[MUSIC PLAYING]

MARCIO SOMMER BITTENCOURT: Hi, everyone. My name is Marcio Sommer Bittencourt. I'm a cardiologist. I'm an associate professor of cardiology and radiology at the University of Pittsburgh at UPMC. And my talk today is about the diagnostic testing in coronary artery disease.

These are my disclosures. None of them is really related to diagnostic testing on CAD, except that GE does technologies that are used in diagnostic medicine. But before we go directly to testing in coronary artery disease, I would like to step back and go towards the pathophysiology of the coronary artery disease and atherosclerosis just to situate where we are in the process and what we're looking for when we're doing diagnostic testing.

And this cartoon on the slide is the classic continuum of atherosclerosis pathophysiology concept, where you go from a completely normal endothelium on the far left of the slide. And the process goes from completely normal to fatty streak in the lesion and an atherosclerotic plaque that grows from the vessel wall towards the inner lumen reducing the lumen until one time in the end of the figure where you see a complicated lesion that ruptures and forms a trombone and you have an acute coronary event. And that is the classic idea that the disease progresses and progresses into a certain moment when there's a plaque rupture, where kind of the story ends on an obstructive plaque leading to rupture.

And that is not really accurate. That's where we start because that's the classic idea. But that's not really how we understand the process nowadays. Nowadays we understand the process in more of a back and forth idea. You still go from a normal vessel, the fatty streak in an early atheroma, as you can see in the cartoon on the right.

But once you are in the atheroma, this plaque can develop in different ways. And it can develop in ways that get it to be more stable if you go towards the right on a stabilized plaque. Or it can develop as a vulnerable plaque going down to the bottom where a plaque gets a thin fibrous cap and can rupture and get to be thrombus and have an ACS. But the vulnerable plaque can also become stabilized and develop as a stabilized plaque. And parts of a stabilized plaque can further become vulnerable and go towards the process of an acute coronary event again.

So rather than a continuum, this is a back and forth process between stable and vulnerable plaques that eventually might become unstable and rupture. And this idea of the process going back and forth also goes to the idea that some of the vulnerable plaques that might rupture and get to be an event might be non obstructive plaque. So this idea that first you become obstructive to then have a ruptured plaque doesn't really represents the truth.

That can happen, but that can also happen with non-obstructive plaque. So the idea of predicting future events is not necessarily only through the pathway of detecting an obstructive lesion. It's a bit more complex.

This is another simple cartoon and probably not as accurate as the prior one. But I like this cartoon in explaining the pathophysiology because it delineates clearly different clinical presentation. So, again, the same idea from a normal vessel towards having some plaque. And then this plaque can either stay non-obstructive on top, get to be obstructive on a more chronic slow progression pattern. Or on the bottom, it can become unstable and rupture.

And although the process goes back and forth between them, it's not really in one group or the other. I like separating the idea on this figure because this correlates with the different clinical scenarios that we usually see in practice. And those clinical scenarios are where imaging might be applied one way or the other.

So on the top is the kind of patient that you usually get for risk stratification because they are completely asymptomatic. They have no symptoms. They are with or without plaque depending on how the patient comes in but definitely without obstruction leading to symptoms, acute or chronic.

The second group is the group that we usually call chronic coronary syndromes or stable engine. Or there are patients that have chest pain, but they are stable pattern, usually come on the outpatient clinic complaining of chest pain for the last weeks or even months. And the approach for this patient is the stable CAD, which is the most common form of presenting to the physician the second group. And the third and last group is when the patient has an acute event, what we usually call acute coronary syndrome. When a patient can present with an unstable angina, myocardial infartion or even sudden death. And the approach to each of these clinical scenarios is completely different.

So I will go on this talk from here onwards starting with the first group of patients, how do we usually approach them for diagnosis or prognosis. Then I'll go to the stable patients, and I won't talk much about the acute patients because they're completely separate. But I'll give some idea of why they're different and why not everything applies the same way to this group of patients.

And before we get to each group of patients, I think if the talk is about diagnostic testing, we first have to take a step back and think why do we do any testing in medicine and how does that apply then to coronary heart disease? And we usually do testing in medicine for three main reasons, first, because the patient has a symptom that we want to find out what is the cause. We're testing for a diagnosis. We want to know what the patient has.

Second, we test because we're looking to understand what is the risk and what are the future implications of our findings. We usually call it prognosis. This might be a definition of risk on the short term, like we have a patient admitted for a myocardial infarction. We want to know what's the risk during an admission or during the first 30 days. Or it might be a longer term prognostic evaluation like in asymptomatic patients where when we're discussing risk of myocardial infarction over the course of 20 years or 10 years or even a lifetime risk.

And the third which is related to the other two, but is a more practical question is what do I do with the patient? Given the diagnosis that I've found out in my test, given the prognosis that I have estimated, what is the best way to manage this patient? So use the test to guide your therapy. And this is actually the ultimate reason why we usually test because we want to treat the patients better with more adequate therapy.

