

Hi Lipidaholics; Those of you in Primary Care will appreciate the following case I received. A clinician writes: "I'm stuck in a power struggle with a patient's cardiologist." The patient, an obese 59 year old, post hysterectomy, white female has undergone numerous angioplasty procedures and now has 4 stents; all in the past 2 years. I continue to follow the patient peripherally, as she is no longer in the right insurance plan. She continues to end up in the ER frequently with angina vs esophageal symptoms.

Further information on patient: BMI is 33.

Labs: Homocysteine 7.3, fasting glucose has always been below 110. I went back as far as I had records and these are her fasting sugars: 104, 99, 101, 104, 96, 103.

Before her last angio her lipids (on Lipitor 20 mg) were:

TC-----199
Trig-----204
HDL-C -----43 Non HDL-C = (199-43) = 156
Lp(a)----17
LDL pattern A/B
VLDL-C = 26
CRP----1.8

She is on Plavix + ASA. I recommended changing her from Lipitor 20 mg to a hydrophilic statin as she was having CNS problems on Lipitor. I thought she might get more benefit from Crestor plus Niaspan and made this suggestion. The patient got up to 1000 of Niaspan and her panel on this plus Crestor 20 mg was:

TC-----184
Trig---253 (???)
HDL-C --56 Non HDL-C = (184-56) = 128
Lp(a) 15
VLDL-C = 26
CRP 0.285

Can't explain the rise in triglycerides on Niaspan but since the PATIENT was tolerating it I thought it was worth keeping in light of the improved HDL-C. She presented to the ER again and this time her angio was unchanged and her cardiologist said she was having esophageal symptoms related to the Niaspan and wants her off the Niaspan and to increase her current omega FA to 15-20 gms per day. And to raise the Crestor to 40 mg.

I don't believe it's the Niaspan that's causing her GERD in the first place and increasing her Crestor isn't going to benefit her Trigs or HDL-C.

The cardiologist doesn't want to take advice from an internist. Any advice would be helpful.

DAYSRING ADVICE

You present a very challenging case of a postmenopausal woman having multiple clinical CV events who obviously will require more aggressive therapy. The case elucidates numerous points of proper lipid management. And can we all agree that someone who has had four angioplasties is certainly in need of more aggressive therapies! My assessment is as follows:

Using the new NCEP Addendum, the patient is clearly in the very high risk category and qualifies for extremely aggressive therapeutic assault. She is a woman with advanced atherosclerosis who is a metabolic syndrome. The hs-CRP is of no importance in ascertaining risk in patients who already are high risk. It is a waste of money to keep repeating it. CRP at this time is simply a risk tool; it is not a goal of therapy.

With respect to the first set of lipids (on Lipitor) TC = 199 Trig = 204 HDL-C = 43 Lp(a) = 17 LDL pattern A/B VLDL-C = 26. You did not provide and LDL-C, but using the Friedewald formula (LDL-C = TC minus HDL-C plus TG/5. Thus the calculated LDL-C = 118

The fact that I see a Pattern A/B LDL size tells me you have done a VAP analysis, which as my readers know I consider to be of no help. One of the great shortcomings of VAP is everyone has intermediate particles!!! This person should have LDL quality (size and composition) determined by more accurate methodologies such as NMR spectroscopy (LipoScience) or by Berkeley Heart Lab. Since only NMR LipoProfile will provide individual particle concentrations which are absolutely essential to manage this case I opt for it over Berkeley which unlike VAP at least provides an apoB. I can tell you with great certainty, the VAP analysis is in error and this patient almost certainly has very small LDL (Pattern B) particles. I know that because of the abnormal TC/HDL-C ratio, elevated Non HDL-C value with an LDL-C of 118, and TG/HDL-C which should be well under 3.0,

If I had to **guess** (which I prefer over VAP): the Non HDL-C is (199-43) or 156. The goal in this very high risk patient would be 100. Anyone who has an elevated Non HDL-C and a normal LDL-C almost certainly has very small LDL particles and/or atherogenic remnant lipoproteins (VLDL, IDL). The HDL-C of 43 is well below the AHA Women's Guideline suggestion of 50 and NCEPs value of 50 in metabolic syndrome patients. The TG's are also at a high risk area (NCEP & AHA Woman's Guidelines). Such abnormalities of the TG/HDL axis are highly and significantly associated with insulin resistance. Her BMI is elevated, but 20% of IR cases have normal weight (BMI between 21 and 26). This lady has 4 of the five criteria for metabolic syndrome: (weight, IFG, low HDL-C and elevated TG).

