Transcript Details
This is a transcript of an educational program. Details about the program and additional media formats for the program are accessible by visiting: https://reachmd.com/programs/lipid-luminations/clinical-decisions-cardiovascular-disease-risks-or-causes-your-guide/7646/

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

Clinical Decisions on Cardiovascular Disease: Are Risks or Causes Your Guide?

ReachMD

Lipid Luminations

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 Health Care.

Dr. Brown:

You're listening to ReachMD, and this is Lipid Luminations, sponsored by the National Lipid Association. I am your host, Dr. Alan Brown, and with me today is Dr. Allan Sniderman, Edwards Professor of Cardiology at McGill University in Montreal, Canada, and our discussion today is going to focus on why we should pay more attention to the causes of cardiovascular disease and less to the risk of cardiovascular disease.

Welcome, Allan. Thank you for taking time out to talk with us.

Dr. Sniderman:

Thank you so much for reaching out to me.

Dr. Brown:

So, I was very intrigued by the topic. Almost every set of guidelines, particularly for primary prevention, has focused on assessing the level of risk to determine the intensity of treatment, going back to World Health Organization, the ATP III, the new ACC/AHA guidelines and even the NLA document, which has several strategies for risk assessment. So, why do you think we should focus more on the causes and less on the risk? And I'm very, very much looking forward to your thoughts on that.

Dr. Sniderman:

Well, first, the idea that we should focus on risk is a strong one, because as physicians, we want to treat people who are likely to get into trouble, so the core concept makes complete sense. It also makes sense that you want to take into account all of the factors that contribute the likelihood that an event will occur. So, the different organizations have somewhat different formulas for doing it, but they are all pretty much the same, and they take into account one's age, gender, cholesterol level, blood pressure, diabetes and so forth, smoking. And so they take all those numbers, they put them together, they generate an estimate of risk for that individual patient based on their individual data so that the doctor looks at the patient and says, “Dear patient, here is your likelihood of having a cardiovascular event, a heart attack or a stroke in the next 10 years.” And what could be more reasonable than that approach? And, perhaps, because

it sounds so reasonable and everybody agrees on it, we haven't thought about it as carefully as I think that we should, because when that number is generated, that number will, depending on what number is calculated, that will determine whether or not pharmacological statin, for the most part, therapy is given to lower LDL. So it's a calculation with consequence. If you fall above the dividing line, threshold, then statin therapy will, all things being equal, be recommended, and if you fall below it, then statin therapy, all things being equal, will not be recommended.

So, my question back to you, Allan, is: When you calculate that number in the patients that you see, what are the confidence intervals of the estimate that's produced? If you calculate, for example, a risk estimate of 4%, what's the range, what's the error in that calculation?

Dr. Brown:

I suspect it's significant, probably enough to move you from as many patients from not treating into a treatment range.

Dr. Sniderman:

Well, good answer, but what are they?

Dr. Brown:

Yes, I don't know the confidence intervals. It's an intriguing question.

Dr. Sniderman:

Because they don't appear in any of the calculations.

Dr. Brown:

Right.

Dr. Sniderman:

And that struck me a little while ago, and I started thinking about it. And I've been so fortunate to be able to work closely with Michael Pencina, who was first at Boston at Framingham and now is at Duke in the Cardiovascular Research Institute. Michael is a biostatistician who thinks like a clinician, or thinks like a clinician should think, and Michael and I and Ralph D'Agostino started to work this through. And when you think about it, to put it straightforward, the risk estimate that's generated, if it applies to anything, it applies to a group of people. If you generate, for example, a risk estimate of 10%, you can validate in 100 people at that risk that 10 suffer an event, so you can say, “Look, my algorithm works,” but you can't actually validate it for any individual. And the question then becomes: If you've got 100 people at 10% risk, were they all at the same risk, or were they actually at different risks, and it only turns out that 10 of them out of the 100 actually had the event, but their risks were different than the other 90?

And we thought about that, and we were able to demonstrate—and this is a viewpoint that appeared recently in *JAMA*—we were able to demonstrate that the risk isn't uniform, that if you take a group of folks who were all given the same number, they're not at the same risk. They're likely at highly variable risks. And when you look at the factors that drive the calculation of risk, age and gender, by far, account for most of what determines your risk in a conventional risk algorithm. It isn't that the algorithm isn't telling you information that's of value. It is telling you good information, but because there is an imprecision in the estimate, then it means, I think, that we can't base our decisions simply on that estimate, but we should be looking at other features of the patient with much more interest and attention than we have to date.

