Non-Invasive Imaging: Risk Assessment

Dr. Michael J. Blaha MD MPH

Professor of Medicine

Director of Clinical Research, Ciccarone Center for the Prevention of Cardiovascular Disease

Johns Hopkins Medicine

Baltimore, MD

Non-Invasive Imaging: Risk Assessment – Module Overview

MICHAEL J. BLAHA, M.D., MPH: Hi, everyone, my name is Dr. Michael Blaha. I'm the director of clinical research for Johns Hopkins Ciccarone Center for the Prevention of Heart Disease. I'm also the director of the cardiometabolic clinic at Johns Hopkins. And thanks for joining our session today. We'll be talking about non-invasive imaging for the purposes of risk assessment in your cardiometabolic patients. And of course this is part of the certified cardiometabolic health professional course.

The importance of this series of lectures is to talk about how we use non-invasive imaging tests in practice to try to figure who's at the highest risk. But also who's at less risk, where we might be able to be less focused on aggressive pharmacotherapy, maybe more focused on therapies like lifestyle. I wanted to talk about the outline for this course before we dive in.

In part one of the section on non-invasive imaging, we're going to be talking about risk assessment in the asymptomatic patient in the primary prevention setting. In other words, those patients that come to you with a cardiometabolic complaint, for example the metabolic syndrome, but they've never had a heart attack or stroke before. And the question is how high risk is that patient and how can I use non-invasive imaging to help with that assessment.

Then we'll move into the symptomatic patient, the patient who comes to see us with a cardiometabolic disorder who has some complaints, shortness of breath or chest pain, for example. And there non-invasive imaging plays a big role in trying to determine the cause of those symptoms and what to do next. And to make this clinically relevant, at the end we're going to have a discussion about some case vignettes and decide as a group how we would proceed with non-invasive imaging in those cases and then what we would do with those results. Thanks for joining for this three-part module on non-invasive imaging. and next we'll dive right in.

Module 1: Risk Assessment of the Asymptomatic Patient-Primary Prevention

MICHAEL J. BLAHA, M.D., MPH: Here's the first part of our three-part module series on non-invasive imaging for risk assessment in cardiometabolic patient. Module 1 here is about risk assessment of the asymptomatic patient in the primary prevention setting.

Let's start with a quick case discussion. Who is it that we're talking about when we say primary prevention in the cardiometabolic space? Let's consider a 52-year-old, non-smoking, non-diabetic man with reasonably good exercise and diet habits, that has a family history of premature coronary disease. And furthermore, when you examine this gentleman in the clinic, his blood pressure is starting to rise and his LDL is higher than you'd want it to be, but it's not extremely high.

The question is, in such a patient, how would you proceed? You heard me talking about different tests that you could be doing in a patient like this and how valuable they are for risk assessment. And we're going to start, as you can see here, with the 12-lead electrocardiogram. What role does the 12-lead

electrocardiogram have in risk assessment in the primary prevention patient? We just talked about a middle-aged man, a family history, and borderline high cholesterol. Does the EKG play a role in this case?

Well, let's talk about the EKG. Of course the EKG is a cheap and rapid non-invasive assessment of the electrical signature of the heart. Because it really talks about the electricity of the heart, it's most useful for looking at things like arrhythmias or evaluating symptomatic complaints. Like I said here, it's most useful really in evaluating symptomatic patients, particularly those with chest pain, for looking for things like acute cardiac ischemia or injury, or of course arrhythmias of the heart, like atrial fibrillation. But it really has limited value in the asymptomatic patient. And we don't really recommend it for everyday use in the cardiometabolic practice in primary prevention. For example, in the patient that we presented here, it's not clear how the EKG would help us so much. Perhaps if left ventricular hypertrophy was detected we would focus on the blood pressure a little bit more. But you can't really learn how high-risk the patient is from an atherosclerotic point of view with just the EKG. We usually say that the EKG has no clear role for routine risk assessment in primary prevention. And maybe only if you detect left ventricular hypertrophy will it make a difference in your assessment.

In general, for the 12-lead EKG, we say the advantages are that it is fast and cheap. It can detect myocardial injury in the symptomatic patient. And sometimes it's useful to get as a baseline measure for someone who you think will be high-risk in the future. But the disadvantage of the EKG is many of the findings are non-specific in the absence of symptoms. And it doesn't really have a role in primary prevention because it doesn't really help us evaluate, for example, the 10-year risk of atherosclerotic cardiovascular disease.

The patient might say, okay, I understand about the EKG, now what about an echocardiogram, should I have an echocardiogram because my dad had a heart attack at a young age? It's worth talking about the echocardiogram and its place in primary prevention. Of course the echocardiogram is a non-invasive, ultrasound-based, relatively low-cost test of the heart. What the echo does is that it allows you to look at both the structure and the function of the heart in real time, for example looking at valves or myocardial function. It also enables you to look at the diastolic function of the heart. And as such it's an excellent tool for evaluating the left ventricular ejection fraction or for working up suspected valvular complaints like a patient with a murmur. And, yes, it's useful when you have a suspicion for, let's say, cardiomyopathy, valvular heart disease, particularly in symptomatic patients whose symptoms fit those complaints, with those disorders. But really it doesn't have as much of a role, once again, in the primary prevention setting. We don't usually use the echocardiogram as a tool to screen for let's say atherosclerotic cardiovascular disease risk. While the echo can, in limited patients, tell you about someone who has maybe bicuspid aortic valve in the screening setting, or you might be able to screen for cardiomyopathy, for example, someone on chemotherapy. In the general, primary prevention population that doesn't have complaints, there's very low yield in finding, for example, valvular heart disease when you don't suspect it, or low ejection fraction in a patient with no symptoms or prior complaints. We consider it to be a relatively low value test in primary prevention.

This patient that I mentioned who was middle-aged with a family history of coronary disease, the echocardiogram won't be particularly helpful for determining the 10-year risk of atherosclerotic cardiovascular disease. Of course the pros of the echo are that there's no radiation. It's relatively low cost. It gives you a functional assessment of the heart, so it won't harm the patient. But the cons are it can be very operator-dependent based on the body habitus of the patient, for example. And once again,

it just doesn't tell us much about primary prevention. It doesn't tell us much about the risk of the patient from an atherosclerotic point of view in primary prevention. We don't routinely record either an EKG or an echo in your standard patient who comes in, in primary prevention.

Now I want to talk about cardiac computed tomography, which is a cardiac-gated, dedicated CT scan of the heart. Now this comes in a few different flavors that I want to talk about. Cardiac CT can be done with or without IV contrast. The patient needs an IV for the contrasted part. If they're getting a non-contrasted CT, they don't need an IV at all. It's a much more rapid test. When we do a cardiac CT without contrast, we call it a calcium score. We generally do CT scans without contrast to look for calcium within the coronary arteries, which signifies how much atherosclerosis burden someone might have in their coronary arteries. Now when we inject contrast and do a more a sophisticated scan on a more highly sophisticated piece of CT equipment, we call it a coronary CT angiography or coronary CT angiogram. There we're trying to mimic invasive angiography to reveal not just calcification, but also the degree of stenosis or the amount of plaque within the wall that might not narrow the coronary arteries. Really, they have different applications. The calcium score is really for risk stratification in the asymptomatic patient to look for plaque burden. And generally speaking, we use the coronary CT angiogram to evaluate symptomatic complaints in someone who we suspect might have obstructive coronary disease. As I said here, the calcium score has emerged as the primary tool for routine primary prevention and risk assessment. It's the best predictor of risk amongst other tests that you could consider. And it's very useful for guiding treatment decisions. Generally speaking, we reserve the CT angiogram for the symptomatic patient, because we don't need to know about vessel stenosis in someone without symptomatic complaints. We just need to know the plaque burden.

The cardiac CT in general is a very useful tool, as you can see. It's relatively fast. It's broadly available to CT scanners everywhere. And actually the amount of radiation is relatively low. It's much less than you get from a nuclear stress test, for example. The downside of cardiac CT is that it is not universally covered by insurance, although increasingly it is being covered by almost all insurers. And you can have incidental findings, for example, if you do a CT scan of the heart, you might find a nodule in the lungs that needs further evaluation, which can be frustrating to the patient and the provider. But it's part of doing the cardiac CT.

I'm going to spend a lot of the rest of the time of this module one on the asymptomatic patient talking about the calcium score. Because the coronary calcium score, as you can see, is the preferred test for risk assessment for atherosclerotic cardiovascular disease in primary prevention.

And why is that? Well, one of the reasons is that the calcium score is nearly universally available and very rapid to do. It can be done on any modern multidetector CT technology as long as you have cardiac gating software to gate to the cardiac cycle. It only takes about 10 or 15 minutes of room time to do and the actual acquisition time is only a second or two. And it comes at the expense of only about 1 millisievert of radiation, which is about like a bilateral mammogram. And the advantage is the calcium score is done the same way around the world. If you get it done at your institution or my institution, or when you're traveling overseas, the protocol for the calcium score will be exactly the same. Theoretically you should get the same score no matter where you are; it's very fast to interpret by design. This is supposed to be a simple test that you can do very rapidly in the outpatient setting.

