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Defining Cardiovascular Risk: Where Inflammation Meets Lipids

Announcer:
You're listening to ReachMD. This medical industry feature, titled "Defining Cardiovascular Risk: Where Inflammation Meets Lipids," is sponsored by Quest Diagnostics-Cleveland HeartLab. This program is intended for physicians.

Here's your host, Dr. Michael Roizen.

Dr. Roizen:
Joining me to examine the inflammatory markers alongside advanced lipids in the assessment of cardiovascular risk assessment are Doctors Atul Sachdev and Mimi Guarneri. Dr. Sachdev practices family medicine in his private practice and is a clinical assistant professor in the Department of Family and Community Medicine at the Baylor College of Medicine in Houston. Dr. Sachdev, thanks for being here today.

Dr. Sachdev:
Thank you. Glad to be here.

Dr. Roizen:
And Dr. Guarneri is an integrative cardiologist, perhaps the most famous integrative cardiologist, the cofounder and medical director of the Guarneri Integrative Health Center. She's also president of the Academy of Integrative Health and Medicine. She practices in La Jolla. Dr. Guarneri, welcome to you.

Dr. Guarneri:
Thank you. Glad to be here.

Dr. Roizen:
To kick off our discussion, Dr. Sachdev, can you just walk us through why inflammation is so critical to defining a patient's cardiovascular risk and the importance of inflammatory testing?

Dr. Sachdev:
Sure. I think to accurately define a patient's cardiovascular risk, you really have to look at 2 aspects of what drives cardiovascular disease: the injury and the response to injury. Now, this is the approach first proposed in 1976 by Dr. Russell Ross. Now, our current standard of care is to focus on common risk factors that cause the injury. These are things like diabetes, hypertension, smoking and high cholesterol. But what isn't traditionally included in our assessment of a patient's cardiovascular risk is a measurement of injury response, which is what we call vascular inflammation, and we know that assessing vascular inflammation complements a thorough and accurate risk factor assessment, so we really need information about both lipids and inflammation to have a clear picture of a patient's overall cardiovascular risk. In other words, it more accurately tells us who we need to worry about and who we may be less worried about in the near future. And there is strong science supporting this approach. Take the JUPITER trial, which was the first large-scale clinical trial in 2008 to show improved risk stratification with inflammation testing. In that trial we saw that while lowering LDL did indeed reduce cardiovascular risk, independently lowering hsCRP reduced that risk as well, and lowering both reduced the risk even further. Now, more recently, in 2017, the CANTOS trial really cemented the role of inflammation in cardiovascular disease by demonstrating that lowering inflammation independently of cholesterol reduces cardiovascular risk.

Dr. Roizen:
And turning to you now, Dr. Guarneri, how do you describe the continuum of cardiovascular risk?

Dr. Guarneri:

Well, I think the arterial wall is a great place to start to describe this process. The left-hand side shows a healthy blood vessel, and as we work our way off to the right, we begin to see disease progression. A healthy blood vessel has a healthy endothelium that could produce nitric oxide. On the other hand, as we progress in disease, we begin to see thickening of the artery wall and then ultimately the initiating stages of plaque development, plaque progression, until we finally end up with a rupture-prone plaque, and we know that when a plaque ruptures it results in clot formation within the blood vessel. The end result, of course, is a heart attack or a stroke, and this is exactly what we want to prevent. We never want to be at this stage, so we like to look at what kind of markers will help us characterize the progression of disease along this continuum. So there are 3 broad categories to think about, which are the risk of disease—who's at risk?—the presence of disease, and disease activity itself. Using these markers we can now move along this continuum and get a snapshot in time of where someone is and where their risk lies.

