Rationale for the APEX-AV, HI-PEITHO, and PE-TRACT Trials

A review of the objectives, study design, outcome measures, and potential impact of three upcoming pulmonary embolism studies.

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Intermediate-risk (submassive) pulmonary embolism (PE) has been the subject of active clinical study over the last 8 years. In 2014, the small, randomized controlled ULTIMA trial demonstrated the promise of catheter-directed thrombolysis (CDT) delivered via the Ekos catheter (Boston Scientific Corporation).[1] The SEATTLE II trial followed in 2015, leading to FDA clearance of the Ekos catheter, the first percutaneous endovascular medical device with a specific PE indication.[2] In 2018, the OPTALYSE PE randomized uncontrolled trial explored the safety and efficacy of Ekos-delivered low-dose CDT.[3] In 2019 and 2021, two studies (FLARE[4] and EXTRACT-PE[5]) described the safety and efficacy of two novel aspiration thrombectomy devices, the FlowTriever device (Inari Medical) and the Indigo aspiration system (Penumbra, Inc.), resulting in two additional devices being cleared for PE.

This article describes the rationale of three upcoming PE studies, one investigating a novel thrombectomy device seeking a PE indication (APEX-AV) and two others aiming to address long-standing deficiencies in our knowledge of catheter-based therapy for intermediate-risk PE (HI-PEITHO and PE-TRACT).

APEX-AV

APEX-AV is a new clinical study aimed at evaluating the efficacy and safety of the AlphaVac multipurpose mechanical aspiration (MMA) F18[85] system (AngioDynamics) in the treatment of acute intermediate-risk PE. The study is being initiated in partnership with The National Pulmonary Embolism Response Team (PERT) Consortium™. Mona Ranade, MD, and William Brent Keeling, MD, are the Co-Principal Investigators of the study.

The AlphaVac F18[85] system is a mechanical aspiration thrombectomy device redesigned with the benefits of the AngioVac system, allowing for rapid large-volume aspiration without the need for extracorporeal bypass.

The AlphaVac MMA F18[85] device uses an 18-F, 105-cm cannula with an 85° angled tip to access the pulmonary circulation*, with the goal of large-volume mechanical thrombus extraction. The cannula retains a nitinol basket–reinforced, self-expandable, funnel-shaped distal tip similar to the AngioVac device, with the addition of a proprietary handle designed to create an off-circuit method of action. The device encompasses features such as a volume-limiting switch, which limits blood loss during the procedure. The AlphaVac F18[85] cannula is currently indicated for the removal of thrombi or emboli from the venous vasculature.

APEX-AV is a single-arm investigational device exemption study that will enroll patients with confirmed acute intermediate-risk PE at up to 20 hospital-based sites in the United States. Patient enrollment is anticipated to commence in summer 2022. The primary efficacy endpoint of the APEX-AV study is the difference in right ventricular/left ventricular (RV/LV) ratio between baseline and 48 hours postprocedure. The primary safety endpoint is the rate of major adverse events, including device-related death and major bleeding within the first 48 hours. Patients will be followed for 30 days after the index procedure. The study will also evaluate secondary efficacy endpoints, including thrombolytic use within 48 hours of the procedure, length of stay in the intensive care unit/hospital, and change in modified Miller Index from baseline to 48 hours postprocedure as assessed by CTA. The secondary safety endpoints include rate of device-related complications, comprising clinical deterioration, cardiac injury, pulmonary vascular injury, major bleeding, and device-related death within 48 hours of the index procedure.

Despite the extensive work done thus far to assess novel catheter-based therapies, we remain without clear societal guidelines dictating use of these devices in intermediate-risk PE. The primary reason is the lack of large randomized clinical trials evaluating their efficacy and safety compared to anticoagulation (AC) alone and best supportive therapy. More than 1,500 patients have been randomized to systemic thrombolysis trials, whereas (prior to current trials in recruitment) only 59 have been randomized to catheter-based therapy versus AC

alone. A second reason is the use of surrogate outcomes rather than clinical ones. Since SEATTLE II, the standard outcome measure has been RV/LV ratio 48 hours postprocedure. However, to understand the value (and the risks) of catheter-based therapy, we need data on short-term fatal and nonfatal clinical deterioration, serious bleeding, and recurrent thromboembolism and longer-term exercise tolerance, functional capacity, and quality of life in the year after PE. An understanding of these outcomes is absolutely required to truly assess catheter-based therapy and advance clinical guidelines for intermediate-risk PE.

