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VENOUS THROMBOEMBOLISM

High incidence of bleeding with fibrinolysis in intermediate-risk pulmonary embolism

Results from the PEITHO trial show that fibrinolysis in intermediate-risk patients with pulmonary embolism reduces the risk of haemodynamic decompensation, but significantly increases the risk of major bleeding and stroke. The investigators conclude that "great caution is warranted when considering fibrinolytic therapy for haemodynamically stable patients with pulmonary embolism".

Individuals with pulmonary embolism are considered to be high risk if they have overt haemodynamic instability that warrants immediate therapy, possibly including fibrinolysis. Conversely, anticoagulation is generally adequate therapy for patients with pulmonary embolism, but no systemic hypotension or haemodynamic compromise. In between these two categories of patients are those with acute right ventricular dysfunction and myocardial injury, but no overt haemodynamic compromise. The PEITHO trial was designed to investigate whether these intermediate-risk patients would also benefit from early fibrinolytic reperfusion therapy.

A total of 1,005 patients who were enrolled in the multicentre, double-blind PEITHO trial were included in the final analysis. The diagnosis of pulmonary embolism was generally confirmed using CT pulmonary angiography. Echocardiography or CT was used to diagnose right ventricular dysfunction, and levels of cardiac troponin I or T were measured to confirm the presence of myocardial injury. Patients were randomly allocated to receive unfractionated heparin plus fibrinolysis with tenecteplase ($n = 506$) or unfractionated heparin plus placebo ($n = 499$).

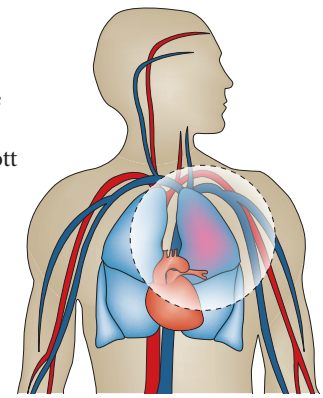
The primary end point (the combination of all-cause death and haemodynamic decompensation or collapse within 7 days of randomization) occurred in 2.6% of the tenecteplase group and 5.6% of the placebo group (OR 0.44, 95% CI 0.23–0.87, $P = 0.02$). Mortality did not differ between the two groups, so the significant difference in the primary end point was driven by a difference in the rate of haemodynamic compromise or collapse (1.6% in the tenecteplase group vs 5.0% in the placebo group; $P = 0.002$).

In the first 7 days after randomization, major bleeding occurred in 11.5% of the tenecteplase group and in 2.4% of the placebo group. Major extracranial bleeding occurred in 6.3% and 1.2% of patients in each group, respectively. The rate of haemorrhagic stroke was tenfold higher with tenecteplase (2.0%) than with placebo (0.2%). Two patients in the tenecteplase group and none in the placebo group had an ischaemic stroke.

Harry Büller, from the Academic Medical Center in Amsterdam, the Netherlands and who was not involved in the PEITHO trial, believes that "the benefits of fibrinolytic therapy in intermediate-risk patients with pulmonary embolism do not outweigh the risks and, therefore, this therapy should not be used". Büller particularly notes that "fibrinolysis was associated with a high rate of bleeding", even in the carefully controlled setting of a clinical trial. He cautions that "the risk of bleeding is likely to be even higher in real-world practice". In an editorial that accompanied the trial report, C. Gregory Elliott recommends "a strategy of initial anticoagulation and rescue fibrinolysis for haemodynamic decompensation. This approach averts the increased risk of major bleeding, especially haemorrhagic stroke, for the majority of patients."

Gregory B. Lim

> "...fibrinolysis was associated with a high rate of bleeding..."



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Original article Meyer, G. *et al.* Fibrinolysis for patients with intermediate-risk pulmonary embolism. *N. Engl. J. Med.* **370**, 1402–1411 (2014)