Dr. Roizen:

So, with that being said, Dr. Sachdev, let's dive into the inflammation markers that are used to discuss early risk and oxidative status. What do we need to know about the use of F2-isoprostanes, oxidized LDL as markers? And can you speak to the assessments around the presence of disease using ADMA? \

Dr. Sachdev:

Sure. So, F2-isoprostanes are prostaglandin-like compounds excreted in the urine. They are considered the gold standard for measuring oxidative stress in the body. High F2-isoprostanes have potent biological effects associated with inflammation and can therefore mediate chronic disease initiation and progression. Now, oxidized LDL specifically measures protein damage due to the oxidative modification of the ApoB subunit on LDL cholesterol. LDL oxidation is the initiating event for foam cell formation, and high oxidized LDL levels precede development of metabolic syndrome and insulin resistance. Finally, ADMA gives us a way to assess chemical dysfunction of the cells of the endothelial lining. This marker is simply a methylated form of the amino acid arginine, and because of this, it can actually block L-arginine's availability in the cell, which ultimately leads to lower levels of circulating nitric oxide. And it's important to keep in mind here that elevated ADMA concentrations have been associated with subclinical atherosclerotic disease in studies looking at both carotid and coronary artery disease.

Dr. Roizen:

Dr. Guarneri, what are your thoughts on hsCRP along with markers for disease activity, such as Lp-PLA2 activity and MPO?

Dr. Guarneri:

So hsCRP is a nonspecific marker for inflammation. That means it can be inflammation anywhere in the body. And I just want to be clear about one thing. Inflammation is not always bad. Inflammation can be there to protect us—for example, following an injury—but what we're concerned about is low levels of inflammation that are present all the time, and these can be picked up by measuring the hsCRP, and it's an indicator of atheroma burden. So we saw this in the PROVE-IT study, and we saw this again in the JUPITER trial, where we learned that not only just lowering LDL is good, but if we lower LDL and we lower the markers for inflammation, the hsCRP, that we're going to be more effective at mitigating cardiovascular risk.

Lp-PLA 2 is a little bit more specific. Lp-PLA 2 is specific for arterial inflammation, so this is telling us that the actual plaque within the arterial wall has active inflammation, and this is a precursor to plaque rupture and a cardiovascular or cerebrovascular event. Myeloperoxidase, or MPO for short, is released from white blood cells, and myeloperoxidase also circulating in the blood is an indicator that something is going on in the plaque lining, and that something is usually related to plaque fissures and plaque erosion, again a predictor of vulnerable black, so both Lp-PLA 2 and myeloperoxidase help us to determine who is likely to have plaque rupture and where the vulnerable plaque is.

Dr. Roizen:

For those just tuning in, this is ReachMD. I'm Dr. Roizen, and today I'm speaking with Doctors Atul Sachdev and Mimi Guarneri about the use of inflammatory markers alongside advanced lipid panels in the assessment of cardiovascular risk. Can we prevent disease?

So, Dr. Sachdev, let's consider the primary care impacts for this assessment. As a primary care physician yourself, when do you think inflammation should be assessed, and are all the markers relevant in your primary care practice?

Dr. Sachdev:

Yes, I believe that inflammation testing should be routinely assessed regardless of age or clinician's perception of a patient's risk because the presence of vascular disease and the risk factors that drive it are both asymptomatic and ubiquitous in our population even at younger ages, and I'd say that as primary care physicians, we're in a unique position to identify cardiovascular risk at an early stage so that we can institute interventions that will prevent the disease before it manifests as a tragic vascular event.

Dr. Roizen:
And Dr. Guarneri?

Dr. Guarneri:
It comes down to this, is that cardiovascular disease is an inflammatory disease, and we need the inflammatory risk markers to identify disease, not only early but who has vulnerable plaque, and this is not picked up by traditional testing. I look at these consistently along with my advanced lipid profile, so hsCRP; I'll look at whole body inflammation and so on. Typical screening only captures about 50% of the risk. We've known this for years. Early on in my career as an interventional cardiologist, we treated disease after it occurred, but now we have the tools in our toolbox that can transform how we practice, and these tools need to not only be in the hands of cardiologists, but they also need to be in the hands of all of our primary care physicians.

Dr. Roizen:
So, what can be done once we've identified a patient, Dr. Guarneri, with vascular inflammation?

