PANEL DISCUSSION

Understanding the Endpoint: Deep Dives on Modern PE Outcomes

Reflections on defining pulmonary embolism outcomes in today's evolving practice, including most meaningful endpoints, pros and cons of RV/LV ratio and composite endpoints, and patient and payer priorities.

With Wissam A. Jaber, MD; Soophia Naydenov, MD, FCCP; and Peter P. Monteleone, MD, FACC, FSCAI

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What is your impression of the current degree of consensus regarding which endpoints are most meaningful in pulmonary embolism (PE) care?

Dr. Jaber: There is general consensus on the major clinical endpoints, including death, major bleeding, and functional limitation, but agreement on the degree of importance of the other endpoints varies: right ventricular/left ventricular (RV/LV) ratio, clinical deterioration, dyspnea score at 24 or 48 hours, etc. Disagreement on the importance of these surrogate endpoints is exemplified by the fact that many experts do not recommend interventional or thrombolytic treatment in patients with intermediate-risk PE, despite trials showing their salient effects on these surrogate measures.

Dr. Naydenov: All-cause mortality and major bleeding remain the most meaningful endpoints in PE care and clinical trials. For obvious reasons, there is a broad consensus around these two measures. However, the challenge lies in their low event rates—especially in intermediate-risk PE—which makes it difficult to design trials powered to detect meaningful differences. As a result, surrogate endpoints such as the RV/LV ratio or composite measures have become important.

That said, consensus on PE endpoints is evolving, as reflected in the primary and secondary outcomes of newer trials like HI-PEITHO and PE-TRACT, which aim to capture the broader impact of this disease on patients' lives, both in the short term and long term.

Dr. Monteleone: There is some foundational consensus but certainly a lot of active discussion. I think we all agree that RV/LV ratio is a very useful and practical outcome and has allowed us to efficiently and effectively drive the initial rounds of study for these therapies. We also know that RV/LV ratio is associated with prolonged RV dysfunction, increased inpatient and PE-related mortality, and recurrent deep vein thrombosis and chronic

pulmonary artery (PA) hypertension. However, we also know that this ratio is not a clear direct clinical outcome. As we have progressed in the advanced treatment of PE, the available therapies and treatment protocols are increasingly more available and more nuanced; as such, we now need hard clinical endpoints to allow us to broadly implement and compare these treatments.

As a field, we are all thankful for the early work that has been focused on RV/LV ratio and for the opportunities this outcome created to achieve robust early answers. However, we are all looking forward to the next generation of clinical trials in which success is only reported through achieving concrete, specific clinical benefits. HI-PEITHO will include for the first time in the PE literature analysis of change in the NEWS (National Early Warning Score) score, an internationally recognized, objective measurement of a patient's clinical status and course. I believe this will be transformative to the field. It will be an excellent clinical science tool to allow objective measurement and understanding of a therapy's clinical trial treatment result; perhaps more importantly, it will also help us in the future to better characterize the patients in front of us and how they are responding to our therapeutic decisions.

In your opinion, which endpoints are the most indicative of successful interventional treatment, and why?

Dr. Jaber: Quick improvement in oxygenation, vitals, and symptoms as a short-term endpoint. These are the main reason for intervention and why we choose to do it early in the first place in intermediate-risk patients. For high-risk PE patients, it is stabilization of blood pressure, avoiding death, or progression to extracorporeal membrane oxygenation (ECMO).

At some point, and as we assess different devices, we have to see comparative efficacy in action, for instance, tangible results like clot resolution/PA obstruction relief at 24 to 48 hours, early improvement in pulmonary vascular resistance, and speed of improvement in oxygenation, together with comparative device safety data.

Dr. Naydenov: The first question always must be *why* the intervention was done. If you are treating an intermediate-risk PE patient because of certain clinical features or significant RV strain on imaging, then improvement in those specific abnormalities is a very reasonable marker of success.

More broadly, I tend to think about successful interventional treatment across three domains.

- **Efficacy:** Does it work? That includes objective improvement in RV strain, such as a reduction in the RV/LV ratio on CT or echocardiography, as well as meaningful symptom improvement—particularly, how quickly and how durably patients feel better.
- **Safety:** Was it safe to do? That means low rates of major bleeding and minimal device- or procedure-related complications.
- **Prevention of long-term sequelae:** Does the intervention provide benefit beyond the acute hospitalization? Ideally, we are reducing the risk of persistent RV dysfunction, post-PE functional limitation, or other longer-term consequences that matter to patients.

Success in interventional treatment is multifaceted with a combination of such factors as mentioned above.

