

Dr. Goldberg

From: TDayspring@aol.com
Sent: Sunday, April 25, 2004 1:52 PM
To: TDayspring@aol.com
Subject: Lipid Case of the Week #106 Young Man with Significant Atherosclerosis

Hi Lipidaholics: I hope spring is treating everyone well. Every once in a while I have to discuss a case involving a man. Virtually everything I say pertaining to this case would apply to women. I was contacted by a clinician about the following patient:

"I have a young 32 yo construction worker gentleman who just had a leg bypass by our vascular surgeon for symptomatic claudication and superficial femoral artery occlusion!
 He has a significant family history of father who has had several MI's in his 40's and PTCA's (percutaneous transluminal coronary angioplasty). He has no HTN, stopped smoking (former 20pk/yr). He is 5'10" with a weight of 195. On no medications. He drinks 4-6 alcoholic drinks/wk.

I sent him for lipids and NMR with the following results:

TC = 197 LDL-C = 119, HDL-C = 38, TG= 293

The NMR LipoProfile (Nuclear magnetic resonance spectroscopy) was:

LDL part # 1768 (Elevated: would want this well under 1100 in such a patient)
 LDL size 19.1 (very small)
 Large HDL 6, (very low: patient lacks large HDL particles)
 Large VLDL 102 (Extremely elevated: large VLDL become small LDL)

Lp(a) = 3.7, Surprisingly normal in a family with bad genes
 hs-CRP = 13.9 (off the chart: consistent with very high risk atherosclerosis and both insulin resistance and the metabolic syndrome)

Homocysteine= 7.3 (normal is < 10)
 ALT/AST= 40/36 (no serious fatty liver or other liver disease)

"I want to start him on a baby ASA, Pravachol 40/day, TriCor 160/day, Omega 3FA supplement and stop alcohol. I know he's at high risk but do you think I'm being too aggressive without giving him an opportunity for lifestyle changes first? Isn't it surprising that his Lp(a) isn't higher?

DAYSRING ANALYSIS

Yes, I would have bet that an Lp (a) would have been elevated and always remember when lab tests do not support your clinical suspicions, it is worth repeating the test! With respect to being too aggressive, there is no such thing in this patient. At a very young age he is a genetic and metabolic wreck with a drastically shortened lifespan unless he gets very aggressive CV advice. If one simply followed NCEP: Secondary prevention patients need aggressive lifestyle and pharmacologic advice on day one. If their lipid parameters are not at goal, drugs ARE required. Of course the magic question is what drug.

This person's CV risk is due to the multiple metabolic perturbations seen in the metabolic syndrome coupled with his tragic use of cigarettes. We were not given any glucose data, but it would have to be watched closely. He must give up his favorite source of sugar: ALCOHOL. If he is a beer drinker, maltose is the most rapidly absorbed sugar which becomes fatty acids - TG post haste! It will be very hard to manage this person if he does not cease alcohol intake. Hopefully his smoking is also history.

Screen all his first degree relatives

NCEP Recommendations: He is high risk as he has CHD and PVD. He is not at LDL-C goal (<100 mg/dL or non

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HDL-C goal (< 130 mg/dL). NCEP would advise therapeutic lifestyle changes along with medication to normalize the above parameters: With the LDL-C up a statin or statin/Zetia would be appropriate and if the two goals were not reached, a fibrate or niacin would be advised as additional therapy.

NOW LETS GET INTO A MORE SERIOUS DISCUSSION

His triglycerides are no doubt causing the following:

1) Intestinal production of numerous large TG rich chylomicrons, that after lipolysis (exposure to lipoprotein lipase and partial hydrolysis of TG) become numerous small chylomicron remnants. These are highly atherogenic betalipoproteins (have apoB on their surface). They are not readily removed by hepatic receptors and thus have prolonged half lives or circulation time.

2) VLDL remnants: his liver is almost certainly producing too many large (TG rich) VLDLs to get the fat out of the liver (liver's way of preventing fatty hepatitis) and too many intermediate sized VLDL particles. Since he is insulin resistant, it is likely that his liver also over produces apoCIII, an apoprotein that delays the degradation of TG-rich lipoproteins (chylol, VLDL, and IDL). The intermediate sized VLDLs are very similar to the chylomicron remnants described above. If you are doing NMR LipoProfiles, remnants are quantitated as VLDL 1 and 2 and IDL particles. They are all atherogenic if present in elevated concentrations. Indeed, NCEP states that in persons with TG > 200 mg there are increased concentrations of atherogenic remnant lipoproteins that convey risk SUBSTANTIALLY ABOVE THAT PREDICTED BY LDL-C.

3) LDL particles: The Large VLDL are TG-rich and cholesterol-poor and when lipases remove all of the TG, the resulting lipoprotein is a small, dense, highly atherogenic LDL particle. LDL particle concentration will be elevated because most of the VLDLs which have half lives of several hours become small LDLs which have half lives of 3-4 days. In other words the LDLs accumulate. This is why no one should be surprised when they do NMR LipoProfiles in persons with even subtle TG levels that LDL particle concentrations is so elevated. It is a large part of the risk associated with hypertriglyceridemia.

4) TG are being transferred to HDL particles: from VLDL, IDL to HDL particles via cholesteryl ester transfer protein (CETP). This makes the HDL particles TG-rich and cholesterol poor (which will lower HDL-C levels). Such HDL particles are subject to lipolysis by hepatic lipase which converts them to small HDL particles: they are so small many pass through renal glomeruli and are excreted. Thus in patients with elevated TG, the HDL particles tend to be small: HDL-C and apoA levels are decreased. Hepatic ApoA mediated reverse cholesterol transport, via hepatic scavenger receptors (SRB1) will be decreased.

