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

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

We searched Medline, Web of Science, Cochrane and EMBASE databases and included studies on outpatient treatment of pulmonary embolism. The outcomes were 3-month recurrent venous thromboembolism, major bleeding and all-cause mortality. We identified 13 studies (1657 patients) with outpatients (discharge <24 h), three studies (256 patients) with early discharge patients (discharged within 72 h) and five studies (383 patients) with inpatients. The pooled incidence of recurrent venous thromboembolism was 1.7% (95% CI 0.92–3.1%) in outpatients, 1.1% (0.22–5.4%) in patients discharged early and 1.2% (0.16–8.1%) in inpatients. The pooled incidence of major bleeding was 0.97% (0.58–1.6%) in outpatients, 0.78% (0.16–3.7%) in early discharge patients and 1.0% (0.39–2.8%) in inpatients. The pooled incidence of mortality was 1.9% (0.79–4.6%) in outpatients, 2.3% (1.1–5.1%) in early discharge patients and 0.74% (0.04–11%) in inpatients.

Incidences of recurrent venous thromboembolism, major bleeding and, after correction for malignancies, mortality were comparable between outpatients, patients discharged early and inpatients. We conclude that home treatment or early discharge of selected low-risk patients with pulmonary embolism is as safe as inpatient treatment.

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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 randomised controlled trial [4–8]. 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 nonfatal recurrent PE [9]. Fatal major bleeding occurs in 0.2% of patients within 3 months after PE, with a nonfatal major bleeding rate of 2.0% [9, 10]. Before outpatient treatment in low-risk PE patients can be accepted as standard patient care, comparable safety to inpatient care has to be proven [11]. Two systematic reviews concerning outpatient treatment in patients with acute PE have been published [12, 13]. 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 randomised controlled trial, were not included in these reviews [5–8].

This meta-analysis compared the risk for adverse outcome in specific low-risk patients who were selected for outpatient treatment (discharge within 24 h) with the risk for adverse outcome in patients with a comparable risk profile who were discharged early (discharge within 72 h) and with the risk in patients treated in the hospital. This second category is relevant in hospitals in which discharge within 24 h 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

We performed a systematic literature search in Medline, Web of Science, Cochrane and EMBASE to identify all studies on clinical outcome of PE patients either treated at home or discharged early. The search was performed using predefined search terms, which can be found in the online supplementary material.

Selection process

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

Only randomised controlled trials or cohort studies that included patients with acute, symptomatic, objectively proven PE were selected. To be eligible, at least a part of the study population had either to be treated with anticoagulants at home or had to have been discharged early. We did not include studies in which the definition for home treatment or early discharge allowed for a hospital admission of >3 days. Also, studies that 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 that 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.

Data extraction

We developed a data extraction sheet containing items on risk of bias, patient characteristics (age, sex and comorbidities), study characteristics, inclusion 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. Zondag and J. Kooiman). The Cochrane collaboration tool for bias risk assessment was used in order to assess the risk of bias in the individual studies [14]. More information on the risk of bias assessment is given in the online supplementary material.

Statistical analysis

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. More extensive information on study outcomes can be found in the online supplementary material. Meta-analysis and meta-regression were performed using an exact likelihood approach. A logistic regression method with a random effect at the study level was used [15]. 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 [16, 17]. The rationale behind the value of 15% was that studies that included >15% patients with malignancies were not deemed representative of the general patient population as this percentage was generally observed in recent large studies on VTE treatment [18, 19]. The outcomes according to the intention to treat principle were used in the meta-analysis. Confidence intervals of 95% around the reported incidences of recurrent VTE, major bleeding and all-cause mortality in the individual studies were calculated using the Fisher's exact test. All analyses were performed with STATA 12.0 (Stata Corp., College Station, TX, USA).

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 [4–8, 20–29].

All included studies were published in English. All but two studies reported outcome measures at 3 months; one study reported outcomes at 6 months [28] and one study reported outcomes at the end of the acute phase (mean 6 days) [23]. All but one study reported on the three outcome measures: recurrent VTE, major bleeding and all-cause mortality [24]. Four studies reported both inpatient and outpatient groups [5, 20, 25, 27], of which one study randomised the patients for inpatient or outpatient treatment [5]. Another study reported early discharge and outpatient groups separately [22]. Finally, one study reported an early discharge group only [21] and eight studies reported an outpatient group only [4, 6–8, 23, 24, 28, 29].

