

## Case # 276 AIMING HIGH Trials and tribulations

Before I get into the AIM HIGH discussion below, I would like you all to review an excerpt of what I call ApoA-I mediated trafficking of cholesterol which comes from my review of the topic. Understanding HDL flux may make it easier to understand HDL-C complexities pertinent to niacin. This is from High-density Lipoproteins: Emerging Knowledge in J Cardiometabolic Syndrome (JCMS) 2007;2:59-62. I strongly encourage you to get a copy of the paper with illustration.

*"If one looks at this overall efficient flux process of peripheral cholesterol transport, where HDL particles are formed, are lipidated, exchange lipids, and are then delipidated, one can understand that the overall process will not affect the total HDL-C level in a predictable fashion, as there is constant remodeling or shifting of HDL particle size and cholesterol content. The final stage of HDL-mediated peripheral cholesterol transport is an increase in steroidogenic tissue cholesterol or in biliary and ultimately stool cholesterol. This final stage will result in very small, delipidated HDL for excretion or relipidation. What if one had very large HDL particles that were not being delipidated? HDL-C would be high, but RCT might be impaired, and cardiovascular risk could increase. It should also become obvious that what a drug does to HDL-C levels may have no relationship to cardioprotection offered by that drug. Drugs that delipidate HDL particles (fibrates, probucol) will not raise HDL-C as much as drugs that hinder large HDL particle remodeling or delipidation (niacin, statins, CETP inhibitors). Of course, the HDL-C level would also have no relationship to what a drug might be doing to the surface proteins that mediate numerous aspects of HDL functionality."*

I apologize for taking so long to get my detailed thoughts on AIM HIGH out to you all but I gave this study serious thought, talked to some of my more expert colleagues and reviewed a lot of literature. Thanks much as always to two of the best lipoproteinologists that I know, Bill Cromwell and Jim Otvos (mentioned above) for helping me better understand this trial. My analysis is long but I hope it provides facts you need to know. At the end I have enclosed with permission the exact thoughts of Bill and Jim. You will learn a lot and gain a different perspective.

Now on to the discussion: How could Niaspan/Statin fail to improve outcomes in AIM HIGH? Should I immediately stop my 2000 mg dose of Niaspan? What should I tell my patients? Is there a role for niacin anymore? I do not think there has been a trial using lipid modulating therapy that has shaken core beliefs so much. So either this trial was a colossal error or some of **our core beliefs were wrong**. Although I am not one of them I have met thousands in my journey lecturing throughout the US and trust me the overwhelming majority of practicing docs who think you have to raise HDL-C or make HDL particles large to get benefit beyond what a statin can do. There have been more than a few thought leaders who have staked their reputation that niacin's effect on HDL-C make it a phenomenal drug. Over the last decade many have heard me write and lecture that what a drug does to HDL-C is unlikely to be related to any outcome benefit. But I am not alone: please go to [lipidcenter.com](http://lipidcenter.com) and see a posting that has been there for a few years quoting innumerable thought leaders about how erroneous it might be to draw any

conclusions that a drug that raises HDL-C is necessarily good or that large HDLs are cardioprotective. Visit:

[http://www.lipidcenter.com/pdf/HDL\\_Thought\\_Leader\\_and\\_NCEP\\_Statements.pdf](http://www.lipidcenter.com/pdf/HDL_Thought_Leader_and_NCEP_Statements.pdf)

Are we ever going to get a positive clinical outcome trial on combo lipid therapy or should we simply conclude that we should never add anything to a statin, especially ezetimibe, a fibrate, niacin or prescription strength omega 3 FA as they seemingly add nothing to outcome reduction? But who is ecstatic with statin monotherapy? We have not closed a single CCU in America since statin monotherapy became the standard of care. Despite statin use, we collectively still fail to prevent the overwhelming majority of CV events that occur. Obviously there are reasons to get more aggressive with both lifestyle and to still use combination lipid/lipoprotein modulating therapy: but which combo therapies?

I admit that based on niacin monotherapy angiographic data, not the extremely unlikely implausible outcome findings of HATS or FATS (which I always considered as tiny hypothesis generating rather than fact finding trials), I have stated that "if you have CAD, give me a reason after your statin you are not on niacin." Unfortunately I have heard many speaker, clinicians and reps talk about HATS and FATS as if they were the 4S or West of Scotland Study (i.e. large, empowered randomized trials from which definitive conclusions can be made). So based on AIM HIGH do I have to retract or simply reconstruct my quote above?

