Therapeutics

In intermediate-risk acute PE, tenecteplase plus heparin reduced hemodynamic decompensation but increased stroke

Meyer G, Vicaut E, Danays T, et al; PEITHO investigators. ***Fibrinolysis for patients with intermediate-risk pulmonary embolism.*** *N Engl J Med. 2014;370:1402-11.*

Clinical impact ratings: C ★★★★★★☆ H ★★★★★★★★

Question

In patients with intermediate-risk acute pulmonary embolism (PE), what are the efficacy and safety of adding fibrinolytic therapy with tenecteplase to heparin?

Methods

Design: Randomized placebo-controlled trial (Pulmonary Embolism Thrombolysis [PEITHO] trial). EudraCT 2006-005328-18; ClinicalTrials.gov NCT00639743.

Allocation: Concealed.*

Blinding: Blinded* (patients, clinicians, and outcome assessors).

Follow-up period: 30 days.

Setting: 76 sites in 13 countries.

Tenecteplase vs placebo added to heparin in patients with acute pulmonary embolism (PE)†

Outcomes	Event rates		At 7 d	
	Tenecteplase	Placebo	RRR (95% CI)	NNT (CI)
Death or hemodynamic decompensation	2.6%	5.6%	55% (12 to 76)	33 (24 to 145)
All-cause mortality	1.2%	1.8%	35% (–82 to 77)	Not significant
Hemodynamic decompensation	1.6%	5.0%	69% (31 to 85)	29 (24 to 65)
Recurrent PE	0.2%	1.0%	80% (–67 to 98)	Not significant
			At 30 d	
All-cause mortality	2.4%	3.2%	26% (–54 to 65)	Not significant
Serious adverse events	11%	12%	8% (–29 to 35)	Not significant
			At 7 d	
			RRI (CI)	NNH (CI)
Stroke‡	2.4%	0.2%	108% (56 to 7780)	47 (7 to 879)
Major extracranial bleeding	6.3%	1.2%	426% (126 to 1065)	20 (8 to 66)

†Abbreviations defined in Glossary. RRR, RRI, NNT, NNH, and CI calculated from control event rates and odds ratios in article.

‡Ischemic or hemorrhagic stroke, including hemorrhagic conversion of ischemic stroke.

Patients: 1006 patients ≥ 18 years of age (mean age 66 y, 53% women) who had objectively confirmed acute PE with symptom onset in the previous 15 days, right ventricular dysfunction confirmed by echocardiography or spiral computed tomography, and myocardial injury confirmed by positive troponin I or troponin T tests. Exclusion criteria included hemodynamic decompensation at presentation, significant risk for bleeding, thrombolytic use in the past 4 days, or uncontrolled hypertension.

Intervention: Tenecteplase, 30 to 50 mg (single weight-based IV bolus over 5 to 10 s) (n = 506), or placebo (single IV bolus) (n = 500). Both groups received unfractionated heparin adjusted to achieve and maintain activated partial thromboplastin time 2.0 to 2.5 times the upper limit of normal range.

Outcomes: Primary outcome was a composite of all-cause mortality or hemodynamic decompensation at 7 days. Secondary outcomes included death, hemodynamic decompensation, and recurrence of PE at 7 days; death and serious adverse events at 30 days; and stroke (ischemic or hemorrhagic) or major extracranial bleeding at 7 days.

Patient follow-up: 99.9% (intention-to-treat analysis).

Main results

The main results are in the Table.

Conclusions

In patients with intermediate-risk acute pulmonary embolism, adding tenecteplase to heparin reduced hemodynamic decompensation but increased stroke and intracranial bleeding. All-cause mortality did not differ between groups.

**See Glossary.*

Sources of funding: Programme Hospitalier de Recherche Clinique (France); Federal Ministry of Education and Research (Germany); Boehringer Ingelheim.

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Commentary

The PEITHO trial illustrates the limitations of relying on a single RCT—even the largest available RCT, with low risk for bias—as well as the need to use systematic summaries of the best evidence to guide clinical practice. PEITHO failed to demonstrate a reduction in mortality, with benefit restricted to hemodynamic decompensation (an outcome of questionable importance to patients). With a 2% absolute increase in stroke and a 5% absolute increase in major extracranial bleeding, the balance is clearly against thrombolytic therapy.

The subsequent systematic review and meta-analysis by Chatterjee and colleagues of 16 RCTs comparing thrombolysis to heparinoids in patients with PE, including the PEITHO trial, tells a different story: a large relative risk reduction in mortality (46%, 95% CI 12 to 67), warranting moderate confidence. The findings are consistent across the available trials, including PEITHO, none of which had sufficient power to provide a statistically significant result. The results were similar in trials that enrolled only hemodynamically stable patients with documented right ventricular function and trials with broader eligibility criteria.

The findings for intracranial hemorrhage (1.3% absolute increase) and major bleeding (5.8% absolute increase) are also consistent with PEITHO results. The systematic review authors suggest that the relative increase in the bleeding outcomes with thrombolysis is greater in patients > 65 years of age than in those ≤ 65 years of age. However, this hypothesis fails some of the criteria for credibility of subgroup effects (e.g., the systematic review authors don't report a test for interaction) (1). Still, patients > 65 years of age are expected to have a higher absolute increase in bleeding outcomes due to higher baseline risk, suggesting a less positive net effect of thrombolysis in older patients.

