

Hi Lipidaholics: here is a case to challenge all of us. I have been asked what to suggest to a 52 y/o white female, aerobic instructor for 25 years, who is in very good shape. Her BMI is approximately 23. She eats extremely healthy except for mild hypertension, well-controlled on Cozaar 50 mg. Patient's PMH and ROS completely negative (except for the recently diagnosed mild hypertension). FH negative for any known CV disease except her mom (over 75) with hypertension.

During a recent complete exam her clinician discovered a prominent bruit over abdominal aorta and loud bruits over both femorals. She has no claudication.

LAB:

TC = 177, TG = 89, HDL-C = 71, LDL-C = 95 Non HDL-C = $177-71 = 106$
FBS 95
LP (a) 0,
Homocysteine 6.5, hsCRP .17, plus all other lab normal.

Incidentally, no evidence of target organ damage (eye, heart, kidney). EKG okay, US of aorta - normal, US of femorals - mod plaque on right, mild plaque on left, ABI (ankle-brachial index) on right .90, left .91 NCEP uses $<.90$ as the criteria to diagnose atherosclerosis. An abnormal ABI is considered diagnostic of PAD.

The physician states that she is at the cut-point for diagnosing PVD but clearly has disease. He has put her on ASA and asks: Would you Rx with statin, and if so to what goal, and any further w/u (stress test, EBCT)?

DAYSRING ADVICE

This is a tough case. Can one have atherosclerosis without abnormal lipids or CRP? There does not seem to be a genetic basis (unless she is adopted and has not been made aware of that). There is no mention of smoking so I have to assume that she does not have the #1 risk factor for PAD. The history is not compatible with some other type of vasculopathy. Let's look very closely at what we have. I am also presuming she is not on estrogen therapy and because of her age is likely postmenopausal menopausal status will matter when we decide on treatment).

Are the lipids absolutely perfect? Since she has PAD, she is considered to be a coronary heart disease equivalent by NCEP. Using their recommendations all of her lipids seem to be at goal. However I would like to quote a statement from NCEP: "It should be noted that these guidelines are intended to inform, not replace, the physician's clinical judgment which must ultimately determine the appropriate treatment for each individual." Thus it is my judgment that this lady has metabolic abnormalities and requires further workup and very aggressive treatment.

1) Although there is no family history, phytosterolemia (sitosterolemia) has to be ruled out and her dietary history of plant, yeast and shellfish sterol ingestion may be useful. If this is the problem, the therapy is Zetia which is our only therapy to block sterol absorption. (Resins have been used in the past with less than fantastic results).

2) would probably repeat the Lp (a) another time to make sure there was not a lab error).

3) Her race is not mentioned, but especially in Japanese, disorders of CETP or hepatic lipase are associated with high levels of HDL-C and atherosclerosis

4) Insulin level and oral GTT. I think a glucose of 95 in a person with a BMI of 23 is very unusual. In the West Of Scotland Study (men) a glucose of 86 or higher predicted a more than doubling of the onset of diabetes over a 5-6 year period. She is also hypertensive. I think we may well have insulin resistance in this lady. One does not have to be obese to be insulin resistant.

5) Some would say, she is a CAD equivalent. Thus, a more appropriate goal of therapy (using data from REVERSAL, PROVE-IT and ALLIANCE studies) in such a patient is an LDL-C less than 70, maybe even 60. Recently, I was part of a faculty during a lipid symposium, where one of the speakers (a member of NCEP) stated an Addendum to ATP-III would be available early next year with a new goal of 70 in CAD patients and 100 in everyone else.

I say why guess or debate LDL-C? If anyone needs advanced lipoprotein testing, it is this patient. I had a similar case a few years ago and advanced lipoprotein testing, using the NMR LipoProfile revealed significant lipoprotein pathology (small LDL particles), as I suspect will occur here. A physiologic TG is well under 70. It is not impossible to have small LDL particles with a TG of 89. I really think we will find increased numbers (perhaps very significantly) of small LDL particles in this patient. One could order an apoB but that would only collectively quantify the beta-lipoproteins, not individually as does NMR: VLDL, LDL, IDL.

I am going to assume that we will discover increased numbers of very small LDL particles and she is insulin resistant. Continued aggressive BP control with a goal of <120/80. The angiotensin-receptor blocker is an excellent choice although Cozaar may require BID dosing.

