

Hello Lipidaholics: Spring is getting closer. I received a telling case from a practitioner a recently. The doc was having some trouble in controlling all lipoproteins in a female patient with mixed dyslipidemia on a statin: Lescol XL 80 mg (fluvastatin).

She is 61.5 inches tall, weighs 140 lbs and she has controlled hypertension on Ziac 2.5mg one per day, Levothyroxine and stable TSH, and Premarin 0.45mg and Lescol XL 80 mg. Glucose is WNL

No lipid profile was done, but the lipoprotein (NMR LipoProfile) analysis revealed:

LDL-P (LDL particle concentration) = 1321 (perfect < 1000)
LDL Size = 20.2 nm (small or Pattern B)
Large HDL-P = 6 (desirable in a drug naive patient >30)
Large VLDL-P = 42 (perfect < 7)

There was also an increase in intermediate VLDL and small LDL-P and small HDL-P

Based on the above lipoprotein concentrations, the practitioner tried Niaspan (extended release niacin) and just a few days later the patient stopped it because of intolerance, and a few weeks later Lofibra (fenofibrate) 200 mg capsules was prescribed for a brief time but she stopped that because her ankles were weak.

The clinician next turned to Zetia (ezetimibe) 10 mg one per day and fish oil 1000 mg two capsules twice per day to the Lescol XL. A repeat NMR LipoProfile revealed dramatic improvement which seems to be due to the synergistic effects of Zetia and/or omega-3 FA.

LDL-P (LDL particle concentration) = 688 (perfect < 1000)
LDL Size = 22.5 nm (large or Pattern A)
Large HDL-P = 56 (there is no specific goal of therapy for large HDL-P): the goal is to increase HDL-P
Large VLDL-P = 2 (perfect < 7)

There was a dramatic reduction in all sized VLDLs and there were no small LDLs. The small HDL-P remained in the 90th percentile.

NMR derived lipid concentrations were:

TC = 183 LDL-C = 88 HDL-C = 82 TGF = 79

The practitioner was stunned by the dramatic improvement.

Since the lipoproteins are now perfect, a traditional or chemical lipid profile would be very similar. NMR derived lipid concentrations differ from traditional profiles in insulin resistant states and in those cases it is the NMR lipids (not the traditional lipids) that are more related to risk. Only those fully versed in the reasons why there are differences between traditional and NMR lipid concentrations should order the NMR-derived lipids. LipoScience now gives you the option and as always when you have lipoprotein concentrations, lipid concentrations should have little if any influence on your risk assessment or therapy.

The physician's plan is to try her off of Lescol about 4-6 weeks before I recheck her lipids to see how she does with just Zetia and fish oil alone.

DAYSRING ANALYSIS

This is a fascinating case that nicely demonstrates a physiologic principal that many are unaware of. It also gives me an opportunity to discuss sterol absorption and what happens to lipid and lipoprotein concentrations when we alter such absorption.

We do not have lipid or lipoprotein values before Lescol was started nor do we have the traditional lipid profiles in the above case (we have NMR derived lipid concentration on the last profile). However, based on the first lipoprotein analysis (on Lescol) one can assume the HDL-C was low and the TG were quite high. TC was probably high but LDL-C was probably unremarkable (because she has too many small LDL particles). Very likely the non HDL-C was significantly elevated. The pre-Lescol profile was probably similar but with even more abnormal concentrations.

When fats (triglycerides) enter the intestine (in our food) they are immediately emulsified by lecithin (a phospholipid in biliary secretions) and then hydrolyzed (changed into mono or diglycerides and fatty acids) by salivary and intestinal lipases (enteric and pancreatic). The fatty acids (FA) and dietary sterols are organized or surrounded by bile salts into Micelles which are obviously collections of cholesterol and non-cholesterol sterols and monoglycerides and fatty acids, surrounded by bile acids. The micelles "ferry" the sterols and FA to the brush border of the jejunal intestinal epithelium. Once there, FA are absorbed by passive diffusion through the lipid cell membranes.

The sterols in the micelles are absorbed via a protein called the Neimann-Pick C1 Like 1 (NPC1L1) protein which is a sterol permease (a protein involved with absorption of sterols). NPC1L1 has absolutely nothing to do with the absorption of fatty acids. Most humans typically absorb about 50% of the sterols in the gut, but some people are hyperabsorbers (60-80%) and some are hypoabsorbers. Zetia (ezetimibe) blocks sterol absorption (by about 50%) from micelles by interfering (binding to) with NPC1L1 in the intestinal epithelium. Less cholesterol is delivered to the liver forcing upregulation of hepatic LDL receptors and subsequent reduction of apoB and LDL-C. Since LDL receptors and LDL receptor like protein can also remove TG-rich lipoproteins (using apoE on the particles as a ligand), Zetia is know to reduce TG and remnant lipoproteins in insulin resistant patients.

