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Year in Review: Key Lipid Clinical Trials of 2008

YEAR IN REVIEW: KEY LIPID CLINICAL TRIALS OF 2008

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Hi this is Dr. Thomas Bersot, President of the National Lipid Association and I would like to welcome you to Lipid Luminations hosted by Dr. Larry Kaskel and presented by the National Lipid Association.

My guest today is Dr. Peter Toth, Director of Preventive Cardiology at Sterling Rock Falls Clinic and an Associate Clinical Professor at the University of Illinois School of Medicine and we are going to talk about the key clinical lipid trials of 2008 and beyond.

DR. LARRY KASKEL:

Dr. Toth welcome back to the show.

DR. PETER TOTH:

Well, thanks Larry, glad to be here.

DR. LARRY KASKEL:

Why don't we start with what's making news all over the place, the JUPITER Trial. I am wondering how you think the JUPITER Trial will actually change the use of statins, if at all, in primary prevention?

DR. PETER TOTH:

Well JUPITER clearly is an extremely exciting trial. It took AHA by storm and we have great reason to be very enthusiastic about the results. How can you argue with looking at a primary prevention group and seeing a 44% reduction in the primary composite M-point including risk for MI, stroke, unstable angina, need for revascularization, cardiovascular death over a median of just 1.9 years of followup.

DR. LARRY KASKEL:

Not to mention there was some actual mortality data.

DR. PETER TOTH:

Yeah, 20% reduction in all caused mortality also statistically highly significant, so this is truly-truly remarkably important for how we manage our patients in the primary risk pool.

DR. LARRY KASKEL:

So what are you doing in the clinic as we speak a little differently since you read the results of JUPITER, anything changed?

DR. PETER TOTH:

Well, I think we have to look at what the inclusion and exclusion criteria of the trial were, and I think when you look at men over 50, women older than 60, folks, who have a baseline LDL on no therapy less than 130. They have hs-CRP that exceeds 2.0. They are not diabetic. They do not have systemic inflammatory disease, do not have a history of cancer within the previous 5 years, etc, etc. Among patients who meet these criteria and are treated with a statin, we can except to see very impressive results in terms of risk reduction and I think what is fascinating about the trial is that the average LDL was 108, triglycerides 118, baseline starting HDL of 49. So this is a lipid profile that I think most people would tell a patient was really quite good and actually did not warrant any form of lipid-lowering therapy.

DR. LARRY KASKEL:

How does this play with the whole lipid hypothesis that perhaps arthrosclerosis as we have been talking about the last few years is an inflammatory disease and the lipids are bystanders?

DR. PETER TOTH:

Yeah, I can't go there. I disagree with that supposition because really I am not sure JUPITER tells us much about whether cooling inflammation gave this results or whether hs-CRP is a therapeutic target. I think what the trial tells us is that statin therapy is remarkably effective when you look at a group like this and my guess is that the great majority of the patients in JUPITER where at minimum moderate risk and probably the average level of risk was moderately high risk and so ATP III in its addendum has already instructed us that among patients, who are of a moderate high risk when you look at Framingham risk scoring, bottom line it's your therapeutic option to drop the LDL below 100 and when you look at the data, really HDL did not change much. You had a huge drop in LDL with the rosuvastatin at 20 mg daily going from 108 to an average 55, I can't say I would be convinced that dropping triglycerides in this trial had a very dramatic impact on overall risk distribution, so I would still have to favor the hypothesis that the bulk of the risk reduction we are witnessing in this trial really was due to the LDL reduction, which was a huge, whopping reduction going from 108 to 55 among patients with predominantly moderately high risk and you also have to consider the fact that you are looking at men older than 50, women older then 60, so if you did some form of imaging, odds are good at least in a percentage of the patients you would see occult disease.

DR. LARRY KASKEL:

Sure. So where did you see CRP now, do you see it as a screening test, do you see it as a therapeutic target, how are you going to use it differently?

DR. PETER TOTH:

Well, I see it as a screening test and we do have nationally defined guidelines as expounded upon by CDC, AHA, and I think those guidelines were really quite reasonable and so JUPITER shows us, and actually one of the tenets of the trial were, why bother treating people with a CRP as we see in AFCAPS, a CRP that was very low with a low LDL because you are really not going to see any type of a benefit. AFCAPS already showed us that; however, if you look at a population with a relatively low LDL here less than 130, and a CRP that is defined as high as being greater than 2.0 in AFCAPS/TexCAPS, which was also a primary prevention study, that did lock in a subgroup of patients, who did experience remarkable benefit from lovastatin therapy over an average followup of about 4-1/2 to 5 years, so that the was the starting tenet and then JUPITER took it farther. So do I think that screening with CRP is valuable in patients of moderate risk consistent with the guidelines, and I would say, absolutely JUPITER does lock that in very, very nicely and remember the bulk of the patients in JUPITER were at least moderate risk, so I think JUPITER supports the existing guidelines, but again, does JUPITER tell us whether or not you should check a CRP in a low-risk population? No, it doesn't tell us that, so I think the guidelines still hold if someone is low risk. We still don't have much reason to check a CRP, but if they are high risk, we also don't have much reason to check a CRP because you should already be assessing global cardiovascular risk burden in treating patients very, very aggressively to move their projected level of risk for heart, CHD events downward.

