

Dr. Underberg

From: TDayspring@aol.com
Sent: Thursday, May 05, 2005 10:43 AM
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Subject: Lipid Case # 137 Young Woman - NCEP: When to Treat & Goals of Therapy

Happy May Lipidaholics: This week I have been asked by a gynecologist about a 23 year old white female who is 4'11", and 160 lbs. She was diagnosed with "elevated lipids" 3 years ago by an internist when working her up for hypothyroidism and fibromyalgia. I became involved due to irregular, heavy menses. The patient does appear to have the metabolic syndrome and COS, with no insulin resistance. She has been regulated on Ortho Evra (chosen by me for less affect on lipids, hopefully) and is happy. However lipids continue to be problem. All panels that follow are fasting. She does have a cardiac Family History in an aunt.

Internist caring for pt: 7/03 TC =173, HDL-C = 27, LDL-C = 105, TG = 342
 12/03 (exercising now) TC =204 HDL-C = 42 LDL 149 TG = 168

I became involved for menstrual irregularities , placed on Ortho Evra
 3/04 TC = 239 HDL-C = 44 LDL-C = 134 TG = 304 VLDL-C = 61
 11/04 menses great, pt happy, yet... TC = 212 HDL-C = 36 LDL-C = 134 TG = 211.

Pt declined medical treatment; wanted to work more on diet, exercise. She was doing a pretty good job at this point so I gave her one more try.

01/05 TC = 232 HDL-C = 41 LDL-C = 152 TG = 193. She was started on Lipitor 10 mg

04/05 TC = 176 HDL-C = 36 LDL- C = 98 TG = 211.

The practitioner asks: Why didn't Lipitor have better effect on raising HDL and lowering TG? I thought it would be a great drug for all her problems. I realize not every drug works for every pt and I might go higher, but she feels terrible on it, primarily fatigue, and wants to stop. Am I overreacting to needed treatment in this pt.

DAYSRING DISCUSSION:

This is a typical but very interesting lipid case, illustrative of many principles.

This is a very typical PCOS with the metabolic syndrome and insulin resistance (which is very evident in the lipid profile). The provider is worried that her lipid profile seems abnormal despite treatment with a statin. In reality, according to the National Cholesterol Education Program Guidelines, she never qualified for pharmacotherapy. Yet even if one considers her at high risk, she has responded nicely to the statin and is at NCEP goals of therapy for a high risk patient. Let me take you all through the case.

What is the CV risk of this patient? Using NCEP criteria, she has but one major risk factor for CHD, namely the low HDL-C. She does not have the others: elevated BP, smoking, age 55 (woman) or premature family history in first degree relative. Therefore she does not qualify for further risk stratification using the Framingham risk equation: you need to have two major risk factors for CHD. She would be considered as low risk and would not qualify for pharmacotherapy unless her LDL-C was > 190 mg/dL or TG > 500 mg/dL on diet.

However, one must always keep in mind that NCEP risk tools only project risk over the next ten years: not long term risk. For sure this woman is extremely unlikely to have a coronary event by age 32. But she is very likely to have one at 52. So do we wait until then to treat or do we start now? This is a major dilemma providers face every day when they encounter young folks with lipid abnormalities.

However, NCEP is a flexible guideline and by that I mean it gives clinicians further options in fine tuning risk assessment. When one encounters a "low risk" patient using initial screening tools, one may then look at what NCEP terms "emerging risk factors." These are lab parameters, supported by significant literature, which can

modify risk, especially when present in multiples. Their purpose is to help us spot high risk patients that are missed when conventional risk factors are looked at. They include lipid and non-lipid categories

- 1) Triglycerides
- 2) TC/HDL-C ratio
- 3) Remnant lipoproteins
- 4) Small LDL
- 5) apolipoprotein B and A1 abnormalities
- 6) HDL subparticles
- 6) Lipoprotein (a) elevations or Lp(a)

- 1) Inflammatory markers such as CRP
- 2) Glucose or glucose tolerance
- 3) Coagulation markers (fibrinogen, PAI-1)
- 4) Homocysteine

As we shall see in the discussion that follows, I believe this woman has the first 5 lipid emerging risk factors and several if not all 4 of the non-lipid emerging risk factors.

