

**NAVEEN PEREIRA:** Greetings and welcome, everybody. My name's Naveen Pereira. I'm an assistant professor of medicine and pharmacology at Mayo Clinic in Rochester. And today on Medscape, we'll be discussing a very pertinent and interesting topic on coronary calcium testing with my colleague-- a professor of medicine, a strong research interest in preventive cardiology, Dr. Iftikhar Kullo. And he has especially shown an interest in using biomarkers for identifying cardiovascular risk. Welcome, Dr. Kullo.

**IFTIKHAR KULLO:** Thanks, Naveen.

**NAVEEN PEREIRA:** So let's go straight into the meat of the matter, if you may. Why do we see calcium associated with atherosclerosis?

**IFTIKHAR KULLO:** Sure. A calcification is part of inflammation and repair processes, which are ubiquitous in atherosclerotic lesions. In fact, calcification occurs early on in atherosclerosis. But we are not able to detect it with imaging until it increases in quantity. And that occurs typically after the age of 40 in men and women. So we can detect that with imaging in later years, but it's present in the very early stages of atherosclerosis.

**NAVEEN PEREIRA:** So is CT scanning amongst the most sensitive imaging technologies that we have to pick up calcium?

**IFTIKHAR KULLO:** Well at this moment, it is the standard test to detect coronary calcification. And what we've seen through even histology confirmation is that it accurately quantifies the amount of calcification. And as you know, by quantifying calcium, we get an idea of how much atherosclerotic plaque burden there is. And although it's not a marker of plaque vulnerability, but by telling you the extent of disease, it does give you an insight into the patient's risk.

**NAVEEN PEREIRA:** So I order a calcium score, Dr. Kullo. What do I expect when I look at the report? What do I see?

**IFTIKHAR KULLO:** Well there are two things we need to consider. One is the absolute score. And then the other is the percentile for that person's age, gender, and now even ethnicity-- we can percentile to those three factors. What we consider abnormal is anything that is greater than the 75th percentile for age and gender and ethnicity, or an absolute score of 300, which is what's mentioned in the guidelines.

Some people have an issue with that. They would say that any detectable or even any calcification score greater than 100 is abnormal. And the scoring is based on the intensity of the calcium signal and the area of where that signal is. So in essence, it gives you the quantity of calcification present.

**NAVEEN PEREIRA:** And so how strong is this data linking calcification that's identified by CT imaging and real clinical outcomes? What should the practitioner believe in that help with that association?

**IFTIKHAR KULLO:** Sure. So the recent guidelines for risk assessment that came out recommended four modalities for scenarios, where there's uncertainty about the patient's risk. The first one being coronary calcium, family history, c-reactive protein, and an ankle-brachial index. Of those four, the strongest data are for coronary calcification. And it's clear that this is by far the best modality in terms of refining risk estimates when you're not certain about the patient's risk or when the patient's in an intermediate risk score.

So the data are pretty good. And in fact, a term that we use is, how often does this reclassify individuals when you're assigning risk based on risk calculators. And it does that fairly often. In the Mesa study, for example, 25% of the time risk was reclassified based on the calcium score. And in fact, in the intermediate risk group it was even more so. Nearly half were reclassified.

So the data are very good that it is a marker of adverse outcomes. That goes above and beyond what you can get from the risk calculators.

**NAVEEN PEREIRA:** So not only does it identify atherosclerosis, but it identifies the possibility of real events, adverse cardiovascular events that can occur in that particular person.

**IFTIKHAR KULLO:** Exactly, because it gives you the extent of subclinical disease. And that in turn obviously determines the prognosis in that patient.

**NAVEEN PEREIRA:** So with the incremental value of getting a score by doing coronary calcium imaging with other risk factors, can you integrate risk factors with coronary calcium? Would that make it a better predictive, too?

**IFTIKHAR KULLO:** That's an excellent question, and I don't think we really know the answer. So for example, the guidelines say calculate the risk using the Pooled Cohort estimator. And then if you want to do the coronary calcium score-- it's not clear how we should integrate that with the Pooled Cohort estimate.

One suggestion was to use the vascular age that you derive from these imaging modalities, like calcification or carotid ultrasound, and then put that age instead of the chronological age.

The other suggestion has been that we use a relative hazard of having an abnormal coronary calcium score. Let's say that the relative hazard is two times what would be expected. And then you would multiply your pooled estimate with that relative hazard. So if the patient's risk is 7.5% over 10 years, but they have a high coronary calcium score, that will essentially double their risk. So you would now estimate the risk to be 15%.

There are some issues with these and we, at this point, don't know exactly how to integrate the coronary calcium score into the baseline of the Pooled Cohort estimator.

**NAVEEN PEREIRA:** So what the guidelines say, Iftikhar?

**IFTIKHAR KULLO:** So it's interesting. The guidelines gave it a 2B, which is a pretty good recommendation, but not a flat out 2. Some of the concerns were that they didn't have enough data for what is the relationship between excessive coronary calcification and stroke. As you know, the new guidelines incorporate stroke as one of the adverse outcomes.

They also feel that there's more data that are needed for whether you can actually change outcomes when you do coronary calcium scanning. There's still trials to be done. And then secondly, the degree of reclassification, I think, still needs some additional data. There are some additional concerns-- cost effectiveness, the cost of radiation, and that may have tipped it into a 2B category rather than a 2.

And I know many people in the imaging world are somewhat disappointed by that. They had expected this to get a 2. And many in this area would prefer that risk estimation should basically be driven by imaging in most people.

**NAVEEN PEREIRA:** Right. And so we are traditionally taught that if someone has higher coronary calcium scores for age and sex et cetera adjusted, we should go towards getting a noninvasive stress test, for example, to see what that means that that really translated into ischemia. Is that still generally the approach?