DR. LARRY KASKEL:

If you have just tuned in, you are listening to Lipid Luminations on ReachMD XM160, The Channel for Medical Professionals. I am Dr. Larry Kaskel and I am speaking with Dr. Peter Toth, Director of Preventive Cardiology at Sterling Rock Falls Clinic and Associate Clinical Professor at the University of Illinois School of Medicine and we are talking about an update on key clinical lipid trials of 2008.

Peter, let's move on to the enhanced trial, which stirred up the lipid community and the stock markets substantially this year, what are some of the lessons that you have learnt from the enhanced trial?

DR. PETER TOTH:

Well, I think a key lesson from enhanced was we need to look at the totality of the information that we have from carotid intimal medial trial. To look at enhance in isolation, I think was a mistake and certainly there was a camp that insisted upon looking at enhanced and trying to shoot ezetimibe therapy on the water, but in the process I think they did a few things. (1) They hijacked debate on this whole thing, which is very unhealthy for medicine in general. (2) I think it lead to this false message of discouraging the use of lipid therapy in patients at risk because actually with this trying to shoot ezetimibe down, they also unfortunately produced this negative light on statin therapy and lipid lowering therapy in general, and in some camps, called in to question the entire LDL hypothesis, which is not a consequence we want because we know that lipid-lowering therapy works, lipid-lowering therapy saves lives, and the last thing we need is for a group of physicians to actually bring some of this into doubt, so what did enhanced show us? Well, the problem with enhanced is that you are starting with a baseline carotid IMT of about 0.7 mm, very, very low. You know I am not going to call that normal, but it's very, very low. You are looking at a patient population of heterozygous, familial hypercholesterolemics, who for the most part were already chronically being treated with very effective therapies, so here you got a group of folks chronically treated, probably they would have done better looking at a group of statin-naïve patients, but be that as it may, when you then compare enhanced to say ASAP or METEOR, the beginning CIMTs and ASAP were 0.92 and METEOR 1.17, so just by way of extension you have got a lot thicker starting CIMTs in all likelihood also have considerably more lipid in the wall of the vessel to mobilize and you have a higher likelihood of being

able to detect an effect. In enhanced, the CIMT is very low and bottom line is instead of seeing regression, which is what they were hoping for, you see identical effects between high-dose simvastatin monotherapy and high-dose simvastatin combined with a ezetimibe, so was it fair to expect progression, probably not, and I think when you compare this study to CASHMERE, and obviously it's very difficult to compare studies, but there too, beginning CIMT of 0.7 you are comparing atorvastatin 80 to placebo among the group of postmenopausal women, and again it's a negative study, no effect. So I think in all likelihood, the CIMT was simply too thin to detect a difference in. I think another disturb is that stemmed from interpretation of the study in the press was this suggestion that actually combination therapy with ezetimibe led to more rapid rates of CIMT progression, which was not true because there was no statistically significant difference between groups and moreover the difference ultimately was 5/1000s of a millimeter and I would like to suggest that if anyone can explain to me what the meaning of 5/1000s of a millimeter is, over the course of the followup period, I would love to hear with that means. The other thing is when you tell people that the incidents of acute events or mortality was higher in the combination therapy group when there is statistically no significant difference, then you are talking about differences of 2 versus 1 and 3 versus 2; that again I think is a profound disservice and is very misleading.

DR. LARRY KASKEL:

Let's move over to a different disease state and based on recent studies looking at glucose control in terms of how it will affect cardiovascular events, what have we learnt this year and what do we hope to learn in the very near future?

DR. PETER TOTH:

Well, I think we have seen 3 very interesting findings, and I think the most important thing that we learnt from long-term extension studies from the diabetes control and complications trial, which looked at type I diabetics and also from the United Kingdom prospective diabetes study, which of course looked at type II diabetics, when you do longer term extension studies after the trials have concluded you see 2 phenomena: (1) You see that the less aggressive groups are treated just a little bit more aggressively and the more aggressively treated groups wind up being treated somewhat less aggressively, but during the course of those 2 trials they did not see glycemic control as beneficially impacting rates of acute macrovascular events.

DR. LARRY KASKEL:

And with that, Dr. Peter Toth, Director of Preventive Cardiology at Sterling Rock Falls Clinic, thank you very much for coming on the show.

DR. PETER TOTH:

Well, thanks Larry, glad to be here.

DR. LARRY KASKEL:

Thank you for listening to Lipid Luminations, presented by the National Lipid Association. For more information, visit www.lipid.org.