Critical Review Form
Meta-analysis

Can Selected Patients with Newly Diagnosed Pulmonary Embolism Be Safely Treated Without Hospitalization? A Systematic Review, *Ann Emerg Med* 2012;60:651-662

Objective: **"To examine the evidence about the safety of exclusive ambulatory management for patients with acute symptomatic pulmonary embolism." (p. 651)**

Methods: **This systematic review (SR) included prospective studies that enrolled patients with acute symptomatic pulmonary embolism (PE) with radiographic confirmation of PE diagnosis and with explicit inclusion/exclusion criteria including risk assessment tools. PE therapy had to be *exclusively* outpatient after ED or clinic assessment (rather than expedited inpatient management) and investigators described well-defined pharmacotherapy and follow-up treatment protocols and objective outcomes including recurrent VTE, major hemorrhage, and all-cause mortality during the follow-up interval. Studies using atypical management models like hotel near hospital were excluded. Studies reporting mixed VTE cohorts (DVT and PE) were excluded when they did not report PE outcomes separately.**

The SR authors searched MEDLINE, EMBASE, Scopus, CINAHL, Web of Knowledge, Cochrane library, and clinical trials.gov thru March 2012 without language restrictions. They also queried MEDLINE "related articles" feature, as well as the studies included in previous SR's on this topic (Janjua 2008, Squizzato 2009), as well as 4 years of conference proceedings from SAEM, ACEP, and CAEP. Three experts in the field were also consulted in the search for additional research evidence.

Two investigators independently screened titles and abstracts for inclusion and measured inter observer agreement via Kappa analysis. A third author brokered discrepancies. Two reviewers independently abstracted data from selected studies using a predesigned data collection instrument, including site of treatment, patient characteristics, diagnostic criteria, use of risk-strtification instruments, outpatient ineligibility criteria, and outcomes. Authors were contacted if important variables were not reported in the study. The SR authors followed the PRISMA reporting guidelines and assessed the quality of original studies using the GRADE criteria.

Guide	Question	Comments
I	***Are the results valid?***	
1.	Did the review explicitly address a sensible question?	Yes, can a subset of newly diagnosed PE patients be safely and effectively treated at home?
2.	Was the search for relevant studies details and exhaustive?	Yes, the authors followed PRISMA guidelines and searched multiple electronic database and conference proceedings.
3.	Were the primary studies of high methodological quality?	As noted in Table 2 (p. 656) only one RCT was identified and it was moderate quality using GRADE criteria with potential bias from lack of allocation concealment and lack of blinding. Seven observational trials were "very low" quality of evidence with concerns for failure to develop and apply appropriate eligibility criteria, failure to measure all known prognostic variables and control for confounders, and imprecision (wide CI's).
4.	Were the assessments of the included studies reproducible?	Yes, authors used GRADE criteria, which is reproducible.
II.	***What are the results?***	
1.	What are the overall results of the study?	• Original search identified 2286 titles from which 24 prospective studies were identified, but 17 excluded (1 because hotel used 16 because PE and DVT outcomes are reported separately), although the SR authors were able to obtain the PE data from one study from the original investigators. ▪ Kappa = 1 (95% CI 0.85-1.0) for study selection. ▪ 8 studies (1 RCT, 7 observational studies) including 777 adult patients were included, all but one in academic settings and only four initiated from the ED. Only one study included U.S. patients. Mean ages varied from 47-69 across studies. • Three studies used risk stratification instruments. ▪ Beer used the 6-variable Geneva score ▪ Agterof used NT-pro BNP <500 pg/mL to define "low-risk". ▪ Aujesky used the 11 variable Pulmonary Embolism Severity Index (PESI). • All 3 of the studies that used risk-stratification instruments **also used social or medical conditions to preclude outpatient treatment** including PE characteristics (massive, receiving thrombolysis, or

		diagnosed >23° prior), patient symptoms requiring parenteral opioids, vital sign abnormalities (hypotension, tachycardia, hypoxemia), contraindications to anticoagulation (active bleeding, acute anemia, thrombocytopenia renal insufficiency, severe liver disease, stroke within 10 days-4 weeks, GI bleed or operation within 2 weeks, heparin intolerance, comorbidities (heart failure, arrhythmia, pregnancy, extreme obesity, (life-expectancy <3 months), and barriers to adherence/follow-up (lack of telephone or transport support, lack of around-the-clock caregiver, substance abuse, psychosis or dementia, homelessness, imprisonment) or patient preference. • Treatment consisted of LMWH for 5 days and warfarin with arranged clinic follow-up within 7-10 days, preceded by researcher initiated telephone calls. • All studies included patient/caregiver education on medication usage and signs/symptoms requiring medical attention. • Four studies used an adjudication committee to define outcomes. • No patients in any study were lost to follow-up. • Seven studies with 90 day follow-up on 741 patients found zero cases of thromboembolic or hemorrhage-related death (95% CI 0 - 0.62%). • One study with 180 day follow-up reported 2 deaths. If these had occurred within 90 days the event rate would have been 0.26% (95% CI 0-1%). • 90-day non-fatal recurrent venous thromboembolic rates ranged from 0 to 6.2%, non-fatal hemorrhage 0-1.2%. • In the RCT patient satisfaction did not differ between groups (92% outpatient vs. 95% inpatients, p=0.39) were satisfied or very satisfied with the medical care received.
2.	How precise are the results?	See 95% CI above.
3.	Were the results similar from study to study?	No. "The significant heterogeneity between the study populations precluded outcome-level assessments." (p. 654). These studies were conducted in different settings on variable PE risk strata with heterogeneous methods of following up patients.

III.	***Will the results help me in caring for my patients?***	
1.	How can I best interpret the results to apply them to the care of my patients?	In select and agreeable *non-geriatric* adult patients with newly diagnosed PE, transportation access to outpatient anticoagulation care, and a reliable caregiver at home, outpatient management of PE is safe: PE or hemorrhage related deaths occur in <1%.
2.	Were all patient important outcomes considered?	Yes, including patient acceptability.
3.	Are the benefits worth the costs and potential risks?	Yes, if appropriately low-risk patients with access to care can be reliably identified real-time in the ED. This will require an algorithm/protocol agreed upon by EM, PCP's, Hospitalists, Firm, and anti-coagulation services.
4.	How will you communicate the findings of this study with your patients to facilitate shared decision-making?	One effective method: "Multiple studies have demonstrated that treating your pulmonary embolism (blood clot) at home with shots and pills is as safe and effective as treating you with the same medications in the hospital, *if* you meet certain criteria (i.e. meaning that you are low-risk for a bad outcome), have the ability to follow-up within 7-10 days as scheduled, and have somebody at home to help you monitor your care."

Limitations

1) **Heterogeneous, poor quality study with only 4 ED-based settings and limited external validity for community ED's.**

2) **Failure to assess publication bias.**

3) **No assessment of how many urban ED patients in the U.S. would be eligible for this protocol given the stringent inclusion criteria.**

Bottom Line

In select and agreeable non-geriatric adult patients with newly diagnosed PE, transportation access to outpatient anticoagulation care, and a reliable caregiver at home, outpatient management of PE is safe with PE or hemorrhage related deaths <1%.

Multiple uncertainties remain. Can and will EP's reliably risk stratify PE patients? Which risk-stratification instrument should be used? Is LMWH available to destitute ED patients 24/7? Who will provide LMWH teaching and is this instruction reliable? How will follow-up be assured and what QI process will close the loop?