NCEP also puts heavy emphasis on recognizing the metabolic syndrome because it modifies risk and is so amenable to lifestyle interventions. It is interesting that NCEP discusses emerging risk factors and the metabolic syndrome under different headings, because the metabolic syndrome is a "constellation" of risk factors that includes all of the above emerging risk factors except Lp (a) and homocysteine.

The patient under discussion has at least three of the five criteria required to diagnose the metabolic syndrome: (no mention is made of her BP or glucose level).

Hypertriglyceridemia (>150 mg/dL)
 Low HDL-C (< 50 mg/dL)
 Obesity

Keep in mind that the WHO definition of MS includes microalbuminuria, which I believe would be a useful test to do in this women.

However, do you really need anything more than the hypertriglyceridemia? In a just published editorial in Circulation by Michael Criqui: "There is a growing consensus about the importance of triglycerides, particularly in women, and we have shown in a national US sample that triglyceride level was the single most predictive component of the MS-NCEP for CVD in multivariate analysis". Circulation 2005;111:1869-1870.

Her lipid profiles are:

1) July 2003: TC = 173 LDL-C = 105 HDL-C = 27 TG = 342
 The Non HDL-C = 173-27 = 146 and the VLDL-C would be calculated as TG/5 = 342/5 = 68.

This profile indicates some CV risk as the elevated Non HDL-C (aha Preventive CHD Guidelines for Women recommends a Non HDL-C < 130 MG/D) is a surrogate for having too many betalipoproteins. These are apoB containing lipoproteins and are potentially atherogenic if present in increased concentrations. The most atherogenic of the apoB particles are small VLDLs (called remnants) and especially small LDL particles. The patient has both. I know this because of the following abnormal values

Increased TC/HDL-C (>4.0) in the face of an unremarkable LDL-C, Elevated TG/HDL-C ratio (>3.8), and an elevated Non HDL-C in the face of an unremarkable LDL-C. Such patients are now termed disorders of the TG/HDL-C axis. The underlying abnormality is almost always insulin resistance. It is likely her BP is >130/85. The last component of the metabolic syndrome (impaired fasting glucose > 100) usually takes many years to appear. NCEP uses increased VLDL-C as a surrogate of remnant lipoproteins (smaller, cholesterol enriched VLDL and chylomicron particles). VLDL-C should never be more than 30 mg/dL.

NCEP states: A TG of 200 mg/dL or higher are associated with significant quantities of remnant lipoproteins that convey CV risk **SUBSTANTIALLY** above that predicted by LDL-C.

If we had not done a lipid profile but rather advanced lipoprotein testing using the NMR LipoProfile from LipoScience (www.lipoprofile.com) we would have seen:

- 1) Way too many small LDL particles (small LDL are more atherogenic than large)
- 2) Reduced HDL-P (without HDL particles, atherosclerosis is unchecked)
- 3) Increased large VLDL (V5 AND V6) which are associated with coagulation abnormalities and which adversely effect the lipid composition of LDL and HDL
- 4) Increased small and medium (V1-V4) VLDLs (atherogenic remnants)

Those lipoprotein abnormalities are very typical of insulin resistance and occur very early after the onset of insulin resistance: often before obvious lipid abnormalities (high TG, low HDL-C) and decades before glucose goes up.

Lifestyle is never to be discouraged and is the appropriate first step in the management of this patient. We now have a new food pyramid which she should become familiar with or we can recommend the DASH program or South Beach Diet. Her profile changed to:

12/03/03 TC = 204 LDL-C = 149 HDL-C = 42 TG = 168 Non HDL-C = 162
 Note the VLDL-C = $168/5 = 33$

At first glance the lipids look better (HDL-C up and TG down), but the two best indicators of trouble, the Non HDL-C and the LDL-C (apoB surrogates) have increased. This is a dramatic example of why NCEP uses LDL-C and Non HDL-C as goals of therapy when treating people with high TG or low HDL-C, rather than normalizing the TG level or HDL-C level. In this case despite a seemingly beneficial change in TG, her Non HDL-C (surrogate of apoB level) is elevated.

Ortho Evra was appropriate to manage her symptoms (menstrual irregularities) without aggravating lipids. I saw no evidence of weight loss on follow up I would have added metformin (titrated up to 2 grams). This would improve the insulin sensitivity and likely helped with weight loss. I understand the patient may have refused my medical therapy. Upon follow up she reportedly is feeling great and with normal menses but in reality nothing has changed with the lipids, especially if you use apoB (LDL-C and especially Non HDL-C) as the proper surrogates of risk.

