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### A Critical View of JUPITER

You are listening to ReachMD, the Channel for Medical Professionals. 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. The results of the recent Jupiter Trails showed a strong association between high sensitivity C-reactive protein and patients at risk for cardiovascular disease. However, the results of the Jupiter warrant using HS-CRP tests as a broad-based clinical screening tool for cardiovascular risk. Joining me today is Dr. Elliot Brinton, Director of the Metabolism Section of Cardiovascular Genetics and Associate Professor of the University of Utah School of Medicine and a Fellow of The American Heart Association, and he is here give a critical view of Jupiter and reasons practitioners may want to give pause screening all patients for CRP levels.

#### DR. LARRY KASKEL:

Dr. Brinton, welcome back to the show.

#### DR. ELLIOT BRINTON:

Thank you very much it's pleasure to be here.

#### DR. LARRY KASKEL:

Well, let's start with what new information we have gained if any about the use of statins in preventing cardiovascular disease from the Jupiter Trial?

#### DR. ELLIOT BRINTON:

Well, I think, it's important to stress the fact that statins work and there have been times when there has been pretty good concerns of when times of people scratching their heads and saying Jesus is this true, but I think that is definitely a reminder that stains reduce cardiovascular disease, there were super-stain or Crestor works just like the other statins in that's ability to reduce cardiovascular disease risk is proportional to it's LDL cholesterol lowering. So, I think, we've got that very, very important take-home message. Those who say that statins are \_\_\_\_\_ that we shouldn't use them. I think we need to take a careful look at this trial, which did indeed show very impressive results.

#### DR. LARRY KASKEL:

So, based on the trial do you think that everybody with an elevated LDL cholesterol should be put on a statin even if they've never had any disease?

**DR. ELLIOT BRINTON:**

Well that's a very very tough question and because doubles in the details here, statins do reduce cardiovascular disease and they can reduce it quite dramatically, quarter to third or maybe even close to a half, the question is how do know who to treat it, who not treat. A large percentage of the population has an elevated LDL cholesterol, can we treat everybody, well we have certain guidelines. This study was actually done outside the guidelines and the sense that it took patients with LDLs at baseline below 130.

**DR. LARRY KASKEL:**

But may got benefit, now what does that mean?

**DR. ELLIOT BRINTON:**

Well, the real question is here is what are the other risk factors and a single strongest risk factor we forget this is age. Age is the strongest predictor of cardiovascular disease risks. It turns out that the patients in Jupiter even though they were "healthy" were on average older. They're averaged age is 66 and in that age group the risk is relatively high and it's relatively easy to see risk reduction. So, I think that's an important takeaway if you're treating a 25-year-old, it's a very different matter than if you're treating a 65-year-old. One of the other questions is how much are you paying for your statin? The statin that was used in the Jupiter Trial was branded or supra-stain or Crestor, which sells for about \$3.5 a day, which is on the high side in expense wise and even with the dramatic risk reduction, probably not cost effective if we used this standard benchmark at \$50,000 per year of life saved.

**DR. LARRY KASKEL:**

On the flip side of that what would happen if you used a cheaper generic?

**DR. ELLIOT BRINTON:**

Well, the generics are cheaper. You can get many of the generic statins for 4 or 5 dollars per month but they are not quite as effective, so the questions is a little hard to answer specifically from the Jupiter study, but looking at all the statin studies together it's probably cost effective to take these relatively high risk patients, these older patients that were studied in Jupiter and considered treating them with the statin. Now that does not mean everybody at age 66 has to be on a statin, no, but may be if you can find that at least one or two of the risk factors 40% of the patients in the study has a metabolic syndrome, you know that's a high risk state and may be there are other situations possibly even with CRP screening or you could say will this put the patient over that line and now becomes cost effective, another very important thing is to talk to the patient. Some patients are very fearful of cardiovascular disease, very willing to pay for and put up in the nuisance of daily treatment, others feel the opposite way.

**DR. LARRY KASKEL:**

But, you mentioned price and you know if you look at it per month, it's more than a \$100 per month and then if you looked at it per how much it would cost per event, per year, it would be about \$300,000 per event per year and it would be more than \$500,000 to prevent one death and you said, you know the benchmark of \$50,000 is what's considered normal for preventing a death. So, this really is, you know 10 times as much money.