NCEP ATP-III states that the best way to alleviate lipid/lipoprotein mediated CV risk is to treat patients to their lipid goals (the specific goals are based on the patient's risk). Never forget that at present there are only two NCEP goals: LDL-C and non-HDL-C, not any specific HDL-C or TG goal. Of course both LDL-C and non-HDL-C are simply lipid surrogates (and often not good ones) for LDL-P. Allan Sniderman has shown that despite good LDL-C efficacy statins as monotherapy are much less efficacious at achieving apoB or LDL-P goals (Journal of Clinical Lipidology (2008) 2, 36–42).

NCEP ATP-III Guidelines advocate lifestyle and when needed FDA approved drugs (regardless of outcome data), not outcome evidence per se when choosing a therapy to achieve goal (just like BP or glycemic goals). We will see where ATP-IV goes. ATP-III encouraged use of fibrates and niacin added to statin therapy when non-HDL-C was still high in patients on statins in the face of high TG and also for use in those high risk patients with isolated low HDL-C. At the time there was no ezetimibe or prescription strength omega-3 products available. Of course we now have FIELD, ACCORD, AIM-HIGH, JELIS and SHARP and are better prepared to make combination therapy decisions. As I get into the use of niacin, be it known that every day I take 2000 mg of Niaspan along with Trilipix, Zetia and Lovaza (for treatment of low Omega-3 index, not high TG). I cannot tolerate any statin. I do not plan on stopping Niaspan based on AIM-HIGH results because that trial did not investigate Niaspan and fibrate and ezetimibe.

For this newsletter I have been reviewing some of the lipoprotein data that exists on the drugs that we have all been adding to statins to try and achieve ATP-III and AHA lipid goals or better yet the ADA/ACC, AACC lipoprotein goals. The NLA at its recent scientific sessions also rolled out its new position statement which advocates using apoB and LDL-P (in pretty much all but low risk folks) as better risk assessment tools than cholesterol measurements. The LDL-C/LDL-P debate is over and the sooner we stop over relying on any type of basic or advanced cholesterol testing the better. I laugh at those who say such thinkers (including me) are too "LDL" centric (meaning looking at LDL-P and ignoring LDL-C).

As an aside, I beg anyone who thinks LDL-C, be it measured or directly assayed, is a highly valid methodology, to go on-line in Journal of Clinical Lipidology and read (and then weep) "Reliability of LDL-Cholesterol, NonHDL-Cholesterol, and Apolipoprotein B Measurement" by John H. Contois, G. Russell Warnick, Allan D. Sniderman doi:10.1016/j.jacl.2011.05.004. I hope the ATP-IV folks read that article. Then get a hold of Clinical Chemistry 57:3392–410 (2011) and check out the Special report on HDL measurement and the accuracy (or should I say inaccuracies) of HDL-C measurements we all use

Any of you who have heard me lecture or read this newsletter know that I always point out that NCEP ATP-III in their evidence-based wisdom provided no specific HDL-C goals of therapy. All of my suggested drug treatment regimens in persons with TG < 500 mg/dL start with LDL receptor (LDLr) upregulation therapy as they are the best therapies at reducing apoB/LDL-P. That means the best first line drugs to help us get to LDL-P/apoB goal are statins, with statin/ezetimibe (or statin/colesevelam) being significantly better than statin monotherapy. I encourage all to re-read the EXPLORER trial authored by Ballantyne et al (Am J Cardiol 2007;99:673– 680). Rosuvastatin 40 mg lowered apoB by 45% and Rosuvastatin 40 + ezetimibe 10 mg lowered it 56%. There is no better apoB reducing therapy available on the planet at this time. Once LDLr therapy is at play (some would say maxed out) there is emerging data that raising HDL-P (not necessarily HDL-C) is likely beneficial (presuming the HDLs are functional which at this time cannot be measured). Part of that HDL functionality is called macrophage RCT, which refers to the delipidation of arterial wall sterol laden macrophages. Is it possible to raise HDL-C without raising HDL-P? Sure by simply making the HDLs larger and cholesterol-rich: there will be no change in HDL-P despite the rise on HDL-C (exactly what niacin does). Is there a way to make HDL-P go up with minimal rises in HDL-C: sure - simply make the HDLs smaller (exactly what fibrates do): exactly what gemfibrozil did in VA HIT and it correlated with event reduction. So much for the BS that you MUST increase HDL size.

