**ROBERT D. SAFIAN:** What I wanted to do this morning is talk a little bit about STEMI and in particular a subgroup of patients with multivessel disease. And we face this quite commonly. This is a patient that we took care of at Beaumont about 10 days ago, a young guy, 52 years old, a smoker, no other risk factors.

And this was his first presentation with coronary artery disease. He presented with an inferior STEMI. Had a little bit of borderline hypertension [INAUDIBLE] infarction as well. In the initial shot here, you can see shows a very large thrombus in the proximal right coronary artery. It's a pretty big vessel.

And then there's an anomalous circumflex as well that comes off the right coronary artery and there is a moderately severe stenosis in the circumflex as well. So one of my partners treated this man with an angiojet. You can see the pacemaker, because the heart always stops with the angiojet. And then after the angiojet, you can see the residual plaque. And it looks like what we would recognize as an unstable plaque, with scalloped margins, ulceration.

And a stent was deployed with a nice result. And the patient did fine. And you can probably see here, when he's not in the [INAUDIBLE] the ST segments have come down. And he did very, very well. Had an ejection fraction of about 50% or 55% and did well clinically. So this is all straightforward. I think we've resolved the issues about what to do and how to do it with the culprit lesion.

And one of the other residual issues that we're faced with is what to do with this type of lesion here at this point. And the choices are to do an intervention at the same sitting, not do anything, see if the patient has provocable or spontaneous ischemia, then do an intervention, use an FFR wire to assess it. So we have a lot of tools in our hands to try to evaluate this.

The problem is a fairly common problem, though, in terms of facing patients with multivessel disease and STEMI. And you can see here based on three large studies that looked at the prevalence of coronary artery disease in patients who present with STEMI, that about 50% of the patients have multivessel disease. About 30% have two vessel disease, and the rest have three vessel disease. So this is not an uncommon situation that we face on a nearly daily basis.

If you look at the universe of data that's out there, it's been expanded lately by some recent randomized trials which I'll cover in a moment. But this is sort of a summary, a meta-analysis of existing trials that were-- some were prospective, some were retrospective studies-- that looked at the issue of what to do during the index procedure, whether you should do a culprit-only approach or a multivessel approach to PCI. And the data in these studies seem to favor doing corporate lesion only. And then if you look at it in terms of how you approach multivessel PCI per se, so doing it as an indexed or a staged procedure, most of the data favor doing this as a staged procedure.

And in fact, if you look at the guidelines that are out there for ACC/AHA that are on the left and the European guidelines that are on the right, they're fairly concordant, although the level of evidence that's applied to the different recommendations is somewhat variable. But you can see that our societies in the US give non-culprit lesion revascularization a Class III recommendation, so not indicated in patients without hemodynamic compromise in terms of doing the intervention at the same time as the culprit intervention.

And then there's the out, if you have patients who develop spontaneous ischemia or if they have a high risk stress test after the infarct, and then it's considered acceptable by both European and American guidelines to go in and treat those patients. And this has really been the standard of care. This is really how we approach patients. And the primary reason was that there was thought to be an excess of complications, contrast [INAUDIBLE] with the stroke bleeding complications and other things, by doing another lesion at the time of the culprit lesion.

And then PRAMI was published, and you're all familiar with this, published in the *New England Journal of Medicine* in 2013. And this raised a lot of eyebrows, and a lot of people were skeptical about the study. But it did show that if you used a preventive strategy, which is really complete revascularization of all the-- revascularize the culprit and the non-culprit lesions greater than 50%.

But there is a outcome advantage if you follow these patients out to about three years. And the decision about doing a preventive PCI was really based on the angiogram. So an angiographic diameter stenosis of 50% or more, that qualified the patients for randomization. And then half the patients got multi-vessel PCI during the index procedure. And some just got medical therapy, that primary PCI.

And then there was the cuplrit study that was just published earlier this year in *JAC.* And same idea-- take patients with multivessel disease. The diameter stenosis range was slightly different, but the same principle that half the patients with multivessel disease got PCI. The intent was to treat them during the index procedure, and if not, during the index hospitalization. And then you can see the difference in the outcomes as well favored the patients who received complete revascularization.

And when you look at the in-hospital outcomes and you look at the components of the primary endpoint, which are all shown here, most of the benefit was thought to be in terms of repeat revascularization. But you can see that there's a fairly dramatic improvement in the hazard ratio. So for the combined [INAUDIBLE], about a 55% relative risk reduction for the patients who had a complete revascularization, as opposed to culprit revascularization.

