

Dr. Underberg

From: TDayspring@aol.com
Sent: Sunday, August 14, 2005 11:54 AM
To: TDayspring@aol.com
Subject: Lipidaholics Weekly: Lipid Case # 144 When do you stop worrying about TG?

Hi Lipidaholics: Ready for some more "lipolytic" discussion during the Dog Days of summer? I received the following from a colleague in down South regarding a 45 year old Caucasian woman. with irregular periods. She is using Mircette for irregular periods: a low dose OC, which uses 20 mcg ethinyl estradiol (EE) and 150 mg of desogestrel for 21 days, no hormones for 2 days and 10 mcg of EE for 5 days). Her mother has coronary disease and type 1 diabetes.

Her BMI is 38 with a weight of 224 lbs and height of 64". She takes metformin and has been instructed on lifestyle, but this has been ignored. The labs are as follows:

TC = 251 HDL-C = 90 LDL-C = 129 TG = 193
 Non HDL-C = 251 - 90 = 161 TC/HDL-C < 4.0 TG/HDL-C < 3.0

The NMR LipoProfile (www.lipoprofile.com and also available at LabCorp)

Here is how to find the NMR on LabCorp's web site Click on N for NMR LipoProfile.
<http://www.labcorp.com/dos/index.html>

LDL-P = 1138 (perfect < 1000) LDL size Pattern A (large)
 Small LDL-P = 231 (desirable < 700)
 Large HDL = 58 (desirable in drug naive patient > 30)
 Large VLDL 71 mg/dL (desirable < 7)

Glucose = 104 HgbA1C = 5.4 hs-CRP = 1.35

The clinician states: "Although her small LDL-P is very good, and with large particles, do I continue to push her triglyceride level lower? Is this just a diet phenomenon? I am sure she is an insulin resistant patient. Does this force me to keep pushing her levels further down, or is this just the result of fasting for a day or so and if I did a random profile would I get trigs that are out of sight. If my LDL-P is at goal, do I need to do anything more than continued follow up, and wt loss. I could also change her from Mircette to Prometrium."

DAYSRING DISCUSSION:

This almost morbidly obese perimenopausal woman is significantly insulin resistant and has several NCEP criteria for the diagnosis of metabolic syndrome (ICD-9 277.7): obesity, elevated TG and impaired fasting glucose. But I am going to keep shouting this till everyone gets it: **there is no specific TG nor HDL-C goal of therapy in NCEP**. Much of the risk associated with elevated TG or low HDL-C is related to an associated increase in atherogenic apoB lipoproteins and they (apoB or apoB surrogates become the target of therapy. Why is this so hard for everyone to comprehend? I believe it is because it is not being taught and PHARMA reps and way too many speakers, not cognizant of lipid and lipoprotein relationships, keep telling clinicians there is an NCEP TG and HDL-C goal of therapy.

Theoretically this patient does not have at least two major risk factors for atherosclerosis (low HDL-C, smoking, age > 55, HTN, premature family history CHD or) and does not qualify for Framingham risk scoring. That is a joke. Her LDL-C level is not high enough to justify initiation of therapy in such a patient. So leave her alone?

Of course not. NCEP has put emphasis on the metabolic syndrome. This diagnosis certainly elevates her to at least a moderate risk category. Perhaps if she was not on metformin her glucose would be > 126 mg/dL establishing the diagnosis of diabetes and elevating her to a high risk (coronary heart disease

equivalent) category.

If she is a moderate risk patient, is she at NCEP goal? The goals of therapy for moderate risk are an LDL-C < 130 mg/dL and if the TG are elevated (> 200 mg/dL) the secondary target is a non HDL-C of < 160 mg/dL. So guess what? This woman is at NCEP goal and should be left alone and encouraged to improve lifestyle.

However, if you follow the AHA Women's Guidelines her goal of therapy becomes and LDL-C < 100 and a Non HDL-C < 130 mg/dL. Using these recommendations, more aggressive therapy (lifestyle and/or drugs is strongly encouraged).

