Lipidaholics: By now you have likely heard something about the ARBITER-6 HALTS trial which was just presented at the AHA and published in the New England Journal of Medicine. Basically this is a trial designed to show what happens to carotid IMT when either Zetia or Niaspan is added to a long term statin use.

For those who do not know, I am a consultant and National Speaker for both Abbott Labs and Merck (Schering Plough). I educate professionals all the time about aggressive use of lipid drugs to achieve goals. I believe Niaspan, Zetia, fenofibrate, Trilipix, and Lovaza are grossly under prescribed. They are all potential "statin-helper" drugs. Without outcome data no one can ever state one combination is superior to another. Readers of my newsletters know by now that statins have serious residual risk in all their trials and only get a minority of patients to apoB or LDL-P goal. Per all guidelines combination therapy is indicated to achieve goal. There is zero Level One outcome data with any of the potentially available combination therapies that are out there right now. So the only sane way to know what drugs to add to a statin is will the combo help me get to lipid goals (non-HDL-C or lipoprotein goals like apoB or LDL-P and perhaps an emerging goal - HDL-P (not always the same thing as HDL-C)).

I happen to very much like both Niaspan and Zetia as wonderful statin-helping therapies. I personally take 2000 mg of Niaspan as well as Zetia 10 mg every day (along with TriCor) along with once weekly statin (because of myalgia). I prescribe Zetia and Niaspan a lot in my practice to help achieve goal. Based on multiple existing angiographic trials and now the ARBITER 6 trial it is my belief that if you have CHD, I want to know why Niaspan, unless it is not tolerated, is not part of your regimen to help achieve goal (except for unusual circumstances I never use niacin or Zetia monotherapy).

This small, open-label (impossible to do a blinded trial with niacin) randomized trial enrolled CHD patients (with high or very high risk) who were on a statin for several years (mostly atorvastatin with some simvastatin) at or near LDL-C goal (all < 100 mg/dL). They received either Niaspan (extended release niacin) titrated to 2000 mg (a dose rarely used in the real world) or Zetia (ezetimibe) 10 mg daily. As expected there were more Niaspan dropouts due to drug side effects in the trial compared to Zetia. The endpoint was change in carotid IMT over a year. Unfortunately the trial was stopped prematurely, for no good reasons (both of the editorialists in the NEJM and the discussants at the AHA meeting agreed on that). Premature stoppage likely means whatever findings occurred are over-exaggerated. The morons in the press are running around telling people they can take an over the counter vitamin for C and cannot be considered a vitamin at that dose and certainly has issues that must be followed.

Patients in the study had at goal or near goal LDL-C and borderline low HDL-C at the lower end of normal (remember baseline HDL-C was assayed while on a statin - not in a drug naive state). Tragically the author did not see fit to measure the far more important parameters apoB or LDL-P or apoA-I or HDL-P. That is a mind boggling oversight in 2009 and it also makes it much more difficult to truly interpret what are the benefits of statin/Zetia or statin/Niaspan. Most of these patients were on statins for over 5 years and thus their carotids have many years of statin therapy. Over the very short 14 month period of this trial the CIMT changes regressed on Niaspan/statin while statin/Zetia caused non-progression or miniscule regression (just like Crestor, a proven outcome therapy, did in METEOR). Thus neither combination therapy failed, but Niaspan/statin induced what certainly seem to be more favorable changes than the statin/Zetia. However there is no data that event reduction would be any different in patients with no progression versus regression. So until we have outcome trials, no one can conclude which combo therapy is in reality the best therapy. Both editorialists and all discussants at AHA made that clear. However, let's be also be very clear that based on IMT changes statin/Niaspan was the winner.

