

Well lipidaholics, there is plenty of news this week.

**1) President Clinton:** Of course had Mr. Clinton been under the care of any of my readers, the bypass team at Columbia in NYC could have had the weekend off. Let me share with you the results of the recently published GENOA study:

Conclusions: Dyslipidemia is highly prevalent in hypertensive =adults. Fewer than one-third of these adults are drug-treated, and fewer than half of those treated achieve recommended goals. Our findings suggest that an alarming 9 of 10 dyslipidemic hypertensive adults have untreated or undertreated dyslipidemia. Arch Intern Med. 2004;164:1313-1318

Did Mr Clinton receive care from one of the GENOA docs? You would think the ex-president of the United States would have a medical team that understood CV risk and would be cutting edge and aggressive with therapy. Now, I have no knowledge that Mr Clinton was hypertensive or not but it is obvious that his lipids were never taken very seriously. He was temporarily put on Zocor when his LDL-C hit an astonishing 177. He lost some weight and then was taken off the statin! When will we all learn that, with rare exception, you just cannot achieve the required apoB (non HDL-C) lowering in people with levels that high with lifestyle alone. Pharmacotherapy is required. Please visit <http://www.doctorzebra.com/prez/t42.htm> for partial info on the case.

Even more astonishing **never once** did anyone do advanced lipoprotein testing, advanced insulin resistance testing or even an EBCT on him. Certainly NMR LipoProfile and EBCT could have picked up his disease long before all arteries were totally clogged. His medical team relied on STRESS TESTING to assure him that his CV health was good? What century are they living in?

Above I said pharmacotherapy is required. I am rapidly coming to the conclusion at least two lipid drugs are necessary in almost all of the higher risk patients. No drug by itself (even with lifestyle changes) can reduce events or atherosclerosis progression by more than a third. We need at least dual if not more approaches to correcting all of the lipoprotein perturbations present in our patients. In the President's case, Zocor little chance of completely correcting his lipoprotein pathology by itself. Since his HDL and TG seem OK, statin plus Zetia should have been prescribed, never a statin alone. With his family history which includes diabetes, he needed (and still needs) tests to r/o insulin resistance (NMR LipoProfile, GTT with insulin levels).

Tragically I'll bet his docs are now sending him home on a gorilla statin at high dose. It would be a big mistake to simply give him Lipitor 80 or Zocor 80 by itself. They will be content to drive his LDL-C to below 70 and congratulate themselves. They should go read PROVE IT, HPS and A-Z study to see how much residual risk remains after using Gorilla Statin monotherapy. I did hear some reporters mention the word Vytorin and I sure hope Mr Clinton gets statin plus Zetia. Indeed, as per standard of care they started statin with admission. Better get the Zetia on board after discharge and then do the IR workup in a few weeks.

To conclude: Read the GENOA Study. If Mr Clinton gets this type of ridiculously non-aggressive care, the average patient has no real prayer. Why does CVD remain our number one disease when it is highly, highly treatable if not even curable?

**2) A - Z Study:** Available on line at JAMA and to be published Sept 15th and hopefully to be read by Mr Clinton's docs. People with ASHD were randomized to placebo or Zocor 40 mg for 4 months and therapy was altered: The Zocor 40 group was switched to Zocor 80 mg and placebo were put on Zocor 20 mg. . Astonishingly there was no benefit of Zocor vs placebo over the first 4 months and then for the rest of the trial Zocor 40 to Zocor 80 mg group had no statistically significant superiority (outcome reduction) to placebo 4 months -Zocor 20 thereafter group. However as expected with a lipophilic statin, there was significantly more myositis and rhabdo in the Zocor 80 than the Zocor 20 mg group.

Remember in the most recent addendum by NCEP the experts clearly stated that PROVE IT and HPS should not be taken as the final word on lower is better with respect to LDL-C. They look very prophetic right now.

