Ceramides as a New Biomarker for Cardiovascular Risk Prediction

Announcer: Welcome to the Mayo Clinic cardiovascular continuing medical education podcast. Join us each week to discuss the most pressing topics in cardiology and gain valuable insights that can be directly applied to your practice.

Dr. Kopecky: Hello. I'm Stephen L. Kopecky, M.D., a preventive cardiologist at Mayo Clinic in Rochester, Minnesota. It's my great pleasure today to be speaking with Vlad C. Vasile, M.D., Ph.D., who is also a preventive cardiologist and has a dual appointment here in Cardiology and also in our cardiovascular laboratory. So welcome, Vlad.

Dr. Vasile: Thank you very much, Dr. Kopecky. I appreciate me being here today.

Dr. Kopecky: Well, I'm very excited about this topic, about ceramides. And ceramides, we use quite a bit here. Could you tell us, what are ceramides?

Dr. Vasile: Ceramides are sphingolipids. They are lipids that are ubiquitously expressed. They are present in all cell membranes. Some of these ceramides have been associated with risk of atherosclerotic disease in patients with known coronary artery disease. Our group here at Mayo Clinic and others have also demonstrated that ceramides can predict negative events in patients without known coronary artery disease. We have developed, validated and have used ceramides now for a couple of years as a simple blood test, which we call the ceramide score. One of the advantages of using the score as a predictor biomarker is that it takes into account the lipid pathway, the inflammatory pathway, and also the thrombotic pathway. All these pathways are known to be involved in plaque formation and plaque rupture. While some of the risk stratification biomarkers look at specific pathways — for example, high-sensitivity CRP at the inflammatory pathway and the reputed LDL at the lipid pathway — the ceramide score assesses all these pathways in a very comprehensive manner. Therefore, I believe that ceremides are really are a robust biomarker for assessing risk.

Dr. Kopecky: So you say assess risk. What specifically, you mentioned that it's both primary and secondary risk. What specific events would it, does it predict?

Dr. Vasile: So we are looking at atherosclerotic events. We're talking about myocardial infarction, stroke. We're talking about, also about, death.

Dr. Kopecky: Ok. Now, who do we recommend that should be, have their ceramides checked?

Dr. Vasile: I use ceramides in patients that are at intermediate risk. For example, patients that are assessed by the ASCVD risk calculators and have a risk intermediate, I use the ceramide score in a similar way to using other risk stratification tools such as the high-sensitivity CRP or the coronary calcium score. The ceramide score is an accurate, reproducible test. It is inexpensive and recently has been approved to be reimbursed by insurance companies. As a personal experience, it is also user-friendly and very easy to interpret by us physicians. Additionally, it motivates patients to continue the interventions I recommend.

Dr. Kopecky: So have you, then, you'll draw ceramides, you'll treat the patient, have them change their lifetime. Check lipids again, maybe check ceramides again. And how do you put those together when you explain it to a patient?

Dr. Vasile: So one huge advantage of testing the ceramide score is that it is modifiable. I use it as a baseline when I assess the patient and then as a follow up. Mediterranean diet, aerobic exercise training, and some lipid-lowering agents, some statins. All have been studied and have been shown to modify, to reduce the ceramide level and ceramide score. This is important because lowering the score with various interventions show both the provider and the patient the decreased risk. It also motivates patients that they are on the right track with healthy lifestyle choices and/or pharmacologic interventions.

Dr. Kopecky: And you mentioned Mediterranean diet. In the PREDIMED study, all the benefit was seen in the patients that had high ceramides at baseline. So it's very interesting. Do you ever have patients and you'll treat their lipids and their lipids go down, but their ceramide score stays up, and what does that mean if that's the case?

Dr. Vasile: And this is a very good question because it happens. It doesn't happen, I wouldn't say it happens very often, but sometimes it does happen. As I mentioned previously, ceramides look at different pathways. And so you may target one pathway by reducing the lipids, for example, if they're elevated, but not necessarily the other two pathways that are, have been involved in plaque formation. Therefore, there is a residual risk that at follow up ceramides would give, would provide additional information.

Dr. Kopecky: That's fascinating. And then how often or how quickly will it change, will ceramides change? We know that lipids will change within a month if you start them on a statin.