THERAPY

1) Priority one is to reduce the number of LDL particles to under 1100 using NMR or an LDL-C well under 100 mg/dL. The clinician suggest using Pravachol and TriCor. Both reduce apoB particles with the statin acting mostly on LDLs and the fibrate on VLDLs, and remnants. This is certainly a very reasonable choice. Gemfibrozil or Lopid cannot help the LDL as much as TriCor and gemfib is not as safe as TriCor so it is not a consideration.

How about starting with statin and Zetia: That would almost certainly get the LDL particle number and LDL-C to goal. Because of the dual mechanism of actions (inhibition of cholesterol synthesis and absorption) the liver is denied all sources of cholesterol and thus would have to upregulate large numbers of LDL receptors. The Zetia could also keep all noncholesterol sterols out of the body. At ACC in March a study was presented showing that Zocor/Zetia combination significantly reduced remnant lipoproteins in metabolic syndrome patients.

At this time there is no evidence that Zetia has as many pleiotropic (non-lipid) effects as do fibrates especially in insulin resistant patients. So in this patient I favor TriCor over Zetia as the statin add on.

However, more and more I am recommending Zetia as an add on to a statin in virtually all cases requiring LDL-C or LDL particle number reduction. The dual mechanism is very effective and keeping out noncholesterol sterols is likely very important. Blocking cholesterol absorption (by upregulating HMG-CoA reductase) will enhance the efficacy of any statin. So In the above patient I would start a hydrophilic statin (as this patient is apt to be a polypharmacy patient subject to drug-drug interactions) with Zetia.

The Crestor advocates would say just go with Crestor and it is the most impressive statin in reducing all of the abnormal lipoproteins present in this patient as well as significantly increasing apoA. However, Zetia also makes Crestor a much more effective statin for the aforementioned reasons. Of course Pravachol has a much longer

and impressive existing safety record than the new Crestor.

So: any of the following are acceptable

1) Pravachol 40 - 80 mg plus Zetia: recheck NMR in a month
No doubt then add TriCor

2) Crestor 10-20 mg plus Zetia: recheck NMR in a month
No doubt then add TriCor

3) Some would use Advicor (Niaspan and lovastatin combo), perhaps with Zetia. I almost never prefer niacin above fibrates or statins in insulin resistant patients.

4) Aggressive platelet inhibition with ASA and Plavix (if no contraindications)
Omega-3 FA
South Beach or Mediterranean diet

My goals: NMR well under 1000 LDL# Normalize large VLDL

If using a fibrate like TriCor, HDL particles will remain small but HDL mass (apoA) will increase. You do not see nor should you expect an increase in large HDL with a fibrate.

References of the week:

Lipid Control in the Management of Type 2 Diabetes Mellitus: A Clinical Practice Guideline from the American College of Physicians Ann Intern Med. 2004;140:644-649.

Recommendation 1: Lipid-lowering therapy should be used for secondary prevention of cardiovascular mortality and morbidity for all patients (both men and women) with known coronary artery disease and type 2 diabetes.

Recommendation 2: Statins should be used for primary prevention against macrovascular complications in patients (both men and women) with type 2 diabetes and other cardiovascular risk factors.

Recommendation 3: Once lipid-lowering therapy is initiated, patients with type 2 diabetes mellitus should be taking at least moderate doses of a statin.

Recommendation 4: For those patients with type 2 diabetes who are taking statins, routine monitoring of liver function tests or muscle enzymes is not recommended except in specific circumstances.

Why some patients respond poorly to statins and how this might be remedied. European Heart Journal (2002) 23, 200–206 Nicely ties in cholesterol absorption & synthesis

Antidiabetic Actions of Estrogen: Insight from Human and Genetic Mouse Models Current Atherosclerosis Reports 2004, 6:180–185 Postmenopausal women develop visceral obesity and insulin resistance and are at increased risk for type 2 diabetes mellitus, but hormone replacement therapy leads to a reduction in the incidence of diabetes. In various spontaneous rodent models of type 2

PPARS and the Complex Journey to Obesity Natur Medicine 2004;10:1-7

Dayspring Travels

Houston TX (4/29) (Optima Ed CME Dyslipidemia Conf)
National ACOG Meeting: Philadelphia Part of CME Panel Discussion 5/2 Evening
St. Louis, MO including Grand Rounds at St John's and St Lukes
Atlanta, GA
Chattanooga, TN
Pascack Valley Hospital Grand Rounds (New Jersey) 5/7
Columbia and Greenville, SC
Anaheim, San Diego & LA Week of 5/17
Dallas - Tyler TX (last week May)

I just did (April 24) a CME presentation at the Annual MidAtlantic Nurse Practitioner Meeting at the University of

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Maryland. The lecture on Atherothrombosis in Women: Effects of Estrogen Receptor modulation was taped and is (will be) available from (I get no benefit)

All Star Media 9470 Campo Rd PMB #118 Spring Valley, CA 91977
619-723-8893
www.allstartapes.com

The selection number is 812-47 G2
The audio CD is \$12 and mp3 file \$10 plus shipping

This week I close as always with prayers and thoughts for our troops. This week, the death of Pat Tillman brought to light the special makeup of our protectors. Each and every one of them who have made the supreme sacrifice and all of those still serving have decided that they will give up all of their tomorrow's so you and I can safely enjoy ours! Where do we find such men and women?

Happy Lipiding,

Tom

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