And the other important point was if you look at the safety indices, you can see that there's really no difference in safety. So the benefits of mulitvessel PCI during the index procedure or the index hospitalization were not achieved at the expense of greater complications, which seem to be in contrast to existing data.

And then a larger study was done called DANAMI, prime multi. It was sort of a complicated acronym. But this was a study that was done. They originally screened almost 4,000 patients with STEMIs. The patients, if they had a successful primary PCI of the infarct-related artery and they had multivessel disease, which was defined as a 50% stenosis or more in a decent sized artery, these patients were then randomized to undergo a strategy that included on the one hand PCI of the culprit vessel, or FFR-guided PCI of the other vessels.

And you can see in this group here that about a third of the patients who were randomized to this multivessel group when they had their FFR, the FFR was considered non-physiologically significant. So these patients did not actually undergo intervention of the multivessel disease, but they were considered in that group because of the intention to treat principle.

And the endpoint of this study was a composite of all caused death not fatal in my ischemia-driven target lesion revascularization, sort of the standard endpoints for this kind of a trial. And what the authors found in this study again was about a 45% reduction in the risk of the primary endpoint by doing complete revascularization, as opposed to infarct-only revascularization, in contrast with the guidelines from all of our societies.

And when you look at the components of the primary endpoint again, a lot of this was driven by ischemia-driven revascularization, but about a 45% reduction in the combined endpoint. And looking at the complications, really no difference in the complications. So these excellent results were achieved, but not at the expense of increasing complications.

And if you compare these three studies, there are some differences in terms of the primary endpoints minor differences. The lesion criteria that were used in PRAMI was basically just sort of an oculus stenata kind of things, stenosis greater than 50%, put a stent in it, which is not really concordant with how most of us practice nowadays. But this is what they showed. And then in culprit, the definition was diameter stenosis greater than 70% or diameter stenosis greater than 50% in multiple views.

So again, using the angiogram to make the determination about whether to intervene on the non-culprit arteries. And then in the DANAMI3 prime multi-study, they used the diameter stenosis greater than 50%, but then all the patients got FFR. And so the decisions about revascularization were driven primarily by the FFR. And this, I think, is in keeping with what interventional practices today.

There were some differences in terms of the timing of the intervention. So in PRAMI it was immediate, so during the index procedure during the primary PCI procedure. That has its own set of tissues, which we can discuss. In culprit, the intent was to use an immediate strategy but staging them at a later time during the index hospitalization was also considered acceptable.

In DANAMI, the intent was to stage that intervention. And the majority of patients were treated within 48 hours after the primary PCI. And you can see the results are fairly dramatic-- 65% reduction, 55% reduction and 44% reduction in the relative risk for patients who underwent complete revascularization. So I think these data are quite impressive. I think one of the questions is why-- what is it?

I think the FFR component is easy to understand, but how often do we see a truly 50% or 60% lesion where the FFR is going to be 0.7? It's not just not that common. So one of the possibilities is that we're dealing with a situation where patients have acute coronary syndromes have what's called vulnerable plaque and other lesions.

And I think that the two most common buzzwords that we hear now in interventional cardiology are culprit lesion and vulnerable plaque. And you can hardly pick up any issue of *CIRC* or *JAC* and not come across an article that deals with one of these issues in some fashion.

So this is a schematic illustration that's taken from a really beautiful review article by Nagavi and Feuster and others that was published in *CIRC* a few years back. And basically, this is not meant to represent a timeline. So this is not a progression from left to right. These are the types of plaques that are considered vulnerable. And in this context, vulnerable plaque is considered the precursor of the culprit plaque.

So it's a thrombus prone plaque or some other type of plaque with high probability of rapid progression. So this is not just a single morphology. It's not just one type of plaque, but it's a spectrum of disease of thrombus-prone lesions and high grade stenosis that are at risk for becoming culprit lesions leading to MI and death. So that's the overriding principle in terms of vulnerable plaque.

It turns out that most of the plaques, most culprit plaques are characterized by a ruptured thin cap fibroatheroma TCFA, with overlying thrombus, which is the morphology that's shown in panel B here. So one of the notions of the vulnerable plaque is whether this lesion, which is a simile lesion, but doesn't have thrombus, whether it would be reasonable to expect that this might progress to that. So that would be one type of vulnerable plaque.

