Information for online appendix

Extension of methods section:

Data sources

We performed a systematic literature search in Medline, Web of Science, Cochrane and EMBASE to identify all studies on clinical outcome of PE patients treated at home or discharged early. The search was performed using predefined search terms: “pulmonary embolism” or “pulmonary thromboembolism” and “home treatment” or “outpatient treatment” or “ambulant treatment” or “early discharge” (Appendix I). The search was developed and conducted by the authors in conjunction with a librarian with experience in meta-analyses. The search was restricted to English, French, German or Dutch articles. The last search was performed on July 5th 2011. There were no restrictions on publication date or status.

Study outcome

The outcomes of this meta-analysis were objectively proven recurrent VTE, all cause mortality and major bleeding during the first three months after the initial PE diagnosis. Symptomatic recurrent VTE was the main outcome. Recurrent VTE was considered present if recurrent PE or DVT were documented objectively, or in case of death in which PE could not be confidently ruled out as a contributing cause. The objective criterion for the diagnosis of recurrent PE was a new filling defect revealed by pulmonary angiography or spiral computed-tomography pulmonary angiography or a new high probability perfusion defect revealed by VQ-scan or any new defects after earlier normalizing of the scan. The objective criterion of a new DVT was a new venous

segment of the thrombus on ultrasonography or a new intraluminal filling defect on contrast venography.

Major bleeding was defined as fatal bleeding, and/or symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial or intramuscular with compartment syndrome, and/or bleeding causing a fall in hemoglobin level of more than 2.0 g/dL (1.3 mmol/L), or leading to transfusion of more than two units of whole blood or red cells (E1).

Assessment of bias

The Cochrane collaboration tool for bias risk assessment was used in order to asses the risk of bias in the individual studies (E2). We adapted the Cochrane collaboration tool for the use in cohort studies. The following items were included: assessment of exposure, clear selection for outpatient treatment, consecutive patients, adequacy of follow-up and assessment of outcome. Assessment of exposure was considered adequate when the index PE was diagnosed with one of the following imaging techniques: pulmonary angiography, CT angiography, high probability V/Q scan or intermediate probability V/Q scan combined with a positive compression ultrasonography for DVT. An unambiguous selection for outpatient treatment was present if predefined exclusion criteria were used to select whether or not a patient could be treated as an outpatient. A study population was considered adequate if it consisted of consecutive patients or included a random sample of all potentially eligible patients. At least 80% of patients had to have had a complete follow-up to decide that follow-up was adequate. Assessment of outcome was

adequate when objective criteria were used, comparable to the international criteria for assessing recurrent VTE or major bleeding (E1, E3).

Statistical analysis

Meta-analysis and meta-regression were performed using an exact likelihood approach. The method used was a logistic regression with a random effect at the study level (E4). Given the expected clinical heterogeneity, a random effects model was performed by default, and no fixed effects analyses were performed. For meta-analysis of proportions, the exact likelihood approach based on a binomial distribution has advantages compared with a standard random effects model that is based on a normal distribution (E5). First, estimates from a binomial model are less biased than estimates from models based on a normal approximation (E6). This is especially the case for proportions that are close to 0 or 1. Secondly, no assumptions are needed for the exact approximation when dealing with zero-cells, whereas the standard approach needs to add an arbitrary value (often 0.5) when dealing with zero-cells. Adding values to zero-cells is known to contribute to the biased estimate of the model (E7, E8).

The outcomes according to the intention to treat principle were used in the meta-analysis. 95% confidence intervals (CI) around the reported incidences of recurrent VTE, major bleeding and all cause mortality in the individual studies were calculated with the Fishers Exact Test. All analyses were performed with STATA 12.0 (Stata Corp., College Station, TX).

References Online Data Supplement

E1 Schulman S,Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost* 2005;3:692-694.

E2 Higgins JP and Green S. Cochrane Handbook for Systematic Reviews of Interventions; Version 5.0.1 (updated September 2008). 2008. The Cochrane Collaboration.

E3 Buller HR, Cohen AT, Davidson B, Decousus H, Gallus AS, Gent M, Pillion G, Piovella F, Prins MH, Raskob GE. Idraparinux versus standard therapy for venous thromboembolic disease. *N Engl J Med* 2007;357:1094-1104.

E4 Hamza TH, van Houwelingen HC, Stijnen T. The binomial distribution of meta-analysis was preferred to model within-study variability. *J Clin Epidemiol* 2008;61:41-51.

E5 DerSimonian R,Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7:177-188.

E6 Chang BH, Waternaux C, Lipsitz S. Meta-analysis of binary data: which within study variance estimate to use? *Stat Med* 2001;20:1947-1956.

E7 Platt RW, Leroux BG, Breslow N. Generalized linear mixed models for meta-analysis. *Stat Med* 1999;18:643-654.