I also teach that if you want to raise HDL-C because you thought that was a necessary step to improve CV outcomes that such thoughts were speculative and far from scientific fact. Many in the lipid community presumed based on both niacin monotherapy data and data from the niacin/statin arm (all 28 of the patients) vs placebo in HATS and the great IMT benefit seen in ARBITER studies that event reduction in AIM HIGH would be stupendous. By the way, where is there any evidence what a drug does to carotid IMT or

any other image of an artery is related to outcome benefit (but that is a story for another day)?

We have been down the route of watching one HDL-C raising drug after another fail to reduce clinical events starting with oral estrogen (extolled for years as a cardioprotective agent because as it raises HDL-C), Dilantin, torcetrapib, fenofibrate statin and now niacin/statin. I remember a fantastic editorial by David Herrington (*Arterioscler Thromb Vasc Biol* 2004;24;1741-1742) entitled "all that glitters is not gold" addressing how estrogen in the ERA trial in women with CHD despite raising HDL-C was not associated with angiographic benefit. We have to be very careful assuming what a drug does to HDL-C would explain any of its benefit. I have repeatedly surmised that I suspect niacin's benefits are not related at all to what it does to HDL-C, but rather apoB (via its TG benefits) and macrophage reverse cholesterol transport (which has no effect on HDL-C (check out [http://www.lipidcenter.com/pdf/Niacin\\_MOA.pdf](http://www.lipidcenter.com/pdf/Niacin_MOA.pdf)). Let me remind all how niacin raises HDL-C: Most studies (one does) show no increase in apoA-I synthesis. There is significant upregulation of hepatic ABCA1 which lipidates prebeta HDLs (thus niacin helps fill HDLs with liver cholesterol). Niacin inhibits both CETP activity (through its TG benefit) and inhibits hepatic lipase. Thus niacin gets to keep that liver cholesterol and the particle stays very big. Niacin down regulates the hepatic apoA-I beta chain synthase receptor (holoparticle receptor) preventing hepatic endocytosis of the large HDLs. Large HDLs have more apoA-I than smaller ones, so niacin increases apoA-I via a delayed catabolism effect. Most amazing of all is niacin does not increase total HDL-P. So the reason niacin raises HDL-C is it makes HDL particles large. There is no data where large HDL size if adjusted for total HDL-P has outcome meaning or is beneficial. Indeed, in IDEAL and EPIC Norfolk folks with very high HDL-C and low HDL-P (apoA-I) had increased CHD risk.

Despite the lack of benefit seen in AIM HIGH (a study of older folks with stable CAD and aggressive LDL-C control), let's not forget there is certainly a lot of positive level II evidence that niacin monotherapy (for example, the Coronary Drug Project or CDP when looking at the secondary outcomes, not the primary outcome which niacin failed to move), or combination therapy with niacin/bile acid sequestrant (FATS angiographic trial) and niacin/fibrate combo (Stockholm Ischemia Trial on outcomes: *Acta Med Scand* 1988;223:405-418). Now if the null result of AIM HIGH is to be believed we now should conclude that when added to serious LDL receptor therapy (statin or statin/ezetimibe) adding niacin seemingly brings **no** additional CV benefit. I think we would know a lot more if we had on-treatment LDL-P rather than LDL-C values. The ezetimibe (Zetia) haters who want to blame Zetia for failure of AIM HIGH ) are nuts (just over 500 folks required Zetia to achieve LDL-C goal in AIM HIGH: there was exactly equal use of Zetia in the statin only arm and statin/Niaspan arm. So why did niacin/statin fail to do anything of benefit in this specific population?

It is unarguable that we must lower LDL-P (apoB): 4 guidelines or position statements now advocate that. Thank goodness that the NLA is about to release a statement (unveiled at NLA Scientific Sessions) that in all but low risk folks measured apoB and LDL-P are advised. It matters little what one does to LDL-C or any subfraction of LDL-

C (small, medium or large LDL-C) if they are not concomitantly lowering LDL-P. Although LDL-C sometimes correlates with LDL-P, the discordance is huge in IR populations (like AIM HIGH) and when discordance is present risk always follows LDL-P, not LDL-C. So were these AIM HIGH patients with excellent LDL-C at or not at LDL-P goal -- doubtful. How much does niacin further reduce LDL-P (apoB) when added to a statin or indeed by itself? Stay tuned.