Another is a situation where you have superficial erosions on the surface of the plaque. And that can lead to formation of thrombus. And again, whether this would be a reasonable conclusion that this type of lesion would be a vulnerable plaque that would ultimately lead to this type of lesion or to that type of lesion.

And there are a few others, varieties of these kinds of things. This is a plaque that has inter-plaque hemorrhage, plaques that have calcified nodules, and then plaques that are highly proliferative types of plaques with fibrosis, calcification and very severe stenosis. So that one is easy to understand as well.

So this is the notion. So in these patients who have multivessel disease and STEMI, the lesions that are not the culprits, the other lesions that are greater than 50% in the non-infarct vessels are these vulnerable plaques in vulnerable patients. If we can identify what the vulnerable feature is in those plaques and treat that, does that make a difference in outcome? And that's one of the biggest questions that's out there. And there's a lot of trials out right now that are being done to address this issue in different ways.

This is sort of a highlight schematic of the more common vulnerable plaque, which is the TCFA. So not necessarily a severe stenosis, but a very large lipid core plaque, which is covered by a thin fibrous cap. And these plaques are infiltrated by monophages, monocytes that are converted to activated macrophages and oxidized LDL, which is sort of the characteristic of this type of vulnerable plaque. And these turn out to be the more common of the vulnerable plaques. And there's a couple of assumptions in this whole vulnerable plaque hypothesis.

And that is that first of all, that the morphological features of the plaque, with culprit lesions and the vulnerable lesions, are similar. And we think that's true, but we don't know for sure that that's true. Well, what are those characteristics? We've mentioned some of them, so the TCVA is one, a large lipid core plaque, thrombus, surface problems, whether it's a ruptured plaque or erosions, and then the burden of plaque itself.

So these are all things that are recognized as being features of vulnerable plaque. And the inflammatory component is something that's probably important, but we don't have a real good way of assessing that by our current imaging techniques. And that's why I have left that as a sort of an open box. So these features are relatively easy to assess. We have the tools that allow us to do that, at least the invasive tools that allow us to do that.

The other assumption is that patients with vulnerable plaque are at risk for and MI and death. And we think that's true and that's a reasonable assumption. And this is where it gets a little sticky. So the identification of vulnerable plaque may permit pharmacological or mechanical interventions to prevent those bad things from happening. And we don't know if that's true, but PROSPECT was a study that was designed to evaluate that. And the plaque study is another study that's out there that's looking at that as well.

So one of the ancillary questions in this is, can we identify vulnerable plaque and non-culprit lesions, and as corollaries, which patients? Are these the unstable patients or the stable patients? Well, you would think that it would be the unstable patients, because that's the unstable plaque in the unstable patient that you're more likely to find features of vulnerable plaque in unstable coronary patients than you will in stable coronary patients.

And then what technique? Are we going to use noninvasive or invasive technique? Is there going to be a single modality or a multi-modality? And I'm going to go through some of these issues. And then, which vessels? So if you have a patient with an acute coronary syndrome, are you really interested in the culprit lesion and the adjacent culprit vessel?

Is that really the high risk environment? Or is it the other artery in the same patient? We don't know that. And there are different studies that have been published looking at different definitions of non-culprit, whether it's in the same artery as the culprit lesion or in a different artery. So it can be very, very confusing.

And then finally, what are the parameters you use? I already mentioned there's a lot of characteristics of vulnerable plaque. Do you have to look at all of them? Is one of them better than the other? So how do you do that? And these are things that are really uncertain. And this is part of the reason why this area has not been clearly defined, but then also one of the reasons why this area is very suitable area for clinical research.

So this is a table that lists the different types of techniques for noninvasive assessment of atherosclerotic plaque, plaque characterization. And I'm not going to talk about any of these. These are really, really important, but not really why I wanted to speak today.

But I think if you think about this from a patient viewpoint, the idea of evaluating vulnerable plaque and patients at risk in terms of broad populations is going to have to be done with noninvasive techniques at some point, because we're not going to take everybody and just take them to the cath lab.

For the unstable patients, it's different, because a lot of those patients go to the cath lab anyway. So it's not such a stretch using invasive techniques. But I think ultimately, if this area of research pans out and it turns out we can identify vulnerable plaque and then do something about it, then a lot of the focus is going to shift towards the noninvasive assessment. But I'm going to put this aside for the moment.

