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RAJIV GULATI: Hello, and welcome back to the Mayo Clinic Medscape video series. I'm Rajiv Gulati, Interventional Cardiologist and Professor of Medicine at Mayo Clinic, and today we'll be discussing the controversy surrounding the use of paclitaxel devices in peripheral arterial disease. I'm joined by my colleague, Sanjay Misra, Vascular Interventional Radiologist and Professor of Radiology at Mayo Clinic and a renowned expert in this area. Welcome, Sanjay.

SANJAY MISRA: Thank you, Rajiv.

RAJIV GULATI: So Sanjay, what are these paclitaxel devices, and what are they used for?

SANJAY MISRA: Yeah, so excellent question. Paclitaxel coated devices are being used primarily now in the lower extremity for revascularizing atherosclerotic disease, and they've been used to limit restenosis, and there are different formulations of the technology and delivery methods that are being used currently.

RAJIV GULATI: So balloons and stents?

SANJAY MISRA: Yes.

RAJIV GULATI: OK, fantastic. That's helpful, and why was there a rapid uptake in these devices compared to prior technology?

SANJAY MISRA: Yeah, so there were several randomized controlled trials in patients with occlusive disease that showed that restenosis rates are reduced when you use these devices. So the blood vessel stayed open longer, and the patient had better outcomes.

RAJIV GULATI: Better outcomes in terms of limb function and symptoms?

SANJAY MISRA: Yes, so they were able to walk farther and have less interventions once they were used.

RAJIV GULATI: So let's fast forward to now, and there's this controversy based on some data. This systematic review and study level meta analysis suggesting, I believe, a mortality concern. Perhaps you could outline the controversy and where we are now.

SANJAY MISRA: Yes, so late last year in December, a meta analysis was performed by the Katsanos group in*Journal of American Heart Association,* and it showed that there was an increase all cause mortality in patients that received paclitaxel coated technologies. The authors lumped all the technologies together, looked at the available data and found that patients that received the devices had higher all cause mortality. What the authors were unable to provide us was why this was happening and what could be a possible hypothesis.

RAJIV GULATI: Got it. So this was a meta analysis of randomized trials of both balloons and the stents and five year outcomes showing mortality. But the mortality signal didn't emerge early on if I'm right.

SANJAY MISRA: Yes, so the early signal, there was no signal in one year, no signal at two years, or a ramping up of the signal at two years. And at five years, it became a larger signal. One of the challenges of this meta analysis is at that time, there were two studies that had completed five year enrollment. And the majority of the studies, approximately two dozen or so, were in the one to two year follow up range. So a lot of the patients were not included in the longer term data.

RAJIV GULATI: I think that's an important thing for our audience to note. The other question to you is that all these peripheral arterial disease studies of interventions, they're not powered for mortality, and mortality isn't generally considered an endpoint worthy of primary outcomes. Is that right?

SANJAY MISRA: Yes, so that's a very good point for our audience. The trials are all powered for restenosis TLR. Mortality is censored. However, what we don't know is what is the cause of mortality. And what I tell my patients is that if you got one of these devices, walked across the street, got hit by a car, you would be associated in the group that got all cause mortality.

So as you know, Rajiv, all cause mortality can be anything from cardiovascular events to non-cardiovascular events. What's unclear in this data set is how many were linked to the device and were true cardiovascular events or plausible cardiovascular events and how many weren't. So the cause of mortality is really not known.

RAJIV GULATI: And I guess one of the issues is that this meta analysis was a study level meta analysis and not a patient level meta analysis. So that won't account for changes that might have occurred during the follow up period, for example, crossovers if I'm right, and you won't account for perhaps lost to follow up. Is that correct?

SANJAY MISRA: Yeah, so about when the meta analysis was done, approximately 20% of the patients were lost to follow up, and we did not know what happened to them. And so if you're looking at small data sets, approximately 4,000 patients or so, 20% is 800. And so one, it was empowered for mortality, and two, a significant amount of patients were lost for follow up, three, we didn't know at a patient level what happened to these patients and what were their outcomes.

RAJIV GULATI: That's an important caveat when we interpret that meta analysis, I'm sure. So despite that, despite the methodologic issues that are out there, there's still a signal, and I guess our bar for concern should be very low when it comes to a signal for harm. So as a result of that meta analysis, the publication, a whole bunch of groups have got together, and perhaps you can enlighten us as to what the discussions have been, who's been involved, and where we are right now.

SANJAY MISRA: Yes, so there are two different groups that are working in synergy on this task force or this problem, and there's others. I'll only mention the two that I'm working with. One is to Viva Faster Leaders forum. They have obtained all the data at an individualized patient level from all randomized controlled trials done in America, and we're in the process of looking at is there a signal or not, and that's a paper that will be coming forward soon.

The second group is a multi societal group, a paclitaxel coalition of different specialists including-- in no particular order-- American College of Cardiology, SCAI, American College of Radiology, American Heart Association, Society of Vascular Medicine, Society of Interventional Radiology, and an Endovascular Surgical Society, and the goal of that group is really to partner with the FDA and help understand what we should do next now that we have some concerns about this technology. Number one, who should be the patients they get treated? Number two, what should that consent process look like? And number three, what should the follow up process look like? And so those are three major things that are happening in the background.