In contrast to the PEITHO results viewed in isolation, the results of the meta-analysis present a trade-off worth considering. The death rates in the anticoagulation groups of the trials in the meta-

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Review: In pulmonary embolism, thrombolytic therapy reduces all-cause mortality but increases major bleeding

Chatterjee S, Chakraborty A, Weinberg I, et al. ***Thrombolysis for pulmonary embolism and risk of all-cause mortality, major bleeding, and intracranial hemorrhage: a meta-analysis.*** *JAMA. 2014;311: 2414-21.*

Clinical impact ratings: EM ★★★★★★★ C ★★★★★★☆ H ★★★★★★☆

Question

In patients with acute pulmonary embolism (PE), what are the effects of thrombolytic therapy compared with anticoagulation?

Review scope

Included studies compared thrombolytic therapy with anticoagulation with low-molecular-weight heparin, vitamin K antagonists, fondaparinux, or unfractionated heparin in patients with PE, and reported mortality. Exclusion criteria were comparisons of different thrombolytic therapies or different doses of the same therapy. Outcomes included all-cause mortality and major bleeding. Subgroup analysis was done for patients at intermediate-risk (hemodynamically stable with objective evidence of right ventricular dysfunction) and by age.

Review methods

PubMed, EMBASE/Excerpta Medica, Cochrane Library, EBSCO, Web of Science, and CINAHL (all to Apr 2014) were searched for randomized controlled trials (RCTs). 16 RCTS (n = 2115, mean age range 49 to 68 y, range of 22% to 63% men, mean follow-up 82 d) met selection criteria; 8 RCTs included patients at intermediate risk (n = 1775). 10 RCTs had low risk for bias for randomization and allocation concealment, 14 for blinding of participants and personnel, and 15 for blinding of outcome assessors. 14 reported adequate follow-up.

Thrombolytic therapy (thrombo) vs anticoagulant (anticoag) therapy in patients with pulmonary embolism*

Outcomes	Group	Number of trials (n)	Weighted event rates		At a mean 82 d	
			Thrombo	Anticoag	RRR (95% CI)	NNT (CI)
All-cause mortality	All	16 (2115)	2.1%	3.9%	46% (12 to 67)	56 (39 to 222)
	Intermediate risk†	8 (1755)	1.4%	2.9%	51% (8 to 74)	67 (46 to 440)
	Age > 65 y	5 (1331)	2.0%	3.6%	44% (–5 to 70)	NS
	Age ≤ 65 y‡	11 (784)	2.3%	4.3%	46% (–17 to 75)	NS
					RRI (CI)	NNH (CI)
Major bleeding§	All	16 (2115)	8.8%	3.4%	158% (85 to 256)	19 (12 to 35)
	Intermediate risk	8 (1755)	6.8%	2.2%	204% (102 to 352)	22 (13 to 44)
	Age > 65 y	5 (1331)	12%	4.1%	185% (101 to 298)	14 (9 to 25)
	Age ≤ 65 y	11 (784)	2.8%	2.3%	24% (–50 to 199)	NS

**NS = not significant; other abbreviations defined in Glossary. Weighted event rates, RRR, RRI, NNT, NNH, and CI calculated from control event rates and Peto odds ratios in article using a fixed-effect model.*

†Hemodynamically stable with objective evidence of right ventricular dysfunction.

‡RRR and CI calculated using event rates; odds ratio was not reported.

§As defined in individual trials. Intracranial hemorrhage was added as a major bleeding event if trials did not indicate it was included in this outcome.

Main results

Main results are in the Table.

Conclusion

In patients with pulmonary embolism, including those who were hemodynamically stable with right ventricular dysfunction, thrombolytic therapy reduces all-cause mortality but increases major bleeding.

Source of funding: No external funding

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analysis ranged from 100% (patients in shock) to < 2% in PEITHO. In patients with signs of hemodynamic stress (in PEITHO, elevated troponin levels and echocardiographic signs of right ventricular dysfunction) and stable blood pressure, the decision is a close call: a mortality reduction of about 1.5% vs a 1.5% increase in stroke and a 5% increase in serious extracranial bleeding. The weak recommendation in favor of thrombolysis in the 9th iteration of the antithrombotic guidelines (2) seems appropriate for this group in which varying patient values and preferences are likely to mandate varying patient management.

The decision is clearer both in patients without signs of right ventricular strain and in those with hemodynamic compromise. The data—as well as experience in a wide variety of other treatments—suggest that the relative risk reduction with thrombolysis will be similar across risk groups. In patients without signs of right ventricular strain (a low-risk group with mortality < 1% [3]), the bleeding complications of thrombolysis far outweigh the possible benefits. In contrast, the higher mortality risk in hemodynamically unstable patients means greater mortality benefit: For instance, those with a 20% risk for dying can expect an absolute reduction in risk for death of about 10%. Consequently, the trade-off in hemodynamically unstable patients clearly favors thrombolysis.

The rapid publication of the systematic review after the PEITHO trial illustrates the living evidence synthesis model, swiftly combining new evidence with existing evidence, and facilitating clinician access to systematic summaries of the best current evidence.

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