Chapter 4

Outpatient versus inpatient treatment in patients with pulmonary embolism: a meta-analysis

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Abstract

Background

The aim was to study the safety of outpatient treatment in low risk patients with acute pulmonary embolism (PE) compared to inpatient treatment, the current clinical standard.

Methods and results

We searched Medline, Web of Science, Cochrane and EMBASE databases and included cohort studies or randomized controlled trials on outpatient treatment of PE. The outcomes were recurrent venous thromboembolism (VTE), major bleeding and all cause mortality in a 3 months follow-up period. We identified thirteen studies with a total of 1657 PE patients treated as outpatients (discharge <24 hours), two studies including 184 patients discharged within 72 hours (early discharge) and five studies totaling 455 patients treated as inpatients. The pooled incidence of recurrent VTE was 1.7% (95% confidence interval 0.92-3.1) in outpatients, 0.48% (95% CI 0.02-11) in patients discharged early and 1.2% (95%CI 0.20-7.9) in inpatients. The pooled incidence of major bleeding was 1.0% (95% CI 0.58-1.6) in outpatients, 0.48% (95% CI 0.02-11) in early discharge patients and 1.1% (95% CI 0.46-2.6) in inpatients. The pooled incidence of mortality was 1.9% (0.79-4.6) in outpatients, 1.6% (0.53-4.9) in early discharge patients and 0.80% (0.06-9.9) in inpatients. The outpatient mortality risk decreased to 0.60% (0.22-1.6) after excluding studies that exclusively included patients with malignancies.

Conclusion

Incidences of recurrent VTE, major bleeding and, after correction for malignancies, mortality were comparable between outpatients, patients discharged early and those after full inpatient treatment. We conclude that home treatment or early discharge of selected low-risk patients with acute PE is as safe as inpatient treatment.í

Introduction

Traditionally patients with pulmonary embolism (PE) are initially treated with anticoagulants in a hospital setting, with a mean length of hospital stay of 6 days.[1] The outpatient treatment of patients with deep vein thrombosis (DVT) is internationally accepted and graded with a 1B recommendation by the American College of Chest Physicians (ACCP).[2] Because of limited evidence, the international guidelines give only a grade 2B recommendation regarding the early discharge of PE patients.[2,3] Notably, in recent years several large studies were published on this matter, including the first completed randomized controlled trial.[4-7] Results from those studies suggest that outpatient treatment is as safe as standard inpatient treatment.

Patients with PE treated in the hospital have a low risk of 0.4% for fatal recurrent PE within the first 3 months and a 3% risk for non-fatal recurrent PE.[8] Fatal major bleeding occurs in 0.2% of patients within 3 months after PE, with a non-fatal major bleeding rate of 2.0%.[8,9] Before outpatient treatment in low risk PE patients can be accepted as standard patient care, comparable safety to inpatient care has to be proven.[10] Two systematic reviews concerning outpatient treatment in patients with acute PE have been published.[11,12] These reviews demonstrated low incidences of recurrent venous thromboembolism (VTE), major bleeding and mortality, but the quality of the included small observational studies was low. The most recent and largest studies, including one randomized controlled trial, were not included in these reviews.[4-7]

This meta-analysis compared the risk for adverse outcome in specific low risk patients who were selected for outpatient treatment (discharge within 24 hours), to the risk for adverse outcome in patients with a comparable risk profile, who were discharged early (discharge within 72 hours) and to the risk in patients treated in the hospital. This second category is relevant in hospitals in which discharge within 24 hours is not possible due to logistical reasons. Our aim was to evaluate whether outpatient treatment and early discharge are as safe as traditional inpatient treatment in patients with PE.

Methods

Data sources and searches

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”. 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. We also hand-searched the reference lists of the two previous systematic reviews.[11,12]

Study selection

Two investigators (W.Z. and J.K.) independently performed the study selection. A third investigator was consulted in case of disagreement (F.A.K.).

Only randomized controlled trials or cohort studies which included patients with acute, symptomatic, objectively proven PE were selected. To be eligible, at least a part of the study population had to be treated with anticoagulants at home or had to be discharged early. We did not include studies in which the definition for home treatment or early discharge allowed for a hospital admission of more than 3 days. Also, studies which did not explicitly mention the outpatient setting of the anticoagulant treatment were excluded. If relevant, outcome data had to be reported for in- and outpatients separately. In studies including both patients with DVT (without PE) and PE, outcome parameters had to be reported for DVT and PE patients separately.