But wait a minute! We have lipoprotein concentrations so why are we wasting time looking at lipid concentrations? Never forget that the reason one orders advanced lipoprotein testing is that lipoprotein concentrations are better surrogates of risk and goals of therapy than lipid concentrations. So stop looking at lipid values when you have particle concentration data.

The NMR profile demonstrates a mild increase in large LDL particle and a significant increase in large VLDL and HDL particle concentration. Of course because of their much longer half life and much smaller size (relative to VLDL), LDL particles are the most atherogenic apoB particles that exist in plasma. Of course small LDLs are even more atherogenic than large but please memorize the following: **IF LDL-P IS NORMAL THERE IS LITTLE RISK PRESENTED BY ANY LDL PARTICLE (SMALL OR LARGE)** as particle number (concentration) is the major determinant of arterial wall penetration and entry. This simple concept is why the NMR LipoProfile or apoB is so much better than lipid concentration tests.

This woman with metabolic syndrome has an LDL-P of just over 1100 and the predominant LDL size is large and increased large VLDL. I would absolutely treat this woman with drugs. The best way to decrease large LDL-P is to upregulate LDL receptors. This is most easily accomplished by decreasing the hepatic pool of free cholesterol: inhibiting cholesterol synthesis or absorption or both. So the most frequently used (by most) first line drugs are statin or statin/ezetimibe. Your favorite statin at standard starting dose would be appropriate. I would use Crestor 5 mg or Pravachol 40 mg or Vytorin 10 mg. I prefer the hydrophilic statins like Pravachol and Crestor for their almost total lack of drug interactions but Zocor 10 (in the Vytorin) is a very safe statin at a 10 or 20 mg dose. Keep in mind that Postmenopausal women may hyperabsorb cholesterol and non-cholesterol sterols, and that would suggest the sterol absorption inhibitor, ezetimibe (Zetia) be part of the therapy.

Would you consider or use fibrate monotherapy: TriCor 145 mg (fenofibrate)? The VA-HIT data (a study of high risk men) revealed that fibrates reduce CV events very nicely in patients with insulin resistance and impaired fasting glucose (as well as any statin has in similar patient types). Also, the benefit of the fibrate was independent of baseline HDL-C in the insulin resistant patients. But there is another reason to consider a fibrate. Note the extremely elevated large VLDL-P concentration on NMR. Does this alarm anyone? In analysis of epidemiological trials, large VLDL is a definite risk factor. Such patients typically have significant postprandial hypertriglyceridemia (> 200 mg/dL), elevated apoB and endothelial dysfunction. .

The risk seen with large VLDL excess is related to many metabolic perturbations including the fact that large TG-rich VLDL has a major influence on the creation of small LDL and small HDL. Increased numbers of small LDL are very atherogenic and the small HDL is prone to renal excretion resulting in very low HDL-P (HDL particle concentration). This case is unusual because, when one sees very large VLDL one also expects to see predominantly small LDL and/or small HDL particles (and low HDL-C). Thus one should think that the patient has something else going on: such as a lipoprotein lipase deficiency (cannot hydrolyze the TG in the large VLDL) or a CETP deficiency (the VLDL cannot exchange TG for cholesteryl ester with LDL or HDL). In both of these scenarios the VLDLs remain full of TG (vary large). In CETP deficiency the HDL-C will be quite increased. Usually lipoprotein lipase deficiency disorders are associated with TG levels well above 500 which is not the case in this patient.

Fibrates inhibit the synthesis of hepatic TG, reducing the formation of numbers and size TG composition) of VLDL. Through PPAR alpha agonism fibrates increase beta-oxidation of fatty acids (lowering their concentration). With less FA available, TG production will decrease. Fibrates also non competitively inhibit DGAT2 the enzyme that facilitates FA attachment to monoglycerol forming TG. Fibrates can also increase hepatic production of lipoprotein lipase enhancing lipolysis of TG-rich lipoproteins in certain vascular beds.