HI-PEITHO

The HI-PEITHO study is a multinational, multicenter, randomized controlled trial that has enrolled 27 patients at 29 active sites as of May 11, 2022.[6] It is currently the only funded and actively enrolling randomized clinical trial studying optimized endovascular therapy of patients with PE. Patients with intermediate-high–risk are identified and defined as having (1) confirmed acute PE, (2) evidence of RV dysfunction on imaging, (3) elevated cardiac troponin, and (4) clinical criteria indicating an elevated risk of early death or imminent hemodynamic collapse. Patients are identified and randomized 1:1 to treatment with a standardized protocol of ultrasound-facilitated CDT (USCDT) with the Ekos catheter plus AC versus AC alone. The primary outcome measure is a composite of PE-related mortality, cardiorespiratory decompensation or collapse, or nonfatal symptomatic and objectively confirmed PE recurrence within 7 days of randomization. Secondary outcomes include assessment of bleeding risks and longer-term outcomes, including all-cause mortality, functional status, and quality-of-life indices out to 12 months. Through this study design, HI-PEITHO seeks to not only assess safety and efficacy of USCDT with Ekos but also provide the landmark randomized data for high-value clinical outcomes necessary to impact clinical guidelines and change standards of care.

Although randomized data on interventional versus conservative therapies are required to change guidelines and advance clinical practice, champions of advanced interventional therapies for PE may have reservations about randomizing intermediate-high–risk PE patients to AC alone. The design of HI-PEITHO ensures safe escalation of care without implicit bias of treatment through implementation of the National Early Warning Score (NEWS). The cardiorespiratory collapse or decompensation primary outcome for the trial is composed of (1) cardiac arrest, (2) signs of shock, (3) extracorporeal membrane oxygenation initiation, (4) intubation or noninvasive mechanical ventilation, and/or (5) a NEWS score ≥ 9 between 24 hours and 7 days confirmed after randomization on two consecutive measurements performed 15 minutes apart. Implementation of a standardized, easy-to-use clinical tool recommended by the National Health Service in the United Kingdom allows HI-PEITHO investigators to clearly and reliably identify decompensating patients and escalate care without awaiting progression to a highly morbid clinical stage. NEWS scores prevent patients from being "crossed over" between treatment arms unnecessarily or for vague clinical reasons, which would complicate interpretation of trial results. However, most importantly, use of the NEWS scores will help prevent patients from severely deteriorating clinically without recognition and escalation of care as directed by their clinical teams. The HI-PEITHO investigators have also developed a unique and class-leading iPhone-based application tool to allow for both facilitated trial patient identification and rapid and easy calculation of NEWS scores.

HI-PEITHO is a bold step in the progress of our understanding of PE and PE therapies. Randomized data evaluating high-impact clinically and patient-relevant outcomes will help advance our understanding of not only USCDT but also interventional therapies for this patient population. These results will be central to the development of clinical guidelines in treatment of PE and will impact use of all interventional PE therapies, including both USCDT and thrombectomy.

PE-TRACT

PE-TRACT is in submission to the National Heart, Lung, and Blood Institute within the National Institutes of Health (the same institute that funded the ATTRACT and C-TRACT trials). PE-TRACT, if funded, would randomize approximately 500 patients to catheter-based therapy plus AC versus AC alone. Although it will describe short-term outcomes such as fatal and nonfatal clinical deterioration, bleeding, and recurrent venous thromboembolism, it is powered and designed to detect differences between the two groups in peak oxygen consumption (measured via cardiopulmonary exercise testing) and New York Heart Association class at later time points (3 months and 1 year postrandomization, respectively). Quality of life, 6-minute walk test, and cost-effectiveness are secondary outcomes among many other exploratory outcomes.

PE-TRACT seeks to (1) clarify the long-term natural history of PE—we are just now starting to understand the scope of the long-term toll PE takes on patients, with nearly 50% having a below-normal peak oxygen consumption during exercise 1 year post-PE per the ELOPE study[7]; (2) identify novel risk factors (eg, blood biomarkers, baseline comorbidities, hemodynamic parameters) for the development of long-term disability and short-term deterioration; and (3) offer biological insights that will

drive research toward novel device and pharmacologic therapies. Consequently, PE risk stratification will become more refined and precise, delineating which submassive PE patients are at highest risk for short-term deterioration and death, which are at highest risk for long-term disability, and which will truly benefit in the short and long term from targeted reperfusion therapy. PE-TRACT will also begin to offer insight into some of the technical aspects of catheter-based therapy, including correlating the amount of thrombus removed with clinical outcomes. PE-TRACT will also increase precision around major bleeding estimates.

CONCLUSION

Ultimately, the PE community must demand more rigorous studies of catheter devices used to treat intermediate-risk PE. Studies such as APEX-AV introduce important and promising devices, but these studies cannot be the "last word." HI-PEITHO and PE-TRACT offer the opportunity to gain a deeper knowledge about PE, potentially improving the short- and long-term cardiopulmonary health of many thousands of patients and, at the least, pointing us toward the next steps in reducing morbidity and mortality from this vexing disease. ■

**The AlphaVac MMA F18^{85} system is not indicated for treatment of PE and is considered off-label.*

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