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## Roles of Non-HDL Cholesterol in Risk Assessment and Treatment

Alan 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 joining me today is Kevin Maki. He has a PhD and the Founder and Chief Science Officer for the Midwest Center for Metabolic and Cardiovascular Research. He's also Adjunct Faculty in Biostatistics and Applied Epidemiology at DePaul University in Chicago, Illinois.

So Kevin, thank you for joining us. We've had the pleasure of interviewing you several times on the show, and it's always fascinating and we have, I think, an important topic to discuss today which is on everyone's minds with regards to lipid management. We've had sort of a paradigm shift to use a cliché going from targeting specific lipid proteins to using appropriate dosages of statins based on the evidence review by AHA and ACC. Now I know that you've been heavily involved in the writing of a document for the NLA that'll be some expert opinion additional recommendations. I also know that you're penultimate scientist and epidemiologist and statistician, so you've had a chance to weigh in on the data.

So I guess the first thing I would ask is it looks from a preliminary release of the NLA recommendations that you are working on recommendations for targets and can you talk to us a little bit about what those targets are and how that interfaces with the ACC/AHA recommendation.

Kevin Maki:

Sure. Well, thank you very much Alan for that kind introduction. It's great to be here again and with regard to targets, I'm going to use terminology because people may get confused when they read the document between the targets and goals. So the targets of therapy in the new NLA recommendations are essentially atherogenic cholesterol, which we define as non-HDL cholesterol and LDL cholesterol. Triglycerides are not a target unless they're elevated 500 or higher to reduce pancreatitis risk. So the focus is really on lowering cholesterol carried by atherogenic lipoproteins.

There are two sets of goals for primary prevention, non-HDL cholesterol less than 130, LDL cholesterol less than 100 for secondary prevention, which includes patients with diabetes who have two or more risk factors or end organ disease and organ involvement. In those cases, the targets are less than 100 for non-HDL cholesterol, less than 70 for LDL cholesterol and that is without regard to triglyceride level because in observational studies and in the studies of statin treatment and other types of treatment, the non-HDL cholesterol level has proven to be a better predictor of risk than the LDL cholesterol level and so both are emphasized is elements of non-HDL cholesterol and their goals in the recommendations for both non-HDL and LDL cholesterol.

Alan Brown:

If we dive into those details and we try and put them in the context of people starting moderate or high dose statins assuming they're following the guidelines that AHA/ACC has recommended. You know it seems to me had they added a couple of words to the AHA/ACC recommendations like you know put them on a moderate to high dose of statin to achieve 50 percent in the high risk people reduction in LDL and in a moderate risk 30 percent reduction and/or a non-HDL less than 130 or non-HDL less than 100. With that additional sentence, I think everybody would have said great, right?

Kevin Maki:

I think that's one of the main areas where there is controversy and I agree. A few more words might have resolved a lot of the conflicts.

Alan Brown:

Yeah. When you look back at all of the trials that were done, nobody really did treat those people that had a residual high non-HDL because most of the trials for mixed...using combination therapy that patients didn't really have a high non-HDL. Tell us a little bit about

what you know from the data in terms of observation and risk assessment that makes you feel strongly that we should go that second step and deal with the non-HDL in those people where it's still elevated.

Kevin Maki:

Sure. The observational data show fairly clearly that non-HDL cholesterol predicts risk that is of atherosclerotic cardiovascular disease events better than LDL cholesterol and when you look at the components, non-HDL cholesterol is primarily comprised of LDL cholesterol and VLDL cholesterol. A one milligram per deciliter increase, in either one, gives you roughly the same increment in risk and so there are various possibilities. One is that VLDL may be atherogenic, so triglyceride rich with the protein particles are remnants, maybe atherogenic or they may be reflecting other processes such as differences in the particles that are released by the liver what have you, but from a predictive standpoint, non-HDL cholesterol has consistently been better than LDL cholesterol.

During treatment, the risk seems to follow the non-HDL cholesterol level more closely than the LDL cholesterol level, which is what you would predict from the observational evidence. So if you're discordant and only one is elevated, if that one is LDL cholesterol but non-HDL cholesterol is below the threshold that used in the analyses then the risk looks just like it does if both are low, but if non-HDL cholesterol is elevated and LDL cholesterol is not, risk is elevated as well. So risk follows non-HDL cholesterol more closely than LDL cholesterol.

