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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Lipidology's Advances and Growing Pains: Technologies, Drug Trials, and Guidelines

Narrator:

Welcome to ReachMD. You are listening to **Lipid Luminations,** produced in partnership with the National Lipid Association and supported by an educational grant from AstraZeneca. Your host is Dr. Alan Brown, Director of the Division of Cardiology at Advocate Lutheran General Hospital and Director of Midwest Heart Disease Prevention Center at Midwest Heart Specialists at Advocate Healthcare.

Dr. Brown:

You're listening to ReachMD and this is Lipid Luminations, sponsored by the National Lipid Association. I'm your host, Dr. Alan Brown, and with me today is Dr. Steven Nissen, Chairman of the Department of Cardiovascular Medicine at Cleveland Clinic. Steve, we go back a lot of years. I want to publically thank you for all the support for education and prevention that you've provided, even during your term many years ago as Head of Education for the ACC, but it's a treat to be able to talk to you because you have such a wide scope of interests and wide breadth of knowledge.

Dr. Nissen:

Thank you very much, Alan.

Dr. Brown:

So, I know you're going to be presenting a talk on intervascular ultrasound which is kind of your baby and done so much work with it, so, if I were to ask you, what do you think are the most exciting developments of IVUS and whether or not you think that's ever going to be a surrogate for development of drugs in terms of predicting outcomes and just your thoughts on IVUS in general?

Dr. Nissen:

Well, first of all, in the answer to your second question, will it ever be a surrogate that we can use for approval, I think the answer is no. The world has moved away from surrogate endpoints and that includes even endpoints like LDL cholesterol, which I think the FDA still accepts as a surrogate, but all surrogate endpoints eventually fail. You come along with something that you think is going to work, a drug that lowers blood pressure or lowers blood sugar, some established surrogates, and then when you actually study it in a clinical outcome trial, you find out that it actually harms rather than helps. Now, I think IVUS is a really interesting surrogate in drug development because it allows us to do proof-of-concept studies. To take something unusual, an example would be ApoA-1 Milano which was a really interesting study we did a decade ago, we're now studying again in clinical trial, and you can find out in a small number of patients, in a relatively short amount of time, whether or not the drug actually is going to affect the burden of atherosclerosis in the arteries. And that information can then de-risk a program and allow a developer to then have some confidence that they can move on and do a major clinical outcome trial and have a reasonable probability of success. But I don't think the regulatory community is going to accept this as a substitute for really measuring what counts for patients which is: heart attack, death, stroke, unstable angina. Those sorts of endpoints.

Dr. Brown:

So, I know you have strong interests in some of the novel treatment therapies that are being developed and looking at IVUS as a possible hypothesis-generating project, I guess, what about the flipside? What if you have an agent that affects risk factor that one

would feel is likely going to translate into outcomes and then you do an intervascular ultrasound trial and you find out there's no difference? How discouraging should that be?

Dr. Nissen:

Well, we've done that and I'm going to talk about that at my discussion about intervascular ultrasound. I can give you a couple of examples that I think are going to stand the test of time. You may remember that ACAT inhibitors were very hot for a while. There were a number of studies done; there were a whole bunch of these in development. One of them was developed by Sankyo, now Daiichi Sankyo, called pactimibe and we did a medium-sized IVUS trial, 5, 6, 700 patients, something in that range. When we unblinded the data at the end of the trial, the ACAT inhibitor, not only did it not slow or reverse the progression of atherosclerosis, it actually made it a little bit worse, and industry looked at that and they said, "Gee, something which is actually increasing disease progression is very unlikely to translate into a clinical benefit." And those programs did not proceed. Now, were we right or were we wrong? I don't think we know the answer to that, but I was comfortable that was a good decision. The other was torcetrapib. We did an IVUS trial with torcetrapib. It did not reduce disease progression and, as I think everybody knows, torcetrapib, the CETP inhibitor, developed by Pfizer, ultimately was harmful in a clinical trial. There have now been several additional CETP inhibitor studies, dalcetrapib which was neutral, and I know everybody is aware that we did the evacetrapib trial with Eli Lilly and we've announced that the study was stopped for futility. The data will be presented soon and published and people can then draw their own conclusions. So, the IVUS evaluation of torcetrapib seems to have held up pretty well over time. So, those two examples make me feel reasonably comfortable that if something really is producing no benefit, or even producing evidence of harm in an IVUS trial, it's not very likely to produce a clinical benefit.