11/04/04 TC = 212 LDL-C = 134 HDL-C = 36 TG = 211 Non HDL-C = 176 VLDL-C = 42

Lifestyle was continued and on follow up:

1/05/05 TC = 232 LDL-C = 152 HDL-C = 41 TG = 193 Non HDL-C = 191

In other words, despite the lifestyle changes, the lipid profile is significantly worse. Her apoB level (as evidenced by LDL-C and Non HDL-C) has been rising significantly over time. She was then started on a statin, Lipitor 10 mg daily.

It is my belief that once a patient has proved that lifestyle is not going to happen or not going to work, then I start what I consider very safe lipid medication. So I do agree with the provider on starting a statin (although as you will see in the ensuing discussion I would have used Pravachol, Crestor or Vytorin and not Lipitor).

Three months later, the profile on statin (Lipitor) was:

TC = 176 LDL-C = 98 HDL-C = 36 TG = 211 Non HDL-C = 140 VLDL-C = 42

The Lipitor has significantly lowered her LDL-C and non HDL-C. She is actually at NCEP (but not AHA Women's) goal for both and thus no further lipid therapy is needed. However, the provider asks, why did not the Lipitor raise her HDL-C and lower the TG? Although this is not understood by many practicing physicians, NCEP sets no specific TG or HDL-C level as a goal of therapy. Since low HDL-C and high TG are simply surrogates that the patient likely has increased numbers of atherogenic apoB particles, the therapy is directed at lowering apoB or rather the NCEP proxies or surrogates of apoB which are LDL-C and if TG are elevated, Non HDL-C. To be honest you should not be looking at the TG or HDL-C level as a goal of therapy. If non HDL-C is normalized, the low HDL-C or high TG conveys no risk. One important caveat: The Non HDL-C goal

of therapy does not apply if the TG is > 500.

If you were following the AHA Guidelines of CHD Prevention published in 2004, they suggest all women have a Non HDL-C < 130. You could easily achieve that in the above patient by 1) increasing lifestyle (although she has proven that will not work), 2) by increasing the dose of the statin (and asking for more side effects), or 3) switching to a lower dose of a more potent statin and one that raises HDL-C better (Crestor 5 or 10 mg). One could add ezetimibe (Zetia) to the Lipitor: however it would make much more sense to use the combination statin (simvastatin or Zocor) with ezetimibe: Vytorin 10 or 20 mg. This product is also much better on HDL-C than Lipitor (which is the least useful statin on HDL-C). See reference #2 below.

A reminder to all: A few weeks ago the FDA rejected the petition of Sidney Wolfe to have Crestor withdrawn from the market. In a 36 page letter the FDA bluntly and emphatically stated that since coming on the market there has been no increase in any adversity compared to any other statin: that includes liver, myopathy and renal complications including proteinuria. In every head to head trial ever published (and there are several), Crestor (at lower doses) is more efficacious than any other statin. Ask your AZ reps for a copy of the letter.

However as with all statins total success will only come with combination therapy and Crestor works beautifully with Zetia, WelChol and TriCor (not gemfibrozil).

True insulin resistance fighters would insist that metformin be added. She should be kept her on the contraceptive as fertility will improve on metformin and you do not want to be using statins, etc in women who might get pregnant. Since fibrates add so much to insulin resistant patients through a multitude of pleiotropic effects including improving insulin sensitivity and reducing progression or onset of microalbuminuria, one might simply add TriCor to the statin: if that is the decision I would switch her to Pravachol or Crestor, the hydrophilic statins which are the least likely to cause food and drug interactions in a polypharmacy patient. However, no statin has an interaction problem with fenofibrate.

REFERENCES OF THE WEEK Lots of good stuff!

1) The Challenge of Achieving National Cholesterol Goals in Patients With Diabetes Diabetes Care 28:1029–1034, 2005. CONCLUSIONS— In many patients with diabetes and cardiovascular disease, it will be difficult to attain an LDL goal of <70 mg/dl. Approximately 25% of patients **will require more than two lipid-lowering drugs** at maximal doses to attain this goal, assuming 100% tolerance of lipid-lowering medications.