The included studies (table 1) involved 2296 patients: 1657 were treated as outpatients, 256 were discharged early and 383 were selected low-risk patients treated as inpatients.

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 [6–8, 21–23, 25, 27–29] to select patients for outpatient treatment. In table 2, the clinical criteria for selecting patients for outpatient treatment used in the different studies are summarised. More than 10 studies used at least the following criteria for exclusion of patients from outpatient treatment: haemodynamic 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 comorbid 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

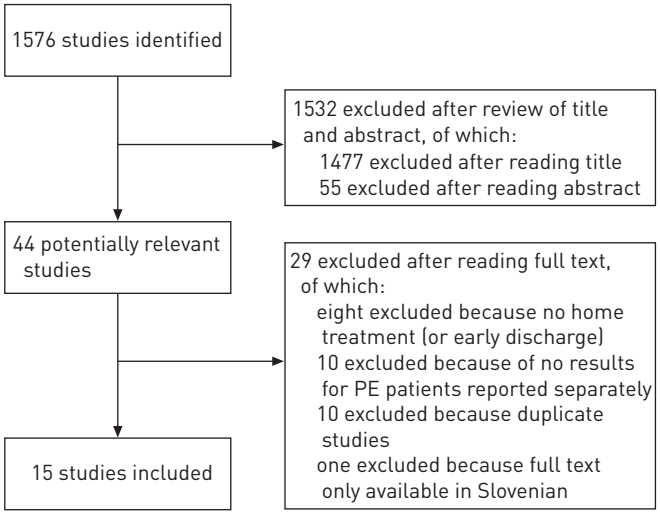

FIGURE 1 Flow chart showing selection of studies. PE: pulmonary embolism.

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TABLE 1 Study and patient characteristics, and risk of bias assessment

First author [Ref.]	Design	Risk of bias (exposure, patient selection, consecutive, follow-up, outcome)	Definition of outpatient treatment or early discharge	Outcome measures and methods	Patients n	Age years	Males	Malignancies
Agterof [4]	Prospective cohort	Yes, yes, yes, yes, yes	Discharged immediately from ED or within 24 h after admission	Recurrent VTE: new intraluminal filling defect on CT, pulmonary angiogram, *V'/Q'*, autopsy or extension of DVT on CUS Major bleeding: according to ISTH criteria [30] Mortality: independent steering committee	152 outpatients	53±14	74 (49)	20 (13)
Aujesky [5]	RCT	Yes, yes, yes, yes, yes	Discharged from ED or within 24 h of randomisation	Recurrent VTE: new intraluminal filling defect on CT, pulmonary angiogram, autopsy or extension of DVT on CUS Major bleeding: according to ISTH criteria [30] Mortality: independent steering committee	171 outpatients 168 inpatients	47±16	84 (49)	1 (1)
Beer [20]	Prospective cohort	Unclear, yes, no, unclear, unclear	Unclear	Not described	43 outpatients 54 inpatients			
Davies [21]	Prospective cohort	No, yes, unclear, yes, yes	Diagnosis of PE confirmed within 72 h of initial assessment	Thromboembolic complications (with objective confirmation)	157 early discharge	58	86 (55)	
Erkens [6]	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 to ISTH criteria [30] Mortality: Consensus of two investigators based on clinical records	260 outpatients	55±17	132 (51)	83 (32)
Kovacs [22]	Prospective cohort	Yes, yes, unclear, 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 [31]	81 outpatients 27 early discharge	57		25 (23)
Kovacs [7]	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 to ISTH criteria [30] Mortality: not described	314 outpatients	54±18	130 (41)	62 (20)
Lui [23]	Retrospective cohort	Yes, yes, yes, yes, unclear	Sent to "hospital in the home" within 24 h 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 [24]	Prospective cohort	Yes, yes, no, yes, yes	Unclear	Recurrent thromboembolism: *V'/Q'* scan	102 outpatients	63	45 (44)	
Ong [25]	Retrospective cohort	Yes, yes, no, yes, yes	Admitted directly into ambulant care programme *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 to ISTH criteria [30] Mortality: clinical records	60 outpatients 70 inpatients			
Otero [26]	RCT	Yes, yes, no, yes, yes	Patients were randomised to hospitalisation 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 to ISTH criteria [30] Mortality: clinical records	132 inpatients	60±17	65 (49)	6 (5)
Rodriguez-Cerrillo [27]	Prospective cohort study	Yes, yes, no, unclear, unclear	Unclear	Recurrent VTE: unclear how diagnosis was established Major bleeding: according to ISTH criteria [30] Mortality: methods not described	30 outpatients 31 inpatients	67	26 (42)	7 (12)