Because of the lack of data correlating therapy-produced, precise imaging changes to outcomes, there are no guidelines advising us to judge the efficacy of our drugs by performing repeat imaging procedures (including IMT). Does everyone remember that estrogen, raloxifene, Fosamax and torcetrapib all have positive IMT data and none have been shown to reduce CVD events? Indeed both estrogen and torcetrapib also raise HDL-C. Statin data on IMT changes are all over the map (positive and negative) yet
all statins reduce outcomes. There does not seem to be much linkage. Pravachol reduces outcomes in its trials but was associated with plaque progression in an IVUS study (REVERSAL).

The lipids concentrations and presumably lipoprotein were beneficially altered with the addition of either Zetia or Niaspan. Zetia helped LDL-C more than niacin and niacin helped TG and HDL-C more than Zetia (what a surprise). Both drugs helped non-HDL-C. My guess is that the LDL-P (apoB) was fairly well controlled by the several years of statin use in this trial and both Zetia and Niacin further improved that crucial parameter (LDL-P or apoB). My guess is also that niacin improved apoA-I and total HDL-P and the Zetia did not. That would likely be a benefit in the Niaspan column.

My conclusions: We grossly under treat our patients. Statin monotherapy, usually nontitrated is the routine therapy in the US. Stents, strokes, bypass and deaths are way too high despite statin monotherapy. We desperately need to get more aggressive to achieve all goals, especially lipoprotein goals.

Want to help lower apoB (LDL-P): Use statins -- if not at goal add Zetia, Welchol, or Niacin in no particular order although if there are not TG or HDL issues, I prefer Zetia first because of ease of use. However if HDL-P (HDL-C) is low in the face of an elevated apoB or LDL-P then Niacin becomes my first add on (which is the exact recommendation made by ACC and ADD position statement published last year). If the TG are an issue (> 200 mg/dL) or TG/HDL axis is abnormal then a fibrate, niacin (or high dose or omega-3) is the likely best choice.

So if I take a drug like Niaspan and can help a statin achieve better apoB levels and raise HDL-P levels, I think I have a great add on. Simcor would save be a copay, but Crestor/Niaspan would be the more potent therapy. ARBITER 6 trial certainly supports Niaspan/statin use. I prescribe Niaspan as they did in the study: get all to 2000 mg ASAP. I suggest you do the same. You cannot expect lower doses of Niaspan to achieve these results. With proper advice, and perseverance Niaspan use is easier done than commonly believed. Abbott also offers a nice program to help patients properly take Niaspan. Talk to your reps.

This study does not change the fact that apoB (LDL-P) reduction is the primary goal but it enforces the belief that raising HDL-P should be the secondary goal (by the way fibrates raise HDL-P more so than niacin, yet fibrates, because of what they do to LDL size, do not raise HDL-C anywhere near what niacin does) - This is one reason HDL-P is more informative than HDL-C. If a patient on statin/Zetia is still not at LDL-P goals of therapy, Niaspan can help even if the HDL-C is not low. Also, if I have a patient on statin/Niaspan and LDL-P is not at goal I add Zetia. There is published data that statin/Zetia/Niaspan is a great lipid modulating triple therapy.

Bottom line: we all need to use a lot more Niaspan (all CHD patients should be on it along with whatever else is needed to get to goal). No one needs to stop Zetia in anyone and no one needs to be afraid of using Zetia to help achieve goal. For your Vytorin users: if HDL-P is not normal or LDL-P is still high: please add Niaspan AND PLEASE TITRATE IT TO TWO GRAMS.

I want to conclude some of the what I consider outrageous statements made in the paper by the author.