To allow for a fair comparison, this meta-analysis was limited to studies with low risk PE patients, i.e. who had a clinical condition which made outpatient treatment possible. Because only low-risk patients were selected in all studies that reported on outpatient treatment or early discharge, patients could only be included in the inpatient cohort of our analysis if they had been selected on the basis of identical prognostic criteria. Hence, studies investigating only high risk PE patients (patients who could not be treated at home due to medical conditions) or mixed high and low risk patients were excluded from the present meta-analysis.

Study outcomes

The main outcomes of this study were the pooled incidences of recurrent VTE, major bleeding and all-cause mortality during 3 months in patients with PE treated at home versus patients discharged early and patients treated as inpatients. 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 computed tomography pulmonary angiography (CTPA) or a new high probability perfusion defect revealed by ventilation-perfusion(V/Q) 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.[13]

Data extraction and risk of bias assessment

We developed a data extraction sheet containing items on risk of bias, patient characteristics (age, sex, co-morbidities), study characteristics, in- and exclusion criteria for outpatient treatment, definition of home treatment or early discharge, length of follow-up, outcome measures and anticoagulant treatment. The data extraction sheet was completed for all eligible studies by two independent authors (W.Z., J.K.).

The Cochrane collaboration tool for bias risk assessment was used in order to asses the risk of bias in the individual studies.[14] We adapted the Cochrane collaboration tool for the use in cohort studies. The following design items were included for risk of bias assessment: adequacy of exposure assessment, clear selection for outpatient treatment, consecutive patients, adequacy of follow-up and adequacy of outcome assessment. Assessment of exposure was considered adequate when the index PE was diagnosed with one of the following imaging techniques: pulmonary angiography, CTPA, 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 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. Complete follow-up in at least 80% of patients was considered adequate. Assessment of outcome was adequate when objective criteria were used, comparable to the international criteria for assessing recurrent VTE or major bleeding.[13,15] Recurrent VTE had to be objectively diagnosed by CTPA, V/Q scanning or pulmonary angiography. Major bleeding had to be defined by the International Society of Thrombosis and Haemostasis (ISTH) criteria or comparable criteria.

Data synthesis and analysis

Meta-analysis was performed using an exact likelihood approach. The method used was a logistic regression with a random effect at the study level.[16] 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.[17] First, estimates from a binomial model are less biased than estimates from models based on a normal approximation.[18] 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.[19,20] Meta-regression analyses were also performed with an exact likelihood approach.

A pre-specified subgroup analysis of studies with low proportions of malignancies (<15%) was performed, because malignancy is a known risk factor for recurrent VTE, mortality and bleeding.[21,22] The outcomes according to the intention-to-treat principle were used in the meta-analysis. Confidence intervals (CI) of 95% 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).

Results

Study selection and characteristics

The literature search identified a total number of 1576 studies; 1532 were excluded after reviewing the title and abstract and another 29 were excluded after reading the full article. The reasons for exclusion of studies are listed in Figure 1. The reviewing process resulted in 15 studies eligible for inclusion in the review.[4-7,23-33]

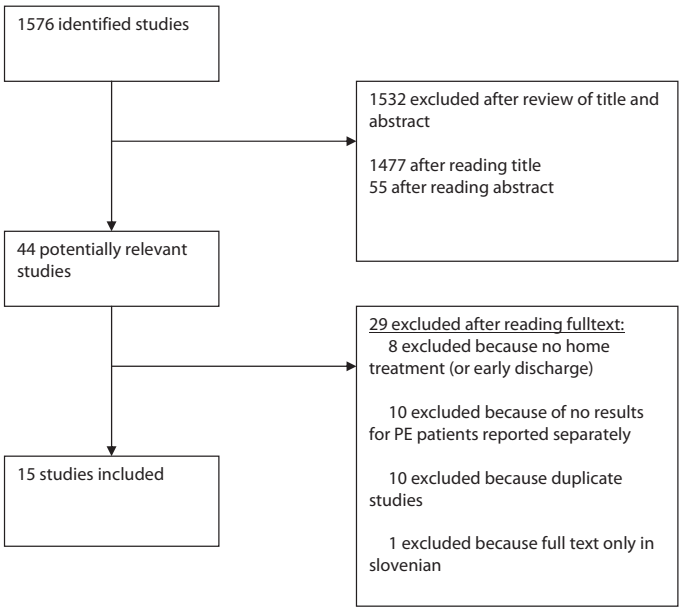

Figure 1: Flow chart: selection of studies

All were published in the English language. All but two studies reported outcome measures at 3 months; one study reported outcomes at 6 months [32] and one study reported outcomes at the end of the acute phase (mean 6 days).[27] All but one studies reported on the 3 outcome measures: recurrent VTE, major bleeding and all cause mortality.[28] Four studies reported both inpatient and outpatient groups[4,24,29,31] of which one study randomized the patients for in- or outpatient treatment.[4] Another study reported early discharge and outpatient groups separately.[26] Finally, one study reported an early discharge group only [25] and eight studies reported an outpatient group only.[5-7,23,27,28,32,33]