Dr. Brown:

So, let me throw something out there, because it's very intriguing, it makes sense. We're always struggling with the fact that when we

look at a population at risk, we can get an estimate of what 100 people like you might do, knowing that not all of them will behave that way, but we're always trying to focus on individual risk. That's why things like calcium scoring seems so intriguing, because you can determine do they or don't they have atherosclerosis, and correlate that better than traditional risk factor analysis, which has been shown several times. It's why you're so enthused by ApoB. It gives you more precise information. But on the flip side of that, when I do the pooled cohort analysis calculator, I'm more struck by the lifetime risk than the 10-year risk in terms of what I use for decision-making. So, my question to you is: If you know that a male in a population has about a 50% lifetime risk and a female between 30 and 40% lifetime risk of a major event, and you've got a treatment that costs almost nothing and is extremely safe, why are we worried so much about individuals? Why don't we treat the whole population? And you can make a case that everybody over a certain age should go on the treatment.

Dr. Sniderman:

Once you start thinking about it, you realize there's a number of different strategies that are out there, not just the risk strategy. As you suggested, once you're over the age of 50, you could argue, well, everybody should be on it, or you can calculate lifetime risk. That also makes a lot of sense. I think those ideas have merit, but it's worth thinking about other ones still, such as focusing on the causes of the disease more carefully, because statins work by lowering LDL, so the more LDL you've got, the more benefit you're going to get from a statin. And the Cholesterol Treatment Trialists, the CTT, they showed that reducing the level of LDL cholesterol by a millimole reduces risk by about 20%, and that's been interpreted as showing that everybody gets the same benefit out of a statin, and I don't think that's what that shows. What that shows is if you've got -- now, here's where Canadian language is better, millimoles, but do the same thing in milligrams per deciliter -- if you had somebody with an LDL cholesterol of 160 compared to somebody with an LDL cholesterol of 80, that person at 160 has got 4 millimoles; the 80 has only got 2, just about 2; and so there's more incremental benefit you can get. There's more juice in that orange at 160 than there is at 80. So that a lot of people who are at “high risk” are older people with low levels of LDL, and nobody's done a trial saying that they're going to get a ton of benefit.

Dr. Brown:

So, let me challenge you on that a little bit, Allan. What about if we remove the primary prevention discussion and we look at somebody where we treat based on risk rather than numbers, which is certainly what the new recommendations are basically pushing, and say the Heart Protection Study where they took patients with established atherosclerosis whose LDL was not very elevated versus patients who had peripheral vascular disease or diabetes? And regardless of the baseline LDL, they all seemed to get the same number needed to treat to save an event, but these were secondary prevention patients in essence.

Dr. Sniderman:

Right, but let me flip you back to primary so you finish that up, okay?

Dr. Brown:

Sure.

Dr. Sniderman:

The downside of the 10-year risk prediction, which is the model we're dealing with right now, is that if you're 40 years old, even if your LDL is high, unless it's sky high, you won't cross the threshold for treatment because the absolute risk of an event for folks like that over the next 10 years is low.

Dr. Brown:

Right.

Dr. Sniderman:

But it's during that period of time that the LDL is building up in their arteries that's going to produce the risk when they are 55. So, this contracting the period, which is what the algorithms do—the decision algorithms are 10 years—it shortens the focus, and it means that younger people are not being treated until their "risk is high," and your risk can't be high until you've developed extensive anatomic disease in your arteries. The risk doesn't come from nowhere. An infarct doesn't happen. I mean, the infarct happens on that day, but there was extensive disease for a considerable period of time before that. And I've argued, and others have argued, that our objective in terms of prevention should be to prevent the disease from developing in which case we don't have to worry about the risk.

Dr. Brown:

If you're just tuning in, you're listening to ReachMD. I'm Dr. Alan Brown, and I'm with Dr. Allan Sniderman, Edwards Professor of Cardiology at McGill University in Montreal, Canada.

So, Allan, that's, I think, the million dollar question. We wait to treat until we think the patient is at significant risk, and that's why I brought up earlier, and I think you've alluded to it, that you almost would want to treat with lifestyle as well as pharmacologic interventions as early as possible, especially in a population where they have a 50/50 chance of having an event over the course of their lifetime. And my question is: Isn't the reason that we have all these complicated risk algorithms and we spend so much money on trying to determine who not to treat because there is a perception that the treatment options have been expensive and potentially toxic? And now that we know that they're not expensive and they're not toxic, should we think more about treating a population?