And what about the invasive detection? Well, these are the tools that we have-- coronary angiography. And Jim Goldstein, one of my partner, published a lot of data on using angiography to identify color vulnerable plaque and I think set the tone for this entire field. FFR, really, is for physiological significance. OCT, near spectroscopy, intravascular ultrasound, are all complementary techniques for looking at different parts of the plaque, which I'll show you. Angioscopy tends to be a pretty good test for looking at thrombus and for the color of the plaque.

I'm not sure there's anybody in the US that's doing angioscopy anymore. It's really big in Korea and in Japan, but we stopped doing it, I think, about 10 years ago. And then this area, which I'm not going to talk about, which is a very exciting area, is micro MRI, which is doing catheter-based MRI using MRI guide wires, which is really cool stuff, but there's not a lot of data published about it. But I think that's a really interesting area as well.

So we're going to focus on the imaging tools that are in our tool box that are relatively and reasonably available, which include FFR, OCT, and [INAUDIBLE]. So this was a figure from one of Jim Goldstein's, the first publication that he had in the *New England Journal of Medicine* a few years back, a patient who came in with an infralateral STEMI.

And it's an ugly looking plaque with thrombotic occlusion. And then in the LAD, you can see this lesion, which we would all recognize as being an unhappy lesion with a lot of surface irregularity and ulceration. And this was characterized by angiographic as being a vulnerable plaque, a non-culprit vulnerable plaque.

So going back to the different types of plaque criteria, there have been a lot of documents out there that have attempted to define major and minor criteria for vulnerable plaque. And these are those criteria. So the ones in the top box here are the major criteria. The ones below are the minor criteria.

And then the ones that are highlighted in orange are the ones that we can assess reasonably, using the invasive tools that we have. And then in this column, it shows what that tool is. Now, I haven't listed all of the tools. I've just listed the best tools. So you have to trust me, rather than go through every study that's looked at this and all the different recommendations for OCT and IVUS.

That this is sort of a reasonable summary, based on the conclusions of those documents. So for TCFA, OCT is highly accurate. Lipid core plaque is really in the realm of near spectroscopy, which is very, very highly accurate and sensitive for evaluating lipid. And then for assessment of the plaque volume, it's done in conjunction with IVUS.

And now there's a [INAUDIBLE] catheter, a single catheter. So that's a good thing. Issues about thrombus on the surface of the plaque are better evaluated by OCT than any other tool. Surface irregularities like fissures are much better identified by OCT. The stenosis severity, obviously an angiogram is useful. And then the FFR comes in there. The plaque burden is in the IVUS wheel house.

These other areas, active inflammation, we don't do such a good job. There are some OCT studies that show that. But this is not one of the strengths of OCT. And even endothelial erosions can be difficult to see by OCT. So these are major criteria, but where we're lacking a tool with a high value for identifying these characteristics. And in terms of the minor criteria, well, these are minor criteria.

And so they are less relevant. Angioscopy is not really an issue, and neither is MRI from a practical standpoint. We don't have good tools for evaluating endothelial dysfunction in the coronaries and culprit lesions. And positive remodeling, I think, is an important area, something that came out of Prospect and this is something that can be done very readily with an intravascular ultrasound catheter.

So we have the tools. So if you look at studies that have been published and what they looked at and what device they used, and then you stratify acute coronary culprits, non-culprits and stable CAD, you can see that there's sort of a gradient of identification of plaque rupture. And the lower end here are the unstable angina type patients and the higher end are the STEMI patients.

So there does seem to be a gradient of being able to identify these types of plaque characteristics. And the same with the TCFA. There does seem to be a gradient of identification. The plaque erosions, minor criteria-- that's not so good with OCT. The OCT experts claim to be able to identify lipid core plaque. I think the NIRS is just much better. Thrombus is readily identified.

And again, you can see a gradient of identification as you go from more unstable to stable patients. So the OCT, I think, does appear to have some value in terms of identifying these types of plaque characteristics. If you look at intravascular ultrasound, I mentioned before this remodeling concept is very easy to identify. Not a huge gradient there, but plaque rupture is not easily identified by ultrasound and neither is thrombus.