Here we see the patient in the diagram is in a hospital gown, but the patient can be in street clothes as long as they have electrodes on their chest. You can do this in the outpatient setting on your way out of

the clinic. And you get images that look like this. They're unenhanced images of the heart. Those things that are bright are highly attenuating of x-rays and generally on an unenhanced image are calcium. And all the operator needs to do is to determine whether that calcium is within the coronary arteries and exclude the calcium that's within the sternum of course, or let's say within that pericardium. And the software will spit out a calcium score after you mark that calcium. And that calcium score is what we use as indicative of coronary plaque.

This observation of the calcium score as useful for measuring the plaque dates back to the '90s with John Rumberger in his early work when he was at the Mayo Clinic that looked at autopsy specimens and looked at the amount of calcium within the coronaries and the amount of plaque. You can see here calcium is on the X-axis. The total amount of plaque is on the Y-axis. And you can see a log linear relationship between the total amount of calcium and the total amount of plaque. The calcium score is a test of plaque burden, that's what it is, it's a test of plaque burden. It's not designed to look for stenosis within the coronary arteries, but just to be a test of plaque burden. But that is why it predicts risk so well in the asymptotic patient.

And studies now have been done over the years with the calcium score. This is data from the multiethnic study of atherosclerosis (MESA). And you can see that while people have more calcium in their coronaries as they age, even young people can have advanced calcification. And some 20 percent of patients above the age of 75 can have zero calcium within their coronary arteries. In other words, it's not just telling you about the age of the patient. It's telling you about the actual burden of diseases within the coronary arteries. And if you look at a study like MESA, you see that the event rate is directly proportional to the amount of coronary atherosclerosis.

Young patients with advanced coronary atherosclerosis have high event rates. Older patients who manage to have a calcium score that's zero, for example, maintain very low event rates. It's really telling you more than just the age of the patient. Some people say it tells you the age of the coronary arteries of the patient. As such it's sort of a measure of the biologic age of the patient.

And that's reflected here as well. As it turns out, the calcium score as an integrator of risk factors, including cardiometabolic risk factors, is a predictor not only of coronary disease, but a predictor of a lot of chronic disease. For example the calcium score also predicts onset of cancer, chronic kidney disease, COPD, and dementia, probably because of the shared risk factor model. And as such, the calcium score can help you determine what the long-term prospects of a patient are. Here you can see in red, patients that are more likely to die of cardiovascular disease than cancer, and in blue, patients that are more likely to die of cancer than cardiovascular disease. You can see, for example, a 50-some-year-old patient, like the patient in our vignette, who has a very high calcium score, is much more likely to die of cardiovascular disease. Hence our interventions to try to reduce cardiovascular risk will be more fruitful. In contrast, a 70-year-old patient with a calcium score that's zero, no calcium in the arteries, is much more likely to die of cancer in their lifetime than they cardiovascular disease. I think it's much less likely that your interventions to prevent cardiovascular disease are going to extend the lifespan.

An important part about non-invasive imaging tests for atherosclerosis like the calcium score, is that they are very strong negative risk markers as well. They tell you not only who's at high risk, but they can tell you who's at lower risk than you thought, too. The calcium score of zero is the strongest negative risk factor the development of ASCVD that we currently have. This is due to the sensitivity of the test. Because

it is so sensitive for atherosclerosis, an imaging test that shows no atherosclerosis is very good about ruling out or downgrading risk estimates.

Hence compared to serum biomarkers or a genetic test, for example, it really can only tell if you're at higher risk than you thought. The imagining test can not only tell if you're high risk, but also it can tell you if you're lower risk than you thought, based on the absence of actual disease. And this is why non-invasive tests, for example, the calcium score, in the primary prevention setting are so useful for personalizing risk assessment.

And we've argued this in the past -- that the calcium score seems to risk stratify patients who would otherwise be eligible for primary prevention pharmacotherapy, and can be used to target the patients that derive the most and the least benefit from interventions like a statin or an aspirin. And then focusing treatment in our cardiometabolic clinics on the substantive of individuals with measurable atherosclerosis, might be a more rational way of personalizing therapy. Because that's what we're talking about here. Non-invasive imaging tests for subclinical atherosclerosis allow you to personalize your therapies in primary prevention.

I want to talk about the 2018 cholesterol guidelines from the American College of Cardiology and the American Heart Association to show you where the calcium score fits. These are asymptomatic patients in primary prevention. Here, first of all, after you exclude patients with familial hypercholesterolemia and those with diabetes, or those with existing ASCVD, you're left with patients that are middle age who you need further risk assessment. The guidance would say to start with an algorithm like the Pooled Cohort Equations that identify a numerical risk for that patient. And most of those patients, many of those patients, after you conduct risk assessment will be in the so-called borderline-to-intermediate risk group. They'll have a 5-20% risk for developing atherosclerotic cardiovascular disease in the next 10 years. And some patients will be low risk, some patients will be high risk, but a lot of them will be in the middle. And you can see here, the guidelines say in borderline and particularly in intermediate risk patients, after considering all their risk factors, the decision about their risk and the decision to treat is uncertain, you consider the calcium score. If the calcium score is zero, you can generally be more conservative. If the calcium score is high, generally you're going to be more aggressive with your preventative therapies.

And that is what is shown here and that's what is stated here. There's a class IIa recommendation in the guidelines nowadays, in intermediate risk and selected borderline risk adults, if the decision about – for example, statin use -- remains uncertain, it's reasonable to use a calcium score in the decision to withhold, postpone, or initiate statin therapy.

And we actually have data from a few studies now showing that people benefit, for example, from statins in proportion to their calcium score, in proportion to their burden of disease. On the left is the St. Francis randomized control trial, the only randomized control trial that measured the calcium score at baseline. On the right is a clinical data set looking at patients who had calcium scores and either got a statin or didn't get a statin or followed-up and their propensity matched. What you can see is patients seem to get more relative risk reduction, both on the left and the right, from a statin, for example, when they have more burden of disease within their coronary arteries. And definitely more absolute risk reduction because patients with high calcium scores are higher risk. You can see on the right, for example, a much larger separation of the curves with a statin when a patient has a higher calcium score. And this is why we use the non-contrast cardiac CT, the calcium score, in asymptomatic patients for risk assessment.

But really, we're talking about more than just statins in the cardiometabolic setting, right? In the cardiometabolic setting, we're thinking about a lot of potential interventions that might reduce the risk of the patient. And what's happening now is that we're seeing a movement away from just primary and secondary prevention. We're now seeing more emphasis on an intermediate group, a group of patients with advanced subclinical atherosclerosis that are neither really primary prevention, and really neither secondary prevention. But they are a unique group that needs to be treated aggressively because they're on their way to a future cardiovascular disease event.

And one of the things where a calcium score can be useful is the decision, for example, about aspirin therapy. In the cardiometabolic clinic, many patients will benefit from aspirin, but many will not. What this shows here in this slide, in the bars, is the number needed to treat to benefit from aspirin. And in the red line, the number to needed to harm a patient with aspirin, because we know that a drug like aspirin can cause iatrogenic harm through gastric dyspepsia or gastric ulcers, for example, or other bleeding events. And as you may have heard, the therapeutic window, the range of patients who benefit from aspirin in primary prevention is actually narrowed over the years. That's shown here in blue. In blue, patients are selected for aspirin based on their pooled cohort equations risk. As you move from left to right, you can see that the blue bar is never below the red line. In other words, the number needed to treat is never below the number needed to harm, regardless of the risk to the patient. And that's because the bleeding risk goes up just as the cardiovascular disease goes up with, for example, the pooled cohort equation. I would say in primary prevention you can't use the pooled cohort equations to select who's more likely to benefit from aspirin. Those patients are more likely to get side effects from aspirin too. However, when you use the calcium score, you can see in green, patients whose calcium score is above 100, that's mildly elevated or moderately elevated, or patients whose scores are above 400, those are severely elevated, those green bars are much lower than the number needed to harm line. In other words, we think they get a big net benefit from aspirin in primary prevention. If you look at the orange bars, those patients with calcium scores of zero, they're much more likely to be harmed from aspirin than they are to receive a benefit. The calcium score can help you further identify, for example, who would benefit from aspirin in primary prevention, too. And we usually say that when the calcium score is above 100. That's what is in the new National Lipid Association guidelines and in the Society of Cardiovascular CT guidelines.

The calcium score can also help you determine your blood pressure goal for the patient. As we know from the guidelines, in patients with stage one hypertension, it says to do risk assessment to figure out how aggressive to be with blood pressure therapy. We know that the calcium score can risk-stratify patients with stage one hypertension quite well. This next study I'll briefly show you was looking at: can we figure out using the calcium score who's more likely, we think, to benefit from strict blood pressure goals. Well, we know from the SPRINT trial that patients who are high risk are more likely to benefit from an aggressive blood pressure goal of around 120 systolic versus a blood pressure more like 130 to 140 systolic. And hence, we know that a strict blood pressure goal is good in high-risk patients, but we know in low-risk patients, you can get less benefit from being very tight with your blood pressure control. Can we use the calcium score to figure out who's at just as high risk as the patients who enrolled in the SPRINT trial? And it turns out you can. A calcium score of about 250, which is moderately elevated, gives you a risk equivalent to that of a patient enrolled in the SPRINT trial. And we think those patients are more likely to get benefit from strict blood pressure control.