**IFTIKHAR KULLO:** That's a very interesting question. And actually the relationship is not linear. It's quite non-linear. And I have patients in my practice that have very high coronary scores, calcium scores in excess of 1,000. So they're above the 99th percentile.

But when I have imaged them, even with the perfusion or echo stress, they have no inducible ischemia at all. And I think this is because some of the excess coronary calcium resides-- in the arterial wall remodels what we call Glagovian remodeling-- and as a result, the lumen remains relatively nonstenotic.

But the excess of calcium is present in the wall, and thereby you don't get any inducible ischemia-- at least to the extent you can detect on these imaging modalities. So there is not a good linear correlation between the extent of coronary calcification, and whether or not you will have a positive stress test.

**NAVEEN PEREIRA:** So you may not have obstructive disease resulting in inducible ischemia, but you still have atherosclerosis, and you're still at higher risk.

**IFTIKHAR KULLO:** Exactly.

**NAVEEN PEREIRA:** So what do you do, Iftikhar, with these patients then?

**IFTIKHAR KULLO:** If your risk absolute coronary calcium score is greater than 300, you are almost like a coronary heart disease equivalent. And so your risk is 2% per year. So you would probably want to treat that as a coronary heart disease risk equivalent, at the very highest risk category, so with moderate to intensive statin treatment.

**NAVEEN PEREIRA:** So aggressive lifestyle modification and all the preventive measures we know in--

**IFTIKHAR KULLO:** Exactly.

**NAVEEN PEREIRA:** --trying to control the disease.

**IFTIKHAR** Yeah.

**KULLO:**

**NAVEEN PEREIRA:** So how do you use coronary calcium in your practice? Because I know there are all these great situations that come up, maybe you can illuminate some of these cases--

**IFTIKHAR** Sure.

**KULLO:**

**NAVEEN PEREIRA:** --that come up where you found this helpful.

**IFTIKHAR KULLO:** Sure. In my practice I try to avoid it at the extremes of age. So typically, I won't do it in individuals that are less than 40.

**NAVEEN** OK.

**PEREIRA:**

**IFTIKHAR KULLO:** There is some concern that they may have plaque, but it may be softer plaque without that amount of calcium that you could pick it up. So you might be lulled into some sense of security. At the other end of the spectrum, I generally won't do it in older individuals, like people that are older than 65. I don't find this to be useful, because actually if you do the Pooled Cohort estimator, they're already at a certain level of risk where you have to treat them.

So I generally use it in that age group of less than 65, greater than 40. And I find it quite useful actually when you're not certain about that patient's risk. So there's somebody whose Pooled Cohort estimator places them at low risk, but they have a strong family history, or women with inflammatory disease, for example-- systemic lupus or rheumatoid arthritis-- this could be a modality, and chronic kidney disease.

So there are multiple scenarios where I find it useful, and family history being probably the most common one. And so I see a fair number of individuals that have family history of early onset disease. And I am finding this information quite useful to see if the genetic predisposition actually translated into excessive coronary artery disease burden. In which case then even if the risk puts them in the low risk category, I would certainly treat them aggressively.

**NAVEEN PEREIRA:** So for example, if you're on the fence regarding committing them to lifelong statins, that would be useful.

**IFTIKHAR KULLO:** Exactly, because you are actually embarking on what could be lifelong therapy with a medication, which is not completely free of side effects. And so as you know, there's also an emphasis on shared decision making in the new guideline. So that helps when you visually demonstrate to the patient that this is the amount of calcification and plaque burden that you have. And that helps the patient then to make that decision with the physician to whether or not embark on that lifelong therapy.

**NAVEEN PEREIRA:** Perhaps improve compliance, too.

**IFTIKHAR KULLO:** Exactly. And in fact, there have been studies trying to establish whether showing patients these pictures actually helps motivate them to do lifestyle changes, which as you know, is extremely difficult.

**NAVEEN PEREIRA:** Iftikhar, why not just do CT angiography with the calcium scores, too? What do you think?

**IFTIKHAR KULLO:** Well CT angiography is a valuable modality, but I think its place is more in the emergency room, where you have individuals with chest pain. And when you're outside of the emergency room, you can use it in select situations. But it does entail more radiation, more contrast. And I think you can get pretty good information with just plain coronary calcium scoring in the majority of individuals that you're seeing for preventive care in the clinic.

So I think that the CT angiography is valuable. But I think the applicability of the plain coronary calcium score is much wider.

**NAVEEN PEREIRA:** I know there's some interesting trivia about coronary calcium from a historical perspective. Iftikhar, can you shed some light on it?

**IFTIKHAR KULLO:** I suppose you're alluding to the mummies. Yes.

**NAVEEN PEREIRA:** Yeah.

**IFTIKHAR KULLO:** Yes. So that's quite interesting, because in the Egyptian Museum of Antiquity they have actually CT scanned several mummies-- I think up to 50. And the surprising finding was that nearly half of them had coronary calcification. And in fact, I think that the oldest recorded case of coronary artery disease is one of them. It's a princess who lived about 1,500 BC. And she had pretty extensive coronary calcification. And they presume her age was maybe 45 to 50. And that was surprising, because one assumes that they ate a trans fat free diet and were physically active.

**NAVEEN PEREIRA:** And true organic food.

**IFTIKHAR KULLO:** And so there are some theories whether they maybe had more inflammatory burden, or maybe there was some pathogens that were responsible as to why. But it does point out that atherosclerosis was present in antiquity, and it's not merely an epidemic of modern times.

**NAVEEN PEREIRA:** Great. Thanks, Iftikhar, for these great insights. And thank you, our viewers. We hope that you will continue to check out future content on Mayo Clinic's page at the heart.org on Medscape. Thank you for spending time with us.