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Flip the Coin: Have Catheter-Directed Therapies Found Their Place in PE Management?

Announcer Introduction:
This is CME on ReachMD! This CME activity, titled, “Flip the Coin: Have Catheter Directed Therapies have found its place in PE Management?” is brought to you by The American College of Chest Physicians and supported by an educational grant from Janssen Pharmaceuticals, Inc., Administered by Janssen Scientific Affairs, LLC.

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Here’s your host Dr. Stavros Konstantinides, Professor of Medicine, Medical Director at University Medical Center in Mainz, Germany.

Dr. Konstantinides:
Risk stratification of acute pulmonary embolism, based on standardized and validated criteria, is critically important because it guides risk-adjusted initial treatment. While all patients with acute PE obviously need anticoagulant therapy, the question is, who needs on top of that and beyond that, immediate, advanced reperfusion treatment to rapidly remove thrombotic material, and thus relieve the patient’s heart from the pressure overload that has resulted, or is about to result, in hemodynamic decompensation. A number of catheter-directed options for reperfusion treatment have been tested for pulmonary embolism. They have been shown to work, to be effective, and they’re now available, and today we want to discuss with our experts their potential and their appropriate use

Dr. Konstantinides:
I’m your host, Dr. Stavros Konstantinides, and I would like to welcome my guests, Dr. Riyaz Bashir who is a Professor of Internal Medicine at Temple University, and Dr. Akhilesh Sista who is the Chief of the Division of Vascular and Interventional Radiology at NYU Grossman School of Medicine. Dr. Bashir and Dr. Sista, thank you for being here today.

Dr. Bashir:
Thank you very much, Stavros, for having us. It’s truly an honor.

Dr. Sista:
It’s a pleasure to be here, Stavros. Thank you for having us.

Dr. Konstantinides:
Thank you. Let’s start by when we talk about risk stratification and risk-adjusted treatment. I would briefly like to remind, as a introduction, that we are talking about acute pulmonary embolism with hemodynamic collapse or decompensation. This is the high-risk PE, or massive PE. And then, at the other end, we have low-risk PE – patients who are clinically stable, patients who have no evidence of, uh, right ventricular pressure overload, of right heart failure. And then, we have the remaining, um, patients, who are in the middle of this spectrum, who may be 50%, or maybe more, of the patients with acute PE – the patients at intermediate risk. We’ve had recently updated guidelines from the European Society of Cardiology, in 2019, on the treatment of acute PE from the American College of Chest Physicians, uh, very recently in 2021.

Akhi, so what’s critical for stratifying a patient into high risk or into intermediate risk? What would you concentrate on?

Dr. Sista:
Well, Stavros, you know, you've really led the way here in many ways., you and your European colleagues, especially in the ESC Guidelines, teasing out the difference between such patients, because what we do know is epidemiologically, high-risk patients face a very high risk of mortality. We saw that from the, large registries that were conducted in the late '90's, and so, really, when a person with high-risk PE comes in hypotensive, the goal is to reperfuse immediately with whatever means possible, most commonly, you know, with systemic lysis. Now there's big difference between a patient who is unable to maintain their systemic blood pressure and a patient who can, and that's obviously the critical differentiator between high-risk and intermediate-risk patients, where intermediate-risk patients tend to have some amount of right ventricular compromise, and it can be in any sort of form. So, critical signs for me, within the intermediate risk, in terms of concern for decompensation into the high-risk category, would include a markedly elevated heart rate, perhaps a – signs of intermittent hypoperfusion, such as an elevated lactate and a rapid, and significant tachypnea. But, I'll stop there, because there's much more that we can discuss here.

Dr. Konstantinides:
Riyaz, what are your thoughts on this? I mean, what are, for you, the important parameters? And once you have diagnosed intermediate-risk or high-risk PE, how would you proceed in terms of the gold or old standard of reperfusion treatment, which is systemic fibrinolysis?