So I think the strength of IVUS is really in the remodelling index and in the plaque burden. And that's very, very easy to do. Now with NIRS, NIRS is a little bit different. NIRS is a spectroscopic technique that identifies lipid core plaque and is excellent for qualitative, so just identification, sort of yes/no kinds of things and also for quantitative assessment using what's been called the maximum LCBI, Liquid Core Burden Index, within four millimeters of the culprit lesions, kind of a mouthful.

But there is definitely a gradient of the quantitative measurements as you go from unstable patients to stable patients. And again, the lower end here is in the unstable angina patients. The higher end is the STEMI patients. So there does seem to be some gradient of identification there that can be leveraged for clinical purposes.

And then in terms of the types of information that you get, well, this is an OCT run from a patient with severe disease in the right coronary artery. And you can see the OCT images taken at various points. And here you can see a thin cap fiberatheroma. This is probably a lipid core behind here, very thin fibrous cap.

Same here at this location, so in this part of the vessel that isn't even severely stenotic, more thin cap fibrous atheroma here. And then a frank rupture, a focal rupture of the plaque, which you can actually see it, I think, on the angiogram and a little bit of thrombus and then fibrous plaque in the other areas.

So the OCT really gives you sort of a nice picture of the surface characteristics and the thickness of the fibrous cap in many of these unstable lesions. So another patient examined by OCT, kind of a hazy, ill-defined area, but it's quite clear on the OCT, you can see a clear plaque rupture here. And here's a cap outside the area of plaque rupture. And you can see this large intraluminal filling defect.

And this is the thrombus in here. And not only that, but if you look at it-- this is a blown up view-- you can actually see differences in the texture of the clot by OCT. So this is a more uniform texture that's consistent with white or platelet thrombus and then this non-uniform texture of thrombus, which is consistent with a red mixed fiber and platelet thrombus. So this is really the strength of OCT.

Some of these other things are a little bit harder to image. So this is a patient who had a acute coronary syndrome. And you can see there's a surface irregularity. There's no plaque rupture. There's some shadowing behind here. And these are thought to represent small erosions in the surface of the plaque.

And OCT is pretty good for this, but not necessarily perfect. And then these are the calcified nodules, which I think are very, very hard-- we've done a lot of OCT, and I find these to be very, very challenging to identify. But this is a case where you see these calcified nodules and a little bit of overlying thrombus in a patient with unstable angina. But again, these are plaque characteristics that are not associated with TCFA, not associated with plaque rupture, but are found in patients with acute coronary syndrome.

And if you look at studies that have compared the different modalities for identifying plaque rupture at least, hands down OCT is the best technology. This is the best IVUS image of a plaque rupture you'll ever see. But this is just incontrovertible. This is really crystal clear. So the different techniques have different strengths.

This is an IVUS chemogram. So the yellow, this colored yellow to represent lipid core plaque. And you can see in a patient with an acute coronary syndrome, the target lesion is down here in the distal part of the AV crew, the circumflex, a lot of lipid in that. Even in a non-target, there's lipid as well. Here's another patient, culprit right coronary syndrome, huge plaque burden. I don't remember what the LCBIs were in this, but very, very high.

And then here's a patient with stable CAD, a culprit lesion patient with stable angina. And there's a nice lipid signature in that plaque, and then another patient with CAD, stable CAD, culprit LAD lesion. There's no lipid in that. So these techniques can be used to identify lipid core plaque and potential other features of vulnerable plaque as well.

And I mention this, if you use the NIRS to stratify the quantitation of the lipid core and then you look at whether the patient's had STEMI, non-STEMI, unstable angina or stable coronary disease for the culprits and also the non-culprits, you can see there's a definite gradient of lipid core plaque in these patients.

So I thought it would be really important to mention the PROSPECT trial. And you're all familiar with this. This was a study published by Greg Stone a couple of years ago in the *New England Journal of Medicine*. And this was an unbelievably ambitious study, just in the way it was designed and implemented, meticulous study of every millimeter of a coronary artery.

Just really an unbelievable effort, a Herculean effort. And what the PROSPECT investigators did, as you recall, is they took patients who had acute coronary syndromes and they revascularized the culprit lesion. And then they did virtual histology IVUS, VH IVUS, on the non-corporate lesions, and then followed the patients for three years.

And one of the endpoints was to determine whether the ischemic endpoints during that time period were related to the culprit lesion or to the non-culprit lesion, and if they were related to the non-culprit lesion, to try to identify plaque features by virtual histology that would correlate with the patient outcome. And the primary outcome, the clinical outcome, was cardiac death or arrest, MI, and then worsening angina, requiring hospitalization. So not precisely the same as the STEMI outcomes, but pretty similar.