What do we think about non-statin therapy? What about LDL cholesterol goals or non-HDL cholesterol goals? How do you determine those in your primary prevention patients? Well, it turns out that the calcium score can also tell you if your patient is just as high a risk as a patient whom in secondary prevention you would recommend strict LDL and non-HDL goals. For example, here is a comparison of the calcium score risk with that of the FOURIER trial. The FOURIER trial was that of a PCSK9 inhibitor in secondary prevention. We can see here a calcium score of about 900 gives you risk equivalent to that to the patients that were enrolled in the FOURIER trial of secondary prevention. In fact, a calcium score of 300 to 500 gives you risk equivalent to the lower risk subgroups within FOURIER who also seemed to have a benefit with strict cholesterol and LDL control here. The emerging picture is that the calcium score can help you make decisions beyond just about statins, but also about aspirin and blood pressure, and maybe LDL cholesterol goals, too.

But also importantly in the cardiometabolic clinic, we use the calcium score also to risk stratify our patients with early onset type 2 diabetes in whom we're going to decide whether we're going to try an SGL2 inhibitor or GLP-1 receptor agonist first or metformin first. What I'm showing here is the ESC guidelines for treatment of a patient with type 2 diabetes with ASCVD or who is at very high or higher risk of ASCVD who's drug naïve. Imagine if a patient came to you in a clinic, maybe just like the patient from our vignette, and you tested the A1C and the patient had early onset of diabetes. How would you treat the patient? These guidelines say if you've got a patient who's high-risk, you're going to use an SGLT2 inhibitor or a GLP-1 receptor agonist as your first drug. If you have a patient who is only moderate risk, it's reasonable to do metformin and other therapies first. Like the other data I've showed you, the calcium score can also help you determine who's more likely to benefit from a GLP-1 receptor agonist, for example, compared to someone who's less likely to benefit from a GLP-1 receptor agonist as the initial therapy, just like the ESC guidelines say. And I'll point out that in the ESC guidelines, it actually says that the calcium score using non-contrast cardiac CT may be considered as a risk modifier for cardiovascular risk assessment in patients with diabetes who would otherwise be considered moderate risk. These are a lot of the patients you might see the cardiometabolic clinic in whom you're going to try to decide whether to use, for example, an SGLT2 or a GLP-1 first. And you might consider in those patients the calcium score, to figure out how high risk the patient is in that primary prevention setting.

Now I want to move to a discussion about our case. Our case was an asymptomatic patient who comes to you in the cardiometabolic clinic seeking risk assessment. Let's take what we've learned and see how we might apply that to this patient. Let's remind you this was a 52-year-old non-smoking, non-diabetic man, who has good exercise and diet habits, but has a family history of coronary disease. His blood pressure is trending higher, and his LDL is also higher than we would like for our high-risk patients. Well, if you calculate the pooled cohort equations risk in this patient, you get about 4.7 percent, which rounds to about 5 percent. That's not high risk. It's actually at the low end of the borderline risk group. And if you looked at the ACC/AHA guidelines, it would generally say to be conservative with a patient like this. But I would say we don't know for sure how high-risk this patient is, because they have that family history, they have that higher blood pressure and higher LDL. This is a place in my practice where I would consider using the calcium score. The calcium score, of course that non-contrast cardiac CT, tells you how much calcium is within the coronary arteries and how much atherosclerosis the patient has, and therefore how high risk the patient is.

This was a patient from our clinic, and perhaps because of the family history, this patient actually had a high calcium score. The calcium score is 325. That put this person at 95th percentile for age, sex, and

race. In other words, they're much higher risk than we would have thought. Now how would we treat this patient?

Let's say the patient is in your cardiometabolic clinic, how would you proceed? Would you recommend lifestyle only? Well, before you knew the calcium score, you might say that's a reasonable approach to this middle-aged man that has a family history, but no other major risk factors. Now if you read the guidelines, it does say that such a patient has a moderate level of evidence for a moderate intensity statin, and you could start a moderate intensity statin in a patient like this and that would be reasonable, too. But I would argue once the calcium score is known, that's probably insufficient for this patient.

What about a high intensity statin and an aspirin? This is reasonable, right? Because the patient's higher risk, because of the calcium score, it's reasonable to be more aggressive with the statin. And since the score is above 100, it's reasonable to use a low dose aspirin, too. I would argue that the last answer is the best. In our cardiometabolic clinic, if you have a patient with a high calcium score, that's where we're going to do intensive lifestyle, maybe with a higher order of intensity of lifestyle recommendations than you might give to your other patients. Probably you would use that high intensity statin and the aspirin, but also consider using an earlier use of antihypertensive for this patient who's got a blood pressure that's nearing 140. And if the statin didn't bring them down to an LDL less than 70, this is the situation where I would consider the addition of non-statin therapy to get that LDL down to our secondary prevention goal of less than 70.

I think this is where we're headed at least with the use of the calcium score for risk assessment in primary prevention. It's not just using the calcium score for decisions about statins, but also for all of the decisions we use in the cardiometabolic clinic. How intensive to be with the statin, should we pursue more aggressive LDL cholesterol goals, should you use an aspirin, how aggressive should the blood pressure be? What about these other medicines, what I call here secondary prevention medicines like the GLP-1s or SGLT2s, or icosapent ethyl, medications like prescription omega-3 fatty acids? When do we use those in primary prevention? Well, I think we should use those selectively in the patients that are the highest risk.

We get a lot of referrals in our practice, like you may do too, for patients who have high calcium scores, and this is the way we approach those patients. We consider therapy almost as aggressive as we pursue in secondary prevention to these patients, because we really want to prevent that first atherosclerotic cardiovascular disease event. If the score is extremely elevated, like we see sometimes the score is over 1000, we treat those patients nearly as aggressive as secondary prevention, routinely.

Now you might ask, okay, this is a lecture about non-invasive imaging for risk assessment, we talked about the calcium score, but we really didn't talk as much about coronary CT angiography. I did mention at the outset that the coronary CT angiogram is really the preferred test for symptomatic patients, where we can learn about the luminal obstruction of the coronary arteries. Well, why not just use it for primary prevention? There are some reasons that we don't. Number one, it's much more expensive. It does require IV contrast. It requires beta blockers, for example, for heart rate control. And usually more sophisticated equipment and a much more trained technologist to do, and as such is less reproducible. But the coronary CT angiogram is a useful test as we'll talk about in our next module.

It turns out when you look at primary prevention patients, when you say, well, how much does the coronary CT angiogram add on top of the calcium score, the answer is not much. Here I'm showing the incremental risk predictive value of the CT angiogram on top of the calcium score. And you can see, it

does not add much. Even if you consider the number of segments with stenosis, the number of vessels with a stenosis greater than 50 percent, plaque type on a CT angiogram, it just doesn't add that much for risk prediction for primary prevention. But we just want to know what is the plaque burden. That's why we don't recommend the CT angiogram routinely in primary prevention. That's why we recommend the calcium score.

This has led to the model that's really come up in primary prevention now that I think is worth mentioning in this lecture series, which is that we care about plaque burden, not plaque stenosis or coronary stenosis, in primary prevention. What we care about is the burden of disease. As you can see here, in this central illustration from an article that was in JACC recently, once you know the calcium score, the added value of knowing plaque stenosis is not much. As you can see in the upper right corner, knowing stenosis, obstructive disease versus not, doesn't really add anything on top of the calcium score in most patients. Once again, a simple assessment of just the plaque burden with the simpler test of the calcium score is probably the preferred approach these days in the cardiometabolic clinic in primary prevention.

Let me summarize the first module of this three-module series on non-invasive imaging with these concluding statements. Number one, non-invasive imaging has a role for risk assessment in primary prevention, after consideration of traditional risk factors, of course, and things like risk enhancing factors, like the metabolic syndrome. But there's currently little role for routine EKGs or echocardiograms in these patients. It doesn't add much for atherosclerotic risk assessment. The calcium score, the non-contrast cardiac CT scan, is the best test for predicting cardiovascular risk in this primary prevention patients. And the coronary CT angiogram, while extremely useful for symptomatic patients, doesn't add much in primary prevention and you're probably not going to get approved by insurance anyway. And we think the calcium score in your cardiometabolic clinic can help you guide the intensity of lifestyle therapy, guide your choices about aspirin therapy, help you select blood pressure goals, help you select cholesterol-lowering therapy, and importantly in this day and age also select your initial choice of cardiometabolic drugs for the patient.

Thank you for joining us for module one of this series. Hope you can tune in for module two, where we'll talk about the symptomatic patient.

Module 2 – Non-Invasive Imaging of the Symptomatic Patient

MICHAEL J. BLAHA, M.D., MPH: Welcome back to our series on non-invasive imaging for risk assessment in your cardiometabolic patients. In module two, we'll talk about the non-invasive imaging of the symptomatic patient. We covered imaging in the asymptomatic patient, where really the goal is determining atherosclerotic cardiovascular disease risk. Now we're going to talk about how you can use non-invasive imaging to further evaluate a patient who has a specific symptomatic complaint, most commonly shortness of breath or chest pain.