Dr. Sniderman:

We should be certainly thinking about treating a lot more people than we're treating now a lot earlier. I totally agree with you. We've moved ahead in our knowledge. We didn't know how effective LDL lowering therapy was. We didn't know how safe statins were. I'm not proud of the fact that we were the gatekeepers on the price, because when the price changed, which was when they came off patent, and suddenly we said a lot was good that should have been good before. Price held up the extension of this benefit to a lot of people, and happily, at least, that should be over.

Dr. Brown:

Do you think that's going to happen with ezetimibe too with all the moaning and groaning? I have a sense that when that goes generic, it will be the best drug that was ever invented.

Dr. Sniderman:

Absolutely. The people that said it shouldn't be will be... You know, memories are short, and that's probably not a bad thing too. I think that there'll be a lot more use of ezetimibe and with statins, and there will be a lot more benefit that's achieved. That's why you alluded to it before. I've argued for ApoB. I think that LDL is -- hypertension is critical -- LDL is critical. And if this thing is critical, then we ought to measure it as accurately as possible. The calculation of LDL cholesterol is unacceptably inaccurate. Non-HDL cholesterol, which is the favorite position of the NLA, I don't agree with that because it's not as good as ApoB. I think a series of studies now, including Framingham, using discordance analysis have shown that ApoB is superior to non-HDL cholesterol. The price for measuring ApoB is trivial compared to accurately selecting and accurately dosing people. I think the debate has been ridiculous and demeaning.

Dr. Brown:

I totally understand where you're coming from on that, and as I'm listening to you, I'm thinking about what the implications of everything you're saying may be. So, first of all, we kind of concluded it for the primary prevention bunch; a 10-year risk calculation probably doesn't give you nearly as much insight as thinking across the lifetime risk.

Dr. Sniderman:

Or let me mention 30 years.

Dr. Brown:

Okay.

Dr. Sniderman:

Thirty years is a powerful, powerful tool, because so many people are at high lifetime risk. Thirty years, if you're 40, it takes you a long way in which you want to go, and it's very, very helpful. Michael Pencina developed this from Framingham, and it's a very useful tool.

Dr. Brown:

So, with that in mind, once you have that kind of a risk assessment and you're doing it on everybody at a relatively young age, presumably for the majority who don't have FH or some other severe disorder that would give them premature coronary disease, then when would the role be there for a more individualized test? So, obviously you've thought a lot about ApoB and many of the other ways that we try to get down to a more personalized risk assessment of an individual patient. So, when would there be a role for a calcium score or doing an ApoB, and is that something that we would also extend to the whole population or only those patients where there's some confusion in our mind?

Dr. Sniderman:

No, I measure an ApoB on everybody. I don't think the lipoprotein status has been assessed if that ApoB hasn't been measured. I don't think you can -- I know you can't -- diagnose a type III hyperlipoproteinemia, a highly atherogenic lipoproteinemia, without measuring ApoB, triglycerides and cholesterol. And with those three numbers you can diagnose any of the dyslipoproteinemias. So, total cholesterol used to be the gold standard. LDL became the gold standard. Lipids are transported in lipoprotein particles, and if you're going to do it, you might as well, you should, measure the particle, because not to do that is to be inaccurate, and inaccuracy should not be acceptable in this day and age.

So, coronary calcium, I have a harder time with because I don't think that should be a routine test. I think coronary calcium can give you information that you don't get from the conventional risk factors. I don't think there's any question about that. I think coronary calcium can add valuable information, but it's telling you that disease is already developed. This is not a signal that you should get in there to prevent the development of disease. It's a signal that you better get in there to prevent the complication of the disease. I have focused my research more on the causes of atherosclerosis. I haven't personally done a lot of research and I don't have a lot of clinical experience using coronary calcium. I think the Hopkins group have just done an amazing job, amongst others, but, in particular, the group at Hopkins has done a great job in outlining the strengths and some of the limitations of coronary calcium, so I tend to look at them for advice on this score.

Dr. Brown:

So, when do you start? I mean, based on what you're saying, you could almost start looking at risk factors at an extremely young age, in the first decade of life. So, what would you recommend in terms of making an assessment and at what age in order to try and prevent atherosclerosis, especially since we know that 16-, 17-, 18-year-olds frequently have early atherosclerosis?