Since we do not have the NMR data from AIM HIGH, let's speculate what it might have shown. These were very IR patients. There is NMR data that 41% of T2DM patients with an LDL-C < 70 mg/dL still have a high LDL-P (> 1000 nmol/L). Numerous studies have shown that discordance is present risk follows apoB or LDL-P not any cholesterol measurement. So it is very likely that in AIM HIGH (which had a lot of metabolic syndromes and T2DM pts) considerable numbers of patients on LDL receptor therapy still had very abnormal LDL-P. Did niacin further reduce apoB and LDL-P? We will have that data one day.

I have reviewed a lot of the published niacin apoB and LDL-P data:

#### Niacin monotherapy data on ApoB or LDL-P

Superko (Am J Cardiol 2004;94:588–594) (apoB)  
vs placebo -- immediate release (IR) niacin -33% Niaspan -17%  
Morgan et al (Am J Cardiol 2003;91:1432–1436) LDL-P  
vs placebo -- immediate niacin -25% and  
Niaspan 1000 mg -15% Niaspan 2000 mg -23%  
McKenny Study Am J Cardiol 2001;88:270–274 LDL-P  
Atorvastatin 10 mg -31% Immediate niacin 3000 mg -14%

#### Niacin plus statin on apoB or LDL-P

FATS: Brown et al. NEJM 1990;323:1289-98 (apoB)  
Colestipol + Niacin -28% Lovastatin + colestipol - 35%  
Bayes. Am J Cardiol 2003;91:667–672. Advicor study (Lovastatin/Niaspan)  
16 weeks: Atorvastatin 40 mg -40% Simvastatin 40 mg - 31%  
1000/40 lovastatin -33% 2000/40 lovastatin -38%  
SEACOAST (apoB): Ballantyne et al. Am J Cardiol 2008;101:1428 –14  
compared to simvastatin 20 mg,  
Simcor 20/1000 reduces it 14% and Simcor 20/2000 -18%  
Capuzzi Study: LDL-P Am J Cardiol 2003;91:1304–1310  
Rosuvastatin vs Niaspan vs Rosuvastatin + Niaspan  
Ros 40 mg -42% Niaspan 2000 mg - 9% Ros 40/Niaspan 2000 -42%  
Ros 10 mg/Niaspan 2000 mg -34%  
HATS: Brown et al. N Engl J Med 2001;345:1583-92 (apoB)  
Simvastatin (10-40 mg) + niacin (slow + IR) -38%  
Unfortunately no statin only arm to compare with  
Jafri et al Journal of Clinical Lipidology (2009) 3, 45–50 (LDL-P)  
Niaspan vs placebo (all patients on statin) LDL-P dropped -8%

No effect whatsoever on HDL-P  
SLIM Study: Knopp et al Journal of Clinical Lipidology 2009;3:167–178  
Atorvastatin 10 mg -39% SloNiacin 1500 mg - 9% Combo -48%  
COMPELL Mckenny et al. Atherosclerosis 192 (2007) 432–437 (apoB)  
Atorvastatin 20 Niaspan 1000 -43%  
Rosuvastatin 10/1000 mg -42%  
Simvastatin 20/Ezetimibe 10 (Vytorin 20) -41%  
Rosuvastatin 20 mg alone -39%

Summary: Niaspan alone ~ 15 % (sometimes greater) apoB drop ~23% LDL-P  
IR Niacin may be more potent  
Niacin IR -14% LDL-P drop No Niaspan monotherapy data on LDL-P  
Niacin IR added to statin ~ -35%  
Niaspan plus statin ~ -5-8 % beyond statin data  
SloNiacin plus statin -9% beyond statin  
Stain/Niaspan no better than low dose Vytorin

In the above studies there were other findings: reductions in VLDL-C and remnant-C: increases in apoA-I and no changes at all in raising HDL-P. Niacin therapy shifted LDL and LDL size upwards (neither LDL or HDL particle size change is known to be significantly associated with event reduction). Niacin lowered Lp(a). No trial data exists showing lowering Lp(a) mass reduces clinical events. No study shows that it does not.

As mentioned before, although statins are fantastic at achieving LDL-C goal they are far less efficacious at reaching apoB or LDL-P goals. From the above data it appears that niacin, Niaspan or slow release niacin can help further lower apoB or LDL-P a bit. With respect to apoB lower dose statin plus niacin is no better than high dose statin or low dose Vytorin. Clearly the contribution of niacin to a statin will get some not all or even most to apoB or LDL-P goal. Thus a better initial strategy might be initiating therapy with meds that can up regulate additional LDLr beyond what a statin can. To maximize LDLr upregulation beyond statins we probably need to use a lot more Zetia, a lot more Welchol or even all three. However what about reducing apoB particle production: that could be accomplished by inhibiting TG (VLDL) synthesis. That is niacin's MOA. So what about adding a fibrate or high dose omega 3 FA to get additional apoB/LDL-P lowering.