The included studies involved 2296 patients: 1657 were treated as outpatients, 184 were discharged early and 455 were selected low risk patients treated as inpatients.

Risk of bias assessment

Of 15 included studies, three were randomized controlled trials, twelve were cohort studies; eight with prospective patient inclusion and four with retrospective patient selection. Only two randomized controlled trials randomized patients between home treatment or early discharge and hospital treatment,[4,30] of which one was stopped early;[30] the trial by Wells *et al.* did not randomize between in- and outpatient treatment, but compared two LMWH regimens.[33] A proportion of the PE patients in both LMWH randomization groups was treated at home. The trial performed by Aujesky *et al.* was well designed with a full score on the risk of bias assessment (Table 1). The main limitation of the trial by Otero *et al.* is that there could be a limited generalizibility of the results, because 30% of patients with PE were not included in the study for reasons unclear.

In the low risk outpatients group, five studies,[4,5,7,23,33] which contributed 59% of the patients, had a maximum score on the risk of bias assessment. These studies represented also the highest proportions of outcomes; therefore it is not likely that possible selection bias in the smaller studies largely affects the magnitude of the outcomes.

The outcomes in the early discharge group are mainly based on the study by Davies *et al.*[25] The main limitation of this study is that there could be an underestimation of the risk of adverse outcome due to selection of low risk patients.

The outcomes in the inpatient group were based for 66% on the inpatient groups of the two randomized controlled trials. These trials had no important sources of bias.[4,30]

Table 1: Study and patient characteristics, risk of bias assessment

Study ID	**Design**	**Risk of bias assessment** (exposure, patient selection, consecutive, follow-up, outcome)	**Definition of outpatient treatment or early discharge**	**Outcome measures and methods**	**N patients**	**Mean age** (SD)	**Male sex** n (%)	**Malignancies** n (%)
Agterof [23]	Prospective cohort	yes, yes, yes, yes, yes	Discharged immediately from ED or within 24 hours after admission	Recurrent VTE: new intraluminal filling defect on CT, pulmonary angiogram, V/Q, autopsy or extension of DVT on CUS Major bleeding: according ISTH criteria [13] Mortality: Independent steering committee	152 outpatients	53 (14)	74 (49)	20 (13)
Aujesky [4]	RCT	yes, yes, yes, yes, yes	Discharged from ED or within 24 hours of randomization	Recurrent VTE: new intraluminal filling defect on CT, pulmonary angiogram, autopsy or extension of DVT on CUS Major bleeding: according ISTH criteria [13] Mortality: Independent steering committee	171 outpatients 168 inpatients	47 (16)	84 (49)	1 (1)
Beer [24]	Prospective cohort	unclear, yes, no, unclear, unclear	Unclear	Not described	43 outpatients 54 inpatients	-	-	-
Davies [25]	Prospective cohort	no, yes, unclear, yes, yes	Diagnosis of PE confirmed within 72 hours of initial assessment	Thromboembolic complications (with objective confirmation)	157 early discharge	58	86 (55)	-
Erkens [5]	Retrospective cohort	yes, yes, yes, yes, yes	Sent home from ED	Recurrent VTE: new intraluminal filling defect on CT, pulmonary angiogram, V/Q, autopsy or extension of DVT on CUS Major bleeding: according ISTH criteria [13] Mortality: Consensus of two investigators based on clinical records	260 outpatients	55 (17)	132 (51)	83 (32)

Table 1: Study and patient characteristics, risk of bias assessment (continued)