Dr. Monteleone: We do not yet have a complete understanding of this. We have all seen cases where a patient is treated with an advanced therapy for PE and by the end of the case or the end of a therapeutic infusion, their heart rate, blood pressure, PA pressure, and respiratory status are improved. But this is not the case for all PE patients, and it is definitely not the sole definition of a successful therapy. There are patients who will improve dramatically but might not improve immediately. We have to remember that many of these advanced therapies are focused on improving tissue perfusion, which is not necessarily defined by immediate clinical improvement. Very exciting work has been done demonstrating improved ventilation-perfusion of the lung parenchyma after therapies for PE. There is also very new work using high-resolution three-dimensional CT scan that has demonstrated improved small- and medium-sized venous outflow from the lung parenchyma after PE therapies. This may be the clearest endpoint to demonstrate improved tissue-level perfusion of the alveoli, which may prove someday to be the best marker of freedom from short- and long-term clinical sequela of PE. However, this direct testing is clinically inconvenient and will not likely become a standard of care.

We are therefore currently reliant on heart rate, blood pressure, respiratory status, or even angiographic results in the short term and functional measures in the longer term. We also cannot forget that perhaps the most important metrics are those of patient experience. Is the patient functionally limited at discharge or at 6 months? How does quality of life (QOL) change for the person? At the end of the day, these are likely the most important metrics we can improve.

What do you see as the pros and cons of RV/LV ratio improvement as a measure?

Dr. Naydenov: The publication of the ULTIMA trial marked a pivotal moment in establishing the RV/LV ratio as an objective surrogate marker for PE treatment suc-

cess. Since then, reduction in RV/LV ratio has been widely adopted in both clinical practice and trials as a clear signal of successful interventional therapy. In the acute setting, reversal or reduction of the RV/LV ratio reflects improvement in RV strain, which we extrapolate to indicate faster recovery of the patient's clinical status—as seen in the recently published STORM-PE trial. We anticipate additional long-term benefits from these interventions as we await results from the PE-TRACT and HI-PEITHO trials.

That said, the RV/LV ratio, while accepted as an endpoint for device approval, is far from perfect. Timing of measurement varies significantly, making cross-study comparisons difficult. Operator variability in calculating the ratio still exists, and discrepancies between CT chest and echocardiogram findings are not uncommon, given that these studies are rarely performed simultaneously.

Overall, this surrogate marker is here to stay, but it should be interpreted alongside other clinical and patient-centered outcomes for a more comprehensive assessment of treatment success.

Dr. Monteleone: The convenience of this outcome has allowed us to transform the field. The same study that allows initial PE diagnosis (the CT pulmonary angiogram [CTPA]) defines the baseline status of the RV/LV ratio. As mentioned, RV/LV ratio status is a very good intermediate metric that correlates well with important clinical outcomes. A minimally invasive follow-up diagnostic transthoracic echocardiogram allows follow-up assessment of changes in the ratio. These are great characteristics for an intermediate outcome measure, but it still does not replace direct clinical outcomes. This is why there is such clear dedication in the upcoming generation of clinical trials to prove that the benefits we have seen in RV/LV ratio with advanced therapies for PE translate directly into advanced clinical benefit.

Dr. Jaber: Pros of RV/LV ratio improvement as a measure are the ease to obtain and use, familiarity of most physicians with such a measure, and the abundance of data behind this measure. The cons are:

- The need for a tight control group given that the ratio will change on heparin alone
- Defining the appropriate time point in obtaining it
- Subjectivity of the measurement, especially in an open-label trial design
- Overall, it is not a useful measure beyond 2 to 4 weeks, as both conservative and interventional groups would have likely normalized that ratio, as well as the fact that it is not sensitive to patient's symptoms or presence of persistent perfusion defects
- It is meaningless to patients as a surrogate measure

How do you weigh the benefits and drawbacks of composite endpoints?

Dr. Jaber: Composite endpoints allow a reasonable sample size, finding a real difference in outcome and combining all clinically important parameters. However, they water down the importance of the trial results and continue to prevent us from finding the difference in outcome that really matters: mortality and intermediate- to long-term functional limitation.

Dr. Monteleone: Composite endpoints can allow us to answer clinical questions and discover clinical benefits with faster, smaller, less expensive clinical trials. But as clinical scientists, we must always be very transparent about what drives a statistical outcome demonstrated solely within a composite endpoint. If a composite endpoint pools mortality, bleeding, intracranial hemorrhage, and hospital length of stay but the only result driving a difference is the hospital length of stay, we have to be thoughtful about how we both present and interpret that statistical result.