Dr. Bashir:
Thank you, Stavros, and thank you, Akhi. Fibrinolytics in patients with acute PE, I think all PE patients who have high-risk PE should be considered for systemic fibrinolysis. I think a very small percent of patients who have intermediate-risk PE may be considered for systemic fibrinolysis at least half-dose. Now that is assuming that they don't have any absolute contraindication to systemic fibrinolysis, or they already received systemic fibrinolysis but are still, hypotensive. And those patients should be considered, for other reperfusion therapies, like catheter-based or surgical embolectomies.

I wanted to emphasize one point, that we need to be carefully assessing what the baseline blood pressure is and many times, these patients who are hypertensive then dropped their blood pressure by greater than 40 millimeters of mercury, but still have a systolic blood pressure that is greater than 90 millimeters of mercury. And these patients might be misclassified as intermediate risk, while they're actually high-risk PE's.

So I wanted to emphasize that point, I also want to emphasize that elevated lactate levels could be an harbinger of acute decompensation.

Dr. Konstantinides:
Thank you very much, Riyaz, and, that is really the perfect transition to our actual topic today.

If you're just tuning in, this is CME on ReachMD. I'm your host, Dr. Stavros Konstantinides, and I have the pleasure of speaking with my colleagues, Dr. Riyaz Bashir and Dr. Akhilesh Sista, on the topic of catheter-directed therapies.

So let's get to the catheter-directed therapies, what is the current status? Riyaz, maybe you would start by telling us a few things on pharmacomechanical options, which include low-dose thrombolysis, and then Akhi, I would ask you to continue with purely mechanical options of treating acute PE.

Dr. Bashir:
Sure, Stavros, you know over the last three or four decades, we have learned one thing with fair amount of certainly, and that is thrombolytic agents dissolve blood clots the best. However, there are two major limitations to systemic fibrinolysis, which includes a high major bleeding rate, and the inability of the fibrinolytics to penetrate deep into a totally occluded vessel. Both these limitations can theoretically be addressed by placing an infusion catheter within the thrombus. And using a smaller dose of fibrinolytic, that could dissolve the clot, hopefully making it a safer and more efficacious alternative. And there are three ways of accomplishing this. One is catheter-directed thrombolysis alone. Second is ultrasound-facilitated catheter-directed thrombolysis, and third is pharmacomechanical catheter-directed thrombolysis. In catheter-directed thrombolysis alone, the operator uses usually a first-generation, single lumen infusion catheter to infuse a fibrinolytic over a prolonged period of time, usually up to 24 hours, and these catheters are primarily designed for use in small vessels, that are less than 10 millimeters in diameter, and therefore, they don't distribute the fibrinolytic over a large cross-sectional area of the thrombus.

The second method is ultrasound-facilitated catheter-directed thrombolysis which again, uses a single lumen infusion catheter, but uses intravascular ultrasound energy to increase the depth of penetration of fibrinolytics. And the third method is a combination of mechanical fragmentation with catheter-directed thrombolysis, called the pharmacomechanical CDT. We have developed a pharmacomechanical catheter-directed thrombolysis device, that is dedicated for large vessel, like IVC and pulmonary arteries. This device is called the Bashir

Endovascular Catheter. It's a 7-French device, which has ten to twelve centimeter infusion basket at its distal end, and this spiral cut infusion basket consists of six nitinol-reinforced, mini-infusion catheters with 48 laser-drilled holes. And once we expand this basket inside a thrombus, we can pulse-spray a fibrinolytic into the thrombus and that dilute TPA gets trapped within the thrombus and continues to dissolve the thrombus, even after the device is taken out. So these are the three forms of catheter-directed thrombolysis, and, Akhi, you want to tell us something about the pure mechanical options?