Let's go over what we'll cover in this module two of this series. First of all, we're going to talk about all of the available non-invasive cardiac imaging modalities in one key slide each, so that everyone remembers the key aspects of different tests. Then we'll talk about how clinical trial evidence has started to inform us about when we should use one test over another in the role of non-invasive imaging that we'll talk about here versus that of invasive imaging like coronary angiography in the cath lab, and where are the respective roles of these tests lie. Then we'll talk about new guidelines, because new guidelines have helped shed light on exactly when we should be using tests in symptomatic patients. We'll talk about the

European Society of Cardiology guidelines, and then the new 2021 ACC/AHA chest pain guidelines, which will give us further information about when to select a non-invasive imaging test for a patient with, for example, chest pain.

Now we'll move into our section on the available non-invasive cardiac imaging modalities and their strengths and their weaknesses.

First of all, what are we talking about here? What do we mean when we say chest pain or stable chest pain? We're not talking about, in this series, how to evaluate a patient in the emergency room. We're talking about a patient in your clinic who comes in with chest pain complaints, for example. All chest pain is not an acute coronary syndrome. When you're in the emergency room and you've got unstable chest pain, that's an acute coronary syndrome. But a lot of the other chest pain we see in the outpatient setting is what we call stable chest pain. These patients are considered to have stable chest pain when there hasn't been an acute onset of the symptoms, there hasn't been an acute change to the symptoms. They've had their symptoms for quite some time. And it may be associated with things like exertion or emotional stress. They come in and say, I'm having these complaints consistently, what should I do about them? That's the definition of stable chest pain, which really turns out to be a majority of the chest pain that we see in clinical practice. This can include patients who come in, for example, to an acute care setting that have a negative EKG or negative cardiac biomarkers, and what do you do next? For example, a patient who's been to the emergency room who's ruled out for an acute coronary syndrome and then comes to your practice, that patient now has stable symptoms and we need to figure out what to do next. Let's dive into our options for now non-invasive imaging and where they have a role in your practice.

First of all, let's talk about the 12-lead EKG. I mentioned in the first module, that the EKG does not have much role in asymptomatic patients, but it's very useful in symptomatic patients. It's this cheap rapid non-invasive test of the electrical signature of the heart, very useful for looking at injury or ischemia to the myocardium or looking for arrhythmias of heart which also can cause symptoms, of course. Not much role in the everyday primary prevention setting, but in every patient who has symptoms, you should get an EKG. It's fast. It can be diagnostic of myocardial injury right off the bat. It's very useful for a baseline for patients who might have changing symptoms over time. Once again, not for primary prevention, but in routine patients, secondary prevention or patients with chest pain, get a 12-lead EKG.

Now let's move into more detailed assessment of these patients. Generally speaking the tests that we'll talk about in the remainder of this module for symptomatic patients can be divided into two categories. One, anatomical approaches. These approaches look to see if there is stenosis within the coronary arteries. These could be, for example, a coronary CT angiogram or an invasive angiogram with a cath lab. And functional approaches, these are tests that look at the function or the myocardial blood flow within the heart to try to see if there's ischemia. As opposed to an anatomical approach which tries to look at the plaque or stenosis directly, these arrive at that indirectly by looking at the function of the heart under stress. Most commonly looking for signs or symptoms of ischemia during some period of either pharmacologic or exercise-based stress. Two big categories, anatomical approach and functional approach and how do we choose between them for our patients.

Let's talk about, first of all, the anatomic approaches to looking at the coronary arteries. Well, the first test I want to talk about is the coronary CT angiogram. We talked about the calcium score in detail in module one. The coronary CTA, we said, didn't have much role in primary prevention, but has a great role in symptomatic patients. The CT angiogram is a non-invasive imaging angiogram that can tell you how

much plaque a patient has, where that plaque is, and how much stenosis of the coronary artery there is, without of course having to be an invasive test. So nowadays coronary CT has become very sophisticated. We can see very great images of the heart. And it can be fast. It can be something that's available to most patients. Even those patients who of course want to avoid an invasive procedure. And it has a very high negative predictive value. In other words, when we do a coronary CT angiogram, and it's negative, we can pretty much assure that that patient doesn't have stenosis from the coronary tree.

And there's some downsides of the coronary CTA, of course. You need heart rate control. You need beta blockers, for example, to bring the heart rate down to about 60 or 70 to do the coronary CT scans. So if a patient has a very high heart rate, this test isn't as good. This test does require contrast, of course. If there's an IV contrast allergy, it's not as good of an option. If a patient has severe kidney disease, you might not want to expose them to contrast as well; that's another limitation. And sometimes the coronary CTA can be limited by severe coronary calcification. If you have a high-risk patient with a lot of coronary calcification, it can be hard for the coronary CTA to determine if there's really a stenosis within the coronary tree or not. These are some of the strengths of using coronary CTA in an anatomical approach to look at the coronary arteries.

Next we'll talk about invasive coronary angiography, going to the cath lab and doing an invasive coronary angiogram. Of course the advantage of the invasive coronary angiogram is that it is the gold standard for assessing luminal stenosis. It's what we compare all other tests to in terms of making the diagnosis of obstructive coronary disease. And of course the biggest advantage being in the cath lab is when you see that stenosis, if appropriate, you can also open it up, for example, with angioplasty or a stent. That's a big advantage of being in the cath lab. But of course there's a risk with any invasive procedure. Usually the complication rate with this procedure is less than 1 percent. But still it can happen, particularly in patients with severe vasculopathies. The advantages of being in the cath lab is you can get definitive assessment of obstructive coronary disease, particularly potentially treat that. But the downsides are it's very invasive and it's very expensive. And you can't really see the earliest forms of plaque in the cath lab. It's really looking for severe stenoses. Technologies like coronary CT angiogram can pick up the early plaque within the vessel wall a little bit better than you can see in the cath lab. These are both anatomic approaches that assess how much disease there is within the coronary arteries.

Of course, other approaches to evaluate symptoms would be functional approaches, to give someone a sense whether the coronary arteries are supplying enough blood flow under stress.

The first test we'll talk about here is the stress EKG, the simple stress test, exercise stress test. You put a patient on a treadmill, they exercise and you watch the EKG and look for evidence of ischemia on the EKG. This is a test I'm sure all of us are familiar with. It can be done with the Bruce or modified Bruce protocol, to get that real-time assessment of the EKG looking for ischemia. It also provides data on the functional capacity of the patient too, how far they can go on the treadmill, which is extremely prognostic. The advantages of the test are that it's very simple, it's cheap, you can do it in the outpatient setting, and it mimics real world exercise, so their symptoms under real actual exercise they might be doing in the real world.

But the cons of this test are that it's not always so easy to interpret. There can be a lot of artifacts on the EKG, making it difficult to interpret. And it's limited by baseline EKG changes the patient might have. And it's not available for the patients who can't exercise because of their arthritis or another reason. And it has a fairly high false positive rate. We can do a fair amount of layered testing. In other words, the stress

EKG appears possibly positive, so you do another test, for example, maybe before you even go to the cath lab. It can lead to layered testing. The stress EKG is a nice test but has some limitations.

Hence imaging has been added to stress tests, too, to provide more specificity to the result after a stress EKG. One way of doing this is with a stress echocardiogram. This can be done on a treadmill, or pharmacologically induced stress, for example, a drug like dobutamine. What you do is you induce stress even with exercise or with a drug, you get that heart revved up, and you see it under maximal exercise, or maximal intensity of stress, if the heart has dysfunction. If the heart has dysfunction, that's a hint that there's not enough blood flow getting to the heart, suggestive of ischemia. Or it a patient is on a treadmill, they quickly lie down, you look at the echocardiogram, and you look for regional wall motion abnormalities within the heart as evidence of ischemia. Wall motion abnormalities are relatively late in the ischemic cascade. This isn't a sensitive test to pick up the earliest manifestations of ischemia. But it does have quite a bit of specificity. When you see a stress echo abnormality, it's much more likely to be true. The pros of this test are it can be done on a treadmill or with a pharmacologic stress. You also get on a treadmill that has a functional capacity assessment. You don't need special equipment; you just need a treadmill and an echo machine. And it has, as I mentioned, very high specificity for having coronary disease. And it has pretty good yield for picking up high risk anatomy, a good yield for picking up left main disease or proximate LAD disease, the disease that we're most concerned about for causing cardiovascular mortality. But the downsides of the stress echo are that it can be limited by baseline wall motion abnormalities that the patient might already have. It has relatively low sensitivity for mild ischemia. And as a result, most of the tests you'll do in your lab for stress echocardiograms will be negative. The vast majority of the tests are negative, so you always wonder if you're missing small amounts of ischemia.