And tests can be used to define the need and the extent of the interventions for non-pharmacologic interventions. They can be used to define pharmacologic interventions. And that can be either preventative risk factor management therapies for coronary heart disease or ischemia directed medications to reduce the symptoms and ischemia burdens and can also be used depending on the information you have to guide the need for an invasive angiography, the need for a percutaneous coronary intervention, and/or the need for a coronary artery bypass graft surgery.

So that's a key reason why we do any test. And that's what we have to keep in mind, anytime you're going to order a test, you have to think will this test change my understanding of diagnosis, prognosis, or management? If it's a no question for all of them, if you know from before what you need to do and what's the expectations, there's no need for testing. This is the real need for testing. And if we go to the current 2021 guidelines of a stable-- or investigation of chest pain, this is their main figure and how we approach these patients.

And as I did, they also separate the patients on the bottom of the pyramid as completely asymptomatic individuals. At the top, those with acute events or acute coronary syndromes. And in between you have a group of patients with chest pain that can be of low probability, intermediate probability, or high probability of coronary artery disease. And the approach of this group of patients is different depending on whether it's an acute chest pain evaluation on your left or a chronic stable chest pain evaluation on the right.

In general, the asymptomatic patients don't need any testing or very selective use of testing in some cases. Those at low risk are either evaluated without any testing or just clinical evaluation. Or you might consider a stress electrocardiography or in some selective cases at least by guidelines, you can use a coronary artery calcium score. The intermediate and high risk are usually investigated with anatomic or functional non-invasive testing and individuals both in the acute and chronic setting.

And once you're on the higher risk, or ACS for the acute setting, you might go directly to the invasive angiography. That's an unusual approach for individuals with chronic coronary syndromes even in the high risk scenario. It's less usual to go directly to invasive angiography, and that's how the guideline is presented.

So now let's move to the clinical scenario starting by the asymptomatic individuals. And with asymptomatic individuals the key part here is there are no symptoms. If there are no symptoms, you cannot improve their quality of life. And each and every intervention you're taking is basically something that will improve prognosis, improve the duration of life or reduce the risk of a future event. And that's an area-- most of the decision is how should I manage this patient on the pharmacologic and non-pharmacologic approach. And this is usually done, or the usual approach is based on the clinical risk factors.

So you look at the clinical risk factors. And usually you use those risk factors to calculate the risk with a numeric value using a risk score. The current risk score recommended in the US is what's called the ASCVD risk score, which is available online and in many documents. And what this score does-- they take the same risk factors that are in the Framingham risk score, diabetes, blood pressure, cholesterol, age, sex, smoking, and estimates your future risk of events and a window of 10 years and with this calculation, we then define the need for most preventative therapy.

In general, the approaches in the cartoon on the top right depends on age, on the presence of very high ADL, the presence of diabetes and then the calculation of risk, which you see in the middle of the figure where you can calculate the risk as being below 5%, which is understood as a low risk. And in general, those patients don't need pharmacologic management for risk factor modification. Then you have individuals with a very high risk above 20% where there's usually a need for aggressive cholesterol treatment.

And then you have in between, which is the most people between 5% and 20%, which are groups that might benefit from the evaluation of ASCVD risk enhancers that are in the table or as it puts in the guideline in the bottom, if you want to consider imaging test, which relates to this talk, then the test if needed-- if one test is needed to further stratify risk of asymptomatic individuals, this test is a coronary artery calcium score. And based on the number from 0, which means low risk to above 100 or above 400 or more, when it really clearly means increased risk, you should manage the patient differently according to each of those scenarios.

The low risk probably needs, again, no therapy. The high risk probably needs aggressive lipid lowering medication. Or as I said, since those individuals have no symptoms, there is no potential improvement of quality of life. And also I didn't mention, but there is in general no evidence that asymptomatic individuals benefit from revascularization procedures. So there is no need for ischemia evaluation for functional stress testing and for invasive angiography in asymptomatic individuals, irrespective of the risk because the risk reduction is mostly done by non-pharmacologic and pharmacologic interventions.

So the clinical risk score plus/minus the calcium score is used to define how aggressive you should be with diet, smoking, exercise, and aspirin and statin for sure. There is some unclear or undefined literature that suggests that maybe aspirin indications can be measured based on calcium score and the clinical risk score. And also the aggressiveness of your blood pressure control in your diabetes can be done based on how high the risk is.

If you look at the American Diabetes Association guidelines, they do mention that increased cardiovascular risks should be a criteria to consider diabetes drugs that are related to reducing the cardiovascular risk. And for blood pressure, the blood pressure guideline suggests a lower target blood pressure if you're at a high risk of future events even if asymptomatic. And then as I said, most of them need no testing.

But if you need any testing, the rationale for a calcium score is most of those patients as in the cartoon I showed before-- and it's down here at the bottom. Most of them have no obstructive plaque. So testing for ischemia you're trying to document presence of obstructive disease. It's not meaningful.