Dr. Sista:
Sure, Riyaz, so, when we talk about purely mechanical options, we're talking about devices that can macerate, that can aspirate, that can capture, that can remove thrombus without the use of a fibrinolytic drug, which is, on the surface very appealing. Many of these devices have just entered the market. Some of them have been FDA-cleared, and I think I'm gonna ask Riyaz to describe some of those studies that have obtained FDA clearance for these – these devices, but many have probably heard of the, Inari FlowTriever device and the Penumbra, Indigo System, as the two devices that have been FDA-cleared., the FlowTriever is a large-bore aspiration device, , that can be maneuvered into the pulmonary circulation and then remove large proximal thrombus through pure aspiration. It does have a component to it that can be used optionally to capture clot and bring it into the catheter itself. The, Indigo Aspiration System is now up – and that – that catheter goes up to 24-French, so quite large bore, to say the least. The Indigo Aspiration System is now up to 12-French, and uses a, mechanical pump from the back end to remove thrombus, and it has a, sort of, smart sensing system to minimize blood loss as well, which was a previously a concern with the device, and it, also uses aspiration as its prime mode of removing thrombus. There are other devices that are emerging, that serve to macerate, chew up, and bring in thrombus, either through a combination of, literally chewing the clot or capturing it through some sort of windsock-type apparatus.

Dr. Bashir:
Sure. Akhi, thank you very much for describing these devices. You know, most of the devices that are cleared by FDA for the use in pulmonary embolism have been cleared through a 510(k) pathway. And as a part of this clearance process, FDA requires a prospective clinical trial using core lab for outcomes analysis, under an IDE or an IND. And most of these trials are single-arm, multi-centered trials that have enrolled intermediate risk PE patients, with the exception of SEATTLE II trial, in which 20% of the patients had high risk massive PE. this trial enrolled 151 patients, used ultrasound-facilitated catheter-directed thrombolysis with an EkoSonic catheter. The other trials included the FLARE trial, which enrolled 104 patients that were treated with suction embolectomy, without thrombolysis, using a FlowTriever device. The third trial was the EXTRACT-PE trial, that you were the principal investigator on Akhi. It enrolled 119 patients, and used an aspiration thrombectomy device called the Indigo Aspiration System. And all of these trials have uniformly shown that there is a significant improvement in RV/LV ratio, and thrombus burden reduction at 48 hours, by CT scan.

And we have also seen very low major bleeding rates with these novel devices. And finally, the RESCUE trial, which is currently ongoing and is planning to enroll up to 125 intermediate-risk PE patients, and this trial is using pharmacomechanical CDT, using the Bashir endovascular catheter, and Akhi, you presented the results of this prespecified, interim analysis at the recent VIVA meeting in Las Vegas., so that's the update for these single-arm trials using these novel devices. Akhi?

Dr. Konstantinides:
So what are we to expect, Akhi? (laughs) Now, in the future?

Dr. Sista:
You know, Stavros, I'm very curious. You've been involved in this field and have seen the evolution of therapy – profusion therapy over the course of your career, and your perspective on this is incredibly unique. Very few can, can really understand the entire arc of what we're discussing right now. I'm very curious, as you hear these mechanical options, and these pharmacomechanical options, what strikes you about the landscape of PE right now, before we talk about future directions?

Dr. Konstantinides:
Yes, thank you. That's a very good question. So, I am really amazed, for the first time, I must say, I think now, finally, after all these years or decades, we have technical innovations that – that are here to stay. So it's not just some, you know, some fireworks of that will disappear. I believe now, interventional treatment of PE, catheter-directed treatment, has come of age, we are getting increasingly better in terms of efficacy, and now what I expect from these devices is to also show – as we expect also from drugs – to also show that patients can benefit clinically from them. I don't know what you think?