The next test we'll talk about is SPECT imaging, the so-called nuclear stress test, where we do a nuclear stress test with a single photon emission computed tomography, a SPECT study. What this does is under periods of stress you inject a radiotracer and you see how that radiotracer gets into the blood pool and distributes within the myocardium. If it distributes unevenly with rest and stress, you have a suggestion of lack of blood flow and ischemia. If it distributes equally, it suggests it's a normal study. You can do these SPECT studies with both exercise or pharmacologic induced stress. Then you do the imaging and you look for, once again, differences in perfusion. It actually directly measures perfusion of blood within the myocardium. This is an earlier assessment of ischemia and ischemic cascade than a wall motion abnormality on a stress echo, and as a result it has higher sensitivity. Pros of this test are once again it can be done with a treadmill, if the patient can exercise, giving that functional capacity assessment, too. It has a high sensitivity. And it's a little bit better for ischemia of localization compared to the stress echo. But the downsides here, there's a lot of radiation involved, about 7 to 10 millisieverts of radiation. It's quite expensive. It can be limited by obesity or gastrointestinal uptake of the tracer, which confuses the images. And in certain circumstances, it can miss what we call balanced ischemia, a three-vessel disease causing diffuse ischemia, because this test only looks for regional differences in blood flow. It doesn't quantify blood flow itself. As a result it can miss, in certain circumstances, balanced ischemia. In certain circumstances, because of its limited specificity, you can get some false positives.

Really the gold standard functional test these days is the PET Study, a PET stress test. Now this isn't available everywhere, but where it's available, it can be a very useful test. It's usually done, of course, with pharmacologic means to induce the test, usually a vasodilator, like regadenoson, to vasodilate the coronary arteries, then look for regional downstream differences in hyperemia with that vasodilation. The advantage of the PET study is that it can actually quantify myocardial blood flow. Not just regional

differences, but actually myocardial blood flow. It's a superior test to look for three vessel disease, or what would be called balanced ischemia. Another advantage is that it can be combined with viability testing in your patients with existing cardiovascular disease to look to see if there's viable myocardium that would benefit from revascularization. The advantages of this test is that it won't miss balanced ischemia, it's much more sensitive and specific and accurate. It's much more consistent imaging. And the disadvantages are, of course, it still involves some radiation. It's very costly. It may not be available in all hospitals because of the limited availability of the tracer that commonly has to be produced at an off-site cyclotron. But the PET stress study remains the gold standard of assessment of myocardial blood flow.

These are the tests that are available for evaluating the symptomatic patient. Next, we'll move into discussion of how best to choose between all of these tests.

In this next session, we'll talk about how clinical trials have helped inform us when we should be choosing an anatomic approach to evaluate a patient with symptoms versus a functional approach to evaluate a patient with symptoms. Let's look at these clinical trials.

The first clinical trial I want to talk about is called the PROMISE trial. The PROMISE trial was a study of patients with chest pain in the acute setting, randomized to an anatomical assessment or a functional assessment for evaluating coronary disease. And this was done at the time where functional tests, like the stress test, were the standard of care for patients with potentially ischemic symptoms. Patients were randomized half to an anatomic approach with a CT angiogram, and half to a functional testing strategy. And the key thing that we learned from the PROMISE study is that there was no difference, over the course of about a few years after randomization, in cardiovascular events. At the time, this was interpreted as the anatomical approach is just as good as the functional approach for evaluating symptoms in the acute setting. This was a change, because at the time, the stress test was the standard approach.

The next trial I want to talk about is the SCOT-HEART study. The SCOT-HEART study looked at once again a standard of care evaluation of patients with chest pain versus a CT angiogram guided approach. What I'm going to show here is the five-year follow-up data after SCOT-HEART, because it became important to follow these patients over a long time to see if there was a long-term benefit of one approach versus the other. And you can see the description of the trial here. And what this study showed was something very important, as we think about patients in our cardiometabolic clinic. It showed that randomization to a CT angiogram versus standard of care actually led to a decreased risk of non-fatal or fatal myocardial infarction over up to five-year follow-up. This is important because it seems to suggest that over the long term, patients benefit from an initial anatomic approach to the evaluation of their symptoms versus a standard of care approach. This was thought to be because using anatomic approach like a CT angiogram, not only identifies obstructive disease, obstructive plaque, but also non-obstructive plaque that might guide more aggressive preventative pharmacotherapy. It leads to that long-term benefit that we associate with things like statins.

And one of the concerns in the past about our strategy, for example, using a CT angiogram, was that maybe more patients would be detected with obstructive coronary disease and require going to the cath lab than if you use the standard of care approach. In the SCOT-HEART study, over a five-year follow-up, no more patients were referred to the cath lab and subsequent revascularization using a CT angiogram versus a standard of care approach. So, the conclusion of SCOT-HEART was: maybe an anatomic approach using a coronary CT angiogram can identify both patients with obstructive disease and non-obstructive

disease who need preventative pharmacotherapy without an increased risk of patients unnecessarily, for example, getting stents or bypass surgery.

After this, the emerging picture that was being adopted, for example, in some places in the United Kingdom, was a more upfront use of anatomic imaging in symptomatic patients. For example, taking a patient who has chest pain, of course patients with acute coronary syndromes need to go straight to the cath lab to address that acute picture. And other patients who had stable chest pain, starting with the CT angiogram, detecting obstructive plaque as needed. But also detecting non-obstructive plaque that might guide more aggressive use of preventative pharmacotherapy with that leading to the long-term outcome benefits in, for example, as seen in the SCOT-HEART study.

The last study I want to talk about here is the ISCHEMIA trial. The ISCHEMIA trial was also important for understanding how best to use non-invasive tests for patients with chest pain. In this case, patients already have at least moderate ischemia, for example on a stress test. What the ISCHEMIA trial did is that it took patients that were stable but had moderate-to-severe ischemia, and all of them got a blinded CT angiogram to exclude patients who had, for example, left main disease. If patients didn't have left main disease, the patients got randomized to an invasive strategy of early vascularization in the cath lab or with bypass surgery, or a conservative strategy with medical therapy alone. The reason why this is important for understanding the use of non-invasive imaging is that the ISCHEMIA trial showed that conservative management was just as good as an early invasive strategy for patients with stable symptoms with moderate-to-severe ischemia.

That's what's shown here. You can see there was not a big difference between patients conservatively managed or in patients invasively managed at first who had stable symptoms. The hazard ratio was not significant here.

But an important aspect of the study was that everyone had a CT angiogram to exclude those highest risk patients with left main disease. And you examine the data from PROMISE very closely, you see that as a risk prediction tool, the degree of baseline ischemia was not that good at predicting risk. It wasn't that big of a difference in risk between patients with, say, mild ischemia or severe ischemia. But there was a big difference in risk between patients who had, for example, one vessel, two vessel, or three vessel disease detected on a CT angiogram. In fact, there was a lot of patients in PROMISE who turned out not to have obstructive disease at all, despite the fact that they had some ischemia.

What this has done is that it has led to the model that maybe patients who come to the outpatient setting with stable symptoms, many of them can be managed or evaluated first with a anatomic approach like a CT angiogram to see the burden of disease. Identify patients who don't have obstructive disease and treat them medically. And in patients who have obstructive disease, look for left main disease. And if they don't have left main disease, once again consider a more thorough medical management of their symptoms.

What I've shown you here is how clinical trials are starting to inform the way we think about non-invasive imaging of the symptomatic patient, in deciding when we might use an anatomic approach and when we might use a functional approach. Next, I want to talk about how guidelines have put together all this data to give you some take-home points about how to consider these test in your practice.

Next, I want to talk about the guidelines of how to select non-invasive imaging tests in the symptomatic patient. First, what I want to do is talk about the European Society of Cardiology guidelines in the diagnosis and management of chronic coronary syndromes.

Here is a stepwise algorithm for taking a patient with, let's say, angina or suspected coronary disease and evaluating them. The evaluation always starts as an assessment of their symptom type, making sure they don't have acute unstable symptoms. Identifying those patients with stable symptoms who don't have severe EKG abnormalities, for example, and trying to select the non-invasive test choice.

And you can see here in step five of these guidelines, it's starting to direct the initial choice of a patient who doesn't have non-obstructive coronary disease towards an anatomic approach, anatomic assessment of their burden of disease. Lower risk patients being preferred for a CT angiogram and higher risk patients, generally speaking, being referred directly to the cath lab for assessment of invasive coronary angiography. This is one of the models that's starting to form, and I'll show you later with ACC-AHA chest pain guidelines, is that the CT angiogram is taking on a greater role, especially in your outpatient evaluation of patients with symptoms with no known coronary disease.

Here are some of the recommendations from the 2019 ESC guidelines. You can see at the top that non-invasive functional imaging, like stress testing, or coronary CT angiography, are both considered class I reasonable tests to do in a patient with whom you need to further assess their symptoms. Also it shows here that, as a class IIa recommendation, that coronary CTA should be considered as an alternative to invasive angiography if a patient has equivocal results from another test, for example, a stress test. It's giving more options for non-invasive anatomic assessment of a patient's coronary arteries.

I want to go through this diagram really quick. It's a little complicated, but I think it breaks down fairly simply. You start in the upper left corner, and you consider the patient's characteristics, their chest pain characteristics and their history of, let's say, coronary disease. If they don't have history of coronary disease, and they have some suspicious symptoms, it shows here you can start with a coronary CT angiogram that can either drive drug therapy if they have non-obstructive disease. For destructive disease, the consideration for functional assessment to see if that coronary disease is associated with ischemia. And only after that assessment, you really move down towards invasive coronary angiography and then a further decision about who would benefit from medical therapy versus who would benefit from revascularization. You can see here how we use non-invasive imaging of a patient with symptoms to figure out who really needs to go onto invasive coronary angiography and who's more likely to benefit from revascularization. This is all a forerunner of the new ACC-AHA chest pain guidelines, which I want to walk through in detail now. These are the most up to date American guidelines on evaluation of a patient with chest pain.

