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Editorial

Ultrasound-Facilitated Catheter-Directed Thrombolysis in Intermediate-Risk Pulmonary Embolism: Insights From HI-PEITHO

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Acute pulmonary embolism (PE) is a major cause of cardiovascular morbidity and mortality [1,2,3]. Annual incidence rates of PE have been reported to range from 39 to 115 per 100,000 population. Mortality varies substantially according to clinical severity and may reach approximately 65% in patients requiring cardiopulmonary resuscitation [3,4,5]. Contemporary management protocols rely on conventional risk categories, spanning from bedside clinical assessment augmented by sonographic imaging and prompt anticoagulation for low-risk groups to emergent computed tomography pulmonary angiography (CTPA) and systemic thrombolysis for high-risk patients presenting with hemodynamic instability [1,6]. While therapeutic recommendations for low-risk and high-risk PE are well-established [1,6], the optimal management strategy for intermediate-risk PE is controversial. The landmark study by Rosenfield et al. [7] evaluated the efficacy and safety of ultrasound-facilitated, catheter-directed thrombolysis (USCDT) in patients with intermediate-risk PE. This multinational randomized controlled trial enrolled 544 patients with acute PE and evidence of right ventricular (RV) dysfunction but without systemic hemodynamic instability. Building on findings from earlier studies and the introduction of the novel risk-stratification system from the multi-society guideline [6,8,9,10], this trial provides important evidence supporting USCDT in patients with intermediate-risk PE.

Although patients with intermediate-risk PE initially appear hemodynamically stable, some rapidly progress to overt cardiopulmonary failure, leaving only a narrow window for intervention [11,12,13]. Prior trials demonstrated that systemic fibrinolysis reduces hemodynamic collapse in this population but increases major bleeding, thus limiting its routine use in intermediate-risk PE patients [14].

Consequently, numerous percutaneous reperfusion strategies have been evaluated, with several ongoing trials continuing to investigate these treatment approaches (Fig. 1A) [8,9,10,14,15,16,17,18,19,20,21,22,23]. Studies have shown that USCDT improves RV function with a low incidence of major complications [8,9,16,24,25]. However, evidence demonstrating improved patient outcomes is limited. Therefore, HI-PEITHO was designed to address this knowledge gap [7].

The HI-PEITHO trial compared USCDT plus anticoagulation with anticoagulation alone in patients with intermediate-risk PE characterized by RV dysfunction, elevated cardiac biomarkers, and evidence of cardiorespiratory distress. The trial demonstrated a significantly lower rate of the primary composite outcome, driven primarily by a reduction in cardiorespiratory decompensation or collapse among patients receiving USCDT plus anticoagulation [7]. Although PE-related mortality was comparable between groups, the reduction in cardiorespiratory decompensation suggests that early USCDT may mitigate progression toward hemodynamic collapse, reducing the need for rescue therapies such as mechanical ventilation, inotropic support, and extracorporeal membrane oxygenation (ECMO). Importantly, this benefit was achieved without a statistically significant increase in major bleeding or intracranial hemorrhage. In addition, the low mortality and recurrence rates in both arms should not be interpreted as a true absence of therapeutic efficacy. Rather, low baseline event rates make the trial underpowered to detect a statistically significant reduction in these outcomes. Nevertheless, these observations do not diminish the efficacy of USCDT in mitigating the rate of cardiorespiratory collapse and optimizing resource utilization. While this reduction in deterioration is compelling, its clinical value is most meaningful when interpreted within the context of the study population.