1) Is it plausible that Zetia is harmful to atherosclerosis: that is the conclusion by the author speculating on lipid issues that I do not believe have any support? The paper hints Zetia impairs reverse cholesterol transport. I can supply several studies show it improves RCT (start with Arterioscler Thromb Vasc Biol. 2008;27:1296-1297). I also hate to remind everyone: a serum HDL-C has no relationship what so ever to the dynamic process called reverse cholesterol transport. Macrophage RCT (removing cholesterol from the arterial wall) has no influence on serum HDL-C levels. Niacin raises HDL-C by increasing apoA-I production, inducing hepatic lipidation of HDLs, reducing CETP activity, inhibiting hepatic lipase (thus making HDLs large) and reducing the apoA-I beta synthase hepatic holoparticle receptor.
2) ACAT (the enzyme that esterifies free cholesterol into cholesteryl ester) inhibition is bad and Zetia is thus bad because it reduces ACAT. ACAT inhibitors, which have failed in clinical trials prevent esterification of cholesterol and the free cholesterol accumulates in macrophages. Zetia reduces ACAT activity and expression because by reducing cholesterol delivery (absorption) ACAT downregulates. There is no cellular cholesterol accumulation on Zetia. In the study quoted, the dose of Zetia that impacted ACAT, was infinitely larger than we use to treat lipids.

3) Author states Zetia affects SRB1 and thus impairs RCT. The study referenced was looking at SRB1 in intestinal cells has nothing to do with reverse cholesterol transport. Niacin inhibits ApoA-I beta chain synthase the hepatic holoparticle (HDL catabolism) receptor which decreases hepatic uptake of HDL trafficked cholesterol and potentially decreases RCT. Yet niacin sure works. Statins downregulate ABCA1 the main HDL lipidation enzyme involved with macrophage RCT yet they work.

4) Amazing the NEJM published a nonsensical post hoc analysis showing too much LDL-C lowering with ezetimibe worsens CIMT. This trial is not empowered to examine such an endpoint in a univariate analysis. Shame on the NEJM and their reviewers for allowing such speculation. This has outraged many respected lipidologists. The author was taken to task by the discussants on the podium for this type of analysis.

3) Implying that Zetia increased CV endpoints in a trial that has no such power to do so is the worst kind of fear mongering analysis and no one should pay any attention to such a statement. The author again was taken to task big time by the discussants on the podium for stating such a thing. The main discussant John Kastelein firmly stated that mortality data has NO MEANING. Shame on the NEJM for letting such statements appear.

In conclusions: FACTS:

1) There is no outcome data for Zetia of any kind
2) There is no level one evidence for Niacin: there is secondary endpoint data from CDP.
3) There is no outcome data relating what a drug does to HDL-C benefits CVD outcomes, but there is level 2 evidence that raising HDL-P is beneficial (see VA-HIT)
4) There is no data relating specific drug induced imaging benefits (including IMT) to CV outcome benefit. Crestor, a drug proven to significantly reduce CV outcomes failed to induce regression in a big CIMT trial (METEOR) but rather inhibited progression (exactly what statin/ezetimibe did in this trial. Yet in an angiographic trial regression occurred with Crestor.
5) Fact: every guideline wants you to get to lipid/lipoprotein goal using lifestyle and FDA approved drugs. Statins first line if TG are < 500 mg/dL. In patients with cardiometabolic risk, niacin is the preferred first add on drug (ADA/ACC consensus statement).

FINAL CONCLUSIONS: NIASPAN is a great statin helper drug and needs to be prescribed much more frequently than it is. Zetia is a great statin helper drug and needs to be prescribed much more frequently. No one should be stopping Zetia, no one should be afraid to use Zetia to get to goal and for sure we need to use a lot more Niaspan at 2000 mg. Guess what: I am not stopping my Zetia - I surely and happy to continue my Niaspan and I'd ask you all to review the great John Guyton study: Lipid-Altering Efficacy and "Safety of Ezetimibe/Simvastatin coadministered With Extended-Release Niacin in Patients With Type IIa or Type IIb Hyperlipidemia: (J Am Coll Cardiol 2008;51:1564–72. Conclusion: Combination treatment with E/S plus N showed superior lipid-altering efficacy compared with N or E/S in type IIa or IIb hyperlipidemia patients and was generally well tolerated aside from N-associated flushing. This combination offers an effective, broad, lipid-altering therapy with improvements in lipid effects beyond LDL-C in these patients.