These guidelines lead off with this pyramid here to remind us that there's a lot of chest pain out there and only a small fraction of it is truly an acute coronary syndrome that needs to be managed aggressively, for example in the cath lab. There's a lot of chest pain that's actually in low-risk patients or in intermediate and high-risk patients that can benefit from non-invasive assessment before, for example, proceeding to the cath lab. And of course reminding us that in asymptomatic patients, there's no real role for coronary CT angiography or stress testing, as I mentioned in module one, in evaluation of these patients.

Let's walk through some of the aspects of the chest pain guidelines. What are the testing options? Well, I think we've talked about this here. In unstable chest pain with no-known coronary disease, we can

consider an anatomic approach to the CTA, or a functional approach with various stress testing modalities. In patients with known coronary disease, we can consider once again the stress testing modalities, including the more advanced stress testing modalities we've talked about, or less likely, but still an option to consider, for example, a coronary CT angiogram. What we see in this first slide is that in patients with no-known coronary disease, we're going to think more about a coronary CT angiography or initial stress testing. In patients with known coronary disease, we're going to think more about how stress testing plays a role in identifying who has substantial ischemia.

Let's start off with the algorithm in the guidelines for patients with stable chest pain and no known coronary disease. Here's the algorithm. It talks about low-risk patients, intermediate, and high-risk patients, and we're going to break this down step by step for you watching this video.

Once again this is the clinical decision pathway for patients with stable chest pain and no known CAD. Let's start off with low-risk patient. What do you do for the evaluation of a patient with stable chest pain and no known CAD who is low risk? After a clinical assessment, you decided their symptoms are unlikely to be cardiac in origin, or they're just a low-risk patient in general. It gives you the option in the guidelines of doing no testing in such a patient. Or it also gives options for doing, for example, a calcium score or an exercise treadmill test to further delineate the pretest probability of these patients. As you can see here, if a patient's low risk, there's a class I indication for no testing. Try and avoid doing a lot of testing in your low-risk patients. And if you do, a simple test like a calcium score or an exercise EKG can help you redefine the pretest probability of that patient. If those tests are abnormal, move you into a consideration of the patient as more intermediate or a high-risk patient with chest pain. And that's what's shown here.

If you determine that your patient with stable chest pain and no known coronary disease has an intermediate or high risk, here are your options. Class 1 indication for both an anatomic approach with a CT angiogram, and a class 1 indication for considering a stress test, for example a nuclear stress test. How do you decide between them? Well, the guidelines give you some guidance of when you would favor the use of an anatomic approach with the CT angiogram, and when would you favor the use of a stress test, a functional approach. Let's look at the left here. When would you favor the use of an anatomic approach, for example, if it's a coronary CTI, particularly if you want to rule out obstructive coronary disease as well as detect non-obstructive disease that might guide your medical management? A CTA is the best test. A stress test can't really tell if you have non-obstructive disease. The CT angiogram can addition tell if you have non-obstructive disease that might guide your medical management as we saw in the SCOT-HEART study. Nowadays CT angiograms have very high image quality, and generally speaking we get good diagnostic images. And because they're particularly good for determining if there's atherosclerotic disease at all, they tend to be preferred in patients that are on the younger side. In the guidelines, it says patients younger than the age of 65 is where you prefer, for example, a CT scan versus a stress test. A CT scan can be particularly useful if a prior stress test was equivocal or abnormal and yet also is helpful if there's any structural problems that you suspect with a patient. For example, an anomalous coronary artery or something like that, where an anatomic approach is preferred. Once again, the CT angiogram is the anatomic approach.

Stress testing here, or functional imaging, is shown on the right. When would we prefer to use a stress test first? Well, if our goal is to guide ischemia-based management, in other words, to define the degree of ischemia and localize ischemia in a patient who we highly suspect has ischemia, a stress test can be useful. Because it's more useful in patients with a very likelihood of having obstructive disease, it's

preferred in the guidelines for patients above the age of 65 in general, or if a CT angiogram is not an option. The further value of a stress test is that it can detect microvascular dysfunction or ischemia in the absence of destructive coronary disease in select patients, particularly women who are more likely to have that syndrome. As you can see, class 1 indications for an anatomic approach or a functional approach, with an anatomical approach being preferred, particularly in patients who are younger who don't have known obstructive disease. And patients on the right who are older, who have a higher pretest probability of having disease, a stress test or a functional approach is more favored.

One question comes up, when is it worth repeating one of these studies if you've done one already and it was negative? It says, generally speaking, don't repeat a CT angiogram if you've had a normal one within two years. Don't repeat a stress test if you had a normal one in the last one year. That's a reasonable thing to approach, especially in that patient with recurrent symptoms.

Let's walk down the rest of this algorithm really quick. Here it shows if you have an intermediate or high-risk patient and you do a CT angiogram, what do you do based on the results. And only if the patient has severe obstructive disease, and a suggestion that it might be causing ischemia, would we be heading to the cath lab, for example. Which is what's shown here. If you move to the right and do functional testing, of course looking for ischemia, generally speaking only the patient who has moderate to severe ischemia and severe persistent symptoms nowadays, are we heading to the cath lab once again. We're trying to medically manage most of the rest of the lower risk chest pain. I'll let you review the rest of this slide perhaps in your notes or in the guidelines themselves, if you want to dive deeper on how to use, or what to do after, a CT scan or a stress test in a symptomatic patient.

I do want to get to the guidelines for stable chest pain in known CAD. Here is where a patient has established coronary disease of some degree and what do we do for those patients to evaluate their symptoms. Well, of course, medical management is always a reasonable thing to do in such patients. But another reasonable thing to do if you have a patient with obstructive CAD and recurrent symptoms, that's where it's reasonable to be more liberal with the use of stress testing, to try to quantify the burden of ischemia in these patients that might guide your medical management. As you can see here in the green on the right, a class 1 indication in this case, where patients have obstructive CAD and recurrent symptoms and not known to have left main disease, you consider a stress test to look at the burden of ischemia. Once again, there's some other complexities in the guidelines. I'll let you review in the notes. Once again, in patients with stable chest pain and known CAD, that's where we're going to move more towards the functional assessment for the degree of ischemia.

I wanted to talk about when you're evaluating patients with symptoms, and of course you find out maybe that they don't have obstructive coronary disease, how else do you evaluate them? What else can we do to try to evaluate their residual symptoms? Well, sometimes patients will come with chest symptoms that are not ischemic in nature, but really are more palpitations that are suggestive of a rhythm abnormality.

That's where ambulatory EKG monitoring can be extremely helpful. Ambulatory EKG monitoring allows for the assessment of rhythm disorders within everyday life. You send the patient home with the device and it records their heart rhythm. It can be very helpful for looking for intermittent arrhythmias or other problems like that. Coupled with a symptom diary, where the patient writes down their symptoms, you can then link when they have symptoms with what you see on an EKG monitor. And it can be very useful for quantifying burden of PACs or PVCs, premature atrial or premature ventricular beats, or for looking

for things like burden of atrial fibrillation. It's very helpful in patients with symptomatic complaints that are more like palpitations or suggestive of rhythm disorders. There's no role for these in primary prevention, once again. We don't want to use them to look for a problem that's not suggested by symptoms. But it can be very easy to use and easy to conceal home monitoring for a patient with palpitation-like symptoms. It's very common nowadays with patch monitors that can be placed right on the patient's skin. Once again, you should be considering an ambulatory EKG monitor in some of your patients with symptomatic complaints who don't have clear coronary disease.

Where does the echocardiogram work in here? The patient, once again, with some symptoms, particularly shortness of breath symptoms, that doesn't have coronary disease. Here's where an echocardiogram can be useful as well. As we mentioned, the echo is a non-invasive ultrasound based test. It's relatively low cost. It can assess for the function of the heart or for valvular heart disease. And in symptomatic patients who have shortness of breath, but no coronary disease, it can be helpful for things like valvular heart disease, cardiomyopathies, etc. And that's where we use echocardiography in the assessment of symptoms, too, particularly when once again you suspect obstructive coronary disease as much as you suspect another cause of potential shortness of breath, for example. And the echocardiogram can be done without radiation, at low cost. But of course it does have some of the same limitations as other tests. It can be limited by the body habitus of the patient. And it can be at risk for overuse, particularly if you're using it in patients without any symptoms.

Let me summarize what we've talked about here about the workup using non-invasive imaging of the symptomatic patient. We've shown you that non-invasive imaging diagnostic procedures are a core component of an evaluation of a patient with, for example, stable chest pain, and how a coronary CT angiogram and the anatomic test can visualize and help to diagnose the extent of severity of non-obstructive and obstructive CAD, as well as the composition of that atherosclerotic plaque. It can be very useful for risk assessment for patients with no known CAD to guide particularly medical therapy.

