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Looking Beyond LDL to Reduce Cardiovascular Events

THE LATEST TARGETS OF LIPID THERAPY

You're listening to ReachMD XM 157, 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.

My guest today is Dr. Alan Brown who is the Medical Director of the Midwest Heart Disease Prevention Center at Midwest Heart Specialists in Naperville, Illinois.

DR. KASKEL:

Alan Brown, welcome to the show.

DR. BROWN:

Thank you very much for having me, I appreciate it.

DR. KASKEL:

We are here in Seattle at the National Lipid Association meeting. Alan, what's your personal history with IMT, do you use it in your practice either to help stratify risk, do you use it to follow patients or is it still really just for the research lab?

DR. BROWN:

That's a great question. I think that IMT still is a research tool, except in those centers where it's extremely well validated, the technicians are well trained, and IMT is really a predictor of risk and we think it follows pretty well with clinical events, but that still remains to be seen before we can jump on that as a surrogate for clinical endpoints so we don't use it on a routine basis. I think what's clear is that it is a good predictor of risk and there is a biological mechanism for reducing the progression of IMT that makes sense in terms of it being a reasonably good surrogate for clinical outcomes.

DR. KASKEL:

Tell me a little bit about the Steno studies, I was unfamiliar with those and I know that you are more familiar with them.

DR. BROWN:

The Steno trials were trials to look at multiple risk factor intervention in patients with diabetes. This was really an attempt to see if we could get better outcomes by attending to all the risk factors, so what they did was they took patients with type 2 diabetes and they tried to aggressively treat everything, their blood pressure, their hemoglobin A1c, their LDL cholesterol, their triglyceride level and both systolic and diastolic blood pressure and then compare that to conventional care, and actually the initial Steno-2 study as well as the followup data showed really striking results with the more intensively treated group, better than you would expect from statin alone, so they had a remarkable reduction in cardiovascular mortality. They had a reduction and need for bypass surgery, angioplasty and MIs they were well beyond what we would have expected and the reductions that were published in that trial were absolute reductions to get to your earlier point they weren't relative risk reduction, so it's really quite stunning and again that returns us to the issue of we want to get all the lipids perfect and we want to get the blood pressure perfect and people losing weight and treat their insulin resistance and no one of them will get rid of the other residual risk.

DR. KASKEL:

Can you tell me a little bit about the CHAMP algorithm that UCLA uses.

DR. BROWN:

Yeah, while we were waiting for MI and we were waiting for long-term clinical outcome data, there were a few examples of people who did things that might not seem scientific, but they had a systematic approach to care. Like we mentioned earlier and I think one of the more striking ones was what Gregg Fonarow did at UCLA, which was just to put a protocol in place for every patient with atherosclerosis to be placed on an aspirin, beta-blocker, ACE inhibitor, and a statin and to be given exercise and dietary counseling. So he had a budget of zero for this project and all he did was come up with standing orders and he told all the cardiology fellows, here's what you are going to do. Anyone who comes in with carotid Doppler that shows atherosclerosis or coronary disease or peripheral vascular disease, you are going to put him on this cocktail of medications and then there was some followup mandated and what they did was removed drugs that had not been shown to reduce cardiovascular events and get the patients put on more of the appropriate risk reducing medications, and within the first year after he implemented that protocol, the chance of dying or having a recurrent MI after being discharged from UCLA went down by more than half from 14.8% to about 6.4% so there was a remarkable reduction in mortality, not to mention reduction in clinical events, and as you know in our lipid trials that we get so excited about, it takes at least 2 years in most of them to see a specifically significant difference and we have measured their benefit over 5 years, so this multiple risk factor approach made a difference in just one year and there are other examples of these kind of protocols to having surprising outcomes, the Steno-2 being one of them and again it pushes us to say that we have to look beyond LDL, even though LDL may be the single most important thing that we have and it's easy to treat, we have to look beyond that.

DR. KASKEL:

And I would like to change paths a little bit and ask your opinion on what I think you are passionate about because you did give a talk entitled "Popular Particle Mechanics" and it seems over the last few years or even the last few months, people are really getting behind

the particle number bandwagon and the particle size as kind of falling by the wayside so that old adage that size isn't important but the motion of the particles seems to be more important than ever.

DR. BROWN:

That's a difficult one to touch, but I will try. I think that the <_____> of evidence is that both methodologies, particle size and particle number predict risk and they do it slightly better than the basic lipid profile. There is going to be groups of patients that you may underestimate their risk based on their standard lipid profile though I think those scripts aren't huge.

DR. KASKEL:

And I think when your LDL gets below 100, there's a pretty big gap in terms of reproducibility for what the real LDL is.

