VDM Interviews Prof. Stavros Konstantinides on the HI-PEITHO Trial, and How it Aims to Help Patients and Inform Guidelines on Intermediate-to-High-Risk Pulmonary Embolism

VDM talks with Stavros Konstantinides, MD, PhD, FESC, FRCP, about the HI-PEITHO trial.



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HI-PEITHO is a multi-center, prospective, randomized, controlled trial, the first international trial of any interventional therapy with anticoagulation for pulmonary embolism (PE) compared to anticoagulation alone. The objective of HI-PEITHO is to assess whether treatment with the EkoSonic™ Endovascular System (EKOS) (Boston Scientific) leads to a significant reduction in the acute composite outcome of the following measures: 1) PE-related mortality, 2) cardiorespiratory decompensation or collapse, and 3) non-fatal symptomatic and objectively confirmed recurrence of PE, compared to anticoagulation alone, within seven days of randomization. Patients will be followed for one year. The trial is a joint research study led by Boston Scientific, in collaboration with the PERT Consortium and the University of Mainz Medical Center, Germany.

VDM: Can you tell us about the impetus for the HI-PEITHO trial?

Dr. Konstantinides: We have been studying and treating acute PE for many years and for me personally, it has been more than three decades. Many times, in our careers and in our daily work, we have encountered patients who are sick and have severe PE. Many of these patients are not (yet) in shock; they still appear to be stable, but they are nevertheless in a situation where they could destabilize and decompensate at any time. This is what we call "intermediate-risk" PE. We simply do not know the correct way to proceed with these patients. Some of the things we grapple with when assessing treatment options are whether we should give them thrombolytic therapy right away or instead try anticoagulation alone first and wait to see if it works, as well as determining how strictly and for how long we have to monitor these patients.

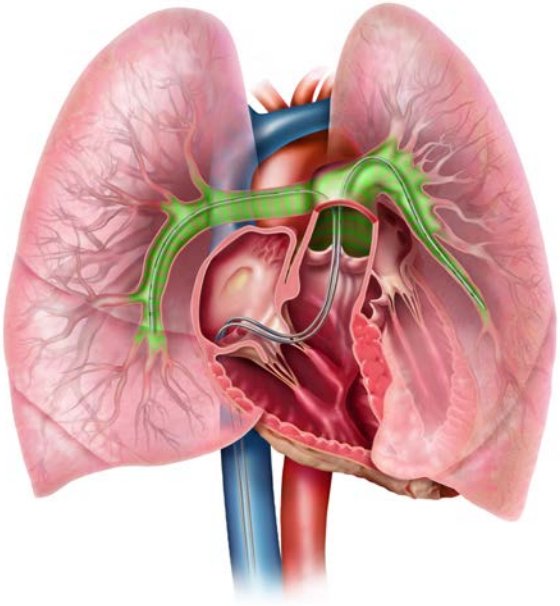


Figure 1. The EKOS Endovascular System was the first interventional device indicated for the treatment of PE.

Systemic thrombolysis is the current standard of care for unstable patients with so-called high-risk or massive PE, and it is also recommended as second-line, rescue treatment for patients with intermediate-risk PE if they decompensate while treated with heparin alone. Catheter-directed treatment has not been established as a proven alternative for treating intermediate-risk PE. However, physicians hesitate to use systemic thrombolysis as a mode of treatment, given its contraindications and potential for life-threatening bleeding. The premise of the HI-PEITHO trial is to test an innovative method of percutaneous catheter-directed treatment using the EkoSonic Endovascular System to deliver a small dose of thrombolytic on site, onto the thrombus in the pulmonary arteries, thus liberating the lung vessels from obstruction without the bleeding risks associated with full-dose systemic thrombolysis.

If the results of the study are positive, physicians will be able to make data-based treatment decisions, as they will have robust clinical evidence to support the use of the EKOS system versus solely relying on anticoagulation.

VDM: Please provide an overview of the trial design and study participants.

Dr. Konstantinides: The HI-PEITHO study aims to target patients with intermediate-to-high-risk PE. These are the sickest patients among those at intermediate risk, the so-called "orange risk category". They appear to be hemodynamically stable, which means that they have low-to-normal blood pressure, they are not in shock, they do not have cold, clammy skin, they are not disoriented, and they have no problem with renal function. These are patients whose circulation is still working, but they are experiencing severe symptoms and abnormalities such as dyspnea, poor oxygen saturation, marginal blood pressure, and signs on an imaging test (echo or computed tomography [CT] scan) showing that the right ventricle is not working well, all meaning that the patient may collapse or decompensate at any time. We also look at laboratory markers, particularly elevated troponin levels in the blood showing that there is already some damage to the heart from PE.