Cholestyramine (Questran), a bile acid resin or Colesevelam (Welchol) a bile acid polymer are termed bile acid sequestrants (BAS). They work by binding or sequestering bile acids, thus blocking their ileal reabsorption. This forces the liver to use endogenous cholesterol to make new bile acids. They have no major effect on fatty acids or sterol absorption. The BAS mechanism of action has absolutely nothing in common with the MOA of Zetia. They (especially the resins) also can cause a loss of fat soluble vitamins and can also interfere with the absorption of many drugs, which is why most drugs have to be administered 2 hours before or 4 hours after a BAS.

Omega-3 FA have many mechanisms of action with respect to lowering CV risk, but at large pharmacologic doses they are PPAR alpha agonists and are very beneficial to lowering TG. The mechanism of action of Omacor® is not completely understood. Potential mechanisms of action include inhibition of acyl CoA:1,2-diacylglycerol acyltransferase and increased peroxisomal β -oxidation in the liver. They may reduce the synthesis of triglycerides (TGs) in the liver because EPA and DHA are poor substrates for the enzymes responsible for TG synthesis, and EPA and DHA inhibit esterification of other fatty acids. A product called Omacor (1 gm of omega-3 fa has received FDA approval and will be detailed to you shortly. The dose is 4 capsules a day to treat hypertriglyceridemia. That's a lot of capsules: I now prefer a very palatable (lemon flavored) omega-3 liquid concentrate:

Visit www.carlsonlabs.com and check out **Finest Fish Oil Liquid Omega 3** Two teaspoons a day provide 4 gm.

There is a certain type of patient that frequently show dramatic LDL-C and thus LDL-P reductions. If one is a hyperabsorber of cholesterol (70-80% rather than the 50%) chylomicrons deliver substantial cholesterol to the liver. There would be little need for hepatic cholesterol synthesis in such patients and thus there is a down-regulation of HMG CoA reductase synthesis. Because of the increased cholesterol absorption, these patients have elevated cholesterol levels and they would be very poor responders to statins, which competitively inhibit HMG CoA reductase. This is the patient whose LDL-C reduction response to a statin is far below what one expects. Since the problem is hyperabsorption of cholesterol, Zetia (by blocking the absorption) usually results in dramatic LDL-C and LDL-P reduction (40-60%). With Zetia induced, less delivery of cholesterol to the liver, HMG CoA is upregulated and like a miracle the statin becomes very much more efficient again. Excellent references on this phenomenon are: *Arterioscler Thromb Vasc Biol.* 2001;21:832-837 and *Am J Cardiol* 2004;93:779-780.

It is also likely that if one is hyperabsorbing cholesterol, there is also hyperabsorption of potentially more atherogenic noncholesterol sterols (ie. sitosterol). Again Zetia can also solve this potential problem.

So is the above dramatic response (beyond the statin) due to Zetia or the high dose omega-3 FA? My guess is both. The Zetia LDL receptor upregulation explains the dramatic LDL-P reduction, but the omega-3 FA shifted LDL size from small to big which enhances the ability of LDL receptors to remove LDL particles. The omega-3 explains most of the TG and VLDL-P reduction (although Zetia helps). Both can help the HDL-P and HDL-C concentrations.

One thing I would not do is stop the statin. I think we need an agent with outcome reduction on board. Neither Zetia monotherapy or omega-3 FA have reduced events in large prospective clinical trials. I have no problem adding them to a statin, but would not use them without a statin in a patient who can tolerate a statin. One might consider Vytorin 20 mg (a combination of Zocor 20 mg and Zetia 10 mg) instead of Lescol 80 mg for cost purposes and compliance issues. .

ADVANCED STUDENTS ONLY: This is lipids 401, but a very recent article gives us some new insight on how Zetia might raise HDL-C (other than by simply reducing TG). In a paper entitled: Reduced cholesterol absorption upon PPAR delta activation coincides with decreased intestinal expression of NPC1L1. *J. Lipid Res.* 2005.46:526-534.

The abstract reads: A PPAR delta agonist treatment resulted in a 43% reduction of fractional cholesterol absorption in wild-type mice, coinciding with a significantly reduced expression of the cholesterol absorption protein Niemann-Pick C1-like 1 (Npc111) in the intestine. PPAR delta activation is associated with increased plasma HDL and reduced intestinal cholesterol absorption efficiency that may be related to decreased intestinal Npc111 expression.