One more issue I want to bring up because my readers are familiar with cholesterol absorption and synthesis and the topic of phytosterols (including their possible adversity). Ernie Schaefer and his team investigated what niacin does to phytosterols in HATS and the data is very interesting: *"Treatment with Simvastatin-Niacin reduced desmosterol and lathosterol levels (cholesterol synthesis indicators) 46% and 36% (P<0.05), respectively, and **elevated campesterol and beta-sitosterol levels** (cholesterol absorption indicators) 70% and 59% (P<0.05), respectively, relative to placebo and antioxidant but not S-N-antioxidant. Results of this investigation demonstrate that S-N treatment significantly alters measures of cholesterol metabolism by decreasing cholesterol synthesis and increasing cholesterol absorption."* Matthan et al. J. Lipid

Res.2003;44:800–806. Such a finding suggest that statin/ezetimibe and Niaspan might be a great triple therapy: I certainly use it a lot in my practice. In a study by Fazio et al there was almost 50% reduction in apoB using simvastatin 20/Niaspan 2000 mg and ezetimibe 10 mg (this was about 8-9% beyond what simva/ezet did. Diabetes, Obesity and Metabolism 12: 983–993, 2010.

Let me discuss fibrates. Many (who should know better) would have you believe they are useless meds. Other than perhaps ezetimibe, no class of drugs have been more bashed by non-lipidologists than fibrates, yet the reality is next to statins no class of lipid-modulating drugs has as much primary or secondary outcome data: WHO (clofibrate), Helsinki and VA HIT (both gemfibrozil) with positive level one evidence and BIP (bezafibrate), FIELD and ACCORD (fenofibrate) with secondary outcome evidence. Keep in mind that WHO, Helsinki and VA HIT had no statin contamination. In all of those trials (except WHO) fibrate monotherapy worked almost exclusively in those patients with high TG and low HDL-C. Despite missing the overall primary endpoints (FIELD and ACCORD) in trials of type 2 diabetics with basically normal TG there was very significant benefit in patients with high TG and low HDL-C (in the face of statin therapy). So at least we have secondary outcome data from two gigantic trials that fenofibrate can reduce macrovascular events in the presence of statins in one subgroup. Niacin has never had any such comparable data and yet fibrates are routinely bashed and niacin routinely (until now) extolled in way too many circles (lectures and publications). This was and is unfair. Even more encouraging is the very positive microvascular benefits of fenofibrate seen in DAIS, FIELD and ACCORD.

Fibrate monotherapy (including fenofibrate) has several positive angiographic trials which seem never to be mentioned while at the same time niacin angiographic data is universally applauded. Why do most not applaud both drugs? Niacin and fibrates share many of the same mechanisms of action but they do differ on certain measurable parameters; how many times have you heard that niacin is good because it increases the size of HDLs (that's good isn't it? Are not the large HDLs cardioprotective? ) and fibrates are bad because they reduce large HDL and increase small HDL (that's bad right?). That was universally believed until Otvos et al showed in VA HIT (Circulation. 2006;113:1556-1563) that the main benefit of gemfibrozil was its ability to increase **total HDL-P** by increasing small HDL-P and reducing large HDL-P. The exact same thing (increased HDL mass but reduced large and increased small HDL) was seen in a substudy of the Helsinki patients in FIELD (2007;50(10):2067-75) The "large HDL" marketing bias was so effective that almost no one knows of or mentions the VA-HIT data. KOS put Niaspan on the map by convincing docs (even though there was zero outcome data to support it) that one had to enlarge HDL size because small HDLs are not protective! Why is this still often stated after VA-HIT? The reason is based on good epidemiological data that **in drug naive persons**, a lack of large HDL is an independent CHD risk factor (all such patients also have low HDL-C, as HDL2-C accounts for the majority of total HDL-C). It was easy to assume (and there was angiographic but no outcome data to support it) that if you simply increased the size of HDLs, there would be outcome benefit: yet estrogen, and torcetrapib all significantly increase HDL size and have failed to reduce events and fibrates reduce HDL size and do reduce events). The truth is almost all

insulin resistant patients, because of TG and CETP activity developed TG-rich HDLs which are subject to lipolysis and renal excretion. Almost all have high LDL-P and thus the risk is due not to a lack of large HDL per se but high LDL-P and low total HDL-P.