Dr. Guarneri:
Okay, Dr. Sachdev mentioned the response to injury hypothesis earlier, which brings home the importance of looking both at the lipids along with other risk factors, most notably inflammation and oxidative stress, and this is how I practice with my patients. I look for inflammatory risk, and that's using things, as we previously discussed, like hsCRP, MPO, Lp-PLA 2, and then once I identify inflammation, I say, "Where is this inflammation coming from?"

Dr. Roizen:
Speaking of risk factors, lipids have become a common target of therapy, but as we mentioned earlier, they can fall short in cardiovascular risk assessment. So, Dr. Guarneri, can you walk us through an improved lipid assessment?

Dr. Guarneri:
Cholesterol needs to be packaged into particles, and the packaging could be efficient, large cholesterol particles, or the packaging could be very inefficient, what we call small particles, and we now have the ability to measure this. We can measure LDL particle number, and the research shows us very clearly that at any LDL level, LDL-P, particle number, is a greater predictor of cardiovascular event. Why? Because the more particles we have, the higher the traffic, per se, in the blood vessel, so the higher the traffic, the more chance of developing a cardiovascular event, so the higher the LDL-P, the higher the risk. And remember that LDL-P tracks with ApoB. ApoB is a protein that surrounds all the atherogenic particles—LDL, IDL, VLDL—so measuring ApoB or measuring LDL-P gives us an indication of who is at risk even at the same LDL level.

Dr. Roizen:
And, Dr. Guarneri, what causes the poor packaging?

Dr. Guarneri:
Okay, we found that people with insulin resistance are the ones who tend to have poor packaging. These are the people where we typically see a low HDL and high triglycerides. They tend to have the high LDL-Ps, and this is where a common mistake could be made, because someone may have an LDL that looks okay, say 70, but their LDL-P may be 1,600, and that person is still at significant risk even at their LDL at goal. So insulin sensitivity is an important part of the lipid panel, and looking at insulin resistance tells us who's more likely to have elevated LDL particle numbers, who's more likely to have elevated ApoB, and honestly, this drives 70% of all vascular disease, so this to me is one of the most important factors in plaque progression.

Dr. Roizen:
Well, as we've come to the end of today's program, are there any takeaways or additional insights you'd like to impart to our audience today? Dr. Sachdev, let's start with you.

Dr. Sachdev:
Well, I would like to say that our current traditional approach to preventing cardiovascular disease falls short. With the resources we have today, there is no reason for cardiovascular disease to be the #1 killer in our country. We've had success in reducing the incidence of smoking and treating common risk factors, such as hyperlipidemia, hypertension, yet cardiovascular disease remains the #1 cause of death in the United States. The primary driver of cardiovascular events today is an epidemic of metabolic disease, and sadly, we don't identify this early enough if we're waiting for an abnormal A1c, so the key is to identify and treat metabolic disease before it has a chance to cause vascular disease and inflammation, and fortunately, these markers we've talked about today allow us to do just that.

Dr. Roizen:
Dr. Sachdev, those are really good insights. I'd really like to take that home in our own practice. Dr. Guarneri, what comments do you

have as a parting comment for people to take away?

Dr. Guarneri:
Our goal is to better define risk, identify the source and the cause of the risk, and in doing so we then could mitigate the whole cardiovascular disease process. At the end of the day, our goal is to save lives, and we can do this now in a much more evidence-based way than ever because we have the tools for assessing inflammation, and adding these inflammatory markers to an advanced lipid profile is placing the best tools in our hands to identify risk, identify active plaque and allow us to put programs into place and treatments into place that are going to prevent a cardiovascular event.

Dr. Roizen:
That's really great insights, both great comments to highlight the discussion on how important these inflammatory markers are when combined with advanced lipid panels in risk assessment and helping prevent disease in our patients. Dr. Sachdev, Dr. Guarneri, it was my privilege and I think our audience's privilege to get to listen to you and to speak to you.

Dr. Sachdev:
Thanks for having me.

Dr. Guarneri:
Thank you.

Announcer:
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