And right off the bat, you can see that at three years, the MACE event rate was about 20% in the patient population. And it was equally divided between culprit lesion events and then events related to the non-culprit vessels. So in the jargon of unstable plaque, event rates that are greater than 5% per year are considered highly significant event rates, 5% per year.

So you'd expect an event rate at three years about 15%. So the event rate is 20%. It's a little higher than that. But the event rate in terms of the non-culprit lesion's about 3% or 4% per year, so not quite that 5% benchmark. But in any case, these are the data. This is what they showed.

Now, the most interesting part of the paper, I thought, was in the appendix, which wasn't published in the *New England Journal* but was available on the website. And I thought this was really interesting. So if you look at the independent correlates of the outcome in the PROSPECT study, they had about 700 patients and they looked at 3,000 lesions. I mean, it's unbelievable study. So the MACE rates at three years-- insulin-dependent diabetes, 41%.

Not many insulin dependent diabetics. But if you had it, that was bad. Hypertension, prior PCI, so these are all sort of clinical markers. And then look at the extent of CAD. So the more CAD you have, the greater the likelihood of a bad outcome at three years. And you can see the hazard ratios here.

Now, look at the lesion level correlates of MACE. So in general, the outcomes are substantially lower than the clinical outcomes. That was one thing that I thought was interesting. But the things that they highlighted in the article were the MLA, miminal luminal area less than four square millimeters a measure of plaque burden. So 5% event rate if you had that relative to the hazard ratio was 5. So 5% of MACE at three years, I mean, that's turned out to be higher than those who had less plaque.

But again, it's not extraordinarily high plaque burden the grade is 70%. Now you're up to about almost 10% and a hazard ratio of almost 9. Lesion length, so another measure of plaque burden, again, it's a significant finding. But still the event rate is not that high. And then even with TCFA, so 595 patients had TCFA. The event rate was about 5% at three years.

So I look at this and I'm thinking, well, either there's an issue with the virtual histology-- maybe it's not really identifying the truly vulnerable plaques. Or maybe what we're calling vulnerable plaques really aren't that vulnerable. And I'm not sure what the right answer is. So the other part of the article that I found really fascinating was the authors really focused on TCFA. So remember what I said. It was highly prevalent in the patient population. So almost half the patients who were studied had TCFA.

But the event rate for those that had it was 4.9%, which turns out to be significantly higher than those who didn't have it, 1.3%, but still not that high for three years in terms of an outcome. But the interesting part was, look what happens if you add more stuff onto the TCFA. And these are all measures of plaque burden. So the minimal lumen area less than four millimeters squared, a plaque burden greater than 70%, or all of those plus TCFA and now your event rates have really skyrocketed up.

So to me, what this suggests in my opinion is that this issue about vulnerable plaque is very, very complicated. We're not going to be able to look at just one feature and say, aha, here it is. We're going to look at TCFA or we're going to look at plaque ulceration or I think we need to look at a combination of things. But if I'm reading their study right, I think that the indices of plaque burden to me seem be the biggest issue. So the amount of plaque, rather than the surface of the plaque to me seems to be the biggest issue.

Now, one of the things that I'm not going to talk about, but this is extremely important, is that vulnerable plaque is dynamic. So what you see today may look completely different six or 12 months from now. Some of it may be related to the antiplatelet therapy, the statins. And there have been OCT studies that looked at various plaque features over time show dramatic changes. And there was also bad things that happened, which is new vulnerable plaques can appear in the same artery at a different spot. Vulnerable plaques in one artery can heal.

Sometimes they'll persist. So it's a very, very complicated issue and it's a moving target. So I think it's not realistic to expect that if we just look at one feature, we're going to find the holy grail of vulnerable plaque. And then the other point is, what about the patient? All we've been talking about is the morphology of the plaque.

But there's a lot of patient factors which are also in that review article, that *CIRC* review article, which is a really interesting review article, but talks about the vulnerable patient and what makes a vulnerable patient. Is it the blood? Is it the flow characteristics in the vessel? Is it inflammation? What's going on at the patient level that influences the plaque performance and behavior? And these are things that we don't really have a good handle on at this point.