The editorialist, Dr Steve Nissen even hints that Zocor 80 should be removed from the market or at least used rarely and with great scrutiny. He also has trouble reconciling how Zocor 80 mg did not work and was fairly toxic compared to Lipitor 80 in PROVE IT and MIRACL. He also gets into a theoretical discussion that CRP may explain the difference and states that he would not advise lower dose statin/Zetia until there is outcome data.

Why? Most docs were using Lipitor for years before it had any outcome data rather than sticking with Pravachol or Zocor. He also states that Zetia does not lower CRP. In fact Zetia/statin reduces CRP about 20% more than statin monotherapy. And although it is being studied, there is no prospective data at this time supporting the use of CRP modulation as a goal of therapy. It is a risk factor to be used for risk assessment at this time. Zetia/low dose statin gives the same apoB, CRP reductions as gorilla statins and of course Zetia keeps out many atherogenic sterols other than cholesterol (something no statin can do).

Look, MIRACL was not a randomized trial and had soft endpoints and should be dismissed as a trial that contributes to our evidenced based knowledge. PROVE IT was a University (not real world) Trial of healthy people with no comorbidities who were on no CYP4503A meds who were given Lipitor 80 vs Prava 40. Of course there were no myalgias in that study. I'd love to see Lipitor 80 given to real world, sick folks having MIs who do take p450 drugs and see how safe it really is. However, the lipophilic Lipitor caused three times more LFT elevations than did the safer hydrophilic, Pravachol. I'd love to see PROVE IT repeated with Pravachol/Zetia vs Lipitor 80. Which regimen do you think would be safer?

All of this emerging data comes to one conclusion: High dose lipophilic statins are not safe, and have no prayer of reducing events more than 40% at best. When are we all going to start using low dose lipophilic statins with Zetia or safer hydrophilic statins (Pravachol and Crestor) at doses (40 Prava or 10-20 Crestor) in combination with Zetia (almost all high risk patients) and TriCor or occasionally Niaspan in our patients with disorders of the TG/HDL Axis?

Late me add the following comment: Vytorin is the combination of Zocor and Zetia and is available at Zetia 10 with Zocor 10,20,40,80. It provides two meds for one co-pay. Do not confuse Zocor 10 or 20 mg with Zocor 40 or 80 mg (especially after you read the A-Z study). Zocor is a very safe statin at 10 or 20 mg dosage and would have few if any p450 interactions or liver toxicity at those dosage. Please also take a look at the apoB, LDL-C lowering of Vytorin 10/10 or 10/20. It is virtually the same as Vytorin 40 or 80. If I have someone with very high LDL-C (familial IIa or IIb patients) I will use Crestor 10-20 mg with Zetia. For patients with lesser LDL-C and apoB Prava40/Zetia 10 or Vytorin (10/10 or 10/20) should be your first line attack.

Also, the Crestor folks must be laughing so hard they can cry. They have been unfairly bashed and labeled as unsafe by their gorilla statin competitors. Remember the old "he who laughs last" statement! Read the A-Z trial and re-think Gorilla statin use.

Here are the FDA approved lipid drugs needed to practice effective lipidology:

Pravachol, Crestor, Vytorin 10/10 or 10/20, TriCor, Niaspan, Welchol  
(to be used alone but mostly in low dose combos)

And do not forget that TG/HDL axis abnormalities are rampant so lots of lifestyle and TriCor (occ Niaspan) will be needed in many

**3) NEW NMR LipoProfile beginning Sept 8th:** For those of you using LipoScience LipoProfile big changes have occur: all will make you better lipidologists.

Not only will LDL particle concentration (LDL-P) be reported, they will also provide the concentration of small LDL (small LDL-P). They have also wisely trademarked the term LDL-P

LDL-P Goals:

1) For high risk persons the new LDL-P goal is < 1000 (was 1100) and the goal for small LDL-P is < 700 (which is the 50th percentile in population studies). LipoScience has changed their reference population from Framingham to the > 6900 patient Multiethnic Study of Atherosclerosis (MESA Study): an ethnically more mixed and diverse population than the Caucasian Framingham study.