In general what is meaningful and what is a stronger marker of events in these individuals is the extent of coronary artery sclerosis, so the plaque burden as we say. And if you want to measure the plaque, you need to go for a method that detects atherosclerosis rather than a method that detects ischemia. And the most widely used method to do that is to indirectly estimate the atherosclerosis burden by measuring the calcified plaques.

That is the calcium score. It's a computed tomography test, no contrast gated to the EKG where you image the heart with a computed tomography and you look for the amount of calcification in the coronary arteries. As you can see in the figure on the top, from the yellow line on the bottom, the red, the purple, and the blue lines, the higher your calcium score, the higher your risk of incidents, coronary, and cardiovascular events. And this is a graph on the five year follow up. We now have data up to 15 years or more follow up from multiple cohort studies, showing basically the same pattern.

Calcium score of 0, your risk is very low, less than 0.5% per year. And if your calcium score is greater than 0 and then greater than 100 or 300 or 400, your risk is even higher than even if you adjust for age for sex and for risk factors. So it is an independent robust marker of risk in the general population. On the figure on the bottom, what you see here are ROC curves, which an ideal ROC curve a perfect agreement would be one that goes towards the top left corner right at the 1. And 1 is, the higher you are up towards that corner, the more sensitivity and specificity, the higher the accuracy of the test for the outcome you're measuring.

And here it's a study looking at incidence of coronary cardiovascular disease in a population of intermediate risk Framingham. So this is only the intermediate risk with a Framingham risk score. And what they're comparing here is just the score or the score combined with any of the markers listed in the figure.

And what you can see in the arrows is that they completely overlap, all of them, with Framingham risk score. So Framingham alone predicts as much as all the other curves except for one. This curve that you can see outside predicting more, adding more accuracy to the identification of your outcome is the combination of Framingham risk score or a clinical risk factor score as it is the ASCVD plus calcium score. So that's the rationale for using calcium score.

And what does it mean to have different levels of calcium score? Calcium score of 0 means that 0.1% events for coronary events and 0.4% for cardiovascular events as a global thing. Calcium scores of 1 to 100, it's double the ASCVD risk and 5 times higher than coronary heart disease risk. And calcium score greater than 100, then you're talking about 20 times more versus 0 for the heart disease event, for the coronary events, and about six times more for the cardiovascular event.

So a very robust, strong marker of increased risk that can be used to guide therapy. In general calcium scores of 0 don't need any additional recommendations. Calcium scores 1 to 100, depending on the clinical risk, you might consider statins. I don't think aspirin fits anymore.

So I'll change this [INAUDIBLE] myself. And above 100, that's where you consider more aggressive statin use and selective use of aspirin depending on the clinical profile, risk of bleeding, and overall cardiovascular risk. And that's where I'll end the evaluation of asymptomatic individuals, which is not really the core of the talk.

The second part of the talk now talking about the chronic coronary syndrome or the so-called stable chest pain or stable engine or stable CAD-- I don't really like the word stable as they put it in the European guidelines. This is a progressive disease. So it's not really stable.

But it's a slow progression. So it's considered a chronic syndrome. And the key thing to start with is to define what is the symptom presentation. It can be chest pain, but it can also be a chest pain equivalent, which is from the most common. It's dyspnea. So the first initial assessment of chest pain is recommended to evaluate those patients and should be based on the likelihood that those symptoms are related to the coronary artery disease or to myocardial scheme.

So question number one is the likelihood of the symptoms based on the clinical score. This is what we call pre-test probability scores. Second, you should never call those patients typical or atypical because that is misinterpreted, in general, as atypical meaning something not important. Instead, you should characterize the pain if you are to characterize as cardiac, possibly cardiac if they're not what we used to call typical, or non-cardiac in origin if you're clearly outside the expectations of that being of a cardiac origin. Those are the terms that should be preferred.

And this table is probably one of the key parts of the new guidelines and the key tools that we should use to define who needs testing and what testing we should use. This is a pre-test probability score that is updated from what we used to use. And this is more appropriate because there is a lower pre-test probability then what we used to have in our scores.

So what you see here is that depending on the clinical presentation and age, for example, individuals with dyspnea and below the age of 40, they're probably 0% to 3% chance of having obstructive disease. So probably not meaningful to evaluate most of them with any testing. And the higher risk or the higher probability of obstructive disease lies on male with chest pain and ages above 70. And that's the only group of individuals that have a greater than 50% pre-test probability. Those in darker green here have above 10% to 12%.

And this is the group that in general should be considered more low to intermediate and should be investigated but also as a group of a lower probability. And those on the lighter green it's questionable if there is a need to investigate. So in general the investigation of potential obstructive coronary disease on the stable setting should be for individuals with symptoms and above the age of 60 or males or females. Or if the presentation is chest pain, then it's above 40 for males. Or if it's dyspnea, then above 50 for males.

For women in general, most of them below the age of 60-- they use for testing-- should be more selective. Then how do we use testing-- if we are on that range, between 10 and above 50%. How do we usually approach testing? Testing can be done with two different groups of testing. You can do the testing with functional tests that, which are stress tests. Or you can do them with anatomical tests where you're looking at the coronary vessel.