TABLE 1 Continued

First author [Ref.]	Design	Risk of bias (exposure, patient selection, consecutive, follow-up, outcome)	Definition of outpatient treatment or early discharge	Outcome measures and methods	Patients n	Age years	Males	Malignancies
Siragusa [28]#	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 shown *via* chest radiograph, blood gases or ECG, or leg swelling with a positive CUS Major bleeding: according to ISTH criteria [30] Mortality: methods not described	36 outpatients	62	67/127 (53)	36 (100)
Wells [29]#	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 underwent further investigations (CUS leg, venography or angiography) Major bleeding: according to ISTH criteria [30] Mortality: methods not described; probably clinical records reviewed by independent committee	90 outpatients	58±17	273/505 (54)	113/505
Zondag [8]	Prospective cohort	Yes, yes, yes, yes, yes	Sent home from ED or within 24 h after admission	Recurrent VTE: new intraluminal filling defect on CT, pulmonary angiogram, *V'/Q'*, autopsy or extension of DVT on CUS Major bleeding: according to ISTH criteria [30] Mortality: clinical record or autopsy report reviewed by independent committee	297 outpatients	55±15	172 (58)	28 (9)

Data are presented as n, mean±SD or n (%), unless otherwise stated. ED: emergency department; VTE: venous thromboembolism; CT: computed tomography; *V'/Q'*: ventilation/perfusion ratio; DVT: deep vein thrombosis; CUS: compression ultrasonography; ISTH: International Society on Thrombosis and Haemostasis; RCT: randomised controlled trial; PE: pulmonary embolism; GP: general practitioner; TTE: transthoracic echocardiography; PIOPED: Prospective Investigation of Pulmonary Embolism Diagnosis. #: 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; ¶: ambulatory care programme.

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TABLE 2 Criteria for exclusion of patients for outpatient treatment

First author [Ref.]	Extra risk tools	Haemodynamically unstable	Respiratory unstable	*i.v.* pain medication	Bleeding risk	Therapeutic OAT	Comorbidities	Social	Pregnant	Renal impairment	Contraindications LMWH
Agterof [4]	NT-proBNP >500 ng·mL^{-1}	X	X	X	X	X	X	X	X	X	
Aujesky [5]	PES index >85 [16]	X	X	X	X			X	X	X	X
Beer [20]		X			X	X		X		X	X
Davies [21]			X	X	X	X	X	X	X		
Erkens [6]		X	X		X		X			X	
Kovacs [22]		X	X	X	X		X	X			
Kovacs [7]		X	X	X	X						
Lui [23]	Massive PE	X	X		X			X			X
Olsson [24]	Large PE (affecting >40% lung perfusion on *V'*/*Q'* scan)			X	X		X				
Ong [25]		X	X	X	X		X	X			
Otero [26]	Clinical score >2, troponin T >0.1 ng·mL^{-1}, RVD on TTE	X	X		X		X		X		
Rodriguez-Cerrillo [27]	Massive PE (two or more lobar branches)	X	X		X		X	X		X	X
Siragusa [28]				X	X		X	X		X	
Wells [29]		X	X	X	X	X	X	X		X	X
Zondag [8]		X	X	X	X	X	X	X	X	X	X

OAT: oral anticoagulant therapy; LMWH: low molecular weight heparin; NT-proBNP: N-terminal pro-brain natriuretic peptide; PES: pulmonary embolism severity; PE: pulmonary embolism; *V'*/*Q'*: ventilation/perfusion ratio; RVD: right ventricular dysfunction; TTE: transthoracic echocardiography.

contra-indications for heparins, such as allergies or previous heparin-induced thrombocytopenia. Some studies used an additional clinical decision rule [5, 20, 26], a laboratory test [4] or imaging test (table 2) [24]. The demographic characteristics of age and sex were variable 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% to 100%. In one study, solely PE patients with malignancies were investigated [28].