How should we reduce the number of LDL particles or get her LDL-C below 70 if you are not going to do advanced testing (for whatever reason)? If we use the PROVE-IT Trial results, should we just go to Lipitor 80 mg? Not at all! In PROVE-IT if the baseline LDL-C was < 120 there was no difference in efficacy between Pravachol 40 mg or Lipitor 80 mg. So I am not going to give this lady a large dose of a lipophilic statin. So I will start Pravachol at the FDA approved dose of 40 mg. My current strategy (based on the proven need to drastically reduce LDL particles) in most patients is to routinely add Zetia to my statin (makes every statin a "gorilla" statin immediately). We also have data that in patients with atherosclerosis or even in first degree relatives and also in postmenopausal women, sterol levels are higher than persons without CAD. Only way to keep sterols out is to routinely use Zetia in high risk patients. So routine use of Zetia gets you to LDL goal almost immediately and also keeps sterols out.

Now for some new emerging data: Ever notice that statins work better in some patients than in others with respect to lowering LDL-C or LDL particle number? Some persons hyperabsorb cholesterol. Their livers therefore have a robust supply of cholesterol and thus there is no need to synthesize cholesterol. HMG-CoA reductase is down-regulated and such people produce little hepatic cholesterol. If there is no HMG-CoA reductase, statins will not work very well (measuring cholestanol levels is a way to ascertain cholesterol absorption and synthesis). If one uses Zetia and denies the liver a source of cholesterol: HMG-CoA reductase levels will increase and the statin will become very efficacious. By denying the liver its only two sources of cholesterol (absorption and synthesis) there will be dramatic upregulation of LDL receptors and dramatic lowering of LDL particle number and LDL-C.

Any use for a fibrate (TriCor) in this case? The VA-HIT study revealed that >40% of the benefits in reducing CV events in insulin resistant patients with a fibrate are pleiotropic (non-lipid). So it would not be unreasonable to use TriCor which can also lower LDL-C. In insulin resistant (or diabetic) patients the fibrate data is as good if not better than the statin data if LDL-C is not high and HDL-C is low. Of course all of the fibrate data is in men for that reason the AHA Women's guidelines advises therapy to begin with a statin. If one measured an apoA level (the main apolipoprotein on HDL) and it was borderline or reduced, one can assume it might be wise to increase apoA production (a PPAR alpha effect of fibrates).

Lastly: I would do a baseline EBCT to see if coronary calcium is present. This could further support the diagnosis, and be followed over time as a judge of therapy efficacy. Because of her profession, she should have an exercise treadmill test to evaluate functional capacity.

Goal of therapy would be an LDL particle count well under 1100 (probably 800) or an LDL-C of < 70 if advanced testing is not done.

REFERENCES OF THE WEEK

1) Initial Low-Density Lipoprotein Response to Statin Therapy Predicts Subsequent Low-Density Lipoprotein Response to the Addition of Ezetimibe (Am J Cardiol 2004;93:779 –780): Patients who are hyporesponders to statin therapy are hyper-responders to ezetimibe therapy and may help identify a patient population in whom ezetimibe would be particularly effective in lowering low-density lipoprotein cholesterol.

2) Effect of Fenofibrate-Mediated Increase in Plasma Homocysteine on the Progression of Coronary Artery Disease in Type 2 Diabetes Mellitus The American Journal of Cardiology Vol. 93 April 1, 2004 848-853 adverse This analysis of the the DAIS reveals that the fenofibrate-mediated increase in tHcy levels does not attenuate the beneficial effects of fenofibrate on CAD progression or clinical events.

3) Scavenger receptor type BI potentiates reverse cholesterol transport system by removing cholesterol ester from HDL Atherosclerosis 173 (2004) 197–202 cells. These results indicate that SR-BI reduces the cholesterol content and size of the CE-rich HDL from CETP deficiency, which ultimately activate reverse cholesterol transport system.

Dayspring Lectures (thru rest of April & May)

Indianapolis and Fort Wayne, IN (Menopausal not lipid lectures)

Houston TX (4/29) and Los Angeles, CA (4/22) (CME Dyslipidemia Conf)

MidAtlantic Nurse Practitioner Meeting College Park, MD 4/24

Bethlehem, PA (4/30)

New Brunswick, NJ

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)

Will be doing a series of evening CME National Teleconferences on Management of Dyslipidemia associated with Diabetes and the Metabolic Syndrome. Call 1-800552-5487 for dates and details

Well, that's all folks! Get out there and prevent CV risk but leave some time to reflect and have a few thoughts about our very special and committed protectors at home and abroad.

Happy Lipiding, Tom

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