Having said that, we have established goals for both because in some patients, the driver may be LDL cholesterol and in other patients it may be a combination of the two and based on the combination of observational evidence and analysis from clinical trials really believe that lower is generally better and that a patient receiving statin therapy, the maximal therapy that that patient can tolerate, who still has elevated levels of non-HDL cholesterol based on limited clinical trial evidence we acknowledge but we still think that the evidence available is sufficient to recommend further lowering of atherogenic cholesterol levels because of the observational relationship and the relationship that's present in analyses from clinical trials such as one that was just published in Journal of the American College of Cardiology recently that showed that the lower you went, even when you get down to LDL cholesterol levels less 50 and non-HDL cholesterol levels less than 75, there's still additional apparent risk reduction. However, there are lots of other factors and other potential explanations, so we acknowledge that the data set is incomplete and we're inferring and using expert opinion to a greater degree than was done by ACC/AHA that really focused on what the clinical trials themselves have shown.

Alan Brown:

So let's say you're a person who's already embraced the current AHA/ACC recommendations. You want to use a monitor or high dose statin in those people that have been shown to get benefit. That seems like a reasonable starting point then you get your follow up lipid profile and I think it's widely misunderstood that AHA/ACC did recommend follow up lipid profiles to try to see if you hit that 50 percent or 30 percent reduction.

Kevin Maki:

And as a measure of adherence, if the patient isn't taking the drug, they're not going to have the response.

Alan Brown:

So you're going to get the follow up lipid profile and everybody agrees with that. Now once you have it and you calculate that the non-HDL is not goal based on the NLA forthcoming recommendations. I look forward to seeing them. I don't have any personal knowledge of what you're writing but I've got a rough idea from conversations with you and others. What are you going to recommend then if the average-practicing physician gets started, has a person on that right dose of statin or maximally tolerated and now they calculate a non-HDL and it's above the threshold that the NLA recommendation suggests. What do you do?

Kevin Maki:

Well, I think the clinician has to apply some judgment and of course, if this a very high risk person, somebody with a history of a coronary event or a stroke, then the approach might be a bit more aggressive and there you might want to consider adding an additional agent to get the non-HDL cholesterol below the threshold. In primary prevention, again, there is a clinical judgment element and one thing that the ACC/AHA pointed out is that we don't have enough information to fully assess the potential benefits.

We can estimate what we think they may be based on epidemiological associations and so forth and the potential risks and so it is a clinical judgment if a person's very close, the approach there might be intensification of lifestyle and more focus on other methods. If the person's fairly far away from the threshold for non-HDL cholesterol then it might be adding another agent and of course, when you add another agent, that can be an agent that either focuses on LDL cholesterol or focuses on VLDL and triglyceride lowering and so there is going to be some judgment based on the phenotype of the patient and other considerations.

Alan Brown:

If you're just tuning in, you're listening to ReachMD. I'm your host, Dr. Alan Brown and joining me today is Dr. Kevin Maki. So let me ask

you your expert opinion. I mean that's what you guys are offering and I think that adds great value and I think one of the other misrepresentations of what AHA/ACC said is that there's no role for drugs other than statins and I've read their document many times.

Kevin Maki:

They don't say that. Yeah.

Alan Brown:

Yeah. They absolutely do not say that there's no role for non-statin. They say that if you don't see adequate response and in that case, 50 percent or so reduction in LDL in the high-risk individuals, 30 percent in intermediate risk people that you could use an additional agent, so once again, when you read the document, you get a little different spin on it than what the people initial interpretation was but with that said, they also said they would recommend using a non-statin agent that has clinical outcomes data if you're going to use one. Right? So do you think that it makes a difference how you lower a non-HDL or LDL in terms of outcomes based on being a trialist and having reviewed the data critically. I'm curious to hear expert opinion on that.

Kevin Maki:

My view and I want to emphasize these are my personal views now so not speaking for the NLA is that it may make a difference. So in fibrate therapy as an example, those with the phenotype of high triglycerides, low HDL cholesterol, it looks as though based on subgroup analyses that there may be some evidence of benefit in that subgroup but that's all based on subgroup analyses and not on a prospective trial that's enrolled people with those characteristics. So we have to be very careful about over interpretation but when you have a patient sitting in front of you, you have to make a decision as to what to do.