We also talked about how the exercise ECG can be useful to assess exercise capacity and can define whether the patient has ischemia or not, particularly in the lower risk patients. We also talked about how nuclear stress testing can actually assess for perfusion abnormalities and measure left ventricular function and particularly would be useful for patients who have a high pretest probability of having ischemia based on their symptoms. We've shown how test selection between an anatomic approach and the CT angiogram, or functional approach, for example with stress testing, should be based on the characteristics of the patient, the contraindications they maybe have, local variability or expertise, and particularly an assessment of the pretest probability of the disease. And now we have guidelines from both the European Society of Cardiology, as well as our new chest pain guidelines that can walk you through the selection of tests for patients with symptoms. Thanks for joining us for this module.

Module 3 - Non-invasive Imaging Discussion Cases: Risk Assessment and Anatomic Versus Functional Approach

Welcome back for module three of our assessment on non-invasive imaging and risk assessment. In this section I'm going to be joined by our fellow who runs the cardiometabolic clinic at Johns Hopkins, Dr. Kunal Jha, for a discussion of some cases where we're going to apply what we've learned about non-

invasive imaging to test selection throughout patients in primary prevention and secondary prevention that you might see in your cardiometabolic clinics. Let's get right into it.

Case Vignette Number One

Dr. Jha: Sure, Dr. Blaha. This is a 49-year-old gentleman with a family history of premature CAD and borderline hyperlipidemia. His LDL was 135 milligram per deciliter. Presented to our clinic for further evaluation. He was on any preventive pharmacotherapy like statin or aspirin. Is there any non-invasive cardiovascular test that we can offer to such patients for additional risk stratification or for consideration of preventive therapies?

Dr. Blaha: I think that's a good case. This is something we see all the time, a middle-aged man with a family history who's worried about cardiovascular risk and whose LDL isn't optimal. It's not that high, but it's not optimal. And they come and say, how high risk am I? And you can start with something like the pooled cohort equations, but commonly you still can't give that definitive answer of how high risk the patient is or how much plaque they have in their arteries.

We go in the guidelines, and I talked about this in module one, if we go down this algorithm, this patient would certainly come out somewhere in that borderline risk zone. We want to look at the risk enhancers, like a family history on the left, and it says, gosh, you have options when the patient haws just borderline risk. And if the risk decision is uncertain, you consider the calcium score. I think in the vignette that you just told me, I would definitely consider the calcium score as the preferred test here. Because if it's right in the guidelines, this patient's risk is uncertain, I think you'd agree. The patient's risk is unclear. We don't know if the person has no plaque in their arteries or a lot of plaque. And the patient's sort of asking us, should I take a statin or not, or should I take an aspirin or not, for example. And you can see here, if you do a calcium score, it kind of gives you some information about how to select the next management for the patient.

What I would say in this case, for this middle-aged man with, premature family history, borderline hyperlipidemia, I would say to do a calcium score. I think that's what we generally would do in the cardiometabolic clinic for a patient like this. We do a lot of non-invasive imaging for primary prevention patients. We don't do stress tests and things. We do a calcium score.

Dr. Jha: I agree with you.

Case Vignette Number Two

Dr. Blaha: Let's move on to case number two. We're picking these case vignettes from our clinic, that will all make sense to you all who see patients in your practice.

Let's talk about a 54-year-old woman with a family history of premature coronary disease again. A very common reason someone comes to us. In this case, the LDL's pretty good. It's 101. But there is a history of having a high lipoprotein A, which we know is a causal risk factor for coronary disease, of 175 nanomoles per liter, so that's mild to moderately elevated. And she's not currently on any preventative pharmacotherapy. She actually says I feel great, but I have this family history and I have this high Lp(a), what do I do? Once again, is there a non-invasive imaging test that you would prefer in a patient like this, or would you just treat the patient as is.

Dr. Jha: Well, this is another great case of primary prevention that we see in our clinic. The patient does have a family history, elevated LDL. But they do come with some risk-enhancing factors, like lipoprotein A is elevated or they have a CKD or some family history of CAD as well. In such cases, there are a few studies that have been done to evaluate the impact of the coronary calcium score.

This study determining the association between the risk-enhancing factors and incident atherosclerotic cardiovascular disease by coronary artery calcium burden, especially among the intermediate-risk individual. On the first figure, it shows that the participant with intermediate risk, even those with elevated lipoprotein A, 50 percent of them have a calcium score of zero, coronary calcium score was zero. And similarly, if we look at another image here, in this image the faint blue line shows the threshold that which the statins would be considered. And the finding of this study showed that among individuals with intermediate risk, with risk-enhancing factors like elevated lipoprotein in our patient, in such patients' atherosclerotic cardiovascular event rates were generally lower than the recommended threshold to start the statins, especially among those with a coronary artery calcium score of zero.

What it shows is that a participant with a calcium score which was greater than one, with risk-enhancing factor, didn't really benefit with a statin therapy. Definitely in our patient, coronary calcium will be a beneficial tool for such participants and patients. What are your thoughts are this, Dr. Blaha?

Dr. Blaha: I think you bring up a really good point with this study. If you look at the patients with calcium scores greater than 100 here, and a high Lp(a), they're high risk. That's a high event rate more like those of a high-risk group. Those two factors can work together to help you decide. Now I don't think a Lp(a) alone sometimes is enough. But combined with non-invasive imaging, you can find the patients that are higher risk. And I like what you said.

It actually fits very closely with the 2020 Endocrine Society guidelines, that says in patients with additional risk-enhancing factors, including an elevated lipoprotein A, risk assessment should consider starting with a 10-year risk assessment. As we talked about, this person was intermediate risk. But then you consider the calcium score and it says it should be considered for risk assessment and treatment when the decisions remain uncertain. I would argue this patient in our vignette, the decision sort of wasn't certain. She came in with an average cholesterol, but high Lp(a) and a family history. And I think what you argued for here, Kunal, was a calcium score.

Dr. Jha: Exactly, yes.

Dr. Blaha: Yeah, so I think the calcium score is reasonable in this case, too, so trying to pick cases from our clinic where we were uncertain about decision making, did a calcium score, and that helped us decide how to treat the patient.

Case Vignette Number Three

Another middle-aged gentleman who is presenting to the clinic with moderate exertional chest pain. The patient also has hyperlipidemia. And the patient reported that he has a family history of late-onset cardiovascular heart disease in family. Again, this patient is also not on any aspirin or statin. The patient is been coming here for primary prevention evaluation. Again, is there anything that we can consider in such patients, like doing an anatomical assessment over the functional assessment for risk stratification in such patients?

Dr. Blaha: Yeah, I think you bought up the most important patient right off the bat, which is the person has chest pain. This is a symptomatic patient. In our series here, this is a module two type of patient here. This patient has symptoms, so we really need to evaluate what's the cause of those symptoms. And furthermore, as you mentioned, the person has highish cholesterol. It's untreated. We don't really know what the patient's burden of disease is at all. In situations where we know, a patient has chest pain but we don't know if they have any coronary disease, that's where the guidelines say there's a class one recommendation to consider, and kind of lean towards an anatomic test like a CT angiogram to both work up a chest pain and figure out the burden of disease.

And that reminds us of what we presented earlier with the SCOT-HEART study. We showed that patients with stable coronary disease, who didn't have known coronary disease, who were randomized for a CT angiogram, got a five-year benefit from that randomization, presumably because we also identified patients with non-obstructive disease and treated them with aggressive medical therapy. These patients start out with chest pain, were further evaluated based on their atherosclerosis burden, and got a benefit. I think this patient sort of fits a little bit to the SCOT-HEART paradigm, where if we did a CT angiogram, we would both, first of all, make sure they didn't have left main disease or something like that, but they would need to go to the cath lab. We can also assess their burden of non-obstructive disease and treat them accordingly. They could have either clean coronary arteries or advanced non-obstructive disease, where, for example, that might guide the decisions about the aspirin and statins and things like that.

Dr. Jha: Exactly.

Dr. Blaha: I think in this patient, I'm going to make an argument, and you can tell me if this fits with the ACC-AHA chest pain guidelines because you're an expert in those guidelines. But a patient who's middle age, pretest probability is mild to moderate, but we don't know anything about the adverse - - burden. I would argue for a CT angiogram. What do you think about that in the guidelines?

Dr. Jha: Yeah, I totally agree with you. The guideline clearly reflects that. The patient with no known CAD and with the risk factors, generally there's a class 1 indication for considering coronary CT angiography in such patients. And our patient clearly fits in that paradigm.

Dr. Blaha: Yeah, I agree. This is great. I think these cases are very relevant to everyone practice. Let's go on to case number four. We'll try to keep these cases short and sweet and you can try to see if they're familiar with patients that you see in your practice. Let's do another one.

Case Vignette Number Four

A 69-year-old woman with consistent exertional chest pain and shortness of breath walking up the stairs. But importantly this patient has a history of coronary disease. She had two stents, two years ago, another one last year, and she has a known reduced ejection fraction of 40%. A little bit different than the other cases we presented, a patient with known coronary disease and symptoms and a low ejection fraction. What would you do in this case?

Dr. Jha: It's a great case. This is a symptomatic patient with known CAD who is presenting here for further evaluation. And not only that, the patient's EF is on the lower side as well. Definitely here in such a scenario, I would rather look for the ischemic burden that will guide us in the further treatment and management.