Clinical trial science is hugely expensive and slow, and advanced therapies for PE have moved incredibly fast. Composite endpoints have been extremely valuable to the space, and as a field, we need to be consistently transparent and thoughtful about their use and the clinical implications of their implementation.

Dr. Naydenov: Composite endpoints are both acceptable and highly valuable in the PE space. They allow us to capture clinically meaningful events as well as additional outcomes that impact health care economics, as demonstrated in the PEERLESS trial, which used composite measures to reflect both patient outcomes and resource use. Composite endpoints improve feasibility and statistical power and better reflect the multifaceted nature of PE outcomes and their impact on health care.

However, the drawback is that not all components of a composite endpoint are equally meaningful. An outcome that matters to health care resources is quite different from one that matters to the patient—although both are important in different ways. Therefore, clarity and transparency are crucial in interpreting which component is driving the observed benefit.

Looking ahead, prespecifying distinctions between patient- and resource-centered endpoints could be a key step toward more transparent and patient-focused research. This approach would make composite outcomes more interpretable and improve the credibility and utility of future PE trials

When speaking with patients, what outcomes are most important to them?

Dr. Naydenov: Patients are clear about what they want. They want to get better (and quickly), avoid complications from the treatment itself, and not be left with long-term consequences from the PE. They want to get back to their normal lives as fast and as safely as possible—and that is the lens through which our clinical success should be judged.

Dr. Jaber: The most frequent reason the patients want an intervention is to get better fast. I am surprised at how often the other outcomes we worry about are not the same as theirs. They do not like being unable to breathe, being on oxygen, or feeling weak. They value the ability to feel better immediately and leave the hospital quickly.

Dr. Monteleone: PE is a very tangible disease state. When you tell a patient that a clot formed in their leg and travelled to their lung, they understand implicitly what has happened. They ask the question immediately, "Can you get rid of the clot?" We have an absolute obligation to inform our patients about what we know and what we do not know, as well as to help them understand the clinical value of the decisions we are making with them. Patients want to be protected from their disease and to be safe to live their lives. Obviously, mortality and safety are our top priorities—particularly in the minutes, hours, and days after they learn what a PE is. But, patients also want to be able to return to their normal functional state quickly. They want to be safe from experiencing another PE in the future. As such, a variety of factors are of great value to patients and thus treating teams—including, but not limited to, functional status, walking distance, exercise capacity, life expectancy, and risk of recurrent venous thromboembolism.

How has QOL assessment evolved with increased understanding based on past trial experiences? What opportunities do you see for improvement in accurately determining this measure?

Dr. Monteleone: QOL is really of the utmost importance to PE therapies. Although we of course must address short-term outcomes and "hard" outcomes (eg, mortality), it is crucial that we also focus on the patient's long-term QOL. This is particularly of value in the setting of diverse patient populations suffering from sequela of PE. In many cases, we are dealing with young, otherwise healthy patients in whom functional status decline can have a transformative impact on their QOL and that of their families. We really have only begun to understand how QOL can be impacted by PE across the broad patient community impacted by this disease.

Dr. Naydenov: Ideally, I would like to see a PE recovery chart—a tool that tracks a patient's progress over time against an expected recovery trajectory. However, the wide variability in PE presentation and recovery makes it difficult to establish a uniform benchmark for all patients.

Our focus in both clinical practice and research has shifted beyond rare hard endpoints such as mortality and major bleeding. While most patients survive the acute event, many experience persistent symptoms, functional limitations, reduced QOL, or chronic thromboembolic pulmonary hypertension (CTEPH). The next major research question is: Which additional interventions, alongside anticoagulation during the acute phase, can minimize or eliminate these long-term sequelae?

QOL endpoints should complement traditional clinical and imaging measures, so we can determine not only whether an intervention works but whether it meaningfully improves patients' lives.

Dr. Jaber: There has been better understanding on how PE affects QOL, and more studies have started capturing such data. QOL questionnaires are frequently part of the design of contemporary trials and registries. Despite that, I don't believe that QOL assessment tools have evolved much, and a lot of the questions are not very pertinent to PE. More PE-specific questionnaires should be developed and studied.

How does the patient's or study population's risk level affect the value of certain endpoints?

Dr. Naydenov: Risk level really determines which endpoints matter most. In high-risk PE, survival is the primary and most meaningful endpoint—everything else is secondary.

In intermediate-risk PE, the focus shifts toward preventing clinical deterioration. Endpoints that capture hemodynamic stability, progression to shock, need for escalation of therapy, or timely intervention become especially important, because the goal is to prevent these patients from becoming high risk.

In low-risk PE, the emphasis is different. Endpoints related to safe care pathways—such as early discharge, home-based treatment, avoidance of unnecessary hospitalization, and patient satisfaction—become much more relevant than traditional hard endpoints.