Dr. Sista:
I couldn't agree more, and I think that sets up the question of what is next for these devices. There are two major gaps right now for catheter-based therapies. The first is a lack of randomization. I like to frequently say that you and your colleagues have done an incredible job, with the systemic thrombolysis trials, of randomizing over 1,600 patients over the past couple decades, and we in the catheter world have only managed to randomize 59. And so that is a massive data gap that we need to – we need to rectify quickly. The

second – you also alluded to – was the lack of clinical outcomes. So, the RV/LV ratio does have, some prognostic capabilities in the first 30 days, but beyond that, it loses sort of its, punch, when it comes to determining whether this therapy should be here to stay. Stavros, you're leading the charge on the HI-PEITHO trial, which is a follow-on from your landmark PEITHO trial, and it's got so many great features, involving sites in both Europe and the United States, so it's the first trans-Atlantic, randomized trial that I know of in PE. It is randomizing patients to catheter-directed lysis with the, EKOS Sonic catheter versus anticoagulants alone. It is looking at clinically relevant short-term outcomes, as the primary endpoint, but involves some amount of safety as well as efficacy. And, is really poised to give us some very important information about when and in whom to use catheter-directed lysis, with the EKOS catheter.

I am privileged to be leading, another trial that we hope to have, patients enrolled by the end of next year, if all goes according to plan, called the PETRACT trial. We haven't come up with an official way of saying it yet, but PETRACT is kind of the easier way to say it, so we're going to go with that for now, which also randomizes catheter-based therapy to anticoagulants, with an emphasis on the medium to long term, looking at cardiopulmonary physiology through cardiopulmonary exercise, testing as well as patient, reported outcomes and functional outcomes, over the course of the year following intermediate-risk PE.

And then finally, there is the PEERLESS trial, which is being sponsored by Inari Medical, the same company that, sponsored the FLARE trial with the FlowTriever device. And they're looking to see whether there's any difference between thrombectomy and catheter-directed thrombolysis, so the technique of catheter-based therapy is what is being, assessed in the PEERLESS, trial.

All of these patients are enrolling approximately 500 patients, so we will go from having 59 randomized patients to well over 1,000. So the future, when we look forward to next six or seven years, if we're successful as scientists and as a field, in advancing these, trials forward, we will be in a very different spot when it comes to understanding these devices than we are now.

Dr. Konstantinides:
Oh, yes. I think so. And as I said, at last, we are moving forward, and I think we will have very good data within very few years from now. So, doctors, as we wrap up our discussion, so may I ask you both to share with us briefly, your key takeaways and final thoughts. Riyaz?

Dr. Bashir:
Sure. Stavros, my key takeaways are that the rapid technological advances that we are seeing in catheter-based therapies are making this procedure safer and possibly more effective for our high, intermediate-risk PE patients. And the contemporary single-arm trials have consistently shown improvement in surrogate endpoints, like RV/LV ratio and thrombus burden reduction, with reduced bleeding rates. However, the major gap in the application of these therapies is the lack of adequately powered, randomized controlled trials, with functional long-term outcomes, as Akhi just mentioned. And I believe these randomized controlled trials will be very instructive in terms of appropriate patient selection for these therapies.

Dr. Konstantinides:
Thank you, Riyaz. Akhi, your thoughts, takeaways?

Dr. Sista:
You know, I would echo what, Riyaz just said. Those are very well put. The, , what I would add is that we are in I think we're entering into a golden age of PE, and holding our communities' collective feet to the fire. The NHLBI is very, very interested in pulmonary embolism, having conducted a State-Of-The-Science PE Summit, in late 2020, hopefully, they will also sponsor the PE-TRACT trial, so that we can really get to the bottom, between high pytho and PE-TRACT, of the clinical benefits in both the short term and the long term, six to seven years from now.

Dr. Konstantinides:
Thank you, Akhi. I like this, the golden age of PE is coming, The challenge is now to identify the right candidates among patients with high-risk, and particularly intermediate-risk PE, who can benefit clinically from these procedures. This is the task of state-of-the-art trials, which you heard about, and some of which are already underway.

I would like to thank my guests, Dr. Riyaz Bashir and Dr. Akhilesh Sista, for speaking with me and our ReachMD audience.

Dr. Bashir:
Thank you very much for the opportunity, Stavros.

Dr. Sista:
Thank you, Stavros. This was a lovely session. Enjoyed being a part of it.

Dr. Konstantinides:
Thank you both.

Announcer Close:
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