Critical Review Form
Therapy

Outpatient treatment in patients with acute pulmonary embolism: the Hestia study, *J Thromb Haemostasis* 2011; 9: 1500-1507

Objective: **"To confirm the results of these small cohort studies in a large study, and provide proof that the incidences of VTE recurrence, major bleeding, and mortality are very low in patients selected with a simple set of exclusion criteria." (p. 1501)**

Methods: **Single arm, consecutive patient prospective cohort study from May 2008 thru April 2010 at 12 hospitals in the Netherlands with 3-month follow-up. Inclusion criteria included adults >18 years presenting with objectively proven acute PE to ED or clinic AND without a "yes" response to an 11-item checklist of exclusion criteria:**

Exclusion criteria for outpatient treatment

Is the patient hemodynamically unstable?*	Yes	No
Is thrombolysis or embolectomy necessary?	Yes	No
Active bleeding or high risk of bleeding?†	Yes	No
More than 24 h of oxygen supply to maintain oxygen saturation > 90%?	Yes	No
Is pulmonary embolism diagnosed during anticoagulant treatment?	Yes	No
Severe pain needing intravenous pain medication for more than 24 h?	Yes	No
Medical or social reason for treatment in the hospital for more than 24 h (infection, malignancy, no support system)?	Yes	No
Does the patient have a creatinine clearance of < 30 mL min^{-1}?‡	Yes	No
Does the patient have severe liver impairment?§	Yes	No
Is the patient pregnant?	Yes	No
Does the patient have a documented history of heparin-induced thrombocytopenia?	Yes	No

Patients were also ineligible if 3-month follow-up was deemed unlikely (no address or foreigner) or if their life expectancy was <3 months.

Treatment was nadroparin (11400 IU for those <70 kg or 15200 IU for those >70 kg) with the first dose administered under supervision of ED or clinic nurse. Phenprocoumon or acenocoumarol were started the same day with target INR 2.0-3.0. Follow-up occurred in outpatient clinic at 1 week and 3 months with telephone follow-up at 6 weeks.

The primary endpoint was objectively proved recurrent VTE at 3 months. Major bleeding was the primary safety outcome (intracranial, intraspinal, intraocular, retroperitoneal, pericardial, intramuscular with compartment syndrome, or intra articular) or bleeding with reduction of Hg ≥ 2 grams resulting in transfusion of ≥2 units PRBCat 14 or 90 days). Mortality was another secondary outcome and included fatal PE, fatal bleeding, cancer, or other established diagnosis. Two physicians constituted the independent adjudication committee and evaluated all outcomes in a non-blinded fashion with access to all clinical data.

The authors set predefined upper limit of the 95% CI for recurrent VTE as the threshold for outpatient management effectiveness based upon their review of the literature: 7% using this 7% upper limit of the CI, a sample size of 257 was needed to achieve 91% power using one-sided α. The analysis was performed according to intention-to-treat principle.

Guide		Comments
I.	**Are the results valid?**	
A.	**Did experimental and control groups begin the study with a similar prognosis (answer the questions posed below)?**	
1.	Were patients randomized?	No. "We initially considered a randomized study design with random allocation to inpatient or outpatient treatment, but concluded that this was not feasible owing to the very large sample size that would be needed." (p. 1506)
2.	Was randomization concealed (blinded)?	No, so finding subject to ascertainment and co-intervention bias.
3.	Were patients analyzed in the groups to which they were randomized?	Yes, study results analyzed using intention to treat principle.
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	No control group with whom to compare prognostic baseline.

B.	**Did experimental and control groups retain a similar prognosis after the study started (answer the questions posed below)?**	
1.	Were patients aware of group allocation?	Yes, so subject to recall bias.
2.	Were clinicians aware of group allocation?	Yes, so subject to co-intervention bias.
3.	Were outcome assessors aware of group allocation?	Yes, since there was only one treatment arm (observational trial).
4.	Was follow-up complete?	Yes. "The 3 month follow-up was completed for all patients." (p. 1503)
II.	**What are the results (answer the questions posed below)?**	
1.	How large was the treatment effect?	• 243/581 (41.8%) were not eligible for outpatient management, mostly because of decreased oxygenation (30%), concomitant illness (26%), hemodynamic instability (12%), or social reasons (10%). • Mean age of eligible patients was 55 years including 26% >65 years and 9% had an active malignancy. • 6.1% treated for the entire period with LMWH, mostly cancer patients. • One non-compliant patient (age 80) had recurrent PE at 1 week (0.3%, 95% CI 0.008 – 1.9). • No patient died of fatal PE at 1 week. • Five patients had recurrent VTE at 3 months for total of 2.0% (95% CI 0.8 – 4.3), none were fatal. • Two patients (0.07%, 95% CI 0.08 – 2.4%) had a major bleeding episode, including 1 fatal ICH at 7 days. • Three patients (1.0%, 95% CI 0.2 – 2.9%) died during 3 month study. None from fatal PE.
2.	How precise was the estimate of the treatment effect?	See 95% CI above

III.	How can I apply the results to patient care (answer the questions posed below)?	
1.	Were the study patients similar to my patient?	No, Dutch patients with ready access to PCP and anticoag service.
2.	Were all clinically important outcomes considered?	No, did not assess patient preferences or satisfaction.
3.	Are the likely treatment benefits worth the potential harm and costs?	If safety and effectiveness results confirmed in RCT's that include urban American healthcare systems, this outpatient protocol for low-risk acute PE patients could save time, money, and inpatient bed space.
4.	How will you communicate the findings of this study with your patients to facilitate shared decision-making?	One effective method: "Multicenter Dutch study of low overall quality indicates that home management of PE with LMWH and oral anticoagulation is effective (although up to 4.3% of patients have recurrent blood clots at 3 months). Home management also appears to be safe with no PE related fatalities, although up to 2.4% have a significant bleeding complication at 3 months. However, verification in the U.S. healthcare system is warranted before extrapolating to our patients."

Limitations

1) **Non-randomized design.**

2) **Lack of blinding of outcome assessors.**

3) **Non-validated risk stratification instrument.**

4) **Insufficient rationale for 7% threshold.**

5) Limited external validity to U.S. healthcare system.

Bottom Line

Based upon this Dutch observational study, in presumably low risk patients with acute symptomatic PE outpatient treatment with LMWH appears safe and effective with a 4.3% recurrent VTE rate at 3-months and no PE-related deaths. The label "presumably low risk" is used because the authors used a non-validated, 11-item checklist to delineate eligible from non-eligible (higher risk) individuals. In addition, this was an observational study and the medical literature is littered with interventions that appear safe & effective in observational trials with effectiveness subsequently disproven by randomized controlled trials (see Guyatt 2008). Furthermore, in the U.S. healthcare system without reliable access to primary care or anticoagulation clinics and without a centralized national medical registry, these results need to be interpreted within the constraints of the U.S. vulnerable patient populations. Furthermore, if the outpatient management protocol is adopted locally, a 24/7 protocol with anticoagulation clinics with a Quality Improvement feedback loop is needed, as is assurance that ED physicians will accurately and reliably risk stratify PE patients.