Ultimately, the value of any endpoint really depends on matching it to the clinical risk profile and the specific goal of care for that patient population.

Dr. Jaber: The higher the patient risk, the more emphasis should be placed on mortality and early deterioration as endpoints. Conversely, as risk decreases,

the emphasis should move to intervention safety, early symptom resolution, and intermediate- to long-term functional limitation.

Dr. Monteleone: It is extremely important. As is often the case with novel clinical therapies, our initiatives begin with patients at high risk of negative clinical outcomes that our therapeutics can target. Over time as therapies are proven safe, we then expand those therapies to patients who are less critically ill. Similarly, we oftentimes begin by introducing therapies into patients who are at low risk for complications or side effects; as comfort grows with a technology, we then extend that treatment to patients who may be more vulnerable to complications but maintain much to gain from proven benefits. As we move through these trial designs, the endpoints naturally change.

For instance, high-risk PE patients have very poor short-term outcomes, even when treated with excellent traditional therapy. These patients are also susceptible to delays in systemic thrombolytic or ECMO initiation that may be precipitated if advanced endovascular therapies are introduced. Therefore, we must be certain that any implementation of advanced procedural care into these patients is justified. Demonstration of short-term benefit may be sufficient to transform the natural history of these patients and justify these therapies. However, if these advanced therapies are extended to more intermediate-low–risk PE patients who have a more favorable natural history with standard therapy, we must be certain that their use does not introduce unnecessary risk; achieves clear, tangible long-term goals; and has a high margin of safety.

Which endpoints likely matter most to payers?

Dr. Naydenov: For payers, endpoints are largely centered around value and resource utilization. As with any disease, the length of the hospital and/or intensive care unit (ICU) stay is a major driver. Thirty-day readmission rates are also critically important, as they reflect both quality of care and downstream costs.

From a payer perspective, interventions or care plans that reduce hospital stay, prevent readmissions, and use resources more efficiently—without increasing complications—are particularly compelling.

Dr. Monteleone: There is quite an interesting balance here. Of course, hard clinical outcomes matter most to the patients and thus the field—and hopefully the payers as well. However, the cost of inpatient therapies for PE explodes when advanced therapies are introduced. To balance that, there is an obvious benefit to evaluating and understanding device and procedural therapy, hospitalization cost, procedural complication cost, posttherapy readmission, and length of stay. The long-term costs, especially in a condition that can strike and sometimes debilitate young, previously healthy patients, cannot be overestimated. These long-term costs, both physical, personal, and financial, must be highly valued by all of us.

Dr. Jaber: Mortality, development of chronic thromboembolic pulmonary disease/CTEPH, and long-term disability.

As more platforms with varying mechanisms of action are developed, how might optimal endpoints differ in trials for each?

Dr. Jaber: The main trial clinical endpoints should not be different, but we need to see comparative effectiveness in the surrogate endpoints and convincing safety data. Single investigational device exemption trials may not be enough anymore, and randomized comparative trials (to other devices or heparin alone) should start being mandated by the FDA.

Dr. Monteleone: Interesting question. We have spent a lot of time looking at "the amount of clot removed" (eg, change in modified Miller score), but we also constantly teach our trainees that it is not the amount of clot that matters. In reality, the amount of clot present preprocedure likely should matter in the selection and predicted success of our interventional therapies. It certainly should not be the only metric we review, but it likely is an important one. The amount of clot removed successfully is likely a beneficial endpoint to understand and compare, but it is only the beginning of the story of successful treatment. There is an evolving understanding now about improving tissue perfusion with PE therapies. I do not think we really know yet which devices or technologies best improve actual perfusion of the lung tissue bed, the alveoli. I hope that someday soon we will understand this result, and I do not think any of us would be surprised if tissue bed perfusion proves to be a better predictor of long-term clinical outcomes than many of the other, easier to measure metrics.

Dr. Naydenov: When we think about endpoints across different PE therapies, they really depend on the intervention.

Mechanical thrombectomy (eg, FlowTriever, Inari Medical) focuses on acute outcomes: clot removal, on-table hemodynamics such as PA pressure, early RV/LV

improvement, ICU-free recovery, and overall safety—especially since this is a nonlytic approach. Trials like FLARE and FLASH provide a good sense of what to measure. But this raises an important question: Are all thrombectomy devices the same, and should endpoints be standardized across them? Can we expect the same clinical benefit from different devices?