**DR. ELLIOT BRINTON:**

It is and so that's why we're not saying and even Dr. Ridker in his enthusiasm for the study, and not saying that everybody had to go on statin. It's a matter of getting a little smatter in terms of risk assessment and frankly one of the things we need and this is not addressing Jupiter but it is a big need we have is some really reliable, noninvasive way of screening for preclinical or subclinical atherosclerosis, if we had that then we'll be way ahead of the game, that's a topic for another day I guess, but it's a very important need and another need that we have is look at the long term consequences of really aggressive LDL lowering. The average of LDL on Jupiter was 55 and \_\_\_\_\_ there are a lot of people who has spent their entire lives with an LDL of 55 but it may be a little different if you get there by aggressive statin therapy, so we need a little more information about this super-aggressive LDL lowering before we can say that bringing LDL to 55 for any particular population is necessarily a good thing, especially if there are somewhat lower risk because they haven't had a prior event.

**DR. LARRY KASKEL:**

I would like to talk a little bit about the number needed to treat? because the number that they are throwing around in this study is based on extrapolating it out to about 5 years and all we have is the number needed to treat for that study, which was 1.9 years, which comes out to about 125 to 129, which I don't think is so impressive and we get into trouble when we extrapolate findings out because we're kind of trying to predict the future and predictions are pretty hard, especially when it comes to the future.

**DR. ELLIOT BRINTON:**

Well, that's why I think it would be really nice if we could subdivide the population of Jupiter. On average, they did fairly well but as you point out, they're really had set the margins, even with a cheap stain so the margins of cost effecting this, so the question is within this group can we pick and choose and there are subgroup analysis in the original publication and they are not very helpful but these are basically taking each factor one at a time, and I think a savvy clinician would say okay and let's look at family history plus, metabolic syndrome plus, you know this plus that and try to put together some sort of score and now we have the framing him risk score, which actually is very effective and one of the questions, which remains outstanding at the moment is exactly how well this CRP add to a standard risk assessment like Framingham. We don't really know that but it will be nice to apply the Framingham to the Jupiter study and then the look within the range of the CRPs that is tested, which is 2 to 10 and see if within that range CRP levels add to the prediction because we need to have some further \_\_\_\_\_ of the population we can't and treat the 50 million or so people the Jupiter would apply to.

If you have just tuned in, you are listening to Lipid Luminations on ReachMD XM160, The Channel for Medical Professionals. I'm Dr. Larry Kaskel and I'm talking with Dr. Elliot Brinton Director of Metabolism Section of Cardiovascular, Genetics and Associate Professor at the University of Utah School of Medicine talking about the Jupiter Trial

**DR. LARRY KASKEL:**

And recent practitioner should apply a more thoughtful approach to screening for high sensitivity CRP levels and I guess one of the other reasons is that it's not reimbursed yet and so patients get really mad when I order that test on them and they get a bill for \$80, and so do you think a.) It will be included in the new guideline and b.) Insurance companies will start paying for it?

**DR. ELLIOT BRINTON:**

You know, the quick answer is that I don't know. The guideline committee has been conveying they are starting to me, it is a big committee. There are a lot of politics as well as science that we slung around and exactly what the committee is going to decide, I don't know. The Jupiter study is an impressive study, but based on what we know at the moment, we really have learned very little about the additional benefit of CRP screening. So, sub-analysis could come out then perhaps we would see some significant movement, but I think based on what we right now the quick answer for that is probably no insurance, don't want to pay for prevention if they can avoid it and they want to pay for extra testing, so they are going to be reluctant to do anything unless the guidelines come out with the very clear statement. So for the moment, I think the answer is likely no but it is possible that further analysis and further data may be move things forward.

**DR. LARRY KASKEL:**

Well, how do you feel Dr. Brinton about Dr. Ridker's interpretation of Jupiter, do you agree with everything or do you have some problems with that?

**DR. ELLIOT BRINTON:**

Well, Dr. Richard is a very, very smart scientist and I agree with most of what he said about the trial. There is one glaring problem and that is the fact that he tells everybody that he is very surprised that the results were so positive. He is expecting maybe a 10% or 15% risk reduction and he was at 45% or so risk reduction. I just have to pause to say you know, relative risk reduction is almost entirely a function of the treatment, and he was using 20 mg a day of Crestor, which is really powerful stuff. It lowers LDL dramatically and so a 45% risk reduction is exactly what you would predict and it really doesn't matter who you are treating. It should be the same risk reduction in any population. Now, absolute risk of course, is a function of the population and then the absolute risk reduction is a multiple of products of the two. So, there is an element here of risk in the population but it is not related to this relative risk reduction of 45% and that is a misinterpretation and unfortunately a very common misinterpretation of the Jupiter study and somehow that was related to the screening and the CRP testing, it had nothing to do that, it was just a function of the drug.