Study ID	**Design**	**Risk of bias assessment** (exposure, patient selection, consecutive, follow-up, outcome)	**Definition of outpatient treatment or early discharge**	**Outcome measures and methods**	**N patients**	**Mean age** (SD)	**Male sex** n (%)	**Malignancies** n (%)
Kovacs [26]	Prospective cohort	yes, yes, unclear, yes	Unclear	Recurrent VTE: new intraluminal filling defect on CT, pulmonary angiogram, V/Q, autopsy or extension of DVT on CUS Major bleeding: according previous reported criteria [36]	81 outpatients 27 early discharge	57	-	25 (23)
Kovacs [6]	Retrospective cohort	unclear, yes, unclear, yes, yes	Unclear	Recurrent VTE: new intraluminal filling defect on CT, pulmonary angiogram, V/Q, autopsy or extension of DVT on CUS Major bleeding: according ISTH criteria [13] Mortality: not described	314 outpatients	54 (18)	130 (41)	62 (20)
Lui [27]	Retrospective cohort	yes, yes, yes, yes, unclear	Sent to Hospital in the Home within 24 hours of arrival	Death, unplanned return to hospital, unplanned staff callout, complications (recurrent PE, bleeding episode or other); methods not described	21 outpatients	56	9 (43)	1 (5)
Olsson [28]	Prospective cohort	yes, yes, no, yes, yes	Unclear	Recurrent thromboembolism: V/Q scan	102 outpatients	63	45 (44)	-
Ong [29]	Retrospective cohort	yes, yes, no, yes, yes	Admitted directly into ambulant care program via GP, specialist or ED	Recurrent VTE: new intraluminal filling defect on CT, pulmonary angiogram, V/Q, autopsy or extension of DVT on CUS Major bleeding: according ISTH criteria [13] Mortality: clinical records	60 outpatients 70 inpatients	-	-	-

Table 1: Study and patient characteristics, risk of bias assessment (continued)

Study ID	**Design**	**Risk of bias assessment** (exposure, patient selection, consecutive, follow-up, outcome)	**Definition of outpatient treatment or early discharge**	**Outcome measures and methods**	**N patients**	**Mean age** (SD)	**Male sex** n (%)	**Malignancies** n (%)
Otero [30]	RCT	yes, yes, no, yes, yes	Patients were randomized to hospitalization or early discharge. Early discharge patients were discharged on day 3 (with TTE) or on day 5 (if TTE was not available).	Recurrent VTE: new intraluminal filling defect on CT or extension of DVT on CUS Major bleeding: according ISTH criteria[13] Mortality: clinical records	132 inpatients	60 (17)	65 (49)	6 (5)
Rodriguez-Cerrillo [31]	Prospective cohort study	yes, yes, no, unclear, unclear	Unclear	Recurrent VTE: unclear how diagnosis was established Major bleeding: according ISTH criteria[13] Mortality: methods not described	30 outpatients 31 inpatients	67	26 (42)	7 (12)
Siragusa [32]*	Prospective cohort	no, yes, yes, unclear, yes	Unclear	Recurrent DVT: extension of thrombus on CUS or venography Recurrent PE: new defect in V/Q or CT lung scan, worsening of signs or symptoms, along with deterioration of chest X-ray or blood gas or EKG or leg swelling with a positive CUS was considered Major bleeding: according ISTH criteria[13] Mortality: methods not described	36 outpatients	62	67/127 (53)	36 (100)

Table 1: Study and patient characteristics, risk of bias assessment (continued)

Study ID	**Design**	**Risk of bias assessment** (exposure, patient selection, consecutive, follow-up, outcome)	**Definition of outpatient treatment or early discharge**	**Outcome measures and methods**	**N patients**	**Mean age** (SD)	**Male sex** n (%)	**Malignancies** n (%)
Wells [33]*	RCT	yes, yes, yes, yes, yes	Unclear	Recurrent DVT: extension of thrombus on CUS; in doubt serial testing or venography was used; Recurrent PE: new defect on V/Q, angiography or CT lung scan according to PIOPED criteria. Patients who did not have high probability on V/Q scan, further investigations: CUS leg, venography, or angiography Major bleeding: according ISTH criteria[13] Mortality: methods not described; probably clinical records reviewed by independent committee	90 outpatients	58 (17)	273/505 (54)	113/505
Zondag [7]	Prospective cohort	yes, yes, yes, yes, yes	Sent home from ED or within 24 hours after admission	Recurrent VTE: new intraluminal filling defect on CT, pulmonary angiogram, V/Q, autopsy or extension of DVT on CUS Major bleeding: according ISTH criteria[13] Mortality: Clinical record or autopsy report reviewed by independent committee	297 outpatients	55 (15)	172 (58)	28 (9)

ED= emergency department; BMI=body mass index; COPD = chronic obstructive pulmonary disease GP= general practitioner; NA= non applicable; NYHA= New York Heart Association; TTE= transthoracic echocardiography; VTE= venous thromboembolism

Categorical data are displayed as number (proportion); continuous data are displayed as mean (standard deviation).