Outpatient anticoagulant treatment

In most of the studies, outpatient treatment was defined as hospital discharge within 24 h. In all 15 studies, patients were treated with a combination of low molecular weight heparin (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 international normalised ratio was in the therapeutic range of 2.0–3.0. Nine studies used once-daily LMWH [4, 6, 8, 20–22, 24, 29] and one study used twice-daily LMWH [5]. The other studies either used more than one LMWH protocol or it was not described. In at least six studies, a proportion of the patients injected LMWH themselves after instruction by a nurse [4, 5, 8, 22, 25, 28].

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 three studies, a total of 256 patients were discharged early, of which three patients had a nonfatal recurrent VTE. The pooled VTE recurrence risk of patients discharged early was 1.1% (95% CI 0.22–5.43%). In the four studies describing 329 PE patients treated as inpatients, six patients had recurrent VTE. The pooled VTE recurrence risk of patient treated as inpatients was 1.2% (95% CI 0.16–8.14%) (fig. 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 256 patients who were discharged early, two patients had a major bleeding; both were fatal. The pooled major bleeding risk of patients discharged early was 0.78% (95% CI 0.16–3.73%). In 383 PE patients who were treated as inpatients, four patients had major bleeding; none were fatal. The pooled major bleeding risk of patients treated as inpatients was 1.0% (95% CI 0.39–2.75%). The pooled incidences did not differ significantly between the groups (fig. 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 256 patients discharged early, six patients died. The pooled mortality risk of patients discharged early was 2.3% (95% CI 1.08–5.12%). In 383 PE patients treated as inpatients, eight patients died. The pooled mortality risk of patient treated as inpatients was 0.74% (95% CI 0.04–11.14). The pooled incidences did not differ significantly between the groups (fig. 2). After excluding studies with an over-representation of patients with malignancy (>15% of study patients), 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% (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% *versus* 0.74%), the confidence intervals are overlapping. Importantly, no fatal PE occurred in the patients either treated at home or discharged early. When outpatients were compared with early discharge or inpatients with comparable malignancy rates (<15%), the incidences of mortality were comparable in outpatients and inpatients (0.60% *versus* 0.74%).

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TABLE 3 Outcome during 3 months following pulmonary embolism

First author [Ref.]	Patients n	Recurrent VTE	95% CI	Mortality	95% CI	Major bleeding	95% CI
Outpatients							
Agterof [4]	152	0	0.0–2.4	0	0.0–2.4	0	0.0–2.4
Aujesky [5]	171	1 (0.6)	0.01–3.2	1 (0.6)	0.01–3.2	3 (1.8)	0.4–4.7
Beer [20]	43	1 (2.3)	0.06–12.3	0	0.0–6.7	0	0.0–6.7
Erkens [6]	260	10 (3.8)	1.9–7.0	13 (5)	2.7–8.4	4 (1.5)	0.4–3.9
Kovacs [22]	81	5 (6.2)	2.0–13.8	4 (4.9)	1.4–12.2	1 (1.2)	0.03–6.7
Kovacs [7]	314	3 (0.95)	0.2–2.8	9 (2.9)	1.3–5.4	3 (0.95)	0.2–2.8
Lui [23]#	21	0	0.0–16.1	0	0.0–16.1	0	0.0–16.1
Olsson [24]	102	0	0.0–3.6	4 (3.9)	1.1–9.7		
Ong [25]	60	3 (5.0)	1.0–13.9	1 (1.7)	0.04–8.9	1 (1.7)	0.04–8.9
Rodriguez-Cerrillo [27]	30	0	0.0–11.6	0	0.0–11.6	0	0.0–11.6
Siragusa [28]¶	36	2 (5.5)	0.7–18.7	11 (30.5)	16.4–48.1	1 (2.7)	0.07–14.5
Wells [29]	90	2 (2.2)	0.3–7.8	3 (3.3)	0.7–9.4	0	0.0–4.0
Zondag [8]	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 [21]	157	0	0.0–2.3	3 (1.9)	0.4–5.5	0	0.0–2.3
Kovacs [22]	27	1 (3.7)	0.09–19.0	0	0.0–12.8	1 (3.7)	0.09–19.0
Otero [26]	72	2 (2.8)	0.33–9.7	3 (4.2)	0.87–11.7	1 (1.4)	0.03–7.5
Inpatients							
Aujesky [5]	168	0	0.0–1.8	0	0.0–1.8	1 (0.6)	0.01–3.3
Beer [20]	54	2/65 (3.1)+	0.4–10.7	0	0–5.5	0	0–5.5
Ong [25]	70	4 (5.7)	1.6–14.0	3 (4.3)	0.9–12.0	2 (2.9)	0.3–9.9
Otero [26]	60	2 (3.3)	0.41–11.5	5 (8.3)	2.8–18.4	1 (1.6)	0.04–8.9
Rodriguez-Cerrillo [27]	31	0	0.0–11.2	0	0.0–11.2	0	0.0–11.2