The clinician seems perplexed that the TG went from 204 to 253 but to be honest such a TG change has absolutely no clinical meaning related to risk. There is no risk difference between a TG of 200 and 300 with respect to risk: both concentrations are simply markers of having too many apoB particles (especially small LDL). Physicians often forget or do not know that the NCEP goal of therapy in treating persons with elevated TG is not, per se, to lower TG but rather to normalize both LDL-C and Non HDL-C. Please note that in this case even though the TG went up, **the Non HDL-C dropped from 156 to 128**. So despite the rise in TG, the therapy is working, but goal has not been achieved. The lipid goals in this case (very high risk NCEP category) would be to achieve an LDL-C of < 70 and a Non HDL-C < 100. In my clinic the goal would be a LDL particle concentration (LDL-P) of < 1000 and a small LDL-P < 700. I'd strive to reduce large VLDL and I would have no goal whatsoever with respect to HDL particles. If I normalize the lipoproteins, I really do not care what the lipid profile looks like.

GI symptoms certainly can be related to Niacin and only cessation of therapy and rechallenge can answer the question. I would be very concerned with such symptoms in this woman because angina in women can present as GI symptomatology. Even if there were no GI side effects, I would not have used Niaspan as a second line drug in this insulin resistant patient with impaired fasting glucose.

A clinical decision was made that therapy should raise HDL-C. However NCEP gives us no specific HDL-C goal for persons with low HDL-C levels at baseline. NCEP suggests that in patients with reduced HDL-C, the suggested targets of therapy are to normalize LDL-C and in patients with elevated TG to then normalize the Non HDL-C. Keep in mind that LDL-C and Non HDL-C are simply NCEP's surrogates for apoB lipoprotein concentrations. Thus our true goal of therapy is to normalize the apoB containing lipoprotein level (which NCEP estimates by looking at Non HDL-C). In my practice I go one step better by normalizing LDL-P and VLDL-P (available on the NMR LipoProfile). **AGAIN NEVER FORGET THE MAJORITY OF APOB CONTAINING LIPOPROTEINS IN PLASMA ARE LDL PARTICLES (because of their 3 day half life).**

Therapy: It is stunning to me that the cardiologist would believe this patient can be managed with statin monotherapy, even with a gorilla dose. In MIRACL, PROVE-IT and A-Z, the majority of events continued to occur even in those on Gorilla statin therapy

With the discussion I have presented above, how should we normalize her LDL-C and Non HDL-C or get her LDL-P to goal. The clinician's thoughts were to get rid of the lipophilic statin which I wholeheartedly agree with. This will avoid drug interactions with the necessary polypharmacy this patient will require. So I also would abandon Lipitor and go to Crestor. The LDL particle concentration in this patient is going to be beyond the scope of Pravachol's efficacy. However instead of using Crestor 40 mg it would make far greater sense to use Crestor 10 mg plus Zetia 10 mg and TriCor 160 mg (which would replace the Niaspan).

Rationale: Postmenopausal women with recurrent events often have noncholesterol sterols such as sitosterol in their plaque. They seem to hyperabsorb such sterols. Only Zetia can keep them out. I would also check a sitosterol level in this lady before starting Zetia. The use of Zetia will let us keep the statin dose lower and this means statin safety. The TriCor (a fibrate) is mandatory in this case. You need a drug that inhibits TG synthesis (options are fibrates and niacin). You need a drug that markedly catabolizes TG-rich lipoproteins (fibrates) and you need a drug which will increase apoA production and also induces proper dynamic flux of the apoA particles (reverse cholesterol transport). Only fibrates do this and fibrates have the only empowered clinical outcome trial that reveals reduction of clinical events in persons with low HDL-C (VA-HIT). Unfortunately neither fibrates or niacin have any outcome data in women. Although fibrates may raise HDL-C, that really does not matter (in VA-HIT the HDL-C rise was only 1.9 mg%). Fibrates cause hepatic delipidation of HDL at SRB1 receptors and thus you do not get the HDL-C rise that niacin provides (niacin delays hepatic uptake of large HDL or in other words delays catabolism of HDL but there is no increase in reverse cholesterol transport). Keep in mind the big picture: fibrates and niacin both have outcome data even though they have different abilities to affect HDL-C. Never forget your mission is to lower apoB.