So the group one, which is the stress test, usually you're measuring the flow and flow reduction. So you're seeing if there is a reduction in flow in the coronary during stress, which is an indirect measurement of luminal stenosis. They're not looking at atherosclerosis. They're not looking at plaque. They're looking at the flow through the coronary, directly or indirectly.

Anatomical tests on the other hand, there are direct measurements of luminal stenosis. They look at the vessel. They look at the lumen. They look at the luminal reduction. But they do not measure flow.

They're not measuring how much blood gets to myocardium. They're just measuring how much reduction there is in the lumen. And they can sometimes evaluate atherosclerosis and evaluate the presence and the extent of plaque.

So let's start with the functional test as a group and then go one by one or the subgroup of the functional test. So the idea on the functional test is if you get this figure here, on the x-axis, you have percente diameter narrowing. On the y-axis, you have coronary blood flow. And the gray line is the flow you get at rest, which is stable even if you have a 40%, 60%, 80% even probably up to 90% stenosis.

There's no change in flow at rest. Your myocardium is getting the blood it needs. So you only see a resting change in perfusion if your luminal reduction is probably above 95% or at least 90%. And even in some of those, you might not see anything at rest.

So the idea is if I stress, I increase the demand in the myocardium for blood, for oxygen. And then you might see a reduction in the expected flow versus the real flow that area will get much earlier on starting at around 50% to 70% at least. So with a high arrhythmia or a stress test, you can detect a reduction in flow in one of the territories even with the lesions that are less than most and that would only cause reduction of flow and pain at stress or during exercise.

So you can see here in the cartoon, the idea that you'd have normal perfusion at rest and an abnormal difference between the normal vessel and the stenotic vessel as represented in the cartoon. And then the question is how can we see this perfusion in the myocardium. So you can see that there is less blood getting to one part of the myocardium versus the other by looking at the electrocardiogram and markers of ischemia. That's the regular treadmill test. You look for EKG changes for ST depressions in the EKG.

You can also look at perfusion itself. You can see how much blood is getting on the myocardium with nuclear testing with SPECT and with PET. And you can also do that with first pass contrast injection of gadolinium in the MRI during stress. And you can also use a different approach. And you can see whether the wall, the myocardial wall is thickening and it's contracting normally during stress, which is the evaluation of contractility during stress. And that's what we do with echo.

So you can do EKG changes. You can do perfusion changes, or you can do wall motion changes as we do in echo. Here are some examples of them. The first one are nuclear imaging. You can see the round donut with it says stress versus the rest. The rest is a completely round image.

At stress you have part of it that is not contrasted that is not marked by the radiotracer. That is the area where there is ischemia, same thing above the crescent, the side of the myocardium. The apical part on the top during stress is getting less blood than the rest of myocardium. And that's this representation of an abnormal perfusion at the regional area related to coronary artery disease.

The view next to it is a cardiac MRI, same idea, rest on the bottom, stress on the top. Just pause here, and we can compare. Just get the middle figure. In the middle below you see the anterior wall, which is the superior in the figure, going towards the lateral where my mouse is. All that area is completely normal. It's all gray.

If you look at the top figure, there is a dark rim below. There's a dark area, sunk in the cardio area. That is lack of perfusion. I'll play it again. But you can see when the contrast gets in, it goes around the myocardium and gets out. The flow is mostly normal on the anterior wall at the bottom panel. But it's not the same on the top. So that's, again, perfusion imaging now with MRI. Let me just play that again.

And then on the bottom here, you have an echo. And you can see this is the stress image. You can see the inferior and the lateral wallwork contracting normally, whereas the septum and the anterior wall are not. This is a wall motion abnormality related to stress. And you can just look at EKG and look for ST depressions on the EKG as demonstrated here.

I talked to you already on the right part of the slide on how do we see the treadmill with nuclear with echo with MRI. But the other question related to function or to stress testing is how do we perform the stress? How do we get the myocardium to need more blood?

And we can do that with the most physiological stressor that we get, which is the physical exercise. We put the patient on the bike or most usually on a treadmill. And we make the patient exercise, increase the heart rate, increase the demand of the heart and put the heart under stress.

The second option on the bottom of the slide, dobutamine, dobutamine is an inotrope. It increases contraction and increases the heart rate. So it increases demand of the heart. The same idea as the exercise test.

And the third group, which is the middle one, which is adenosine, regadenoson and dipyridamole, all of them are vasodilators. So they don't really create a real stress. But they vasodilate the vessels.

And vessels with stenosis cannot get the same amount of blood with vasodilation. So you usually see a relative lower increase or no increase in flow in the area with stenosis when compared with the normal coronary arteries area. So you basically compare the vasodilation of two areas. But in practical terms, all of them if you look at the nuclear or if you look at the MRI, what you will see is one area getting more perfusion than the others.