So as an example, if you are talking about groups for which there are subgroup analyses that suggest the potential benefit, I think that is a reasonable data set to use to justify a decision to add a fibrate as an example and having said that, I think that with other agents, specifically bile acid sequestrants and niacin, we have some evidence from monotherapy studies that they lower risk. We don't know exactly what the mechanisms are that are responsible that may be reduction in atherogenic cholesterol levels and there are lots of things to consider. If it's a patient with mild hypertriglyceridemia, a bile acid sequestrant might not be the ideal agent. With niacin, you have some issues of toleration and so I think that it would be reasonable to consider something like cholesterol absorption inhibitor on the basis of the expectation that you get additional reduction in atherogenic cholesterol. Although, we do know at present we don't have outcomes data to show that there is a benefit of adding a cholesterol absorption inhibitor to a statin, so lots of considerations, lots of clinical judgment.

Alan Brown:

That's the expert opinion that will help our doctors when they try and make a decision of what to do. Tell us a little bit about this simplicity of non-HDL. I think we talk about it a lot. I think the average doctor knows how to calculate it but then doesn't know what the heck to do after that. You briefly alluded to there's two ways to treat it. You can further lower LDL or you can add an additional agent to lower triglycerides. Any bias on which of those two things is more important and then could you review for everybody, once they've done their statin therapy at the appropriate dose, how to calculate non-HDL, and the results and how to think about.

Kevin Maki:

Sure. Well, the calculation fortunately is very simple, total cholesterol minus HDL cholesterol. It's been a struggle to get labs to report that. So many physicians don't have that reported on the lab slip and unfortunately, they're going to have to employ the use of high technology like a calculator to do that and then of course the question is well, once you have the number, what do you do with it and the answer is with the NLA recommendations, there are specific goal levels and so you can compare where the patient is relative to the goal threshold for the person's risk category and then make a decision on how to proceed.

Now, in terms of whether there's a preference for lowering VLDL cholesterol which would primarily happen with the triglyceride targeted drug or further lowering LDL cholesterol which would happen with something that a cholesterol absorption inhibitor. The observational data would suggest you have a similar increase in risk for one milligram per deciliter increase in VLDL cholesterol or LDL cholesterol, so based on that, we don't have a strong view that one approach is better than the other but we acknowledge that this is extrapolation from observational evidence and is not based on any kind of head to head comparison studies and so it is really a matter of clinical judgment as to which approach is taken and then maybe considerations. If the person has diabetes as an example, the fenofibrates specifically has been shown to have some benefits with regard to microvascular complications, so that might enter the equation in terms of making that decision, but again, lots of clinical judgment.

Alan Brown:

Great. I think the average clinician can visualize the non-HDL issue when they think about a patient who has a normal HDL, normal triglycerides, and LDL at 150. They get nervous. In a diabetic patient, if all they could see is the LDL, they may get a false sense of

security because the LDL might be 105 but the HDL is 25 and the triglycerides are 300 and we all know when we see the whole picture that that patient's at higher risk than what we would think if we just saw the LDL of 105. So non-HDL really gives you a way to assess that level of risk.

Kevin Maki:

And it also simplifies the management of the patient with hypertriglyceridemia in the high range, not the very high range. In that you worry about the triglyceride level, which varies quite a bit from visit to visit, and you focus on non-HDL cholesterol as the targeted therapy and that simplifies the process so that you can focus on just those two numbers, non-HDL cholesterol and LDL cholesterol when evaluating the patient's response to therapy.

Alan Brown:

Well Kevin I can't thank you enough for explaining the non-HDL, for giving us some additional insight beyond what we talked about in the past with regard to the project being undertaken by having the expert opinion, and additional review of the science done by the NLA Writing Group. Thank you very much for being with us today.

Kevin Maki:

We very much appreciate the chance to come and spread the word and clarify questions that clinicians may have about the recommendations that will be coming out soon.

Alan Brown:

Great. I'm your host Dr. Alan Brown. You've been listening to Lipid Luminations sponsored by the National Lipid Association on ReachMD. If you've missed any part of this discussion, I would encourage you to visit us at ReachMD dot com slash lipids to download this podcast and others in this series. Thank you all very much for listening.