would be very informative. Women with the metabolic syndrome who have elevated CRP, have far worse survival and CHD event statistics than those without elevated CRP. Not that her aminases are elevated indicating fatty hepatitis is likely present.

So, I am going to approach this lady as a CHD equivalent.

1) She has very TG-rich lipoproteins which would include some very large (probably non-atherogenic) VLDL particles (too big to enter the arterial wall). With such hepatic production of TG, her liver will be producing vastly increased quantities to export the TG (to avoid or minimize fatty hepatitis). Many of these VLDL will wind up as small LDL particles. Since VLDL has a half life measured in hours and LDLs have a 3 day half life, LDL particles accumulate when numerous VLDL are produced. It is also likely that this woman has abnormalities of apoCIII (elevated) and lipoprotein lipase or its ligand apoCII. Increased levels of apoCIII are associated with delayed catabolism of TG-rich lipoproteins, enabling them to stay in the circulation longer and invade the arterial intima.

2) There will also be increased amounts of smaller atherogenic VLDL and chylomicra (remnants).

3) There will be markedly increased numbers of small (highly atherogenic) LDL and very small HDL particles (not carrying much cholesterol). The lab has not reported the LDL-C level because it cannot be calculated with any accuracy with such a high TG (The Friedewald calculation for LDL-C is TG/5, is only accurate with TG levels < 200). No matter how much cholesterol is within her LDL particles, we can assume she will have markedly increased numbers of LDL particles and they will be small.

4) Number 1, 2 and 3 above all result in markedly increased levels of apoB (betalipoproteins). All of the above particles have a single molecule of apoB).

5) The HDL particles will be very small, very few in number and will not be carrying much cholesterol. The TGs invade HDL particles (lessening their cholesterol content). The TG-rich HDL are subject to lipolysis (TG hydrolysis) by hepatic lipase, creating small lipid free or lipid poor HDL particles. Such small particles are very subject to renal excretion. The reduction in HDL particles is accompanied by low levels of apoAI. (ApoAI is the main surface apoprotein on HDL).

6) Because of numbers 1-5 above this lady will have very high apoB, very low apoA and a very high apoB/ApoAI ratio. In the very large primary prevention trial AFCAOS/TexCAPS, apoB, apoA and their ratio were by far the best predictive surrogates of risk and response to the statin used in the trial (Mevacor).

Lifestyle

NCEP would advise therapeutic lifestyle changes (to include daily exercise). I am not a fan of Atkin's. Portion control, avoid simple sweets and exercise. Mediterranean diet is the best (with data). South Beach would be acceptable. How about her lipid and lipoprotein pathology: Indeed this woman has had a phenomenal response to diet advised by her practitioner. The glucose and Non HDL-C have done very well. One might just elect to continue that approach. In the face of her follow-up improved lipids, I would do the NMR LipoProfile test. It is very possible she has significant lipoprotein abnormalities even though the lipids are better. If so, then additional therapy would be advisable.

Pharmacologic Therapeutic Choices in such a patient (with TG > 500)

1) A TG > 500 calls for use of a fibrate and TriCor (160 mg daily if renal function is normal) is by far the safest fibrate on the market. It has no CYP450 baggage and does not inhibit glucuronidation of lipophilic statins, Zetia or Avandia (Gemfibrozil or Lopid does all of that). TriCor would induce lipoprotein lipase, reduce apoCIII and thus markedly reduce TG and the TG-rich lipoproteins. It would significantly increase apoAI production and facilitate all aspects of reverse cholesterol transport (ABCAI, SRBI upregulation).

Very interesting data published this week in Circulation (see below) that bezafibrate (a fibrate used in Europe) significantly delays the onset of diabetes. It is very likely TriCor would do the same to this lady. The only other meds that have shown an ability to delay the onset of diabetes are metformin, TZDs, Precose and Pravachol. You could, make a case for all of them in this lady if lifestyle was not attempted or did not work.

2) Statin will be needed. Everyone knows what a Pravachol fan I am, but I think many would reach for the King Kong statin, Crestor in this case. Although Crestor cannot be used with Lopid, it has no interaction with TriCor. Crestor is the best statin at improving both apoB and apoA, and the apoB/apoAI ratio which is a necessity in this patient.

3) Niaspan could be used if there was difficulty in normalizing the TG or Non HDL-C. Niacin by inhibiting hormone sensitive lipase and DGAT (a TG synthesis enzyme) would reduce TG-rich lipoproteins and apoB. Niacin would delay the catabolism of large HDL particles, thereby increasing apoAI. Niaspan would be a third line choice in my view because of the glucose abnormalities. If used you

would want to keep the dose at no higher than 1000 mg. The new data showing fibrates delay the onset of diabetes will be a big factor in using a fibrate before niacin.

4) Metformin or TZD: yes if the lifestyle had not worked so well. No need for them if the patient continues her weight loss.

5) ASA: absolutely 81 mg is fine

6) Omega-3 FA Absolutely

References of the week:

1) Treating low HDL-cholesterol in normocholesterolaemic patients with coronary disease: statins, fibrates or niacin for courses? *European Heart Journal* (2004) 25, 716–719 This is a great, highly recommended editorial on approaching patients with low HDL-C.

2) Women and Heart Disease The Role of Diabetes and Hyperglycemia Elizabeth Barrett-Connor *Arch Intern Med.* 2004;164:934-942 More must reading

3) Effect of Rosiglitazone on Common Carotid Intima-Media Thickness Progression in Coronary Artery Disease Patients Without Diabetes Mellitus Conclusions—Rosiglitazone reduces common carotid IMT progression in nondiabetic CAD patients, and insulinsensitization may be one contributory mechanism. (*Arterioscler Thromb Vasc Biol.* 2004;24:930-934.)

4) Should Progestins Be Blamed for the Failure of Hormone Replacement Therapy to Reduce Cardiovascular Events in Randomized Controlled Trials? The authors discuss the controversial effects of HRT and ERT on cardiovascular system and provide a hypothesis that the failure of HRT and ERT in reducing the risk of cardiovascular events in postmenopausal women might be because of the stage of their atherosclerosis at the time of initiation of HRT or ERT. (*Arterioscler Thromb Vasc Biol.* 2004;24:1-10.)

DAYSRING TRAVELS

Newport Beach, Solana Beach next week

Pasadena and Westwood, CA next week

Mountain Lakes, NJ

Dallas - Fort Worth and Tyler TX (last week May)

Kansas City AFP Annual Meeting June 3

San Francisco, Walnut Creek, Pleasanton, Fresno, Sacramento

Morristown, NJ

Bridgeport, CT

I just did (April 24) a CME presentation at the Annual MidAtlantic Nurse Practitioner Meeting at the University of Maryland. The lecture on Atherothrombosis in Women: Effects of Estrogen Receptor modulation was taped and is (will be) available from (I get no benefit)

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Happy lipiding and more than ever, positive thoughts about our servicemen and women across the globe

Tom

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