



## Debate: Pharmacological or invasive therapy in acute pulmonary embolism. The clinician perspective



### *A debate: Terapia farmacológica o invasiva en la tromboembolia pulmonar aguda. Perspectiva del clínico*

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**QUESTION:** In the current management of acute pulmonary thromboembolism (PTE) to what extent is thrombolytic therapy used? and what about invasive therapy?

**ANSWER:** During the early management of PTE, we're going after the clinical stabilization of the patient and the alleviation of symptoms, the resolution of vascular obstruction, and the prevention of thrombotic recurrences. The priority of these goals depends on the severity of the patient. Most times (over 90%) these goals can be achieved using conventional anticoagulant treatment to stop the progression of the thrombus while the patient's endogenous fibrinolytic system resolves the vascular obstruction developing collateral circulation. In a minority of the patients (5% to 10%)—often those with hemodynamic instability (high-risk PTE)—aggressive therapies (of reperfusion) can be used to resuscitate the patient or accelerate the lysis of the blood clot.

When reperfusion therapy is advised for a patient with symptomatic acute PTE, the clinical practice guidelines recommend the use of full-dose systemic fibrinolysis as long as it has not been contraindicated.<sup>1</sup> Some of the reasons behind this recommendation are:

a) Numerous clinical trials (with over 2000 patients included) have assessed the efficacy and safety profile of systemic fibrinolysis (compared to anticoagulation) demonstrating a statistically significant drop of the mortality rate. On the other hand, to this date, only 1 clinical trial has been published assessing the efficacy and safety profile of a catheter-directed treatment (ultrasound enhancement fibrinolysis) in 59 patients with acute PTE and echocardiographic dilatation of the right ventricle.<sup>2</sup> The trial used an event of echocardiographic result and was not statistically powered to detect any differences regarding clinical events (mortality, thrombotic recurrences or bleeding).

b) Percutaneous (local fibrinolysis, embolectomy or a combination of different techniques) and surgical (embolectomy) therapies require infrastructure and experience before they can be applied, and most centers and clinicians who often treat these patients just don't have what it takes.

**Q:** Regarding invasive therapy, to what extent is it surgical or percutaneous nowadays?

**A:** RIETE<sup>3</sup> is a real-world, multicenter, and international registry—led by Dr. Manuel Monreal Bosch—of consecutive patients diagnosed with deep venous thrombosis or symptomatic acute PTE. Recent analyses indicate that only 20% of hemodynamically unstable patients with PTE receive reperfusion treatment. Most of these patients (87%) receive systemic fibrinolysis, 10% surgical embolectomy, and 3% percutaneous treatments.

**Q:** On cardiac catheterization, which is the clinical evidence available regarding intravascular thrombolysis? and regarding thrombus aspiration therapies?

**A:** The evidence available on the use of percutaneous treatments is still very weak. As I said only 1 clinical trial has been published to this date on the efficacy and safety profile of a catheter-directed therapy (ultrasound enhancement fibrinolysis) in 59 patients with acute PTE and echocardiographic dilatation of the right ventricle (see answer #1).<sup>2</sup> Recently, the findings of the prospective FLASH registry have been published including 250 patients treated with percutaneous thrombectomy through the FlowTrieve system.<sup>4</sup> A total of 3 serious adverse events occurred (1.2%)—all of the severe hemorrhages—that resolved uneventfully. The 30-day all-cause mortality rate was 0.2% (1 death unrelated to PTE). Although the results of clinical registries—that are hypothesis-generating—provide useful medical information, they are no stranger to several biases

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and confounding factors, which is why they should not be used on a routine basis to assess the efficacy and safety profile of medical procedures. Currently, intermediate-high risk patients are being recruited (sample size, 406-544) with intermediate-high risk PTE for the HI-PEITHO clinical trial. These patients are being randomized to receive conventional anticoagulation or anticoagulation plus ultrasound enhancement local fibrinolysis. The efficacy primary endpoint is assessed by an independent committee 1 week after randomization includes PTE-related death, thrombotic recurrence or hemodynamic collapse.

**Q:** What are today's indications for invasive treatment, and how does your center work in this sense? how important is bleeding risk in the decision-making process?

**A:** At our center we have a PTE code for making decisions on the management of patients with severe PTE (especially high and intermediate-high risk patients). Overall, we follow the recommendations from the Spanish multidisciplinary consensus recently published in *Archivos de Bronconeumología*.<sup>5</sup> We use full-dose systemic fibrinolysis in patients with an indication for reperfusion and without contraindications for use. In patients with an indication for reperfusion and relative contraindications—minor—for full-dose systemic fibrinolysis we use catheter-directed percutaneous treatment (percutaneous thrombectomy, local fibrinolysis or both) or low-dose systemic fibrinolysis. In patients with symptomatic acute PTE, an indication for reperfusion treatment and absolute contraindication for full-dose systemic fibrinolysis we use surgical embolectomy or catheter-directed percutaneous treatment (percutaneous thrombectomy).

From this we can deduce that assessing the bleeding risk is key regarding decision making with reperfusion therapies. In our clinical practice we use the BACS (Bleeding, Age, Cancer, Syncope) scale to identify patients with very low risk of bleeding after the administration of full-dose systemic fibrinolysis.

**Q:** Can you tell us something on what's coming in this field, in particular any ongoing studies you think are relevant?

**A:** As I already mentioned, the HI-PEITHO clinical trial is studying the efficacy and safety profile of ultrasound enhancement local fibrinolysis in intermediate-high risk patients with PTE. Additionally, the PEITHO III clinical trial is currently randomizing intermediate-high risk patients with PTE to receive low-dose systemic

fibrinolysis (r-TPA at doses of 0.6 mg/kg up to a maximum of 50 mg) or placebo plus conventional anticoagulation; the efficacy primary endpoint is the same as in the HI-PEITHO trial.

Also, clinical trials are being conducted to assess the efficacy and safety profile of other procedures (non-reperfusion therapies) in patients with severe PTE. In the DiPER clinical trial, a total of 276 patients were recruited to assess the efficacy and safety profile of diuretic therapy to treat PTE with right ventricular dysfunction.<sup>6</sup> The administration of a bolus of furosemide improved diuresis and did not make renal function worse. The AIR clinical trial (ClinicalTrials.gov identifier: NCT04003116) is currently studying the efficacy and safety profile of the administration of oxygen to patients with PTE and right ventricular dysfunction.

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## CONFLICTS OF INTEREST

None reported.

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