DR. BROWN:

Yes, but all of our clinical trials except for the Lipid Research Clinic's primary prevention trial done in 1984 used calculated LDL, so yes, you can argue that you are not really getting a real LDL, but the data that were used to set guidelines was baseline calculated LDL, so you have to come up with a whole new set of rules to decide what to do with measured LDL, but what you say is true and then the question is what do you do with it and that's been the ongoing dilemma, so with that said I think particle number seems to be even a better predictor than particle size based on some of the clinical data that we see in terms of predicting outcomes. What we don't have yet, however, is a prospective randomized trial of treating those parameters trying to increase buoyancy of particles or trying to reduce particle numbers and then seeing if we focus on those test results, whether we will get better outcomes than we would by doing what the NCEP guidelines say, which is treat LDL to goal and then follow up with non-HDL, and none of the clinical trials that we have had is really focussed on non-HDL, which is as you know a surrogate for APPLE-B, but that's what the current guidelines recommend and what's missing is using these so called novel risk factors or advanced lipid testing in a prospective trial and using them to guide our therapy. We have the prominent CRP, we have evidence of high hs-CRP, shows an increased risk, but then what's the treatment. The treatment is to lower LDL further, but we haven't used CRP as a target yet to determine whether that should be and that most classic scenario was the homocysteine issue where we knew that high homocysteine predicted risk, but we did 2 large trials reducing homocysteine, it didn't reduce cardiovascular risk, so not everything that predicts risk reduces it when you treat it. A horizontal ear lobe crease was always about to predict risk, but if you cut out the ear lobe, you don't reduce it. That's why we need prospective clinical trials to know what to do with some of these tests.

DR. KASKEL:

If a general practitioner is listening to this show and is thinking about getting his feet wet with advanced lipid testing, he can choose a Berkeley, he can choose a VAP, he can choose an NMR and I even think there is a new kid on the block at these meetings, I haven't dropped either <_____> yet, what do you tell him?

DR. BROWN:

Well, what I would say to the general practitioner and what I do in my own practice is that I don't think everybody needs an advanced lipid test, whichever one you choose is up to you. You know, you can go around and talk to the different companies and look at the data. I think there is a fair amount of validated predictive data for both the Berkeley Heart Labs and the LipoScience NMR testing. It's the VAP and some of the others, they do similar types of testing with different methodology and one can talk to them about, which they think is

best, but in whom do you know those tests. I think when you have a clinical question I think if you have a middle aged man, who smokes, has hypertension has an LDL of 160, I don't need that test, I am going to treat that patient. I am going their LDL done to appropriate NCEP goals and be pretty comfortable, but if you have a borderline patient, let's say a middle aged female whose LDL is right on the border and who doesn't want to be on therapy, but yet she has got multiple family members that had coronary disease and you say, well her lipid profile doesn't look that bad, but I am worried about it. That's when doing an advanced lipid test really makes sense because then you can further get information about her risk and if she has high particle numbers or if she has a lot of small dense LDL particles or her hs-CRP is high, in your mind you would say she is actually on the higher end of risk and I am going to treat her more intensively and I am going to try and convince her to take therapy and if those numbers are all normal, you may go along with her and say look you are borderline, but I can't find any reason to push you to take therapy, so I think all of these tests until we have outcome measures of using them to treat and comparing them to our standard approach is, it should be used in those patients where you need the information to make a judgment on how intensively to treat the patient.

DR. KASKEL:

Alan, last question, would like to circle back to HDL and I want you to play a little game with me and pretend your wife comes home with a check for 500,000 dollars and says, Alan this money must be spent on an emerging therapy that's going to raise HDL and you can only put the money on one particular therapy, go do it. What are you going to do?

DR. BROWN:

That's a tough question because there are seven or eight targets, all under development and I don't know how well they are all going, I think that CETP inhibition has had a little stone thrown at it, but nobody is quite sure whether that was the molecule or the class of drugs, we do know that raising HDL was nice and it is quite effective and we have data with gemfibrozil, that raising HDL reduces cardiovascular events further, but that's our pattern, so you're not going to invest your 500,000 there, and I think that the APPLE-A1 mimetics and the attempts to raise the APPLE-A1 are probably going to be the most likely candidate.

DR. KASKEL:

It is to say this is what Alan Brown believes is going to win the race in the next 10 years, if you can?

DR. BROWN:

I don't have an answer for you. I think there is so many exciting intermediary steps in HDL metabolism that we've reasonably come to understand that there are really multiple targets that may turn out to be the right one and currently I can say that HDL is a lot like psychiatry, about half of what we know is correct and nobody knows, which half it is and many people who were betting on CETP inhibition as being the savior to reduce the ventricular risk and how you pull mother nature, obviously, makes the difference. So I think as we learn more about HDL, we will have the answer, but right now I tell her to put that money in the stock market while it is really low and keep it there.

DR. KASKEL:

Alan Brown, thank you very much for coming on the show today.

DR. BROWN:

Thank you for having me, I appreciate it.

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