Peter Jones and I just presented a poster at ATVB and NLA (now published in latest J Clinical Lipidology 2011;5:202) that fenofibric acid (FFA) monotherapy in dyslipidemic patients with TG > 200 mg/dL and low HDL-C lowers LDL-P about 15%. That monotherapy data is better than what gemfibrozil monotherapy did in VA HIT (5%) and comparable to the niacin data presented above. However if the patient is on a low or moderate dose statin adding FFA (unlike niacin) results in no additional LDL-P lowering. FFA lowers VLDL-P considerably more than statin monotherapy and there is VLDL-P lowering beyond what a statin can do if combination therapy is used. Previously published data from the FFA/statin trials (Journal of Clinical Lipidology 2009;3:125–137 showed a 15% apoB lowering with FFA monotherapy and an additional 5% apoB lowering on top of a statin Looking at the two just reviewed studies - one looking LDL-P and the other apoB: the no change in LDL-P induced by FFA added to statin in the face of a 5% apoB drop - implies a VLDL-P reduction.

Here is the potentially good news: In our poster FFA monotherapy elevated total HDL-P (10%) more than did the statin monotherapy (6%). However there was also a very significant increase in total HDL-P (16%) when FFA is added to a statin. Otvos showed a similar 10% increase in HDL-P in VA HIT which used gemfibrozil monotherapy in dyslipidemic patients. The event reduction benefit of gemfibrozil had no relationship to any lipid concentration changes but was related to the reduction in LDL-P and significant rise in total HDL-P (which as mentioned above was due to reduction in large HDL and increase in small HDL). So much for the baloney that one has to increase large HDL-P and panic if small HDL-P goes up. So to summarize: Fibrates have solid monotherapy outcome data (VA HIT) because they raise total HDL-P and lower LDL-P (the outcomes were not related to any of the beneficial lipid changes in that study). Fenofibrate in FIELD and fenofibrate added to statin in ACCORD showed beneficial secondary outcome data in T2DM patients with high TG and low HDL-C (who almost certainly have high LDL-P and low total HDL-P). We have no NMR data from those trials.

There is apoB data from the >9700 patients in FIELD (Diabetologia 2010;53(9):1846-55): Compared to baseline value those on fenofibrate (supposedly monotherapy) had a 17% apoB reduction and amazingly those in the placebo (or should I say supposedly placebo) group had a 11% apoB reduction. I'd like to patent that placebo. As we all know there was a significant statin drop-in in the placebo group - which clearly explains the 10% apoB reduction.

Of course no drug has been treated with as much venom and ridiculous commentary as ezetimibe (Zetia): All of the Zetia vindictiveness stems from a null (not a negative) trial (ENHANCE) using an endpoint (CIMT) that has no known correlation with drug-related CHD outcomes. In ENHANCE both statin and statin/Zetia kept fairly normal arteries normal (somehow few looked at the fact that on five important parameters the combo did better than the statin (TC, LDL-C, apoB, TG and hs-CRP). Some ARBITER aficionados



speak about ezetimibe as if it is a poison - some even made up negative ezetimibe mechanism of action parameters (all of which were absurd). In ARBITER 6, the ER-niacin/statin combo was so much better on CIMT than ezetimibe/Statin that one wondered why the FDA did not immediately remove Zetia from the market but the reason Zetia is still here is that the FDA does not accept drug induced CIMT as a predictor of outcomes.

Why must we in medicine always keep open minds? New data always appears and often shows we are not as smart as we think we are. AIM HIGH sure has us all wondering. Statin/ezetimibe now has positive outcome data in patients with significant renal failure or on dialysis. Three statins have failed to reduce macrovascular events in such patients: Pravachol in PREVENT IT, atorvastatin in 4D and rosuvastatin in AURORA. I am sure ezetimibe had nothing to do with the benefit seen in SHARP - it had to simply be the 20 mg of simvastatin - yea right! I do realize there were somewhat different outcomes looked at in the above statin trials and one must always compare trials with caution. Despite the rants of those who ran around calling Zetia a carcinogen, there was virtually zero negativity with Zetia use in SHARP. It is time to cut statin/Zetia some slack.