Dr. Brown:

So, now that we're on the topic of CETP inhibitors, I mean, you are a clinical trialist par excellence. I've had the privilege of sitting on some ad boards and listening to how you look at trials and very thoughtful, and you've seen the data on CETP inhibitors, at least for these few that haven't borne any fruit. So, you know we've got a couple of more out there. I'd be curious as to your thoughts about the whole concept of CEPT inhibition and whether you think the drugs that are still under investigation are likely to show any benefit.

Dr. Nissen:

Well, I have to be a little bit careful here because we have announced that we terminated the ACCELERATE trial with evacetrapib, but we haven't actually presented the data. And I think that this is one where I believe that the scientific community will need to look at the results of the ACCELERATE trial for evacetrapib, take a look at what the effect was on LDL cholesterol, look at what the effect was on HDL cholesterol, and then look at what happened to the major morbidity and mortality endpoints. And then, I think everybody will have to make their own mind up. It is a reality that when you test a hypothesis you certainly generally don't want to abandon a class of drugs when you have a single trial. You may not even want to abandon it when you have two trials. It starts to get a little tough to believe in the mechanism if you have three trials where it didn't succeed. Now there is ongoing trial with anacetrapib, which is Merck's drug. Although I believe that in, no matter what happens with that trial, anacetrapib cannot be developed as a successful drug. That a drug…

Dr. Brown:

Because of the long half-life.

Dr. Nissen:

Because of the long half-life. It's around for 4 years. If you get one serious allergic reaction or Stevens-Johnson syndrome, or something like that, the whole program blows up and I don't think it's prudent, you know, you give it to a woman, she can never get pregnant, these are all the issues that we face. Drugs that hang around for years in the body represent a risk to patients that is just not acceptable, and so, unless the study were to show some spectacular benefit, I don't imagine that anacetrapib will ever come to market. So, essentially, we've got a problem in that we've got multiple failures and it remains to be seen whether anybody can make this mechanism work.

Dr. Brown:

If you're just tuning in, you're listening to ReachMD. I'm Dr. Alan Brown and I'm here with Dr. Steven Nissen, Chairman of the Department of Cardiovascular Medicine at the Cleveland Clinic.

Well, thanks Steve, for the insights on some of the newer drugs in development. I'm going to shift gears again, because I've actually, I'd love to hear your thoughts on this. So, as you know, there was plenty of controversy about the 2013 ACC recommendations. You may know that there's a new document that will soon be published that sort of, I think, at least for the area of non-statins, gives some guidance and likely will have some thresholds for treatment back in it. But, I'd just like to hear your thoughts about should all our eggs

be in the statin basket and should numbers not be part of the equation? And if they should be, in what types of patients? So, let me hear your thoughts.

Dr. Nissen:

Well, I was one of the people that was probably the most strident in criticizing the 2013 guidelines. And I think there were a number of problems with the guidelines, some of which were related to the process by which they were developed, and of course the results and what they were actually being recommended.

Dr. Brown:

Through no fault of their own for the process, right? This was a process that was thrust upon the group.

Dr. Nissen:

Well, first of all, I'm not going to buy that. When you're on a guideline committee, you have to make your own mind up. Nobody can tell you what you should write. You have to make your own mind up. But I will tell you that the guidelines, there were several things that I criticized about them. One is this sudden abandonment of target levels. Now, obviously, my thinking is colored by some of the studies that we and others have done where more intensive LDL lowering has proven over and over again to do several things including: dramatically slow or reverse the progression of atherosclerosis and reduce morbidity and mortality. I think of trials like TNT, 10 versus 80 mg of atorvastatin. Now, you can believe that it's the dose of the drug, or you can believe that its effect on lipids that made the difference. I happen to think it was its effect on lipids. And so, the idea that it is not appropriate to target lower levels of LDL cholesterol, which was essentially what the guidelines said, I can't accept. The other, what I believe is really pretty unforgivable mistake of the guidelines made, is they included in the guidelines a risk calculator that had never been published. That can't make societal sense. When we used Framingham, the Framingham Risk Calculator in prior guidelines, there were hundreds of manuscripts that had been written testing that calculator and looking at it, and understanding its pros and its cons, and all of the sudden we get a guideline for 300 million Americans with a risk calculator nobody had ever seen before. That can't make any sense from a scientific point of view and it was a very big mistake. What I believe should have happened, and I hope will happen in future guidelines, is what the US Preventive Services Task Force does routinely, is they write a draft guideline, they put it out for public comment, they allow physicians/scientists from around the country or around the world to comment on it, and then based upon that feedback they then refine and finalize the guidelines. The 2013 guidelines was done in absolute secrecy. They literally made people sign in blood that they wouldn't talk to anybody about the guidelines. Now, why is that a good idea? Shouldn't a guideline be something that we all look at together, think about, write about, evaluate and test, and then gets finalized? And so, this idea that a guideline should be a top-secret endeavor is frankly not sensible and I hope it's not the way it's done in the future.

Dr. Brown:

I think we probably learned a lot from the lessons of this, the way this group proceeded in following the Institute of Medicine's recommendations, to a degree. As you know, there is a new group that's getting ready to write another set of guidelines and probably that's the quickest reiteration of guidelines in our history, right? To see something come along. One thing that strikes me that I thought was good about the ACC recommendations was people who had very low guidance what to do when someone had a coronary event and their LDL was not so high.

Dr. Nissen:

Yes.

Dr. Brown:

Right? So, and maybe I could get your thoughts on that. So, the new set of guidelines says treat risk, and if you go back and look at Heart Protection at the same risk, regardless of LDL, they got the same benefit from treatment. So when somebody has an LDL of 95 and has an acute coronary syndrome, do you use 10 of pravastatin or 80 of atorva and, as a scientist and who's looked at all the literature, do you think it makes sense to use the high dose, because at least in clinical trials that's been tested?

Dr. Nissen:

Well, the one thing that's pretty clear on the clinical trials is it doesn't matter where you start. If you look at a pretty good study, PROVE-IT, people who started lower and got intensive statins did better than people who got less intensive statins. And so, I do think that treating people that have had a recent event with high-intensity statins, and I can tell you what our policy is at the Cleveland Clinic. You come in with an MI and you leave on 80 mg of atorvastatin. I don't care what your LDL was when you came into the hospital, because the available data suggests that that approach reduces risk. And so, I think that is an important concept; a concept of intense statin

therapy, but we don't know of any harms. We have people in some of our clinical trials that have LDLs in the single digits and they appear to be perfectly healthy. And so, if there's not really a harm associated with getting LDL down, and if the evidence is there for the benefit, then I think that's what we should be doing.

Dr. Brown:

Can't be skinny enough, you can't be rich enough, and your LDL can't be low enough, right?

Dr. Nissen:

Well, I actually like that. I say the same thing, something very similar myself.

Dr. Brown:

So, actually a hybrid approach is sort of what you're advocating.

Dr. Nissen:

Yes.

Dr. Brown:

If they have high risk, use intensive therapy, no matter where you start.

Dr. Nissen:

Yes.

Dr. Brown:

But if you use intensive therapy and you don't achieve a reasonable number, you've got to add more, right?

Dr. Nissen:

Yes. That's right. And I think we'll know more when we get the results of FOURIER which I believe will be the first PCSK9 inhibitor trial to complete, whether intensive statin therapy with an add-on of a PCSK9 inhibitor produces incremental reduction in risk. That will be really interesting.

Dr. Brown:

Well, Steve, I am very disappointed we're out of time because I could talk to you for hours. I rarely get to talk to you, even personally, for more than 30 seconds as you're flitting from one place to another, so I can't thank you enough for joining us today on Lipid Luminations.

Dr. Nissen:

Thanks for inviting me.

Dr. Brown.

I'm Dr. Alan Brown. You've been listening to Lipid Luminations, sponsored by the National Lipid Association on ReachMD. Please visit ReachMD.com/lipids where you can listen to this and other podcasts in this series, and make sure to leave your comments and share those podcasts. We welcome your feedback, and once again, I'm your host, Dr. Alan Brown. Thank you very much for listening.

Narrator:

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