Critical Review Form
Non-Inferiority

Outpatient versus inpatient treatment for patients with acute pulmonary embolism: an international, open-label, randomized, non-inferiority trial, *Lancet* 2011;378:41-48

Objective: **"To compare the effectiveness, safety, and efficiency of outpatient versus inpatient care for low-risk patients with acute, symptomatic pulmonary embolism as established with a validated clinical prognostic model." (p. 41)**

Methods: **Open-label randomized, non-inferiority clinical trial from Feb. 2007 to June 2010 conducted at 19 EDs in Switzerland, France, Belgium, and the U.S. Consecutive adults >18 years old with acute symptomatic objectively verified PE at low-risk of death (PESI risk class I or II) were eligible. PE was verified by filling defect on spiral CT or pulmonary angiogram, new high probability V/Q scan, or new DVT by venous US or contrast venography in the setting of acute dyspnea or chest pain. Exclusion criteria included oxygen sat on room air <90%, paO_2 <60 mm Hg, SBP <100 mm Hg, chest pain requiring parenteral opioids, active bleeding or high risk of bleeding (stroke within preceding 10 days, GI bleed within 14 days, <75000 platelets, creatinine clearance <30), body mass >15 kg, history of heparin-induced thrombocytopenia or heparin allergy, therapeutic INR when PE diagnosed, pregnancy, imprisonment, or any barriers to adherence or follow-up (current ETOH abuse, illicit drug use, psychosis, dementia, homelessness) or diagnosis of PE > 23° prior.**

Patients were randomized to outpatient or inpatient treatment in a one-to-one ratio at each participating site. Patients in outpatient arm received standardized teaching from a study nurse about enoxaparin self-injection 1 mg/kg BID. In both impatient and outpatient protocols, early oral anticoagulation (warfarin, acenocoumarol, phenprocoumon, or fluidione) was encouraged for a minimum of 90 days. Enoxaparin was discontinued after ≥ 5 days when the INR ≥ 2.0 for two consecutive days as managed by the PCP or coagulation service. Patients were contacted every day for the first week and then at 14, 30, 60, and 90 days.

The primary outcome was the recurrence of symptomatic, objectively confirmed VTE as defined by recurrent PE or new DVT within 90 days. Secondary outcomes were major bleeding (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 PRBC at 14 or 90 days. All-cause mortality within 90 days was another secondary endpoint. Outcomes were defined by a committee of three blinded clinical experts at the University of Lausanne (Switzerland). Investigators also assessed patient satisfaction

with 5-point Likert scale by telephone at 14 days post-randomization. Major medical resource use at 90 days was also assessed.

Based upon a 90 day recurrence rate for VTE of 0.9% in low-risk inpatients with PE and a non-inferiority margin of 4%, the sample size of 160 patients per treatment group would have 80% power to detect 4% non-inferiority margin with one-sided α 0.05 assuming a 5% drop out rate. The authors reported an intention to treat *and* per protocol analysis. The 4% non-inferiority margin was extrapolated from "studies comparing different anticoagulation regimens in acute VTE and outpatient…) (p. 43).

Guide		Comments
I.	**Are the results valid?**	
1.	Did novel and standard treatment groups start with the same prognosis?	Yes, Table 2 (p. 44) demonstrates equal distributions of prognostic risk factors between inpatient and outpatient groups, including the PESI risk stratifications.
2.	Was prognostic balance maintained as the trial progressed?	Yes. "We randomly allocated 172 eligible patients to the outpatient group and 172 to the inpatient group. One outpatient and two inpatients were lost to follow-up and two inpatients withdrew consent during follow-up; therefore, we included 171 outpatients and 168 inpatients in the primary analysis." (p. 44) Even if the 1 outpatient and 4 inpatients were the extremes of disease (outpatient sickest, inpatients least ill or best prognosis) this small number lost is far less than anticipated dropout rate and would not show evidence of effectiveness or safety.
3.	Were the groups prognostically balanced at the completion of the trial?	No report of prognostic distribution at end of trial but with only 5 excluded out of 349, unlikely to imbalance prognostic distributions.
4.	Did the investigators guard against an unwarranted conclusion of non-inferiority?	Yes. "The percentage of time spent in the therapeutic INR range (2.0-3.0) was around 52% in both groups (Table 3)." (p. 44)