RAJIV GULATI: I mean, I think it's commendable how rapidly the societies have got together and how inclusive the leadership forum has been, and involving the FDA, I'm sure, is a very important thing. Perhaps you can tell us where we are right now. So for clinicians facing patients who they believe might benefit from a paclitaxel coated device, what should they do?

SANJAY MISRA: Yeah, so that's a very interesting question that we're asked all the time. You know, what would you do if you see this patient? I think a lot of this is driven by the types of patients you see. If these patients are presenting with claudication, which is pain with walking, or if they're coming with critical limb ischemia, which is the end product of atherosclerotic peripheral arterial disease and they need a limb revitalization. So one is what is the patient that you're treating, how sick is he or she, and what is the best therapy for them? And then finally--

RAJIV GULATI: So let let's go back to that. So that's a really interesting point. So you're saying that the patient who has more to gain with a device would be someone who has critical limb ischemia, for example, and you'd have a lower threshold to use the device?

SANJAY MISRA: Yeah, I think the CLI patient would be a lesser threshold to use the device, because you'd want effective revascularization, and you'd want durable revascularization, and these patients have higher mortality risks than patients that are claudicate. The problem with the data we have is 90% of the data set is in the healthier patients, which are the claudicates, and so you would have to extrapolate from the claudicate group to the CLI group.

And so I think that would be a subset that one would consider revascularizing in. I think the other things are how sick are the patient? Would a repeat revascularization be more hurtful than a very good revascularization, a Cadillac procedure, a priority. And then obviously, what are the risks and benefits of a surgical bypass, and could this patient undergo a surgical bypass? So it's very complex decision making.

RAJIV GULATI: That's really helpful. It's as though it's not as simple as banning all the devices and waiting for more data, but we should be nuanced in our discussions with patients. And so what is Mayo doing right now with regards to both the balloon and stent?

SANJAY MISRA: Yeah, so as you know, Rajiv, were a very large organization in multiple different geographic sites and multiple venues within these geographic sites from cardiologists, surgeons, radiologists practicing in several different centers. Given that we have such complexity of patients and diversity of patients, we've put a moratorium on using these devices until we understand what our data is.

And so we have looked at our data set across the enterprise, that includes Scottsdale, Jacksonville, Rochester in the health system, and we're analyzing our results and trying to decide on what are our results, because there are center to center biases for these data sets. Anytime you do a randomized controlled trial, you're assuming that every patient gets treated with the optimal medical therapy at the same level. And as you know as a cardiologist, a simple thing such as a statin and good hypertensive control could be 30% mortality difference versus someone that's not, and so that's one thing that we're looking at as we speak.

The other thing that we're looking at is what will the FDA say? Currently they're suggesting a very good counseling of the patient, very good follow up of the patients, and then informed consent based on your local environment that you work in. And so while we're waiting for is to understand will the FDA provide additional guidance with additional data sets that are going to be released? So for the short term, we are recommending not using it. Once our data is available, we will look at that data and see where the FDA is and then decide on what to do for our patients.

RAJIV GULATI: So right now, as I understand it, we're sort of in a limbo, and what is the data that we need to help us make a decision about whether these devices should be used and who they should be used in?

SANJAY MISRA: That's a great question. I think it has to be at a level of what is best for the patient? So at least for Mayo, what's our own data show and how did our patients do?

RAJIV GULATI: But that's not going to be randomized data. Do you think we'd be able to get patient level meta analysis, patient level information from the initial trials?

SANJAY MISRA: Yes, so we're going to get-- so there's a couple things-- what we're doing locally and what's going on nationally. I'll talk about the national. We're getting individualized patient meta analysis for randomized trials. We're getting large data sets from Medicare and other providers, and we're also getting large data sets from Germans and other national data sets outside of the US. So I think that's what's happening, that data will help us in conjunction with the FDA.

The local data, I think, will also help us they'll give us an idea of what is our data look like in Mayo. We'll have individualized patient data, and we'll also have a control group of patients that didn't get stents that were coated, and we'll be able to sort out with some level of confidence how our patients did. And I think those two data sets will really help guide the conversation, at least at Mayo, and maybe even outside of Mayo.

RAJIV GULATI: Certainly sounds that way. I mean, more robust data with better follow up I'm sure would be highly informative to the FDA and to our clinicians and patients. Let me ask you one more question, Sanjay, so what does this mean for the field of peripheral arterial disease scientists? Should mortality be considered an endpoint in all future studies of device interventions?

SANJAY MISRA: Yeah, so that's a great question. As you know from the coronary data set, very few trials have ever actually been powered for a mortality endpoint. And what I think what we're finding is that mortality plays a role in anytime we do an intervention. The question is, what is the optimal trial design? How long should we follow these patients, and what are the ways of following patients?

Do you enroll everyone in a registry, NCD or VQI, another registry, and follow all these patients longitudinally for what happens to them? And more importantly, if they were to die, how do they die? And I think these are important questions that are going to need to be discussed and debated. For the short run, if you were to do a mortality trial in this space, we're looking at 10 to 20,000 patients which would probably be very hard to accomplish anytime soon.

RAJIV GULATI: Well, thank you, Sanjay, for highlighting the controversy regarding these devices and also telling us about the immediate future for generating more data and guidance for our clinicians and patients, and thank you for joining us on the Heart.org Medscape Cardiology.