2) Dose-comparison study of the combination of ezetimibe and simvastatin (Vytorin) versus atorvastatin in patients with hypercholesterolemia: The Vytorin Versus Atorvastatin (VYVA) Study. Conclusions: Ezetimibe/simvastatin was more effective than atorvastatin in lowering LDL-C at each dose comparison and provided greater increases in HDL-C at the 40- and 80-mg statin dose. Ezetimibe/simvastatin is a highly efficacious, well-tolerated treatment option for hypercholesterolemic patients. (Am Heart J 2005;149:464-73.)

3) Effectiveness of statins for secondary prevention in elderly patients after acute myocardial infarction: an evaluation of class effect Interpretation: Our results suggest that, under current usage, statins are equally effective for secondary prevention in elderly patients after AMI. CMAJ 2005;172(9):1187-94

4) Nonalcoholic Fatty Liver Disease Is Associated With Carotid Atherosclerosis. Conclusions—Patients with NAFLD show a cluster of risk factors of the metabolic syndrome and advanced carotid atherosclerosis. NAFLD appears to be a feature of the metabolic syndrome, and its detection on abdominal ultrasound should alert to the existence of an increased cardiovascular risk. (Arterioscler Thromb Vasc Biol. 2005;25:1045-1050.)

5) Effects of switching statins on lipid and apolipoprotein ratios in the MERCURY I study. Conclusions: Rosuvastatin 10 mg reduces lipid ratios more than equivalent and higher doses of other statins; switching to equal or lower doses of rosuvastatin produces significantly improved reductions in lipid ratios. International Journal of Cardiology 100 (2005) 309– 316

6) Mechanisms of disease: Inflammation, Atherosclerosis, and Coronary Artery Disease N Engl J Med 2005;352:1685-95.

7) Advanced Lipoprotein Testing Does Not Improve Identification of Subclinical Atherosclerosis in Young Adults: The Bogalusa Heart Study Article. Conclusions: Advanced lipoprotein testing using vertical-spin

density-gradient ultracentrifugation did not improve prediction of carotid intima-media thickness in young adults and may not be useful for assessing cardiovascular risk in this population. *Ann Intern Med.* 2005;142:742-750.

DAYSPRING TRAVELS (next few months)

If you are looking for a great summer vacation idea and want to coordinate it with CME, why not join me at the Mississippi Osteopathic Medical Association meeting. On 6/01/05, at the San Destin Florida Hilton, I will lead off a series of lectures designed to aggressively assist you in reducing cardiovascular disease. Other speakers that same day include Dr. Nassef from Washington University who specializes in stroke reduction, and Dr. Charles Reasner from Dallas who also is nationally noted speaker for CV reduction. Paradise and CME in one package -- come join us for this special Memorial Day Holiday Week event! The contact person for the meeting is Jeffrey LeBoeuf, 601-366-3105, jeffrey@moma-net.org

Voorhees, Rutherford, Madison, Bridgewater, Fair Lawn, NJ
 Omaha, Lincoln, NE
 Mayfield, NY
 Milwaukee, Racine, Madison, WI
 Denver, CO
 Charlotte, NC
 Syracuse, NY
 Fort Myers, FL
 Dallas, Forth Worth, Austin, TX
 Los Angeles, Oxnard/Ventura, Bakersfield, San Fernando Valley

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>

Remember the National Lipid Association www.lipid.org Join: The new syllabus on Metabolic syndrome is ready for release. **Be sure to attend the annual meeting this summer (July) in Chicago.** They are offering a Masters Course for those ready to take that plunge. On line registration is now available.

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

WANT MY SLIDES? Two CME CDs are available for free. You get my animated slides, my voice and slide notes. (1) "Understanding the Influence of Triglycerides on Lipid and Lipoprotein Pathobiology" and (2) "Treatment considerations form TG-rich Lipoprotein Pathobiology" The slides are very much worth the price: **FREE!** Do the Lipoprotein Physiology one first. It is essential to understand the basics before looking at the one dealing with treatments.

If they would like both CDs, **FAX a request to ACCESS Medical Group Department of Continuing Medical Education at 847-392-2257** Request both CDs. If your fax goes unanswered call you can contact Susan Pazderski at Access Medical, (847) 392-2227.

Continued prayers and thanks for the men and women of our Military who continue to make so many sacrifices for our way of life (freedom). Let's also never forget our vets, who have also made that sacrifice. If you ever get to DC, spend some time at the WWII memorial. Bring plenty of tissues!

Happy Lipiding,

Tom

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