So let's go one by one on the test and their meaning diagnostically and prognostically. That that's what matters for us. So far as the exercise testing, which is the most physiological stressor, it also adds on top of the stress information data about functional capacity. And it's known that a good functional capacity indicates excellent prognosis and overall health regardless of all other features.

So this is the preferred method of stressing a patient if the patient can walk, can go on a treadmill, can tolerate the exercise and can reach adequate heart rates with exercise. It's very safe. The risk of complication is below 1. The main complication is below 1 in 10,000.

In general, the use of regular treadmill testing without imaging means that the patient is, first, able to exercise, second, that the EKG is completely interpretable at baseline and third, the lower-- here it says intermediate, but it's probably even more towards the lower pretest probability. That's where that information will be more prognostic useful. You should not use this for the higher pretest probability. But in particular, you should not use this in people that are unable to exercise or that at baseline already have ST depressions or have left bundle branch blocks or are with pacemakers or have pre-excitations or if the baseline EKG is too abnormal, if it is hard to further evaluate the EKGs and stress.

Sensitivity is not as high as other methods, but it's around 70%. Specificity to detect obstructive disease is about 80%. But although it's not as precise, it is very helpful in the prognostic implications.

And here you can see different risk levels, low, intermediate, and high. And the overall event rates over 6 or seven years of follow up. And it's very clear that the low versus the high risk based on the treadmill test is completely different prognosis. And also as I said, there's the additional information of exercise capacity. And individuals with excellent exercise capacity or tolerance, which is usually defined as above 10 METs, they have a very good prognosis regardless.

And this is an additional information on physical capacity on top of the ischemic information. So this is one very good, useful information from the exercise testing. And that is one of the reasons why even if you're doing an imaging with nuclear or with echo, your form of stress, should still if possible be physical exercise if the individual is able to exercise and can reach the adequate heart rates with physical exercise.

The second one is the nuclear testing. In the nuclear lab, what we do is we inject a radiotracer. We can reinject a radioactive agent that will be taken up by the cardiac muscle in proportion to the blood flow. So it will get more blood flow if there is an open coronary unless there is an obstruction. And then we do 3D maps and multiple projections of images to evaluate the myocardial perfusion.

Just to guide you, on how we do the imaging on the right, you can see on top, we're cutting the heart on the short axis and getting the round done images from base towards the apex of the ventricle. Then we do one long axis projection that gets anterior, apical, and inferior walls. And then we do another long axis projection orthogonal to the first one where you get septal and lateral wall and apex on the same image. And if you combine those three projections as you can see here on the map, on the left, you get every segment imaged at least twice and you can compose the area with potential ischemia or reduction in perfusion with multiple projections to avoid reading just an artifact. And they're usually imaged as you can see here on the score on the box with many, many images.

On paired images with stress and rest, you can directly compare the two images, first, on the short axis, then in one of the long axis. And then on the other of the long axis. And you can also, if the test is gated, evaluate the LV function and the LV ejection fraction during the nuclear test. And this can be used with any of the stress agents. And the tracer is usually setamibi although it can also be done with thallium.

And you can do the same idea and the same approach also with stress agents in PET. It's a different nuclear test. And the concepts and idea are about the same, although PET is a bit more precise as the image quality image resolution is a bit better.

Sensitivity and specificity are much higher than the red bars you get for exercise only without imaging. And regardless of that being exercise or pharmacological stress, your sensitivity is above 80%, your specificity is above 70%, so in general a combined accuracy close to 80% something or 90%. This number has always changed a little bit depending on the study but roughly on the range of much better than a regular treadmill only EKG only test.

There's also robust data on the prognostic value of nuclear tests and compared to-- any abnormal perfusion test has some increase in the risk of myocardial death and myocardial infarction. And the larger, the more area of myocardium that is involved the higher the risk, and the more aggressive the patient should be managed. This can be measured counting the number of segments of the precent of myocardial area that is undergoing ischemia.

The next imaging modality is the stress echocardiography. As I mentioned before, it is based on the principle that the ischemic myocardium won't contract normally and will be hypokinetic. We always do a baseline echo to see all the region of motion at rest. And then we stress with dobutamine or with exercise and compare the image post stress with the pre-stress images to see if there are any changes in contraction that could be markers of ischemia.

So as it says in the bottom here, ischemia is detected as a change in wall motion and thickness of the myocardium. You can do it with exercise with dobutamine stress. And the overall idea in terms of implications is similar to the other test. Here's an example. You can see at rest the ventricles contracting normally across the myocardium. And then if we play at stress, you can see the septal anterior wall are no longer contracting, normally demonstrating a stress detected LV dysfunction.

Data on stress, Echo suggests a little bit lower sensitivity but comparable specificity when compared to the SPECT study, so in general comparable to but a little lower sensitivity. And the idea of the lower sensitivity is that small changes in perfusion might not result in reduction in contractility. Under what we call the ischemic cascade, the changes in perfusion come first. They're more sensitive than the changes that we have in contractility. So it is by concept expected that contractility will be seen only in a bit more severe patients with bit more perfusion abnormalities.

