

AN INTERVIEW WITH...

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Dr. Sista discusses the PE-TRACT trial's origin, goals, and current status, as well as what it's like to run a PERT in New York City.



Can you summarize the background and aims of PE-TRACT trial? What stage is it currently in, and when is enrollment anticipated to begin?

We are currently at a stage in submassive pulmonary embolism (PE) treatment where we don't know whether catheter-directed therapy (CDT) should be part of the algorithm or not. It has a lot of promise, is minimally invasive, and uses the latest imaging and device technologies. Some data support its preliminary efficacy and perhaps even safety. However, no short- or long-term clinically relevant outcomes have been described in comparison to anticoagulation alone. Therefore, the PE-TRACT trial aims to determine whether CDT should be routinely performed for patients with submassive PE. It would be the first large-scale randomized trial in the United States on CDT, and we're trying to bridge the evidence gap between systemic thrombolysis for submassive PE and CDT for submassive PE.

Submassive PE is an interesting entity because it has both acute and long-term deleterious outcomes. The literature thus far has focused on the short-term (30 days) rates of clinical deterioration, mortality, and recurrent PE. Studies have not yet focused on the fact that many patients don't do well in the months to years after PE, specifically that they may experience shortness of breath when exercising, have reduced quality of life, or become deconditioned and debilitated (eg, easily dyspneic when walking up stairs). These symptoms are being increasingly recognized, especially in light of recent long-term observational studies that have shown that approximately 30% to 50% of patients have some decrement in their cardiopulmonary status within a year after experiencing a PE.¹

Systemic thrombolysis studies and most studies have not focused on how interventions affect these long-term outcomes. PE-TRACT aims to ascertain whether CDT is the right approach in the acute setting by determining whether it improves short- and long-term outcomes.

Currently, the PE-TRACT team has secured a U34 planning grant from the National Institutes of Health (NIH).

This is a great step because it gives us the opportunity to research alongside talented NIH statisticians, the ability to select an innovative and adaptive trial design, mobilize the site network, organize the infrastructure, and galvanize the PE community toward a pivotal trial for submassive PE. The next step is to apply for a UG3/UH3 award in February 2020. If we are awarded funding, enrollment could begin in late fall 2020 or early 2021.

The time couldn't be more ripe for this type of investigation. With several devices now approved for PE-specific indications, there are several treatment options available, but we still don't have fundamental trial data to tell us whether we should be routinely removing thrombus via this technique.

How has your experience in the other "-TRACT" trials prepared you for or guided your approach to PE-TRACT?

I think these studies were absolutely fundamental. As a new attending at Weill Cornell Medicine, I was tasked with building the deep venous practices in my section. I had done some work as a fellow in the deep venous space, and I remembered that there was a major trial at the time (around 2011/2012) called the ATTRACT trial. I spoke with the principal investigator, Dr. Suresh Vedantham, about the trial. He was understandably a bit skeptical that a second-year attending wanted to join the trial and was not sure that our center at Cornell had the resources and practice space to effectively enroll and conduct the trial because, at that time, we didn't have a reputation for handling acute deep vein thrombosis (DVT) cases. However, this gave me the opportunity to visit my noninterventional physician colleagues and educate them about the current state of the DVT literature and why the ATTRACT trial was so important.

This initial experience recruiting into a major national trial opened doors that wouldn't have been there. Because of ATTRACT, consults came in for complex inferior vena cava filter retrieval and complex ilio caval reconstructions, etc.

(Continued on page 119)

(Continued from page 122)

Another unexpected area that opened up because of ATTRACT was PE. One day, I was admitting a DVT lysis case to the intensive care unit and one of the attendings asked if I had ever performed a similar procedure for a PE, which I had done as a fellow at Stanford University. From there, we started building one of the first pulmonary embolism response team (PERT) programs in the country, performing CDT for PE and obtaining good results.

In 2014, I partook in a clinical trials workshop and decided to work on a protocol for a CDT PE trial. I developed the protocol over the course of a week with resources from the Radiological Society of North America and asked Dr. Vedantham to review my work. He said that he'd been waiting for this type of study to be done for PE, and so he brought in his entire steering committee from the ATTRACT trial, consisting of world-renowned venous thromboembolism experts. This was the foundation that launched PE-TRACT.

Designing a trial in 2020 and beyond, what opportunities are there for advanced data collection and management methods (ie, big data) to be leveraged, and how might this affect the utility of future trials?

There is certainly a focus on big data now, and the NIH is starting to allocate resources toward it. The Clinical and Translational Science Awards (CTSA) network is a network of sites that have attained funding from the NIH to make the clinical research process more streamlined and effective. One of the resources that has come from this is the ability to query electronic medical records (EMRs) included in these CTSA sites. This has many potential utilities; the first that comes to mind is clinical trial planning. For example, if I want to know how many patients I would potentially enroll per month based on the number of patients who are presenting with submassive PE per month, I could query the entire network of CTSA sites (which includes approximately 40 sites). If we are able to enroll 40% of those patients, then we could anticipate the rate of enrollment and an enrollment completion date. Previously, we took our best guess at these figures, because we didn't have the ability to query ICD-10 codes or perform advanced searches via EMRs. We are still in the early stages of using these data for trial design, but this has the potential to revolutionize the way clinical trials are performed going forward.

How would you describe the challenges of determining trial endpoints in this difficult etiology?