5.	Was the effect of the standard treatment preserved?	Yes, the anticipated recurrent PE/new DVT event rate in PESI Class I or II patients was 0.9% and the observed rate in the hospitalized group was 0%.
6.	Did the investigators analyze patients according to the treatment they received, as well as to the groups to which they were assigned?	Yes. "We also did a per-protocol analysis of the medical outcomes, excluding outpatients discharged more than 24 h after randomization and inpatients discharged 24 h or less after randomization." (p. 44)
II.	**What are the results (answer the questions posed below)?**	
1.	How large was the treatment effect?	• Mean age of patients was 48 years and 75% were white with BMI ~ 26.5 kg/m^2 and 75% presented with new or increasing dyspnea and 71% with chest pain. • 89% diagnosed by CT and >60% of PEs were segmental – only 14% (outpatient) and 10% (inpatient) were central. • 65% - 68% were PESI Class I. • Time from presentation until randomization in the ED was 13.9 hours (outpatient) versus 13.3 hours (inpatient, p=0.24) and treatment with LMWH was of longer duration in the outpatient group (11.5 days versus 8.9 days, p=0.04). Primary Outcome • In the primary-analysis intention-to-treat (ITT) 1/171 (0.6%, 95% CI 0-2.7%) in the outpatient group had a recurrent VTE within 90 days meeting criteria for non-inferiority (<4%). • The per-protocol analysis also supported non-inferiority with upper limit of 95% CI 2.9%. Secondary Outcome • Two outpatients and no inpatients had major bleeding within 14 days (upper limit 95% CI 3.8% on per-protocol and 4.5% on ITT/primary analysis)

		which does exceed non-inferiority 4% margin. • One patient in both groups died during 90 day follow-up for 0% difference and 95% CI upper limit 2.1% in both ITT and per-protocol analysis. • 99% completed the satisfaction survey at 14 day with 92% of outpatients and 95% of inpatients either satisfied or very satisfied. • Mean time initially hospitalized post-randomization was 0.5 days (outpatient) versus 3.9 days (inpatient). • No significant differences in hospital or ED readmission within 90 days, or visits to PCP. (Table 5) P. 46)
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?	Yes, ED patients with newly diagnosed PE. However, uncertain how many of our patients are PESI Class I or how this data extrapolates to blacks or urban American with universal healthcare or readily available PCP.
2.	Were all clinically important outcomes considered?	Yes, including patient satisfaction.
3.	Are the likely advantages of the novel treatment worth the potential harm and costs?	Yes, if patients comfortable with home anticoagulation and not wary of slightly increased major bleed risk that extends beyond non-inferior threshold.
4.	How will you communicate the findings of this study with your patients to facilitate shared decision-making?	One effective method: "A single moderate quality study from 19 ED's in Europe and the U.S. demonstrates that certain PE patients can be safely and effectively treated with blood thinners at home, although there is a chance of increased bleeding risk at 90 days (< 5% at most) with home management."

Limitations

1) **Unconvincing rationale for the 4% non-inferiority threshold.**

2) **Lack of ethnic (or socio demographic) diversity amongst patients that were 85% white and mostly from countries with universal healthcare.**

3) **Need to verify safety in post-warfarin era of oral direct thrombin or factor Xa inhibitors (Buller 2004, Bauersachs 2010, Büller 2012).**

4) **Open-label so subject to recall bias, co-intervention bias and other biases.**

Bottom Line

In low risk patients with acute symptomatic PE, outpatient treatment with LMWH is not inferior to inpatient treatment as measured by effectiveness or safety, although outpatient management not non-inferior at 90 days when contemplating major bleeding with upper limit of 95% CI 4.5%. Previous prospective trials (Kovacs 2000, Beer 2003, Zondag 2010, Agterof 2010, Otero 2010) indicate that 13%-51% of ED PE patients would be eligible for this outpatient protocol. However, in the U.S. healthcare system without ready access to primary care or anticoagulation clinic and without a centralized national medical registry, these results need to be interpreted within the constraints of our vulnerable patient populations. Patients without transportation, housing, or a reliable and available caregiver were not studied and these results should not be extrapolated to them. 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 with the PESI.