**DR. LARRY KASKEL:**

Can we get rid of relative risk reduction, when did that creep into medicine and why are we even allowing it to persist when the absolute risk reduction is really more meaningful and in this study it was less than 1%, 0.9%?

**DR. ELLIOT BRINTON:**

It's a good figure in the sense of what I just said, which is if you give a given dose of a given drug, you could have a relatively predictable, relative risk reduction, but you're absolutely right. That is only a part of the equation, the other part of the equation is what is the risk of that particular patient and therefore, what is the actual degree of benefit, because the risk is nearly zero, 45% reduction of something nearly zero is meaningless; if the risk is really high, then a 45% risk reduction is used. So, you have to select your high risk patients and I guess part of the take-home here is that Jupiter tell us it is a secondary prevention, they were not studied in the study but

in secondary prevention aggressive LDL lowering is useful and one of the things to keep in mind is the fact that this 45% risk reduction leaves 55% unprevented.

**DR. LARRY KASKEL:**

So, is statin monotherapy enough?

**DR. ELLIOT BRINTON:**

I think, in the high risk patients, the answer is no. So, yes we need to think more about absolute risk reduction and absolute risk that we do about relative risk reduction, but relative risk reduction remains a good concept if we are not relying on it exclusively.

**DR. LARRY KASKEL:**

So, let's say you have a patient in front of you and you calculated his risk to be 6% and you say let's I can give you this pill, you have to take it for the rest of your life and I can reduce your risk from 6% to 5%. Is that interesting to you patient?

**DR. ELLIOT BRINTON:**

That is a good way to put. Because then the patient is saying, oh, yeah, I see how much benefit I am going to get and turns out lifetime risk is almost always much higher and it is higher than the 10-year risk is which we normally quote so you have to kind of think about 10-year versus lifetime and of course those were two very separate considerations, which you ride. It's helpful to talk to the patient about what is their chance x in a 100 of having an event within whatever period of time and then it will be changed to wipe a 100 over the same period of time, say take treatment in. Often times the patient are surprised to realize that this treatment that they think, they have to take is really giving them relatively little bit of it that being said for the person whose event is prevented obviously to these things. So, it's a 2-edge sword certainly the treatment for any other disease, we have to on the one hand be enthusiastic and positive, on the other hand the reason they are conservative and circumspect that we don't treat everybody who comes in the door. We save our treatment for the high-risk patient, for the patient who truly understands the risks and the benefits.

**DR. LARRY KASKEL:**

Dr. Brinton, you mentioned earlier that you are kind of surprised to Dr. Ridker's reaction of that he was very surprised that the degree of risk reduction and you know, when they design these trials, they know exactly how many patients they need to prove their theory and we kind of knew from the proved trial that the CRP theory would play out. So, it was a kind of \_\_\_\_\_ from the start.

**DR. ELLIOT BRINTON:**

It was in the sense that they selected people with higher CRPs, we know that CRP is a risk factor, so we knew this was a higher risk population Dr. Ridker refers to the \_\_\_\_\_ study, which seemed to show a low risk, but they were 8 years younger on average and the age is a such huge risk factor, that needs to be paid attention to a little bit more. There was this business of excluding 80% of the potential study subjects and what happens to those 80%, well we don't really know what happened to them or what would happen if you took a similar population with the therapy under 2. What happens within the 2 to 10 range that's for some sub-analysis I think would be

helpful. There are an off a lot of things that we need to know even just about the baseline data for this study and what we have is interesting, it's useful, it's intriguing but it's still very, very incomplete in terms of what we need to know about this group in general and CRP testing in particular.

**DR. LARRY KASKEL:**

Do you have any thoughts on why more people in the Crestor arm developed diabetes than the Placebo arm, I can't come up with the good explanation.

**DR. ELLIOT BRINTON:**

We haven't been thinking of stain since being harmful in terms of insulin resistance or betazole function, the two key mechanisms behind type 2 diabetes, but that's again a part of this question of you know, if you took enough people and treat them with enough drug, might we cause more risk and more harm than benefit, and the answer that is possibly yes.

**DR. LARRY KASKEL:**

Dr. Elliot Brinton thank you very much for coming on he show.

**DR. ELLIOT BRINTON:**

Thank you very much. I enjoyed it.

**DR. LARRY KASKEL:**

My gust was Dr. Elliot Brinton, Director of the Metabolism Section of Cardiovascular Genetics and Associate Professor at the University of Utah School of Medicine and a Fellow of The American Heart Association, and we were talking about the Jupiter Trial.

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