Dr. Vasile: I usually retest ceramides at the same time when I retest lipids. So I think three months is a very reasonable cutoff time point when we retest ceramides. Sometimes depending on the situation, I retest them at six months or one year. And again, the purpose is just to show that that score went down, which gives reassurance to me as a provider but also to the patient that they're on the right track.

Dr. Kopecky: And you mentioned how easy it is to use the score. So we draw the patient's blood, we get a score here at Mayo. And it is quite easy. Tell us about this 0-to-12 scale.

Dr. Vasile: Yes. This is a scale that gives a number, a certain number to the patient. And that number will place the patient in a risk group from low to very high risk group. And depending on that, we may do certain interventions, but it is very user friendly in the sense that it just places the patient in a bucket of risk from low risk to very high risk. So it is very, very easy to interpret and use.

Dr. Kopecky: Now, you also mentioned comparison to CRP. We know that CRP is not that specific for inflammation causes. It may be vascular, may be nonvascular. What do we know about ceramides and them going up?

Dr. Vasile: Ceramides are also involved in the inflammatory pathway. And so, when you have elevation in ceramides, so you can look at specific, ceramides species that are involved more in the inflammatory pathway and see whether inflammation is more prevalent in driving the score up. But for the purpose of using the score —again, the score is very comprehensive and looks at all three pathways, inflammatory pathway, thrombotic pathway, and lipid pathway. But when we look at specific ceramide species that compound the score, we can actually pinpoint to specific ceramides that are associated with inflammation, for example.

Dr. Kopecky: Well, that's fascinating. The issue of lipoprotein (a) comes up and what, we don't really have a good way to measure lipoprotein (a). Do ceramides help us with finding out how maybe aggressive or how atherogenic or thrombotic lipoprotein (a) is in an individual patient?

Dr. Vasile: I'm not aware of any data that correlates ceramides or different ceramide species with a lipoprotein (a) particle or size of the particle. So I generally test lipoprotein (a) and ceramides in patients that are at intermediate risk. I test both biomarkers.

Dr. Kopecky: Ok. And so we don't really know if everybody with a high lipoprotein (a) in mass measurement may have a high or low ceramide score. Has that really been looked at?

Dr. Vasile: No, I don't think we've looked at that particular question. What we do know is that the lipoprotein (a) mass carries a certain value of the total LDL. And so if the LDL is elevated, that could be because it is intrinsically elevated, but it could also represent that certain component of that LDL that come or derives from lipoprotein (a). In turn, because LDL is elevated, whether it's elevated intrinsically or it's elevated because of elevation LDL and lipoprotein (a), that may affect the ceramide score. Because ceramides, again, they're looking at the lipid pathway in addition to the other pathways.

Dr. Kopecky: Very good. And then finally, you mentioned that the primary and secondary prevention and the risk that it predicts, ceramides predict, is it the same time scale for primary prevention events versus secondary prevention events, or is there a different time scale involved?

Dr. Vasile: I believe the time scales are very similar because when we do, we see changes in ceramides relatively quickly. There's a recent study that looked at stroke, for example, stroke patients. And they measure ceramides before and after they started a statin and they showed a statistically significant difference in statins at two weeks after initiation — sorry, in ceramides — at two weeks after initiation of statins. So therefore, I think any change that you would do for primary or secondary prevention would manifest relatively fast.

Dr. Kopecky: And when you say relatively fast, are we talking about event reduction? We have a risk predictor for ten years that the ACC, AHA uses. What about the ceramides? When do they predict risk?

Dr. Vasile: Ceramides predict risk at short term. That could be a couple of months, but also long term. Most of the studies have looked at long term, but there's a few studies that also look that short term.

Dr. Kopecky: And long term being three to five years?

Dr. Vasile: Yes. Long term several years.

Dr. Kopecky: Very good. Well, Vlad, this has been a fascinating discussion and I can say from personal experience, you've been a great addition to our cardiovascular prevention clinic and to our relationship with the cardiovascular laboratory both. So thank you very much for joining us on this discussion.

Dr. Vasile: Thank you very much, Dr. Kopecky.

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