So coming back to the spectrum of vulnerable plaque, if we accept the notion that multi-modality imaging may be necessary to allow us to identify these different plaque features, what are they? So here's one. The ruptured plaque OCT NIRS to look at the lipid core burden, surface rupture, same type of lesion OCT, NIRS.

Here's a case where there is maybe a surface erosion OCT. This is a thrombus on the surface OCT for that. We don't have a really good way of looking at plaque hemorrhage, so this is the one type of lesion that we can't really identify. OCT probably for calcified nodules, and then this severe obliterative type of atherosclerosis is probably best suited for the FFR.

So with all of those things in mind, what we decided to do at Beaumont was put together a group where we're going to take all STEMI patients who come to the lab, treat their primary culprit lesion with the standard techniques. And then anybody who has multivessel disease with a 50% stenosis or greater is going to come back to the cath lab. We're not going to do this at the same time.

And we're going to do imaging of all the arteries that are non-culprit arteries. And we're going to use NIRS, IVUS, OCT, and FFR to study all of those lesions. The revascularization decisions are going to be based on the FFR only, because that's really the best evidence that we have. The primary endpoint is we're really looking for the prevalence of vulnerable plaque features in the non-infarct-related arteries.

And it's a small study, so we're not expecting a signal to show us. But we will look at the MACE rates at one year, correlate them with the vulnerable plaque features, and then compare the vulnerable plaque findings with the different imaging modalities. Because this will really be the first large study that will be done that will allow us to compare these non-culprit lesions with different imaging modalities in the same patient.

And then if there's a signal that seems to suggest that there are certain types of vulnerable plaque features that are fairly common, then we can do a different trial and maybe look at a pharmacological or mechanical intervention and look at endpoints thereafter. But right now, we're still trying to figure out, what is it that we're studying? What's the future or the features that we need to be focused on in order to do a larger clinical study, if any?

So the flow diagrams here, so acute STEMI and multivessel disease, they've got a culprit infarct related PCI at that time. And then come back to the 30 days after primary PCI and then have imaging of the non-infarct related artery with NIRS, IVUS, FFR, and OCT and then revascularization based on the FFR. It's a very, very simple study. We decided, based on our STEMI group and our institution not to force the issue in terms of the index procedure, because in the middle of night we don't have a lot of support to do this type of imaging thing. It's pretty labor intensive.

And also, the 30 day issue, we just wanted to make it more clinically applicable. So we realize that the MACE, maybe some patients who have contrast issues or vascular issues or patients that want to come back to the cath lab. So we try to do it in a time that was soon enough so it would still be relevant, but not force doctors and patients it into a box and then lose the patients because they didn't fit into our algorithm. So that's why we've chosen that that time period.

And the techniques that we're going to use and the things that we're going to focus on, OCT to look at fibrous cap thickness, red or white thrombus, TCFA plaque rupture and plaque ulceration, these are the major criteria. These are all the strengths of OCT. Some of the minor criteria we're going to try to look at, I'm not sure how this is going to turn out.

But we're going to focus on the major things. And then the lipid core plaque and the LCBI by NIRS. And then IVUS, we're going to look at plaque burden, the minimal cross-sectional area and the minimal and the remodeling index as well.

And then we're going to record other features, calcification. And one of the things that's been reported about ultrasound is that hypoechoic plaque is supposed to be a marker of lipid core plaque. But if you have calcium, you can't assess that. But you can assess it by NIRS. So we're going to do some comparative things. We have some predefined comparative studies that we're going to do as well.

So in summary, the multivessel PCI approach may actually be better than the culprit approach after STEMI. And early revascularization may actually be better than late revascularization. And this is contrary to our guidelines, but it may be true. And the rationale for benefit is not quite clear yet, and it may be related to complete revascularization of all severe stenosis, which is the FAME 2 approach, using FFR, which makes sense, and/or perhaps a preemptive prophylactic revascularization of vulnerable plaque in these vulnerable patients.

And I think that now, I think that plaque burden really is the most important vulnerable plaque feature. I'm not totally sold on the whole Kool-Aid about some of these high risk vulnerable plaque features, but I think it's an area that's interesting to study. But I am certain that using a single technology will not be the way to go, that we're not going to be able to do this with either a virtual histology or an OCT or NIRS/IVUS. And we're going to need multiple modalities to look at the plaque characteristics and also recognize that there may be a lot of other patient factors that we haven't even clued into yet.