* baseline characteristics (age, male sex, malignancies) described for a mixed group of patients with DVT and PE together, not reported separately for patients with PE

Table 2: Criteria for exclusion of patients for outpatient treatment

Exclusion criterion	Which studies?	Definition
1. Extra tools for risk stratification	Agterof	NT-proBNP>500 ng/mL
	Aujesky	Pulmonary Embolism Severity Index>85*
	Lui	Massive pulmonary embolism
	Olsson	Large PE (affecting >40% longperfusion on V/Qscan)
	Otero	Clinical score >2, Troponin T>0.1 ng/mL, RV dysfuction on TTE
	Rodriguez	Massive PE (two or more lobar branches)
2. Hemodynamically unstable	Agterof, Aujesky, Beer, Erkens, Kovacs 2000, Kovacs 2010, Lui, Ong, Otero, Rodriguez, Wells, Zondag	
3. Respiratory unstability	Agterof, Aujesky, Davies, Erkens, Kovacs 2000, Kovacs 2010, Lui, Ong, Otero, Rodriguex, Wells, Zondag	
4. Intravenous pain medication	Agterof, Aujesky, Davies, Kovacs 2000, Kovacs 2010, Olsson, Ong, Siragusa, Wells, Zondag	
5. Bleeding risk	Agterof, Aujesky, Beer, Davies, Erkens, Kovacs 2000, Kovacs 2010, Lui, Olsson, Ong, Otero, Rodriguez, Siragusa, Wells, Zondag	
6. Therapeutic anticoagulation at time of diagnosis PE	Aujesky, Beer, Davies, Wells, Zondag	
7. Co-morbid conditions requiring hospital admission	Agterof, Davies, Erkens, Kovacs 2000, Olsson, Ong, Otero, Rodriguez, Siragusa, Wells, Zondag	
8. Social conditions	Agterof, Aujesky, Beer, Davies, Kovacs 2000, Lui, Ong, Rodriguex, Siragusa, Wells, Zondag	
9. Pregnancy	Agterof, Aujesky, Davies, Otero, Zondag	
10. Renal insufficiency	Agterof, Aujesky, Beer, Erkens, Rodriguez, Siragusa, Wells, Zondag	
11. Contraindication to heparins	Aujesky, Beer, Lui, Rodriguez, Wells, Zondag	
12. Concomitant deep vein thrombosis	Davies, Wells	
13. Obesity	Aujesky, Beer, Otero	
14. Liver impairment	Zondag	

PE= pulmonary embolism; RV=right ventricular; TTE = transthoracic echocardiography
*Aujesky et al. Am J Respir Crit Care Med 2005;172(8):1041-1046

Selection of low risk patients for outpatient treatment or early discharge

Different methods of defining PE patients as low risk for adverse events were used (Table 2). Most studies used comparable clinical criteria[5-7,25-27,29,31-33] to select patients for outpatient treatment. In Table 2, the clinical criteria for selecting patients for outpatient treatment used in the different studies are summarized. More than 10 studies used at least the following criteria for exclusion of patients from outpatient treatment: hemodynamic instability (mostly defined as systolic blood pressure < 100 mmHg), respiratory instability (mostly defined as hypoxia on breathing room air), severe pain and need for parenteral narcotics, high bleeding risk and co-existing co-morbid diseases or social problems requiring hospital admission. Other important factors to consider when patients are screened for outpatient treatment are: whether they have altered pharmacokinetics due to pregnancy or renal/liver insufficiency or contra indications for heparins like allergies or previous heparin induced thrombocytopenia. Some studies used an additional clinical decision rule,[4,24,30] a laboratory test [23] or imaging test (Table 2).[28] The demographic characteristics age and sex were comparable among the studies: mean age ranged between 47 and 67 years and 30-58% of patients were male (Table 1). Notably, the proportion of malignancies varied widely among the studies: from 1-100%. In one study solely PE patients with malignancies were investigated.[32]

Outpatient anticoagulant treatment

In most of the studies, outpatient treatment was defined as hospital discharge within 24 hours. In the two studies reporting an early discharge group the mean duration of hospital admission was 1.0 days [25] and 2.5 days.[26] The study of Otero *et al.* reported on two groups: the first group of patients was discharged after a mean of 3.4 days and the second group was discharged after a mean of 9.3 days.[30] Because the two groups had a mean duration of hospital admission over 72 hours, both were analyzed in the inpatient cohort of the meta-analysis.