The clinical implications of HI-PEITHO depend on identifying those patients most likely to benefit from early reperfusion. The updated 2026 multi-society guideline introduces a novel American Heart Association

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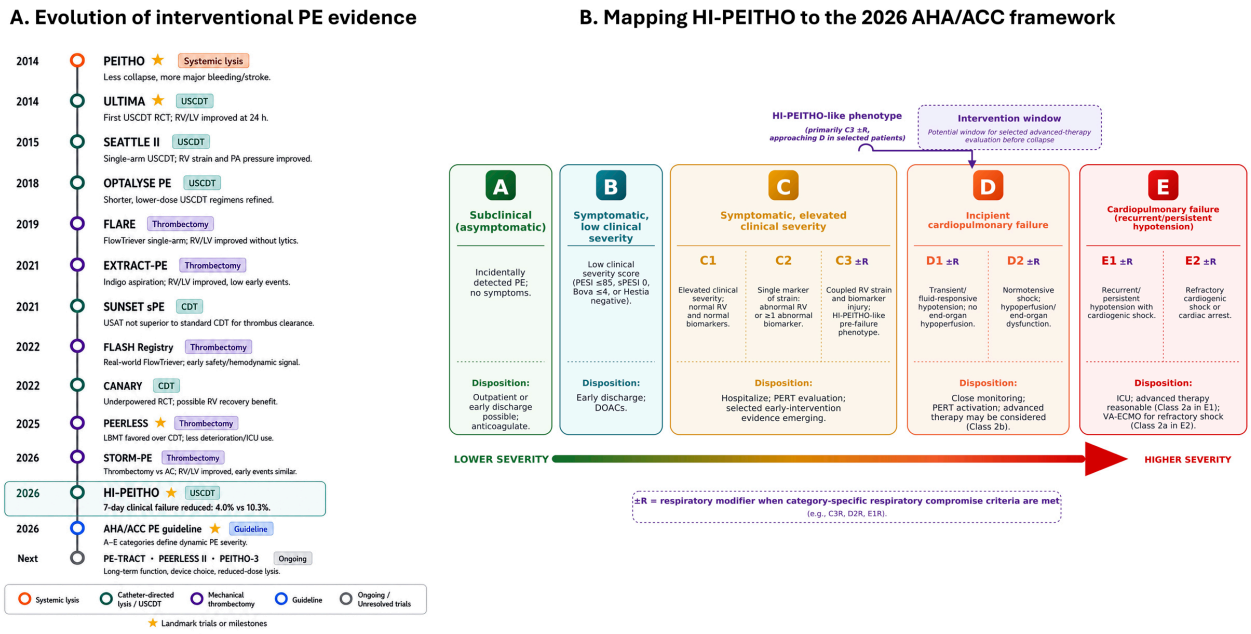


Fig. 1. Interventional management of acute pulmonary embolism: historical evidence and modern guideline integration. (A) Chronological evolution of interventional PE evidence. (B) Therapeutic alignment of the HI-PEITHO trial within the 2026 AHA/ACC Acute PE Clinical Categories framework. AC, anticoagulation; CDT, catheter-directed thrombolysis; DOACs, direct oral anticoagulants; ICU, intensive care unit; LBMT, large-bore mechanical thrombectomy; LV, left ventricular; PA, pulmonary artery; PE, pulmonary embolism; PERT, Pulmonary Embolism Response Team; RCT, randomized controlled trial; RV, right ventricular; USCDT, ultrasound-facilitated, catheter-directed thrombolysis; VA-ECMO, veno-arterial extracorporeal membrane oxygenation; AHA, American Heart Association; ACC, American College of Cardiology.

(AHA)/American College of Cardiology (ACC) risk classification system that may help identify this specific population (Fig. 1B) [6]. The revised classification was developed to better identify patients with impending cardiopulmonary failure, recognize the heterogeneity within intermediate-risk PE, and facilitate earlier intervention before overt hemodynamic collapse [6,11].