The trial is a randomized, controlled trial, with the control arm examining treatment with only heparin anticoagulation, the recommendation of the current guidelines for these intermediate-to-high-risk patients. As already mentioned, full-dose systemic thrombolysis is considered too dangerous for this condition and will not be used in the trial.

In the interventional arm (or treatment arm), patients will be treated with ultrasound-assisted, catheter-directed thrombolysis. Patients in this arm will receive treatment with the EKOS system, using targeted ultrasonic waves in combination with thrombolytic to dissolve the clot. Both groups will receive anticoagulation and all other state-of-the-art therapy based on current guidelines.

A blinded committee will confirm ("adjudicate") the clinical outcomes in both treatment arms of the trial. Comparison of these outcomes within the first seven days will determine if the interventional treatment can reduce death or new-onset shock, or if there is a need for cardiopulmonary resuscitation or intubation.

VDM: What does the HI-PEITHO trial set out to achieve?

Dr. Konstantinides: The HI-PEITHO trial is the first large, randomized trial to evaluate interventional treatment of PE and will seek to understand whether the EKOS system results in a measurable improvement in health, function, or quality of life compared to anticoagulation alone. We hope the trial findings will inform clinicians and future guidelines, improving the safety of active thrombus removal from the lung vessels and, in parallel, advancing the concept of intermediate-to-high-risk PE and the PE severity criteria, with the aim to better identify patients who may clinically benefit from this type of catheter-directed intervention.

In summary, the HI-PEITHO trial sets out to demonstrate a clinical benefit in the treatment of acute, intermediate-to-high-risk PE when using the EKOS system with anticoagulation compared to anticoagulation alone. If this objective is met, it would be a major contribution to cardiovascular medicine.

VDM: What excites you about the study in particular?

Dr. Konstantinides: The steering committee and I are very happy that the trial has begun, as we started discussing and conceiving this project in the clinical and academic community almost three years ago.

We want to evaluate the EKOS system in a state-of-the-art clinical trial so that we will be able to state, with the backing of clinical evidence, "yes, this has been shown to work. It saves patients and it improves patient outcomes, preventing shock and adverse outcomes."

We are hopeful this trial will become a landmark clinical study in the treatment of PE.

VDM: Can you talk to us a little more about the EKOS system? How does it work?

Dr. Konstantinides: The EKOS system has two primary features:

(1) It delivers a small dose of thrombolytic agent directly into the clot or in the proximity of the clot. This is delivered locally, meaning that it is delivered in each pulmonary artery filled with thrombi. If it is only one artery, you will use one catheter; otherwise, we use one catheter for each side, but remain well below the dose used in systemic thrombolysis, which minimizes the dose of the thrombolytic needed. For example, if we were to use 100 milligrams in a systemic dose of thrombolysis, when using the EKOS system, we only use 15-20 milligrams, so it is less than one-fifth of the total dose.

(2) The system also emits ultrasound waves very close to the thrombus. While the ultrasound does not itself dissolve the clot, it allows the thrombolytic drug to penetrate deeper into the clot, which helps to dissolve it. This allows for effective treatment with a small dose of thrombolytic and reduces the bleeding risks of thrombolysis.

VDM: What impact has the EKOS system had in your practice? Are there any specific cases that you can share?

Dr. Konstantinides: In our center, which is a large cardiovascular center that sees many PE cases, we have treated PE with various catheter-directed procedures. My colleagues have shown some hesitation around using interventional treatment, with many saying they would like to wait until we have more evidence. We are hopeful that the evidence collected through the HI-PEITHO trial will eliminate this hesitancy and advance the care of patients with PE. We now have interdisciplinary PE response teams in place so that more specialists are immediately and directly involved in the care of all patients with high-risk and intermediate-to-high-risk PE.

Until now, enthusiasm has been moderate for catheter interventions in PE, but now, my colleagues are hearing about the HI-PEITHO study and interest is rising exponentially — that makes me very happy.

VDM: Are there currently any other unmet needs in treating PE? What additional evidence do you hope the HI-PEITHO trial will provide to potentially help address these unmet needs?

Dr. Konstantinides: This is a critical question, what else is there to learn in PE? Clearly, anticoagulation is more or less complete — I would say nothing is ever 100% complete, but we have had two decades of impressive innovation in anticoagulation, first with low-molecular-weight heparin and then the introduction of direct oral anticoagulants (DOACs). There are no major unmet needs in this category of treatment.

What is still a major unknown is reperfusion — reperfusion of patients in shock and particularly of patients immediately prior to shock. Full-dose systemic thrombolysis has been available for more than 30 years; however, it is not a popular treatment method, given the high bleeding complication rate. Now that we have catheter-directed procedures the question becomes, "What can we do to improve the acute, early prognosis of these patients?"