This is one of the major issues with studying submassive PE. In massive PE, we know that something must be done to address the situation, either by systemically lysing the

patient, aspirating the clot percutaneously, surgically removing clot, or putting the patient on extracorporeal membrane oxygenation. Without one of these interventions, patients with massive PE have a mortality rate of approximately 50%. Therefore, trials where intervention is withheld would be unethical. On the other hand, with low-risk PE, we already know that anticoagulation can prevent clinical deterioration and death, and therefore it's also not appropriate to subject those low-risk patients to a potentially invasive and dangerous procedure.

Submassive PE hits the sweet spot for clinical investigation, because there's enough equipoise surrounding whether we should be intervening or not. However, this also poses some challenges to determining endpoints for the study. The PEITHO trial was a positive trial that combined the short-term death and clinical deterioration endpoints, but the mortality rate was very low (< 2%). If mortality is the primary endpoint, 2,000 enrolled patients would be required, which would probably take 10 years and would likely cost upward of \$25 million. The other problem of designing toward a mortality endpoint is that mortality is an uncommon occurrence and may miss the bigger issue of long-term cardiopulmonary health after submassive PE.

You then look at issues that occur more commonly in terms of the long-term consequences of PE, such as exercise intolerance, that occur in 30% to 50% of cases. However, the problem is that we don't have pilot or preliminary data that clearly indicate that intervention provides better outcomes than anticoagulation alone in the long term. In theory, it makes sense that by removing clot early, the heart and lungs would recover more quickly and more permanently, but we don't know this for certain.

Another issue is that post-PE syndrome, or chronic thromboembolic disease, has not been well-defined in a syndromic way with a validated mechanism of evaluation that could be used as a primary endpoint. Although we believe that this trial is badly needed, we have struggled to determine the best endpoint. This is exactly why the U34 grant is so helpful, as it has been used as an opportunity to set certain trial designs and consider some truly novel, innovative, and impactful endpoints in both the short and long term that will allow for a comprehensive assessment. This, in turn, may potentially define our understanding of long-term cardiopulmonary disability after a patient has experienced a PE.

Will there be mechanisms by which the treatment options and protocols can be modified and kept up to date over the course of the trial?

Absolutely. It's very important that PE-TRACT remains relevant and up to date with the state of the art for

PE care. If new data are published indicating that our protocol is obsolete and that a different approach or device needs to be added to the trial, we have mechanisms to address these issues. Such concerns would be looked at by subcommittees that will continuously evaluate our protocols to ensure that PE-TRACT will not be irrelevant to the modern-day practice of CDT.

With patients consistently seeking improvement in long-term exercise capacity as a top treatment goal for submassive PE, as highlighted in your recent survey,² to what degree do you weigh this factor in your treatment algorithm?

The point we were trying to make with this survey is that we don't want to be too paternalistic as physicians about what outcomes matter to patients. As physicians, we are very concerned about death and bleeding, a concern that sometimes prevents us from being aggressive in terms of actively removing clot or giving local thrombolytics because these interventions subject the patient to certain risks. However, these treatments also offer potential benefit, so we need to discuss with patients the trade-off between the risk of having a complication and the potential to improve long-term exercise ability and how much weight they place on each outcome (presuming a trial such as PE-TRACT shows a long-term benefit with CDT). It was interesting to see how differently physicians and patients weighed these potential risks and benefits. The message to take from this is when we're designing a trial, we need to make sure that the results are not just relevant to physicians' internal struggles and priorities regarding treatment decisions, but also take into account what is important to patients.

How do you currently assess and address post-PE syndrome?

As alluded to earlier, this is still in the early phase of becoming a recognized diagnosis—it's not like the post-thrombotic syndrome, which has the Villalta score to help in the assessment and treatment choice. The most important aspect of PE care is to longitudinally follow the patient, which we do in our local PERT and I know many PERTs around the country do as well. The idea is to monitor patients and assess their well-being in terms of exercise ability and shortness of breath when climbing stairs. By monitoring their progress over time, we can determine if they're not progressing and bring them back for a workup. That workup could include an echocardiogram, ventilation/perfusion scan, and perhaps a CT scan, cardiopulmonary exercise test, or 6-minute walk test. These objective assessments will indicate whether they have a cardiopulmonary problem (eg, poor cardiac reserves on the right side of the

heart, residual obstruction in the pulmonary arteries, or a combination of these), which basically prevents them from achieving optimal exercise capacity.

Chronic thromboembolic pulmonary hypertension could be identified through longitudinal care and has very clear treatments. However, even if patients don't have resting pulmonary hypertension, there are reports of patients with chronic thromboembolic disease undergoing pulmonary thromboendarterectomies. Balloon pulmonary angioplasty has not yet been fully embraced, but perhaps in the future it will be used for patients with the more severe chronic thromboembolic disease who don't meet the threshold of pulmonary hypertension.

This is still evolving and I think PE-TRACT will help define the post-PE syndrome and provide an opportunity to learn more about the disease overall.

What are the unique aspects of being part of an emergent response team in a city like New York?

Our center is one of four or five major institutions in the city, so it's a very competitive environment, but that's just the nature of the beast with New York medicine. However, we're also all partners in this idea that PERTs are the right treatment model. In fact, Dr. James Horowitz runs a chapter of the National PERT Consortium called NYC PERT, and we all come together every quarter and discuss our PERTs in terms of issues we're having and any notable or challenging cases, which we love.

In New York, it's very much the spoke-and-wheel model across the hospitals throughout the five boroughs. So, you're not just isolated to your hospital, you become the PERT for the institution, which is a more modern treatment model and one that is quickly expanding. ■

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2. Taslakian B, Li C, Goldhaber SZ, et al. How the results of a randomized trial of catheter-directed thrombolysis versus anticoagulation alone for submassive pulmonary embolism would affect patient and physician decision making: report of an online survey. *J Clin Med*. 2019;8:215.

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