And last for the function of stress test is the stress cardiac magnetic resonance. That one usually cannot be done with treadmill because you cannot put regular treadmills inside a magnetic resonance area. So usually you have the disadvantage of not being able to do a physiological exercise, where you would also be able to quantify functional capacity. So in general you do it mostly with vasodilator. It can also be done with dobutamine.

With stress myocardial magnetic resonance, what you can do, evaluation of wall motion, so wall motion and contractility. But mostly what we're looking for is myocardial perfusion. So injecting the gadolinium first past perfusion and see if there's any defect in the perfusion of the myocardium.

There is one additional thing that you can do in the investigation of ischemic myocardium with magnetic resonance, which is the evaluation of what we call late enhancement, which is an evaluation of the presence of scar, fibrosis, or the evaluation of how much viability that is in the part of myocardium that is not perfused normally. So we can quantify the area of what is that myocardial, post myocardial infarction that will not contract and get back to normal even if you're vascularized. That might have some use in the more complex case.

Just to show you some images, This as I showed is a first past perfusion. There are arrows on the abnormalities that stress, very clearly comparable to bottom that there is a darker area. Here it's inferior septal, more from the mid towards the apex.

So I said, you can also look for light enhancement which are bright white areas in the late gadolinium enhancement faces like you see here. There's a white area on the myocardium-- round myocardium in the white area on the bottom. And as I said, you can also evaluate contractility. This is just a usual [INAUDIBLE] image of the myocardium where you can see how is the contractility segmental and overall global functioning and ejection fraction.

Sensitivity, specificity as I said always depends on the test. You see the variability across tests. But in this meta analysis, the sensitivity is about 90% specificity, about 80%. As I said, it's always changed test to test as you look across the board of the studies. But that's in general around 80% something to 90% for sensitivity and a bit lower but around 80% to 85% for specificity for the magnetic resonance.

And also there's robust data for prognostic value of cardiac MR in the context of stable CAD. And what you can see here in this slide on this study from JAMA Cardiology, 2019, is that compared to normal, just the presence of ischemia is a marker of worse prognosis. As you can see in the other panel on the right, this is only in individuals with prior MRI, same idea, the detection of an abnormal cardiac MRI being that late enhancement or ischemia indicates increased risk of incident events in the future.

Then last, I want to talk about the non-invasive evaluation of anatomy or anatomical approach to the evaluation of coronary artery disease that on the non-invasive setting is only done in clinical practice with cardiac CT or coronary CT although potentially some studies indicate that this could be done also with coronary magnetic resonance intervention, although most people don't use that in the clinical routine. Here just a simple image showing the RCA and the LAD and one projection in the cardiac CT just as an example of what the image can look like. This is an example of an image with disease.

So you see here in approximate LAD the darker areas around the contrast of the LAD. You can clearly see there is not a normal lumen, same thing on the 3D. And here the invasive angiography is showing exactly the same finding of a very severe type stenosis in approximate LAD. So this is the kind of image we can have from a coronary CT.

As far as diagnostic accuracy, as you can see here on the area, under the AUC curve, there is an area under the curve of 0.9 for all the population evaluated in CT and this large meta analysis. But if you exclude segments where we're limited to evaluate coronary disease-- so the non-diagnostic segments.

If you exclude those, then the precision is even higher. So once you know you're with a patient with no artifacts or no limitations to evaluate the coronaries, it is about 0.95. But in real life, including all patients evaluated is about 0.9.

And what you see on the right is that doesn't change much even with older individuals. The expectations of accuracy are robust to that. Although the individual is above 75, there is a slightly drop from 0.9 AUC in the other groups to 0.86 and the group of individuals above the age of 75. They usually have more calcification, and the precise estimation of aluminum reduction is more complicated. There's also robust data on the prognostic value of coronary CT.

Early studies, this is a meta analysis published in 2011 that shows that from non-obstructive and obstructive plaque, there's an increased risk of MACE of that myocardial infarction and revascularization. And the panel on the right shows that it's not only the presence of plaque or obstructive plaque but also the extent.

The SS is the score of number of segments in the CT. And if you have more segments of non-obstructive disease or more segments in individuals with obstructive disease, there is an increased risk of events even adjusting for sex, age, symptoms, and risk factors. So we can see that the presence, extent, and severity of coronary atherosclerosis detected by CT are all indicative of prognosis.

Unless you can also look in the CT by other characteristics of the plaque-- since this is a method that can see the atherosclerotic plaque per se, and there are four features called higher risk features, which is positive remodeling plaque going outside of vessel. Darker areas which are called low attenuation areas. The signal that is demoninated napkin ring sign and the identification of spotty calcifications.

Usually having two or more of those markers indicate a higher risk plaque. And as you can see in the figure, the higher risk plaque is associated with increased risk of events in both individuals with non-obstructive as well as individuals with obstructive coronary artery disease. So in short the CT can evaluate the presence of atherosclerosis, the presence of obstructive atherosclerosis, the extent of plaque, and also eventually in some cases the high risk feature plaques.