E8 Sweeting MJ, Sutton AJ, Lambert PC. What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data. *Stat Med* 2004;23:1351-1375.

Appendix I: Search

PubMed

("Pulmonary Embolism"[mesh] OR "pulmonary embolism" OR "pulmonary embolisms" OR "pulmonary thromboembolisms" OR "pulmonary thromboembolism") AND ("home treatment" OR "Home Care Services"[mesh] OR "home care" OR "home therapy" OR "outpatient treatment" OR "outpatient therapy" OR "Ambulatory Care"[mesh] OR "ambulant treatment" OR "ambulatory treatment" OR "ambulatory therapy" OR "ambulatory care" OR "outpatient care" OR "outpatient health service" OR "outpatient health services" OR "Outpatients"[mesh] OR outpatient OR outpatients OR "out of hospital treatment" OR "early discharge" OR "early discharges" OR "early discharged" OR "discharged early" OR "out of hospital")

EMBASE

(*Lung Embolism/ OR "pulmonary embolism".ti OR "pulmonary embolisms".ti OR "pulmonary thromboembolisms".ti OR "pulmonary thromboembolism".ti) AND (exp *home care/ OR ("home care" OR "home therapy" OR "outpatient treatment" OR "outpatient therapy").ti OR *outpatient care/ OR exp *Ambulatory Care/ OR ("ambulant treatment" OR "ambulatory treatment" OR "ambulatory therapy" OR "ambulatory care" OR "outpatient care" OR "outpatient health service" OR "outpatient health services").ti OR *Outpatient/ OR (outpatient OR outpatients OR "early discharge" OR "early discharges" OR "early discharged" OR "discharged early" OR "out of hospital").ti)

Appendix II: Risk of bias assessment

First author (ref)	Year	Design	Assessment of exposure	Clear selection for outpatient treatment	Consecutive patients	Adequacy of follow-up	Assessment of outcome
Agterof [4]	2010	Prospective cohort	Yes	Yes	Yes	Yes, 100% completed follow-up	Yes
Aujesky [5]	2011	RCT	Yes	Yes	Yes	Yes, 1 outpatient and 2 inpatients (0.9%) were lost to follow-up	Yes
Beer [24]	2002	Prospective cohort	Unclear, probably yes because PE was "objectively confirmed"	Yes	No, 57 patients excluded because recruitment was not possible in weekends	Unclear, no description of lost to FU	Unclear
Davies [25]	2007	Prospective cohort	No, clinical features of PE and DVT confirmed by was also allowed	Yes	Unclear, not described how many patients were excluded in phase 2 of the study	Yes, one patient lost to follow-up (0.6%)	Yes
Erkens [6]	2010	Retrospective cohort	Yes	Yes	Yes	Yes, 9 (1.7%) patients lost-to-follow-up	Yes
Kovacs [26]	2000	Prospective cohort	Yes	Yes	Unclear, there is a description of how many patients were treated as	Unclear, no description of how many patients were lost to FU	Yes

					inpatients, but not the reason why they were treated as inpatients		
Kovacs [7]	2010	Retrospective cohort	Unclear	Yes	Unclear, consecutive patients were recorded, but unclear if all or only a selection were referred to participate in the outpatient program	Yes, one (0.3%) of the patients was lost to follow-up	Yes
Lui[27]	2007	Retrospective cohort	Yes	Yes	Yes	Yes, none of the patients was lost to follow-up	Unclear
Olsson [28]	2006	Prospective cohort	Yes	Yes	No, patients could only be included if the physician responsible for the study was available and if V/P scanning was possible (technical and logistical)	Yes, none of the patients was lost to follow-up	Yes
Ong [29]	2005	Retrospective cohort	Yes	Yes	No, 130/194 treated at home; unclear why others were not treated at home	Yes, one patient (0.8%) lost to FU	Yes
Otero [30]	2009	RCT	Yes	Yes	No, 284 of 1016 (28%) excluded for “other reasons”	Yes, no patients were lost to follow-up	Yes

					than prespecified criteria		
Rodriguez-Cerrillo [31]	2009	Prospective cohort study	Yes	Yes	No, only 61 of 286 (21%) included	Unclear, no description of lost-to-follow-up	Unclear, only criteria for major bleeding defined in methods section
Siragusa [32]	2005	Prospective cohort	No, clinical features of PE and DVT confirmed by CUS was also allowed	Yes	Yes	Unclear, no description of lost-to-follow-up	Yes
Wells [33]	2005	RCT	Yes	Yes	Yes	Yes 100% of patients completed follow-up	Yes
Zondag [8]	2011	Prospective cohort	Yes	Yes	Yes	Yes, 100% completed follow-up	Yes

RCT = randomized controlled trial; V/P scan = ventilation/perfusion scan