How about Omega 3 Fatty Acids? Are they useless when added to a statin? Maybe unless you happen to be Japanese (see JELIS: Lancet 2007; 369: 1090–98) where omega-3 FA supplementation added to baby statins improved clinical outcomes. So I guess evidence based non-Japanese humans should reject Omega 3s as having CV benefit on top of a statin. I am not Japanese but I sure take my Lovaza every day (with my 2000 mg Niaspan, Trilipix and Zetia). Like the Japanese in that study I do not have nor have I ever had high TG. What does POM3 (Lovaza) do to apoB or LDL-P if a statin is on board: about 4% lowering. Total VLDL-P was lowered 6%. Total HDL-P is not affected despite a rise in HDL-C (Journal of Clinical Lipidology 2009;3:332–340).

So let's honestly compare niacin data and fibrate data: Niacin monotherapy certainly has enough evidence that it improves angiograms and has secondary outcome evidence that it reduced nonfatal MI in the CDP. Fibrates have lots of positive angiographic data but the fibrate outcome data (WHO, Helsinki, VA-HIT, BIP, FIELD, ACCORD) is much stronger quantitatively (#s of patients tested) than what niacin has. Fibrates improve microvascular endpoints, and there is no evidence that niacin does. Fibrates improve insulin resistance and niacin can aggravate it. DO NOT FORGET, the fibrate benefits seems limited to those with high TG and low HDL-C. We await any AIM HIGH subgroup analysis. Yet as mentioned, for whatever reason fibrates are often unfairly dismissed and niacin fairly universally praised (until now). Interestingly, the Stockholm Ischemic Trial showed that niacin and fibrate used together (no statin use) dramatically reduced all CV events including the primary endpoint. I hope the fibrate bashers out there take a second look the above data and use both drugs more appropriately.

We all know what niacin or niacin plus statin does to lipid concentrations: it is universally beneficial on reducing TC, LDL-C, TG and raising HDL-C. I always believed niacin was beneficial because it was such a great TG-lowering therapy (meaning it lowers apoB - by suppressing TG and VLDL synthesis). How about the niacin induced raising of

HDL-C? I know I have been in the minority but I say who cares: HDL-C is certainly not an NCEP specific goal of therapy. I know of no level one outcome data that has shown that raising HDL-C with niacin or any other drug resulted in benefit. I have seen lots of data that lowering apoB/LDL-P saves lives. Low HDL-C is often a major risk factor, but the truth is that virtually all low HDL-C folks who have CV risk are insulin resistant and have very high LDL-P. That is why the ADA/ACC position statement on management of lipoproteins in patients with cardiometabolic risk (Diabetes Care 2008;31:811-822) recommend statins as the appropriate first line drug in such patients who have low HDL-C. Because it enrolled a lot of diabetics and metabolic syndromes, AIM HIGH was likely a study of folks with incredibly high baseline LDL-P (NMR data is being done on all patients and one day we will get that data and make more sense of this trial).

Summary:

- A) Niacin monotherapy lowers LDL-C and raises HDL-C.
- B) Niacin when added to a statin provides some additional LDL-P lowering
- C) Niacin when added to statin has no ability to raise total HDL-P: all it does is makes HDLs larger which will of course be associated with increased HDL-C.
- D) Niacin and statins increase absorption of cholesterol and noncholesterol sterols

- A) Ezetimibe when added to a statin more dramatically lowers apoB and LDL-P beyond the capability of the statin. No other currently available combination therapy is as efficacious at lowering apoB or LDL-B
- B) I have no data on what statin/ezetimibe does to HDL-P - likely not much. We certainly have data that ezetimibe like niacin and fibrates improves "macrophage reverse cholesterol transport."
- C) Ezetimibe reduces intestinal absorption of cholesterol and noncholesterol sterols

- A) Fibrate monotherapy lowers LDL-C and raises HDL-C (not as well as niacin)
- B) Fibrate (feno) when added to a statin provides no additional LDL-P lowering
- C) Fibrate monotherapy or when added to statin has significant ability to raise total HDL-P: however it makes HDLs smaller (by upregulating hepatic SR-B1 which delipidate large HDLs) . So is the benefit seen in the high TG/low HDL-C groups in ACCORD & FIELD due to the fact that it helps the statin further increase HDL-P. Fibrates do increase macrophage RCT.
- D) Fibrates reduce absorption of cholesterol and noncholesterol sterols (by down regulating intestinal NPC1L1 protein). Ezetimibe and fenofibrate together (fully on label approved) drastically reduce sterol absorption and help achieve non-HDL-C goals.