Compared with the 2019 European Society of Cardiology (ESC) risk framework [26], the revised classification provides a more dynamic framework that better captures disease progression, clinical deterioration, and the heterogeneity within intermediate-risk PE [6,11]. Category D, for example, identifies patients with impending cardiopulmonary failure who would otherwise remain within the broader intermediate-high and high-risk groups of the ESC classification. This facilitates earlier intervention before the occurrence of hemodynamic compromise. The addition of subcategories also provides a more precise assessment of disease progression, potentially improving the selection and timing of advanced therapies. Based on the HI-PEITHO enrollment criteria, these patients would be classified as Category C3 or D under the 2026 AHA/ACC guideline based on RV involvement, elevated troponin, and cardiorespiratory distress (Fig. 1B) [6,26]. Taken together, the findings from HI-PEITHO directly delineate the precise, higher-risk population that the new classification aims to identify. Consequently, the demonstrated efficacy of USCDT in preventing cardiorespiratory collapse translates directly to these particular Category C3 or D patients.

The favorable safety profile represents another key finding of HI-PEITHO. Previous randomized trials in intermediate-risk PE demonstrated that although systemic fibrinolysis reduces hemodynamic collapse, it does so at the expense of increased major bleeding [14]. In contrast, HI-PEITHO reported low rates of major bleeding, intracranial hemorrhage, and ischemic stroke with low-dose USCDT, comparable to standard therapy with anticoagulation alone [7]. These findings suggest that USCDT may provide a safer reperfusion strategy than systemic fibrinolysis for selected patients with intermediate-risk PE.

While HI-PEITHO evaluated USCDT, other catheter-based reperfusion strategies have also been evaluated in patients with intermediate-risk PE. The PEERLESS trial demonstrated the superiority of large-bore mechanical thrombectomy (LBMT) over catheter-directed thrombolysis (CDT), including ultrasound-facilitated and non-ultrasound techniques, while maintaining a low rate of complications [21]. However, no trial has directly compared USCDT with LBMT [15], and the findings of HI-PEITHO are specific to the EkoSonic ultrasound-facilitated catheter

system [7]. Subsequently, selection of a reperfusion strategy should be individualized based on patient characteristics, bleeding risk, institutional expertise, and resource availability. Ongoing studies, including STRATIFY, BETULA, and PE-TRACT, will further define the role of catheter-based reperfusion in intermediate-risk PE patients [27,28]. Therefore, we propose that clinicians must move beyond simply asking which intervention to perform, but also focus on identifying specific intermediate-risk subgroups most likely to derive clinical benefit. With the 2026 AHA/ACC guideline proposing a more granular risk classification, we urge healthcare professionals to adopt this novel stratification framework to guide future research directions, refine patient selection, and tailor advanced interventions to those specific populations.

Several limitations of HI-PEITHO should be noted. First, the open-label design may have influenced clinical decision-making. Although the trial reported strict control of confounders, the open-label nature may inevitably influence clinicians' attention and subsequent management decisions. Second, follow-up was limited to 30 days, precluding the assessment of long-term patient outcomes beyond this window. Third, the protocol strongly recommended initiation of USCDT within 2 hours of randomization—a treatment timeline that may be difficult to replicate outside experienced centers or during after-hours care. This constraint is critical, as real-world time-to-intervention will determine the applicability and utility of USCDT in regional networks and national healthcare systems. Finally, the trial was funded by the manufacturer of the EkoSonic catheter system, and the reported findings may not be generalized to other devices.

In summary, HI-PEITHO represents an important advance in the management of intermediate-risk PE. Rather than supporting catheter-directed therapy for all patients, it identifies a higher-risk subgroup that may benefit from early USCDT to prevent clinical deterioration without increasing major bleeding. Along with the 2026 AHA/ACC risk classification, these findings provide a practical framework for patient selection. Ongoing studies will further define the role of USCDT relative to other catheter-based reperfusion strategies.

Author Contributions

LE: Conceptualization, Investigation, Data Curation and Writing – Original Draft. RIAA: Investigation, Data Curation and Writing – Review & Editing. CGN: Investigation, Data Curation and Writing – Review & Editing. JD'AU: Conceptualization, Supervision, Data Curation and Writing – Review & Editing. PMW: Investigation, Data Curation and Writing – Review & Editing. OE: Supervision, Data Curation and Writing – Review & Editing. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

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Conflicts of Interest

The authors declare no conflicts of interest.

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