There is another unmet need, of course, because if you do have an acute procedure — as with the EKOS system — you want to know if it has an impact on the long-term outcome for the patients. This is also something that the HI-PEITHO study will address.

We hope the HI-PEITHO trial will produce evidence for treating intermediate-to-high-risk PE with effective but safe reperfusion that is much safer than systemic thrombolysis, and will help determine the effect this acute treatment may have on long-term outcomes, chronic thromboembolic disease, and other late sequelae.

VDM: Can you talk about the current guidelines for treating PE?

Dr. Konstantinides: I have been involved with the European Society of Cardiology (ESC) Clinical Practice Guidelines since 2006 and I have chaired the past two consecutive task forces on guideline updates. What makes the ESC Guidelines quite popular among physicians, not only in Europe but also in other parts of the world, including North America, Asia, and South America, is the fact that they are interdisciplinary. The guidelines were created not only by cardiologists, but also by experts from many other disciplines. Of course, we follow guideline methodology, but we also try to be as clinician-oriented and as user-friendly as possible.

Our aim is not to overwhelm the clinicians with lots of study findings and hundreds of tables, but rather the role of the task force is to establish and convey the key messages for clinical practice. These are based on the level of evidence and the level of recommendation agreed upon by the experts. We have been able to show, particularly in the 2019 ESC Guidelines, that many aspects of acute treatment of PE have been resolved with the new anticoagulants that we have had the opportunity to use in the past decade. The topic of interventional treatment, catheter-directed percutaneous treatment of acute PE, has not been resolved and this is a clinical gap that must be filled.

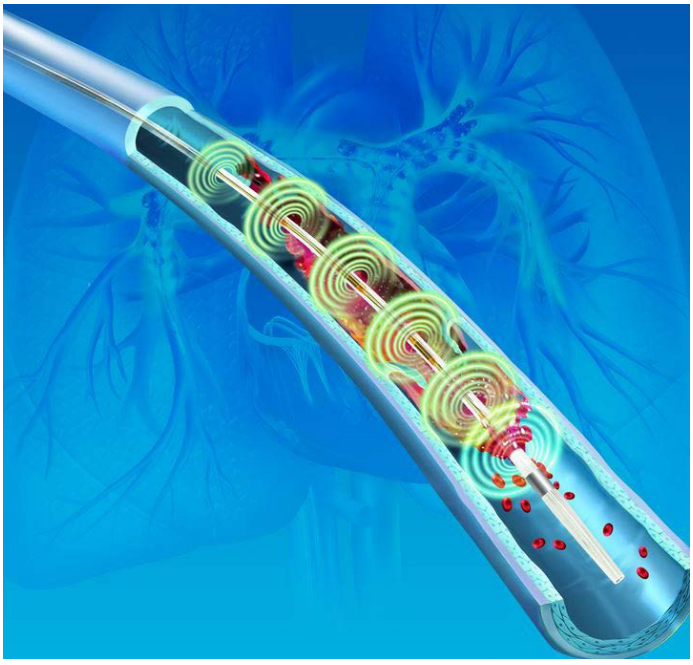


Figure 2. The EKOS Endovascular System ultrasound technology unwinds and thins fibrin strands to expose more drug receptor sites, while acoustic streaming drives the drug deeper into the clot, accelerating clot dissolution with low doses of thrombolytics.

VDM: Do you think that the trial will help with a more aligned approach for treating PE?

Dr. Konstantinides: This is a very important question, because, yes, we do believe that the trial will help with a more aligned, multidisciplinary approach for treating PE. This is the Pulmonary Embolism Response Team (PERT) concept that originated in the United States, but is now becoming increasingly popular all over the world. The PERT teams triage patients with acute PE, identify the patients' level of risk, and align on the best treatment option.

The HI-PEITHO trial aspires to demonstrate that if patients with PE are treated with a catheter-directed reperfusion technique (provided that the expertise, resources, and infrastructure are readily available), this early strategy can improve their clinical outcome both in the acute phase and over the long term. It will not just be the interventional treatment producing this positive outcome; it will be a result of the integrated concept of taking care of acute, severe PE in a multidisciplinary way, and doing it safely.

VDM: What can we expect next for the trial and timing of initial results? Is there anything physicians should be looking out for in particular?

Dr. Konstantinides: I must emphasize that there has been great interest from many parties. I have been doing trials for many years and this is perhaps the first time I have seen so many clinical sites enthusiastically reaching out to us and saying that they want to participate. A site selection committee is currently going through all candidate sites.

Physicians will receive information about patient enrollment from study newsletters and other study correspondence. The sponsor, the steering committee, and the contract research organization are highly motivated and will ensure that the trial is successful in the recruitment of patients; and as such, not a single day will be lost. ■

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