Dr. Sniderman:

I'm going back to the very detailed studies on atherosclerosis that was done in the '70s, '80s and '90s, and you don't start to see complex lesions, the lesions that can really cause clinical events, until the late 30s, 40s, 50s. I know that you can get early changes, because the complex lesions don't come out of nowhere. They come out of a sequence of events that develops over decades. But, by and large, I think for men, late 30s, early 40s, is where with pharmacological agents I'm comfortable, women maybe 5 years later. I

think one of the arguments for causes, I would emphasize how poorly women are served, I think, by the conventional risk algorithms that don't accurately capture their true risk, and women who have elevated levels of LDL are not immune to the consequences of disease.

Dr. Brown:

So, with that in mind, were you somewhat pleased with the pooled cohort calculator in that it at least does a better assessment for women than the prior traditional risk calculators?

Dr. Sniderman:

I thought it was better, but I come back to the limitations of the risk approach. I know that virtually everybody in their 40s is going to be "low risk," and I know that's true even if you had a high LDL. So, my message, what I've learned and what I think that viewpoint established is in the first instance, that estimate has considerable imprecision in it, so don't take it so literally. If you see a 40-year-old man, a 45-year-old woman, who has a high LDL, go back to what we know about the causes of vascular disease, accept the imprecision with which we can select those people who are going to have clinical events, remember how common the disease is over a 30-year period or lifetime, and let's treat those folks. If your blood pressure is 160, you're not going to let it go. If your LDL cholesterol is 160, you shouldn't let it go.

Dr. Brown:

Right. I think this is a very important message, because even though the AHA/ACC guideline doesn't really say it, people have interpreted it to be that in primary prevention, if there isn't a 7.5% 10-year risk, there's to benefit from statins, and that clearly is not the case. What they say is that there's definite benefit over 7.5%, and if it's less than that, you should take into account individual evaluation, including whether or not they might have abnormal ankle/brachial index or a high lifetime risk or an LDL over 160. So, they give a lot of leeway, but as always, we're kind of always looking for the magic number.

And we only have a couple minutes left, and I could ask you a thousand questions, but let's go back to what you said your assessment always is, which is an ApoB cholesterol and a triglyceride level. Since we don't really have any guidance for our audience as to if you do do that, what should you be looking at in terms of numbers, and at what ApoB levels are you concerned and what should your goals be, as the, probably foremost, ApoB expert in the world, I'm going to ask you to give us your opinion on how to use that data when you have it?

Dr. Sniderman:

I think if your ApoB is above 110, your long-term outlook is hazardous. I think that the goal for, if you're treating someone, their ApoB should certainly be below 80, and preferably below 70 milligrams per deciliter. I think the numbers that have come out in some of the guidelines are way out of date and they don't reflect the clinical trial data, and that one of the major advantages of using ApoB is that people with small dense LDL, if you follow the cholesterol, the LDL or the non HDL cholesterol, you'll under treat them; if you have people with cholesterol loaded particles, you'll over treat them, so that there are a lot of people who is LDL cholesterol is "at the right level," but their LDL is still much too high. And that's a tragedy in this day and age when we've got excellent supplemental therapies, and we're going to have additional good ones coming along.

Dr. Brown:

Right, it gets back down to numbers of particles, doesn't it, and not the size and not the total amount of cholesterol in those particles?

Dr. Sniderman:

You know, there's a group of people whose cholesterol levels are high and you look at them and you say, "Gee, they got a high cholesterol, maybe they should be treated," and if you measure their ApoB or their LDL particle number, it's normal. And there's a number of excellent studies that have now shown that their outlook is good, so I don't see the argument for doing this with one hand tied

behind your back.

Dr. Brown:

Well, that's fantastic, and we'll remind everybody that we have a few ways of looking at LDL particles, with ApoB being one of the excellent ones, and as you already mentioned, just measuring LDL particle numbers is another, and non-HDL is sort of a surrogate. It's supposed to correlate well with particle numbers, but as you pointed out, not as accurate as either ApoB or LDL particle numbers.

Allan, thank you very much for being with us today.

Dr. Sniderman:

Thank you so much.

Dr. Brown:

I'm Dr. Alan Brown. You've been listening to Lipid Luminations, sponsored by the National Lipid Association, on ReachMD. Be sure to visit our website at ReachMD.com/lipids featuring podcasts of this and others in this series.

Narrator:

You've been listening to Lipid Luminations, produced in partnership with the National Lipid Association and supported by an educational grant from AstraZeneca. To download this program and others in the series, please visit ReachMD.com/lipids. That's ReachMD.com/lipids.