In all fifteen studies patients were treated with a combination of LMWH and vitamin K antagonists, except for patients with an indication for LMWH treatment alone, for example patients with malignancies. Most of the studies reported a minimum of 5 days of LMWH treatment, until the INR was in the therapeutic range of 2.0-3.0. Nadroparin once daily was used in two studies,[7,24] tinzaparin once daily in two studies,[25,28] daltaparin once daily in one study,[26] four studies used more than one LMWH protocol and in five studies the type of LMWH used was not specified. In summary, nine studies used once daily LMWH[5,7,23-26,28,33] and one study used twice daily LMWH.[4] The other studies used more than one LMWH protocols or it was not described. In at least six studies a part of the patients injected LMWH themselves after instruction of a nurse.[4,7,23,26,29,32] Warfarin was used in seven studies[6,25-28,32,33] and other forms of VKA treatment (phenprocoumon, acenocoumarol, fluidione) were used in five studies.[7,23,24,30,31] In three studies the type of VKA was not specified or more than one protocol was used.[4,5,29] In one study 5% of patients were treated with unspecified experimental drugs.[6]

Table 3. Outcome during 3 months after pulmonary embolism

Study ID	N	Recurrent VTE	95% CI	Mortality	95% CI	Major Bleeding	95% CI
Outpatients							
Agterof [23]	152	0	0.0-2.4	0	0.0-2.4	0	0.0-2.4
Aujesky [4]	171	1 (0.6)	0.01-3.2	1 (0.6)	0.01-3.2	3 (1.8)	0.4-4.7
Beer [24]	43	1 (2.3)	0.06-12.3	0	0.0-6.7	0	0.0-6.7
Erkens [5]	260	10 (3.8)	1.9-7.0	13 (5)	2.7-8.4	4 (1.5)	0.4-3.9
Kovacs [26]	81	5 (6.2)	2.0-13.8	4 (4.9)	1.4-12.2	1 (1.2)	0.03-6.7
Kovacs [6]	314	3 (0.95)	0.2-2.8	9 (2.9)	1.3-5.4	3 (0.95)	0.2-2.8
Lui[27]*	21	0	0.0-16.1	0	0.0-16.1	0	0.0-16.1
Olsson [28]	102	0	0.0-3.6	4 (3.9)	1.1-9.7	-	-
Ong [29]	60	3 (5.0)	1.0-13.9	1 (1.7)	0.04-8.9	1 (1.7)	0.04-8.9
Rodriguez-Cerrillo [31]	30	0	0.0-11.6	0	0.0-11.6	0	0.0-11.6
Siragusa [32]†	36	2 (5.5)	0.7-18.7	11 (30.5)	16.4-48.1	1 (2.7)	0.07-14.5
Wells [33]	90	2 (2.2)	0.3-7.8	3 (3.3)	0.7-9.4	0	0.0-4.0
Zondag [7]	297	6 (2.0)	0.8-4.3	3 (1.0)	0.2-2.9	2 (0.67)	0.008-1.9
Early discharge							
Davies [25]	157	0	0.0-2.3	3 (1.9)	0.4-5.5	0	0.0-2.3
Kovacs [26]	27	1 (3.7)	0.09-19.0	0	0.0-12.8	1 (3.7)	0.09-19.0
Inpatients							
Aujesky [4]	168	0	0.0-1.8	0	0.0-1.8	1 (0.6)	0.01-3.3
Beer [24]	54	2/65 (3.1)‡	0.4-10.7	0	0-5.5	0	0-5.5
Ong [29]	70	4 (5.7)	1.6-14.0	3 (4.3)	0.9-12.0	2 (2.9)	0.3-9.9
Otero [30]	132	4 (3.0)	0.8-7.6	8 (6.1)	3.1-11.5	2 (1.5)	0.2-5.4
Rodriguez-Cerrillo [31]	31	0	0.0-11.2	0	0.0-11.2	0	0.0-11.2

CI= confidence interval; VTE=venous thromboembolism; Categorical data are displayed as number (percentage); continuous data are displayed as mean (standard deviation).
*mean duration of follow-up 6 days (range 3-11), no long term outcome available; †outcome measured at 6 months after diagnosis of pulmonary embolism;
‡2 recurrent PE in total inpatient group (N=65), not specified for high (N=11) or low risk (N=54) group.