We can look at the recent ACC-AHA 2021 guidelines, which give us some guidelines regarding when to consider coronary CT angiography versus stress testing. For example, coronary CT angiography should be considered to rule out obstructive CAD or to detect non-obstructive CAD. In our case, we already know that patient had a CAD, so it will not be a very beneficial tool for us. And, again, this should be ideally considered in a patient who is less than 65 years of age, because, in those patients, the plaque burden is lower in those groups of patients. Likewise, in our case, here the ischemic guided management will be very beneficial for the patient because we know that he has obstructive CAD and he is also 65. I'd rather argue here that stress testing would be a beneficial tool for this group of patients.

The ACC-AHA 2021 guidelines further give us some guidance regarding different forms of a stress test. Like for example, stress CMR, stress PET, or a SPECT test, have a class one indication for the patient who has a known obstructive CAD, like our patient. And based on the result, we'll find they might have no ischemia, a mild ischemia, moderate to severe ischemia burden. And we should individualize the treatment based on that ischemic burden as well. Based on the ACC-AHA guidelines, I believe that for this patient who is symptomatic and had a history of obstructive CAD, I'd rather favor stress testing over CCTA in such patients.

Dr. Blaha: Yeah, I agree with you. I think you've brought up an important distinction here. Why did we choose a CT angiogram on the last patient, where we didn't even know if the patient had any plaque at all? The patient was untreated. This patient has known CD, and presumably is on a lot of medical therapy already. We're just asking the question, as you said here at the top, I like that, it's ischemia-guided management. Does the patient have significant enough ischemia that we need to, for example, up titrate our medical therapy or send the patient to the cath laboratory? I agree with you. I think a stress test in this setting, a functional test, is the right test. I think we see all the time anatomic tests when the functional test should be ordered, or functional tests when anatomical tests should be ordered. These two cases help to bring up some of the distinctions about when we decide between these two approaches.

Case Vignette Number Five

Dr. Jha: This is a 47-year-old lady with a family of hypercholesterolemia and chronic mild chest discomfort, mostly at rest and sometimes with light exertion. Looking at her medication history, she's on high intensity statin and ezetimibe and her LDL is 92. Again, this lady is not on aspirin yet. We see such patients in our cardiometabolic clinic, a young patient with a family of hypercholesterolemia, LDL sub-optimally controlled as such. There should be some tests that we can consider for such patients, not only for allocating this preventive medical therapy but also for the risk of stratification. How would you approach such patients when they come to the clinic, Dr. Blaha?

Dr. Blaha: This is a good one. This is a challenging one. Because I think some people would make the case that you don't need test here. That you could just say we'll just treat the LDL as aggressively as possible, put the patient on an aspirin. But the reality is we don't know for sure what the plaque burden of this patient is right now. We can't tell her exactly where she is on the natural history of the disease and some of the familial hypercholesterolemia. We do know, actually, that a fair amount of patients with high cholesterol can manage to live into their middle adult years without much plaque burden. This shows on the left that 45 percent of patients in this series, in patients with established genetic FH, had a calcium score of zero. Of course, many patients had a high calcium score on the right. We followed patients up for events. Even within this FH group, you can risk stratify them: Patients who are less likely to have events in the next few years or more likely to have events in a few years. We're in the habit of taking

patients with FH who are incompletely treated, as you mentioned. Because her LDL is not below 70. She was not on aspirin. I would argue that we don't know for sure how high risk she is. I would argue for some further risk assessment.

Now the question is would we do a calcium score or straight to CT angiogram. Now in our practice, we're more likely to do a CT angiogram in this setting, because we have a great availability of a CT angiogram. She has symptoms, so we could justify the test. But actually, in the guidelines, there is recommendations to consider a calcium score in such a setting, too. As we talked about, in patients with kind of a low-risk chest pain story, she's young, she had chest pains that were sort of atypical, you can also do a calcium score to change the pretest probability to the risk of the patient. If we did a calcium score and it was very high, in the hundreds range, we might then feel the need to further evaluate her symptoms with for example a CT angiogram.

I think what we're trying to say here is the anatomic approach to actually quantify plaque burden is helpful here, not only to set our LDL goals but to decide if aspirin is indicated. But it makes sense for her chest pain in this patient with FH. We can discuss whether it would be a calcium score or a CT angiogram. I think some sort of a test of plaque burden here would be particularly helpful. And I guess, Kunal, in our clinic, let's just say we did a calcium score or a CT angiogram and it showed pretty substantial plaque, what would we usually do in this case?

Dr. Jha: Well, as we have discussed in module one, a patient with a calcium score of more then 100, those groups of patients are mainly benefited by aspirin. We can consider aspirin for those patients. Even if the patient has diabetes, GLP-1 would be considered based on their calcium score as well. This will not only help in risk stratification but also in picking the right adequate preventative medical therapy for those patients.

Dr. Blaha: Yeah, I agree with you. And I'll add to that. I think it's reasonable in this day and age if you use the calcium score or a CT angiogram in this picture, to use that as leverage for your patient to get access to a PCSK9 inhibitor, too. This patient with FH, she's on statin and ezetimibe already, but not yet at her LDL goal. You might say, well, she's fine, based on her risk factor status. But certainly, if I were to tell you that she's got the diffuse disease, we might say, well, earlier administration of a PCSK9 inhibitor makes sense.

Once again, where non-invasive imaging can be helpful. In our practice, this is one where the answer's a little less clear, but in our cardiometabolic clinic, we're probably going to be thinking about the calcium score or CT angiography to further work up this patient with mild symptoms and a high-risk condition like FH.

Case Vignette Number Six

Let's close things out with the last case. This is a little bit different. Thinking a little less about atherosclerosis, but something that we see all the time in our practice. In this case, it's a 58-year-old woman with palpitations. They occur weekly. They last 30 to 60 minutes at a time. She says she feels her heart rapid in her chest like it's racing. When you listen to her heart, you hear a soft murmur. It's unclear if that's a new murmur or not. You hear at the left upper sternal border where you could start thinking about valvular heart disease. Here we have a woman, she's not complaining of chest pain, per se, but palpitations, heart racing, and a murmur. How would we evaluate this patient?

Dr. Jha: Well, this is a great case. Not only a cardiologists we see such patients in our clinic, but a lot of primary care physicians see such cases in their clinic, also. A middle-aged lady with intermittent palpitations and with a possible soft murmur, could this be systolic versus diastolic, we're not sure about that. In this scenario, rather than anatomic or a functional assessment, there are a few other tools that we can consider for such patients. For example, we can consider an ambulatory EKG monitor, or we can consider an echo ambulatory. For example, there are different ambulatory EKG monitors I have labeled. On the left, it shows a continuous ambulatory EKG monitor that is placed as a patch on the chest. And then it can monitor EKG for at least seven to fourteen days. And it also has a trigger button, like whenever the patient is having the symptoms, if they can trigger that button, we can clearly look at their underlying rhythm once the patient is experiencing those symptoms. And that is very beneficial for the physicians as well. And on the right, we can look at some of the - - labels, two to six EKGs that have been labeled in the market. These are not yet FDA-approved, but they are very beneficial for some of the patients. They can keep it at their home. But, again, these are like a non-continuous EKG monitor. They can just monitor like two or six leads for like probably ten or fifteen seconds and such.

In our patient, we can consider either a patch monitor or a non-continuous EKG monitor. On top of that, also on examination, we found that she had a murmur as well. In such a scenario, maybe we can make up a point that maybe we should do an echocardiogram to rule out any valvular heart disease, look at the LVEF, and then the systolic function of the heart as well. I would argue that we should consider an ambulatory EKG monitor, plus/minor an echocardiogram in such patients. What are your thoughts, Dr. Blaha?

Dr. Blaha: Yeah, I agree completely here. There's nothing here that really points directly to ischemic heart disease, like anginal equipment. She wants an evaluation of her palpitations and we want to know about the murmur. I think, yeah, it is important to remember that in symptomatic patients, it isn't all about stress testing. It isn't all about CT angiography atherosclerosis. Sometimes the patient needs an assessment of heart rhythm. Of course, this could show everything from an SVT to atrial fibrillation, hopefully not, or maybe some early stenosis. Who knows that? But an EKG monitor and an echocardiogram in this patient is probably the right thing to do. I agree with you completely.

Thank you for joining me for these case vignettes. I think it's extremely helpful to walk through these as we try to think about non-invasive imaging for risk assessment. And we've tried to cover the broad sweep in your cardiometabolic clinic, from the asymptomatic primary prevention patient, where you're going to consider more about atherosclerosis risk assessment, for example a calcium score. To the symptomatic patient where there's a lot of questions, but where we found a lot more guidance recently, thinking about do I want an anatomic approach or do I want a functional approach, with kind of a layered approach before you get to the cath lab. And of course not forgetting about appropriate use of things like EKG, EKG monitors, and echocardiograms in appropriate patients too, because you're going to see this throughout your cardiometabolic clinic.

Thanks, Kunal, for joining me. Hopefully everyone enjoyed this three-part series on non-invasive imaging and risk assessment. Thank you very much.

DR. JHA: Thank you so much.