Simply put PPAR delta, which has a beneficial effect on HDL-C and HDL-P also decreases cholesterol absorption in the jejunum. Is it now thought that Zetia (ezetimibe) binds to and interferes with the Npc111 protein. However is it also possible that Zetia also to some fdegree upregulates PPAR delta and not only reduces sterol absorption but thus also increases HDL-C? This is new food for thought and the premise is raised by the author in the concluding paragraphs of the article.

REFERENCES OF THE WEEK

1) The following is a paraphrase from Forbes Magazine: The FDA issued a new package insert for Crestor: The good news for AstraZeneca is that the U.S. Food and Drug Administration apparently did not push for the kind of safety warnings some investors had feared. The new

labeling may be seen as evidence that the worst cries of danger are unfounded. The new label adds a clearer warning regarding the risk of rare muscle-weakening side effects that can lead to kidney damage or death. As the labeling emphasizes, these side effects occur in rare instances not only with Crestor, but with more established competitors such as Lipitor, Zocor and Pravachol. The new Crestor label also contains a boldfaced instruction not to prescribe the highest dose of the drug (40 milligrams) unless patients have not been sufficiently helped by lower doses. Lipitor does not carry such an admonition.

Asians initially should be prescribed the lowest dose of Crestor. New studies of the way the drug works in the body showed that Asians may respond just as well to lower doses. The updated Crestor label recommends that Asians be started on the lowest dose, which is 5 milligrams. In an interview, Blasetto said that AstraZeneca was "pleased" with the new labeling. He also noted that labeling changes are not unusual, and that the other cholesterol drugs had undergone a combined total of 100 such labeling revisions since they were introduced. "These revisions strengthen and add points of information for the practicing physician, and gives them the most accurate information that we have to help them appropriately prescribe Crestor to the appropriate patient population," he said.

Aside from Lipitor, sales of which grew 23% in the fourth quarter of 2004, Crestor is facing tough competition from Vytorin, a cholesterol medicine that combines Zocor with Zetia, a newer medicine from that is generally given on top of the existing cholesterol drugs. Zetia itself has become a blockbuster, and some doctors are prescribing it with Lipitor and Crestor. Crestor still may find its niche: Milligram per milligram, it is the most powerful single-agent cholesterol pill on the market.

2) Contribution of Abdominal Visceral Obesity and Insulin Resistance to the Cardiovascular Risk Profile of Postmenopausal Women Marie-E`ve Piche et al. Conclusions: These results show that although the presence of high IR in its isolated form is associated with some metabolic alterations, it is the combination of both high visceral Adipose Tissue and high IR that is the most detrimental for the metabolic health in postmenopausal women. Diabetes 54:770-777, 2005

DAYSRING TRAVELS

Lipid Lectures:

Louisville and Lexington, KY

Providence, RI

Gary, IN

Chicago and surrounding area (several lectures)

San Diego, CA (2 nights)

Sarasota and Bradenton, FL

Evansville and Terre Haute, IN

Minneapolis, MN

Nebraska Heart Institute Annual Lipid Symposium April 23 (Lincoln NE)

West Hartford, CT

I will be doing a series of CME lectures in person and numerous Web Casts on the challenge of treating menopausal symptoms in postmenopausal women with CV risk factors. The lectures get into lipoprotein physiology in women and the effects of estrogens and progestogens. This will be very much appreciated by primary care professionals including gynecologists interested in better understanding CV risk in women.

My upcoming lectures (March through May) are in Chicago, San Diego, Minneapolis, Philadelphia, Baltimore, Washington DC, Dallas, Houston, Tampa, Cincinnati, Columbus (OH), Indianapolis, Detroit and Denver. If you are interested in the exact times and dates or in logging into one of the many web casts please contact Genesis Healthcare

Phone 908-231-6083 Fax 908-575-0250 or hagan@genesishhealthcare.com

Reminder: My previous cases can be reviewed and downloaded in PDF form at <http://www.nypcvs.org/pages/1/index.htm>

National Lipid Association www.lipid.org Join: The new syllabus on Metabolic syndrome is just about ready for release.

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

WANT MY SLIDES? Two CNE CDs are available for free. (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** 847-392-2257 Request both CDs

ACCESS Medical Group Department of Continuing Medical Education .

Continued prayers and congratulations and respect for our military who through tremendous sacrifice seemingly have initiated a revolution of democracy in the Middle East.

Happy Lipiding,

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