MY CONCLUSIONS: We now have the first well done, seemingly well empowered level one evidence trial on outcomes and it was surprisingly null with a nonsignificant increase in ischemic strokes (which seems implausible but on the NLA web site niacin expert John Guyton reminds us that although not likely there is an association of niacin and atrial fibrillation which certainly can cause ischemic strokes). The trial was stopped because the trial statisticians declared there was only a 1 in 10,000 change that if the trial continued to completion benefit would have been seen. That and the trend to strokes

persuaded the NHLBI to end the trial. Could the data be erroneous? Why not? Remember Lipitor a well proven outcome reducing drug failed to reduce events in the ASPEN trial (Diabetes Care 29:1478–1485, 2006). Pravachol after several positive trials failed in ALLHAT (JAMA. 2002;288:2998-3007). So many were shocked with the AIM HIGH results but in reality there has never been any level 1 evidence one outcome data with niacin monotherapy or statin/niacin. The niacin outcome data that did exist was often over exaggerated. The HATS trial was disingenuously marketed and too many extrapolated too much from it. There is definite apoB benefit and antiinflammatory benefit with niacin or niacin/statin. However despite rising HDL-C and apoA-I there is no increase in total HDL-P whatsoever. There is improvement in macrophage RCT and several other CV surrogates. However there is worsening of insulin resistance (acanthosis nigricans, glucemic adversity including HgbA1c), hyperuricemia, hyperhomocysteinemia, and over absorption of both cholesterol and the potentially more dangerous noncholesterol sterols. Fortunately there is an on-going even larger trial namely the HPS THRIVE study being done in Europe with statin/Niaspan and laropiprant (the anti flush/itch prostaglandin inhibitor). You can bet the data and safety board of that trial is taking a close look at their data. If that trial also fails then niacin added to a statin is a dead therapy. But what if that is a positive trial? Then nothing as changed and statin/niacin will remain in our armamentarium.

We really need to await publication of the full data including the NMR data (done on all) and all of the secondary endpoints and post hoc analyses that will ultimately appear. Maybe like the fibrates there will be some subgroups that showed benefit [high Lp(a) groups]: however if there are groups that benefited, then because of the overall null outcome that would mean there would have to be subgroups that were harmed (diabetics with glycemic issues?). Remember in the FIELD and ACCORD trials: although null there was an overall trend (nonsignificant) to improvement.

So until I get more info (and read other expert opinions which should rapidly start appearing) I will to personally continue Niaspan in my practice for apoB (LDL-P) benefit but closely monitor some of the adversity I described above. For my patients who have niacin on board with a statin who are at lipoprotein goal (please stop looking at lipid concentration or cholesterol goals and that includes subparticle cholesterol measurements) I will maintain the status quo pending the HPS-THRIVE data or other info that will be forthcoming from AIM HIGH.

Medicolegally, until HPS THRIVE is out, I will no longer use niacin in anyone who has significant cerebrovascular disease, or stroke or TIA or a family history of ischemic stroke. When will the first lawyer ads start appearing about Niaspan advising stroke patients to sue their docs? Let me also remind you this trial investigated older folks with aggressive statin induced LDL-C control. The data may not apply to those less well treated LDL (but the recommendation would be to use LDLr therapy first meaning statin or statin/ezetimibe first). It does not apply to the very high risk ACS, MI survivors or to younger at risk folks. Keep in mind folks in their 60s have a lot if insulin resistance which might be aggravated by niacin use. Finally there is positive angiographic and

outcome data with niacin monotherapy and niacin/fibrate and angiographic data with bile acid sequestrant/niacin. So niacin surely deserves a role in the statin intolerant patient.

Although few previous niacin lovers will admit it, **as of this moment** in patients with high TG and low HDL-C the fenofibrate data is incredibly stronger than the niacin data. Few realize that despite the lesser HDL-C efficacy, fibrates raise HDL-P better than niacin. So fibrates are options in TG/HDL-C axis disorders if you believe raising HDL-P makes sense. I encourage all to revisit fenofibrate and its active form fenofibric acid. A great read for those wanting to understand fibrates better is the article by myself and Greg Pokrywka: Dayspring T & Pokrywka G. Fibrate Therapy in Patients with Metabolic Syndrome and Diabetes Mellitus in *Current Atherosclerosis Reports* 2006;8:356-364.

Finally a big take home of the AIM HIGH trial, especially if HPS THRIVE is also null is that it should alert us that imaging (angiography, CIMT) may not be an accurate way to judge drug outcome efficacy and it perhaps should be abandoned for that purpose and only used to adjudicate baseline risk.