2) LDL-P goals for other patients are:

Moderate risk < 1300 (down from 1400)

LDL-P in risk Assessment:

1) New risk category numbers for LDL-P

Borderline high risk 1300 - 1599

High risk 1600-2000

Very high risk > 2000

They no longer report what drugs do HDL size (THANK GOODNESS, as it is very drug specific and largely irrelevant with respect to treatment decisions). The form now lists what the drugs (including Zetia) do to LDL-P and small LDL-P

LDL size numbers will change: (The LDL size range has widened from 19 to 23 nm). Cutpoints between small and large is the same (20.5)

Large is 20.6 through 23

Small is now 18-20.5

LipoScience also believes that if you can get LDL-P to < 1000 and LDL-C to < 100, it is very unlikely that the patient has any lipoprotein risk remaining even if their LDL-C is not below 70.

They have eliminated lipoprotein subclass levels (expressed as TG or cholesterol concentrations). These were the numbers on top of the bar graphs. Physicians found this confusing. Personally I liked it. The bar graphs still exist and allow comparison to the MESA study patients. So you will still know if your patient has too many VLDLs or IDLs and you still get the HDL particle breakdown referent to the MESA population.

On the bar graph absolute concentration small LDL particles (small LDL-P) number is reported. This is fantastic. We will not only be able to get our LDL-P to goal but will also be able to chase the more atherogenic killer small particles more aggressively. I think we are all going to be amazed at how high small LDL-P is going to be in folks with LDL-Cs of 60-70.

The +/- symbols under the various particles have been removed from the graph. They were of no use and I am glad they are gone. ApoB particles are atherogenic and we have to worry about all of them. Also gone is the confusing +/- symbols below HDL. That description was confusing and non-applicable to current knowledge on HDL particles.

**However please beware:** They state in the HDL bar graph that high values of HDL particles are desirable and then they erroneously say: "especially large HDL" That is misleading when a patient is on drugs as fibrates reduce CV risk by increasing small HDL. One should never stop a fibrate like TriCor just because large HDL is not going up.

## RADICAL NEWS ON HDL

In data just published a few weeks ago and the Journal of Clinical investigation and just reviewed in Nature Medicine, we now know for the first time that under inflammatory stress some (not all) HDL particles lose their antiatherogenic function and become proinflammatory rather than anti-inflammatory. Unbelievably these HDL particles worsen atherogenesis.

For some time we have realized that HDL particles have far greater antiatherogenic functions than reverse cholesterol transport. Most of these are anti-inflammatory in nature. This in part explains why apoA is so much a better surrogate than HDL-C. HDL carries several enzymes that are anti-inflammatory especially paraoxonase and platelet activating factor acetyl hydrolase. These enzymes protect against LDL oxidation. About 1 in 10 to 1 in 100 HDL particles carry these enzymes. This helps explain why some folks have low HDL without CHD risk. As long as they have these anti-inflammatory HDL they might be fine.

The new data (see reference below from which I now quote) is "that enzyme myeloperoxidase selectively targets the main protein of HDL, apolipoprotein AI (apoA-I). The consequence of this damage is that macrophages associated with atherosclerotic lesions retain increased amounts of cholesterol. As a result, the lesion is more lipid-rich, and hence more vulnerable to rupture, and causes thrombosis."

Also, Apolipoprotein J (also called clusterin) is an acute phase reactant overproduced in inflammatory states. ApoJ may displace the anti-inflammatory enzymes from HDL. Such HDL particles will now be pro-inflammatory!!! Serum amyloid may do the same. Wow.

This new information will radically change the way we think about HDL and why we have to be very, very cautious in making HDL-C a target of any therapy until there is clear clinical trial evidence as to when that makes sense. Beware, if you increase the number of proinflammatory HDL you may not be doing the patient a favor. No drug other than fibrates (VA-HIT) have empowered (large) clinical trial showing that their MOA is related to what the drug does to HDL-P or HDL-C.