There is more to the story: large TG-rich lipoproteins are often associated with coagulation abnormalities like increased viscosity, elevated PAI-1 (plasminogen activator inhibitor-1) or fibrinogen, all serious CV risk factors. Part of the event reduction seen with fibrates is their ability to improve such coagulation factors. These are just a few of the many pleiotropic activities of drugs acting through PPARS. In VAHIT, 90% of the beneficial action of fibrates was not related to follow up lipid concentration. 50% of the action was not discernable by looking at NMR lipoproteins (message, beware of stopping a fibrate in an insulin resistant patient base don what happens to the lipid profile). So indeed one could easily make the case for initiation fibrate monotherapy in this woman.

A quick look back at the lipid profile:

TC = 251 HDL-C = 90 LDL-C = 129 TG = 193
161 TC/HDL-C < 4.0 TG/HDL-C < 3.0

Non HDL-C = 251 - 90 =

If you use AHA Women's Guideline recommendations, the LDL-C and Non HDL-C are elevated. The normal TC/HDL-C and TG/HDL ratio are very suggestive that LDL size is large. The elevated LDL-C (>100) and Non HDL-C (>130) suggest there are too many apoB (especially) LDL particles. Thus I would have predicted from this lipid profile the patient had somewhat increased concentrations of large LDL which is exactly what the NMR LipoProfile revealed. Also, by noting the elevated TG of >193 in the face of large LDL and very high HDL-C, CETP disorders should be suspected.

How about the OC (Mircette). Ethinyl estradiol can significantly elevate TG and HDL-C. So one might choose a different OC including the patch. However I believe that proper and aggressive pharmacologic treatment of the lipoproteins will negate any risk that the OC might bring (this was seen in HERS).

Lesson learned??? It is not hard to find lipoprotein abnormalities in insulin resistant patients. However one must have a full understanding of lipid concentration relationships OR one must do lipoprotein concentration tests (apoB or better yet NMR LipoProfiles) in all patients. **Use TG or low HDL-C as surrogates of apoB, not as goals of therapy** (please read NCEP).

REFERENCES OF THE WEEK:

- 1) SPECIAL REPORTS AND REVIEWS New Insights Into the Genetic Regulation of Intestinal Cholesterol Absorption RANK LAMMERT and DAVID Q.-H. WANG GASTROENTEROLOGY 2005;129:718-734. This is a fairly in depth discussion of the complexities of intestinal handling of cholesterol. Very important reading for Zetia users.
- 2) REVIEW Serum uric acid and cardiovascular disease: Recent developments, and where do they leave us? The American Journal of Medicine (2005) 118, 816-826
- 3) mechanisms of disease Retinoid X Receptor Heterodimers in the Metabolic Syndrome Andrew I. Shulman, Ph.D., and David J. Mangelsdorf, Ph.D. N Engl J Med 2005;353:604-15. High level basic science review of what we all better start understanding.

DAYSRING TRAVELS

Houston, TX
Pikesville, MD
Calhoun, GA
Gadsden, AL
Chattanooga, Knoxville, Nashville, TN
Albany, NY
Kiawah Isle and Columbia, SC
Bethlehem & York & Pittsburgh, PA
Las Vegas, NV

Reminder: My previous cases of the week discussions can be reviewed and downloaded in PDF form at

<http://www.nypcvs.org/pages/1/index.htm>

North American Menopause Society www.menopause.org Become a certified menopause practitioner!

All my readers should consider joining the National Lipid Association. Great CME materials, great conferences and lipid certification if qualified.

If you sweating and uncomfortable during the late summer. Picture Iraq and out heroes and their military dress. What sacrifices they make for their country (you and me).

Happy lipiding and may the particles be with you,

Tom

Thomas Dayspring, MD, FACP
North Jersey Institute of Menopausal Lipidology
516 Hamburg Turnpike
Wayne, NJ 07470
Tel: 973-790-8604
Fax: 973-790-1488