And last thing I think is an interesting finding from the ischemia trial. So in this trial everyone included had at least 10% area of ischemia. And what is shown in this cartoon is the cardiac CT finding, the coronary CT findings, showing how many vessels were detected with greater than 50% stenosis. And even in the population where everybody has a high burden of ischemia, the more vessels you have with obstructive plaque, the higher the event rate.

So the plaque information is complimentary to and adds prognostic information on top of the images evaluated by stress and the detection of ischemia even in individuals with ischemia. Also there is data comparing the addition of CT to the usual use of stress tests, and here's regular treadmill tests, comparing that just with the treadmill test. And what you can see in this cartoon that adding the CT information of plaque and all the detailed features I mentioned makes substantial changes in therapy.

There are more patients that get more aggressive treatment but also more patients in whom the treatment is changed to less aggressive treatment. So you change the anti-anginal therapy based on the CT findings more than on a usual test. Same thing for preventative therapy, there is substantial increase in some patients but a substantial decrease in some patients. So you're really better restratifying risk in both directions.

And overall if you sum all those, you end up with changes in therapy almost one in every four symptomatic patients who are evaluated for chest pain when you use the coronary CT. This is one of the randomized trials. Here are the two of them.

So the one I presented before is the one on the right. The one on the left is the promise trial that was performed in the US and compared different tests for functional evaluation with anatomic testing. And they have shown that for usual cardiovascular outcomes on the follow up of three to four years, there was basically no difference in the risk stratification. So the prognosis after the test was the same in both groups, so we could say they are equally likely to identify, detect risk, and impact management being that a city or any other method.

On the other panel, as I said, it's a CT plus ETT versus ETT only. And what you can see here is that the blue line has way fewer events on a up to three year follow up year. Although it doesn't formally reach statistical significance, there is a 40% reduction in the risk of myocardial infarction in the SCOT-HEART trial.

And if you do a meta analysis of not just those two studies but other studies that have done the same thing, you will find this 31% reduction or about 30% reduction in the myocardial infarction. And that is accompanied by an increase in revascularization. So you end up intervening more if you start with a CT at least in the randomized trials. You end up having less myocardial infarction.

There is also a large Danish registry that compared individuals that underwent stress testing versus individuals that went CT on the entire country of Denmark for more than 10 years. And you basically the same see the same pattern. Starting with CT leads to a 30% reduction in myocardial infarction, but it's also associated with increasing the use of preventative therapies and the increased use in revascularization.

Whether the benefit comes from one or the other, I cannot tease out from this data. But it's clear that there is a benefit in the reduction of myocardial infarction if your initial choice at least in general is done within a coronary computed tomography evaluation. This is not necessarily applicable to all patients across the board. But this is the information we have at least from the population level of registries and randomized trials.

SCOT-HEART was also continued in the follow up for up to five years. And you can see the curves continue to diverge. And then here it's clearly significant difference, starting with CT versus the usual care. And there was an increase in invasive angiography and revascularizations early on. And there was some concern whether that was something useful and meaningful in terms of impact or whether that was just overuse of testing and procedures. And what we can see in the figure here is that over the course of five years, there's different [INAUDIBLE] and both groups end up with the same number of invasive angiography and interventions.

So basically what CT is doing is pulling forward the amount of interventions that happened probably because of the detection of more disease. So it's basically doing the interventions early because it detected disease earlier. Just to illustrate how we usually read CTs, we cannot precisely measure every stenosis. So we use a semi-quantitative method going from no plaque, below 25, 25 to 49, 50 to 70, 70 to 99, or occluded vessels, so five levels. And we quantify that amount of reduction in all coronary segments, proximal meeting distal RCA, proximal meeting distal LED, proximal and distal CIRC, left main, ramus if there is a ramus, PLV, PDA, diagonals and [INAUDIBLE]. So ideally each and every of those segments if present invisible should be evaluated by the presence of plaque, plaque characteristics and the severity of stenosis.

Here's just an illustration of those different levels, a completely normal coronary artery, one with minimal plaque, one with mild plaque, one with a moderate plaque, and one with a severe plaque. And this is what we use to define the findings in CT. And how we put it all together-- according to the new guidelines, if you have a patient with a chronic coronary syndrome or stable chest pain, first question is does this patient have known CAD. So is there a prior CT that shows obstructive disease is there prior interventions with stents with bypasses or prior myocardial infarction.

If there is no known of those, then you should approach with this algorithm where the first evaluation is the pretest probability. If it's low, in general no testing is needed. But selective use of calcium score or regular treadmill testing can be considered.

For all those intermediate or high pretest probability, you can evaluate either with the CT or with any of the stress imaging methods that are mentioned, stress echo, stress SPECT or stress MR. Pure exercise only stress can be considered in selective cases. And then all the management forward and the need for invasive angiography is all based on ischemia results and CTA results.