Ultrasound-facilitated catheter-directed thrombolysis (eg, Ekos, Boston Scientific Corporation) aims to balance efficacy and safety. We still track RV/LV improvement but also optimize dose and duration to minimize bleeding. Emerging imaging insights—such as increased small- and medium-sized venous vessel volumes—suggest enhanced distal reperfusion with this device.[1]

Systemic thrombolysis remains irreplaceable for saving lives within minutes in high-risk PE. For intermediate-risk PE, as highlighted by PEITHO, endpoints broaden to include composite measures of clinical deterioration, major bleeding, stroke, and mortality—where safety is central.

From a global perspective, systemic thrombolysis and novel pharmacologic options will continue to play a critical role worldwide. Research on fibrinolysis resistance, including the role of alpha-2-antiplasmin, underscores the need for next-generation drugs that overcome access barriers. Development of these agents may require endpoints that capture biochemical markers and clot resolution over time and prevent long-term sequelae. Expanding drug-based strategies is essential to ensure equitable, timely PE treatment globally.

Finally, for anticoagulation, while direct oral anticoagulants are well established, future research should focus on optimizing duration, minimizing bleeding risk, and integrating patient-centered strategies. Opportunities include ultra-low-dose regimens, intermittent dosing, predictive modeling for personalized therapy, and digital tools to improve adherence and monitor recovery.

Overall, the key is matching endpoints to the mechanism and goals of each therapy, while keeping patient outcomes—both acute and long term—front and center.

What will drive the development of the next generation of endpoints?

Dr. Monteleone: There are two things I am hoping for most. First, I want to see improvement at targeting invasive therapies to the patient in front of us. This

may result from advanced imaging capabilities where we know more about the clot or the lung parenchyma we are treating. It seems that some clot is best treated with large-bore thrombectomy, while some are perhaps treated with equal efficacy with smaller-bore thrombectomy and others are likely best treated with introduction of thrombolytic. We also do not really understand what patient phenotypes benefit most or are harmed least by the various technologies we implement. Importantly, these devices are incredibly expensive, and cycling through multiple options in one case raises both unnecessary cost and unnecessary clinical risk. I hope that in the near future we will gain more from our imaging and analytic studies than just the location of the clot and its impact on the right ventricle. I also hope this knowledge drives particular patient-focused therapies, including targeted procedures.

Second, I want us to get better at predicting and tracking the short- and long-term progress of our patients after development of a PE. Wearables may indeed prove to be very helpful in this space, giving us real-time feedback on our patients post-PE hospitalization and helping us make early and thoughtful clinical interventions.

Dr. Jaber: Drivers of next-generation endpoints include big data interpretation, automated measurements of clot burden/obstruction index on CT, results from PE-TRACT with analysis of cardiopulmonary exercise testing results to try to discern any signal for future studies, and reliance on smart devices to monitor a patient's functional status (whether wearables or app-based daily questions).

Dr. Naydenov: I think the next wave of endpoints will be shaped by advances across multiple domains—imaging, biomarkers, artificial intelligence (AI), wearables, and even health economics.

On the imaging side, tools like quantitative CT perfusion and four-dimensional flow MRI can now show us distal perfusion and microvascular recovery—things that may be predict exercise capacity and lingering shortness of breath better than the traditional RV/LV ratio. Automated CTPA analytics will also help standardize RV metrics, making results more reproducible for both trials and everyday practice.

Biomarkers like N-terminal pro–B-type natriuretic peptide and troponin provide dynamic measures of RV strain, and integrating these into composite or hierarchical endpoints could help refine our signal detection. In addition, research is ongoing to identify novel biomarkers that could enhance diagnosis and improve predictive models for long-term PE sequelae.

AI and predictive modeling are going to be game-changers. By pulling together baseline RV strain, clot characteristics, comorbidities, and recovery patterns, AI can help personalize endpoints and make trials more efficient and easier to interpret.

Wearables and digital health open up a whole new dimension—tracking real-world recovery through activity levels, heart rate trends, and exertional symptoms, alongside patient-reported outcomes. This means we can spot post-PE functional impairment early and create endpoints that truly reflect patient experience.

And finally, health system and economic measures —like length of stay, readmissions, excess days in acute care, and cost-utility analyses (eg, quality-adjusted life year)—will keep payer priorities in view and help speed up adoption of high-value therapies.

Put all this together, and we're heading toward endpoints that aren't just clinically meaningful—they'll predict long-term function, QOL, and even health system impact. ■

1. Rahaghi F, Piazza G, Bikdeli B, et al. Increased vascular volumes in response to treatment with ultrasound-assisted, catheter-directed thrombolysis in the OPTALYSE PE trial (OPTALYSE-3D). J Am Coll Cardiol. 2025;85(supp 12).

Disclosures
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