Meta-analysis: recurrent VTE

In 13 studies a total of 1657 PE patients were treated as outpatients and 33 patients had a recurrent VTE (Table 3). None of these recurrent events were fatal. The pooled VTE recurrence risk of patients treated as outpatients was 1.7% (95% CI 0.92-3.1). In two studies, a total of 184 patients were discharged early, in which one patient had a non-fatal recurrent VTE. The pooled VTE recurrence risk of patients discharged early was 0.48% (95% CI 0.02-11). In the five studies describing 455 PE patients treated as inpatients, 10 patients had recurrent VTE. The pooled VTE recurrence risk of patient treated as inpatients was 1.2% (95% CI 0.20-7.9; Figure 2). After excluding studies with a high proportion of patients with malignancies as previously stated, the pooled incidence of recurrent VTE did not change significantly (p=0.053).

Meta-analysis: major bleeding

In the 1657 PE patients that were treated as outpatients, 15 patients had a major bleeding of which three proved fatal (Table 3). The pooled major bleeding incidence of patients treated as outpatients was 0.97% (95% CI 0.58-1.6). In 184 patients who were discharged early, one patient had a fatal major bleeding. The pooled major bleeding risk of patients discharged early was 0.48% (95% CI 0.02-11). In 455 PE patients who were treated as inpatients, five patients had major bleeding of which one was fatal. The pooled major bleeding risk of patients treated as inpatients was 1.1% (95% CI 0.46-2.6). The pooled incidences did not differ significantly between the groups (Figure 2). The pooled incidence of major bleeding did not change significantly after excluding studies with a high proportion of patients with malignancies (p=0.44).

Meta-analysis: all-cause mortality

In the total of 1657 PE patients that were treated as outpatients 49 patients died (Table 3). None of the patients died of fatal PE. The pooled mortality risk of patients treated as outpatients was 1.9% (95% CI 0.79-4.6). In the 184 patients discharged early, three patients died. The pooled mortality risk of patients discharged early was 1.6% (95% CI 0.53-4.9). In 455 PE patients treated as inpatients, 11 patients died. The pooled mortality risk of patient treated as inpatients was 0.80% (95% CI 0.06-9.9). The pooled incidences did not differ significantly between the groups (Figure 2). After excluding studies with a maximum of 15% of patients with malignancies, the pooled incidence of mortality in outpatients decreased to 0.60% (95% CI 0.22-1.6). This was significantly different from the pooled incidence of mortality of 4.2%

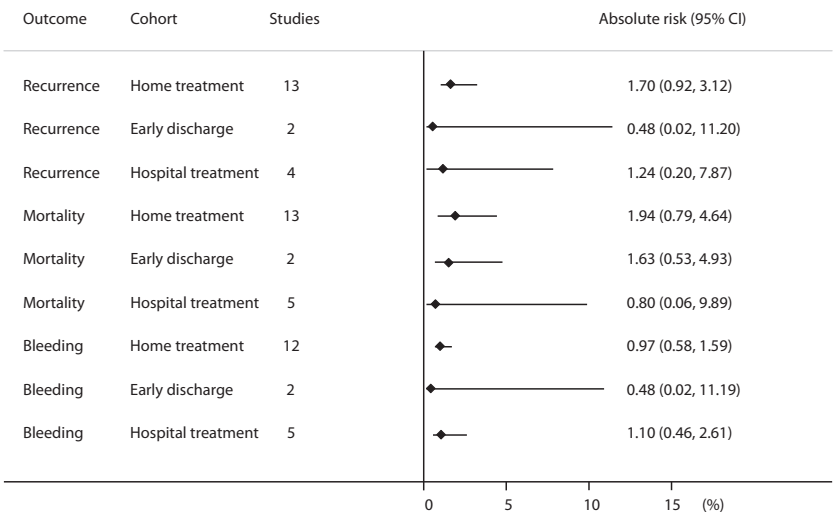

Figure 2: Pooled incidences of clinical outcome after pulmonary embolism in patients treated at home, discharged early or treated as inpatients

(95% CI 2.0-8.6) in the outpatient studies with a high proportion (>15%) of malignancies (p=0.003).

Discussion

The results of the present meta-analysis indicate that the pooled incidences of recurrent VTE and major bleeding in selected patients with PE treated at home or discharged early within 3 days are equivalent to those incidences of comparable selected patients with PE treated in the hospital.