So it depends on how much plaque or how much ischemia you have. If you have known CAD, then the question was the prior plaques or the last evaluation was the disease less than 50% stenosis or more than 50%. If it was less than 50, it's about the same idea. You can go with CT or with stress testing. If it is more than 50%, you already know there's obstructive disease, first, intensified guideline directed medical therapy, preventative therapy, and anti-ischemetic medication to then evaluate if there is any high risk CAD or very limiting angina.

If the symptoms are very concerning or very limited, you might go directly to the invasive angiography. However, everybody else when there is no high risk or very frequent severe symptoms, you should consider, again, a non-invasive investigation with the functional test. And then the management of course, is based on the test results.

Implementation based on the ESC guidelines, a bit different way of presenting idea here is also that all methods are comparable. But they use more of the spectrum of the risk as a continuum and don't give you exact thresholds, or you should go one way or the other. They basically say that in general, the lower the pretest probability, the more likely CT will be the best test. The higher the pretest probability, the more you're going towards preferring ischemia testing associated with imaging. Although it always depends on the patient preference, contraindications to test, availability and local expertise in reading and performing those tests.

You might ask me which one of the tests or which one of the functional tests is better. It's not that easy to compare. There's not that many head to head studies. But there is a couple meta analysis. This is one of them. And what you can see here is that there are two lines, the yellow and this first bluish one that have lower area under the curve compared to the other three. The other three are more comparable and almost overlapping.

So the two that are with a bit lower sensitivity and specificity leading towards lower AUC, our SPECT with 82 and echocardiography with 83. And the best ones are MRI PET and CT. Although as I said, it really depends on the local expertise. And the two on top have the advantage that you can perform them with regular treadmill exercise as a stressor, which has some other advantages. And the other three at the bottom that is not so common. Or the CT doesn't even have stress of course.

And then the other approach was deciding which test can be an approach based on cost effectiveness. So this cost effectiveness model is based on the intermediate to low pretest probability in the video of middle age [INAUDIBLE]. And based on these assumptions, the modeling suggests that the lower cost, higher effectiveness, higher adjusted qualities are these three crosses here that are-- they're both crosses that are related to starting the evaluation of the coronary CTA in the three of them. Then follow that with the imaging, stress test that could be an echo, a SPECT or a cardiac MR.

Regardless of which are the three, they're very close to each other. Only doing the invasive angiography, if the CT detects substantial plaque and stenosis, then you should go for functional. Or otherwise, you don't go to the stress test. And if you go to the stress test, you should only go to the CAT lab if on top of the CT information, you also have detection of ischemia. So invasive angiography should be used selectively only for individuals that have a prior documentation of anatomical evaluation and stress evaluation. Although that's not what we usually do in practice, that has been shown at least in the study, to be the best cost effectiveness approach.

So choosing the right test is a bit more complicated. It depends on the pretest, likelihood of CAD, depends on the goals of other information you want from the test. It depends, of course, on whether the test is available and there's good expertise. It depends a little bit on the age. It depends on whether there has been prior tests and what were their findings and as a short table here on the bottom.

If the patient is or isn't able to exercise, which is the stress for aging you can see you're considering, we'll make you go towards more one testing versus the other. As I said, the coronary artery disease is a spectrum that goes from the asymptomatic, the chronic stable patients and also the acute coronary syndromes or the acute chest pain individuals. This is a different group. I won't get into much details because in this group the evaluation is usually history and physical examination.

If they're really acute, this should be done on the ER setting. And there the first thing you do is an EKG. Based on the EKG findings, you define the need for additional testing. And if there is need for additional testing, you then do a troponin to a lab based on an imaging test. And then based on the troponin on the EKG and the physical examination history, you'll then consider the risk and what is the management. Some imaging modalities might be used selectively in those cases. But I won't get into the detail because that makes the talk too broad.

My conclusions are, first, start with the clinical presentation. Is this an asymptomatic individual, a chronic, or a acute coronary syndrome? In general, for the asymptomatics, clinical risk scores and risk factor modification is what you need with selective use of calcium scores. For the chronic stable coronary artery disease, first you have to define the pretest probability.

Then you have to consider whether a test is needed particularly in the low pretest probability individuals. And then you should think how much of those findings would change your non-pharmacologic, pharmacologic, or invasive management. If you don't expect any changes, you don't need the test. If you're expecting the changes will be based on the test results, then that's when you should order the test. And the acuity individuals should be evaluated usually in the ER setting.

And my second part of the conclusion is that for this group of stable chronic chest pain, the testing choice depends on the pretest probability depends on the contraindications to each modality, depends on local expertise and depends on the need and interesting of the physician to define the use of aspirin and statins. If you're unsure of the need of those, ACT or the detection of plaque might be more helpful than ischemia evaluation.

And the expectations you have for the need of invasive angiography, they're too high because the patient is very symptomatic. There are some cases where you might even go directly to the CAT lab although the vast majority will be managed with stress or anatomical non-invasive testing. I would like to thank you all for listening to the talk. And this is where I'll finish. Thank you.