The cardiologist in this case needs to rethink statin monotherapy. Even in PROVE it and in the recent A-Z trial: The majority of events continued to occur in patients taking high dose statin monotherapy, despite achieving extremely low LDL-C levels. Cardiologists seem to think there is some magic pleiotropic effect of high dose statins: amazing what marketing can get a doc to believe. I want to quote from a just published in Circulation "Update on Statins" by Lipid God, Professor Antonio Gotto: "

"There has been considerable debate as to whether statins possess cholesterol-independent effects. Cholesterol-independent effects of statins have been described most extensively in relation to effects of statins in restoring endothelial function via enhanced availability of nitric oxide. A variety of other pharmacological effects of statins have been described that may promote plaque stability through modulation of macrophage activation, immunological effects, and antiplatelet and antithrombotic actions. Investigators have explored the direct, cholesterol independent inhibition by statins of leukocyte function associated antigen-1 as a novel target for the development of agents that may suppress the inflammatory response in several diseases. Most pleiotropic effects of statins in cell culture studies can be reversed by the addition of mevalonic acid, which restores the antegrade integrity of the cholesterol biosynthetic pathway and its intermediates. The clinical importance of the noncholesterol effects of statins in humans has been notoriously difficult to determine, because in humans, statin treatment is almost always associated with cholesterol lowering, even in patients with initially low cholesterol levels. For now, **it would appear that the majority of the clinical benefit of statins is due to LDL-C lowering.**" (Circulation. 2004;110:886-892.)

Other mandatory therapies:

Omega-3 FA at 1-2gm a day. No one can possibly swallow 15-20 gms.

Consider metformin if patient does not improve lifestyle: Titrate to 2 gms.

I would also consider Altace even if normotensive.

Before beginning the combo therapy, get a baseline CPK and urine microalbumin level. Of course counsel the patient on myopathic symptoms. Do not repeat the CPK on subsequent visits unless myopathic symptoms occur.

REFERENCES OF THE WEEK:

- 1) Randomized trial of effects of estradiol in combination with either norethisterone acetate or trimegestone on lipids and lipoproteins in postmenopausal women. F. Al-Azzawi, M. Wahab, S. Sami, A. J. Proudler, J. Thompson and J. Stevenson: Conclusions: unchanged. Total cholesterol, low density lipoprotein (LDL) cholesterol, lipoprotein(a) and apo-B concentrations were reduced in all treatment groups. The concentration of triglycerides was elevated after treatment with the estradiol/trimegestone combinations but was unchanged after treatment with the estradiol/norethisterone acetate combination. *Climacteric* 2004;7:292–300
- 2) Genetic Basis of Atherosclerosis: Part I. New Genes and Pathways. Aldons J. Lusis, PhD; Alan M. Fogelman, MD; Gregg C. Fonarow, MD. Very nice review. (*Circulation*. 2004;110:1868-1873.)
- 3) Efficacy and safety of ezetimibe coadministered with statins: randomized, placebo-controlled, blinded experience in 2382 patients with primary hypercholesterolemia
M.H. DAVIDSON, C.M. BALLANTYNE, B. KERZNER, L. MELANI, P.T. SAGER, J. STRONY, R. SURESH, E. VELTRI, FOR THE EZETIMIBE STUDY GROUP: alone. At each statin dose, treatment with ezetimibe - statin led to a greater LDL-C reduction compared to the next highest statin monotherapy dose. *Int J Clin Pract*, August 2004, 58: 746–755
- 4) Disruption of cholesterol homeostasis by plant sterols Chendong Yang, Liqing Yu, Weiping Li, Fang Xu, Jonathan C. Cohen, and Helen H. Hobbs. These data indicate that selected dietary plant sterols disrupt cholesterol homeostasis by affecting two critical regulatory pathways of lipid metabolism.
- 5) The effect of statins and fibrates on interferon- γ and interleukin-6 release in patients with primary type II dyslipidemia oguslaw Okopie'n, Robert Krysiak, Jan Kowalski, Andrzej Madej, Dariusz Belowski, arek Zieli'nski, Krzysztof Labuzek, Zbigniew S. Herman *Atherosclerosis* 176 (2004) 327–335. The treatment-induced reduction in the release of both cytokines may contribute to the clinical effectiveness of statins and fibrates in the therapy of atherosclerosis and in the management of organ transplant recipients.

DAYSPRING TRAVELS

Branchburg, Mendham, Wall Twp, Westwood, NJ
Chicago Area (October 12, 13th),
Manhattan, Brooklyn, NY
Annapolis, MD
Atlanta, GA (November)
Monroe LA
Albuquerque, Santa Fe NM
Phoenix (Paradise Valley), AZ
Milwaukee, WI (two different visits)
Sarasota and Bradenton, FL
Salt Lake City

National Lipid Association www.lipid.org

North American Menopause Society www.menopause.org

Continued prayers and thoughts to our magnificent protectors (the armed services) in the jobs they are doing throughout our troubled planet.

Happy Lipiding,

Tom

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