While the point estimates of mortality were higher in the outpatient than in the inpatient group (1.9% vs. 0.80%), the confidence intervals are overlapping. Importantly, no fatal PE occurred in the patients treated at home or discharged early. When outpatients were compared to early discharge or inpatients with comparable malignancy rates (<15%), the incidences of mortality were equal in outpatients and inpatients (0.60% vs. 0.80%).

Most of the studies excluded patients with a high risk for major bleeding. This resulted in low pooled incidences of major bleeding in outpatients, early discharge patients and inpatients of 0.5-1.1%. However, the case-fatality rate of major bleeding is high: 20% (95% CI 4-48) in outpatients and a comparable 20% (95% CI 0.5-72) in patients treated in the hospital. The comparable incidences of major bleeding in outpatients (1.0%) versus inpatients (1.1%) and the comparable case-fatality rates in both groups indicate that treating patients at home may not enhance unfavorable outcome of bleeding events and therefore underlines the safety of outpatient treatment.

Outpatient treatment and early discharge of patients with PE should be restricted to patients with low risk for adverse clinical outcome. In the included studies, different methods for selection of low risk patients were used. All studies used a list of pragmatic exclusion criteria for outpatient treatment (Table 1) which mostly contained items on hemodynamic or respiratory compromise, high bleeding risk, co-morbidity and predicted therapy compliance. In addition some studies used a formal, validated method to select patients at low risk for adverse clinical outcome. The only completed randomized controlled trial used the Pulmonary Embolism Severity Index (PESI), a clinical prognostic score based on signs and symptoms.[4] Patients in the low risk PESI classes have a risk for 90-day all-cause mortality of 1% or lower.[34] Other studies used different clinical risk scores,[24,30,35] the laboratory value NT-proBNP,[23] or imaging parameters like the size of the embolus [27,31] or the size of the perfusion defect.[28] The proportions of patients that could be selected for outpatient treatment varied among the studies from 30% to 55%, depending on the extensiveness of the selection method.

The strength of this study is that it is the first meta-analysis on outpatient treatment in PE patients with pooled incidences of adverse clinical outcome. Another strength is that this meta-analysis discriminates between patients treated entirely at home (<24 hours) and patients discharged early (24-72 hours). Furthermore, a highly relevant control group of low risk patients treated in the hospital was added for the comparison with outpatient

and early discharge groups. The selected control group of low risk inpatients, i.e. PE patients with clinical conditions which make them potentially eligible for outpatient treatment, is relevant because it enhances comparability of baseline risk factors for adverse outcome, like co-morbidity and severity of pulmonary embolism, between the groups.

This meta-analysis also has some limitations. Although the results presented here indicate that outpatient treatment and early discharge may be as safe as treatment in the hospital, the level of evidence of the included studies remains limited. Until now, only one randomized controlled trial on outpatient treatment of PE patients has been completed.[4] The trial by Otero *et al.* was stopped early because of two deaths within 14 days in the early discharge group versus none in the standard hospitalization group, which was too high for their predefined margins, but this proportion had wide confidence intervals and was not statistical significant. The lack of more high quality randomized controlled trials means that our conclusions can not be supported by grade 1A evidence yet. However, well designed cohort studies can also provide reliable evidence. This meta-analysis included five high quality observational studies with many patients and no serious sources of bias (Table 2). Therefore we conclude that the estimates of incidences of adverse outcome are reliable. Another drawback is that one of three treatment groups was small: only two studies described patients discharged early. Therefore the confidence intervals of the incidences in this group were wide. On the other hand, the incidences of recurrence, bleeding and mortality in the outpatients groups are representative, because they were based on 1657 patients form 13 studies. Third, the autopsy rates in all studies were low giving some uncertainty about whether PE related mortality was really absent. Fourth, before outpatient treatment can be implemented in clinical care, close follow-up of patients, especially in the first weeks, must be guaranteed. This could implicate that outpatient treatment of patients with PE will be reserved for countries with a solid network of thrombosis clinics.

In conclusion, the results of the present meta-analysis demonstrate the safety of outpatient treatment and early discharge in selected low risk patients with pulmonary embolism. This conclusion is also supported by the latest ACCP guideline with a grade 2B recommendation.[2] More randomized controlled trials on outpatient treatment of pulmonary embolism patients are needed, for outpatient treatment to be graded with a 1A recommendation.

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