We will all be better off sticking to LDL-P, small LDL-P, VLDL-P, apoB, non HDL-C as goals of therapy. If you want to use HDL: look at overall HDL-P on the NMR or apoA. However neither of those methods can attest to the functionality of HDL particles.

A good friend from Atlanta, Dr Barry Hull, put it very well in a recent e-mail to me: After reviewing some of this new data he states: ***"Just more ammo to try to convince people that HDL is not about the numbers but rather the dynamics whereas apo-B is all about numbers."***

We should all memorize that phrase.

## REFERENCES OF THE WEEK

1) I listed it last week but here it is again: Apolipoprotein A-I is a selective target for myeloperoxidase-catalyzed oxidation and functional impairment in subjects with cardiovascular disease. Lemin Zheng, Benedicta Nukuna, et al. The Journal of Clinical Investigation Volume 114 Number 4 August 2004 p 529: Conclusions: The present results provide the first direct evidence for apoA-I as a selective target for oxidative modification in human atheroma. They also suggest a potential mechanism for oxidative generation of a proatherogenic dysfunctional form of HDL in vivo.

2) Review of article (1): Entitled: "When Good Cholesterol Goes Bad" Conclusion: High density lipoprotein (HDL) is often called the 'good cholesterol.' Products of an inflammatory enzyme, myeloperoxidase, are now shown to selectively target the main protein in HDL, apolipoprotein A-I. This turns the 'good cholesterol' bad.

3) Metabolic Syndrome in Normal-Weight Americans New definition of the metabolically obese, normal-weight individual. CONCLUSIONS— Individuals in the upper normal-weight and slightly overweight BMI range have a relatively high prevalence and are at increased risk of having the metabolic syndrome. Therefore, screening in individuals with normal or slightly elevated BMI is important in the prevention of diabetes and cardiovascular disease. Diabetes Care 27:2222–2228, 2004

4) Unique Pathway for Cholesterol Uptake in Fat Cells. Sergio Fazio, MacRae F. Linton. This is a very interesting review by two great lipidologists that adds more info to the confusion on HDL function. Conclusion: It seems that fat cells consider cholesterol more as treasure than as trash, because they have developed a dual mechanism to extract CE from HDL; one is based on the typical HDL receptor SR-BI, the other is based on a novel "efflux recapture" process that needs apoE and the LDL receptor related protein (LRP). Because apoE and LRP are linked in secretion recapture loops also in hepatocytes and macrophages, there may be a biological advantage for the LRP-mediated entry of cholesterol into the cell. Vol 10 # 9 September 2004 Nature Medicine pp 902-903

DAYSRING UPCOMING TRAVELS Sept & October

Branchurg, Mendham, Bridgewater, NJ  
Chicago (Sept & October), Rosemont, IL (Sept)  
Greenville, NC  
Manhattan, Brooklyn, Newburgh, NY  
Atlanta, GA  
New Orleans, Monroe LA  
West Palm Beach, Indian Shores (Tampa area) FL (hopefully)  
Albuquerque, Santa Fe NM  
Phoenix (Paradise Valley), AZ  
Milwaukee, WI

As always, please consider joining the National Lipid Association: the more lipidaholics on board, the more Lipidology as a specialty will be recognized and the more important lipid information can be promulgated. Very nice prestige and educational benefits come with membership.

<http://www.lipid.org/>

I'll also see all of my North American Menopause Society friends in Washington DC in October at the annual meeting. (Oct 6-9)

<http://www.menopause.org/> Another great organization to join

I end with a continued salute to our brave and sacrificing troops but also a salute to our Florida friends for dealing with all they have been dealt. Please consider a donation to their cause (Red Cross, etc)

Happy Lipiding,

Tom

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