Data are presented as n (%) or mean±SD, unless otherwise stated. VTE: venous thromboembolism. #: 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 (PE); +: two recurrent PEs in total inpatient group (n=65), but not specified for high- (n=11) or low-risk (n=54) group.

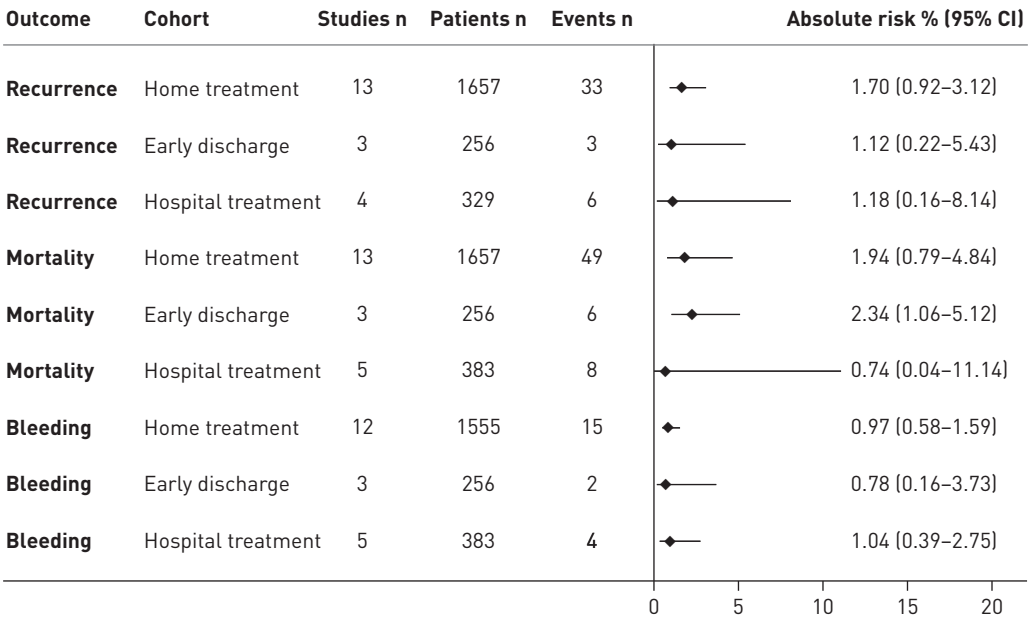

FIGURE 2 Pooled incidences of clinical outcome after pulmonary embolism in patients treated at home, discharged early or treated as inpatients.

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 0.8–1.0%. The comparable incidences of major bleeding in outpatients (0.97%) *versus* inpatients (1.0%) indicate that treating patients at home may not enhance unfavourable 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 a low risk for adverse clinical outcome [32]. In the included studies, different methods for the selection of low-risk patients were used. All studies used a list of pragmatic exclusion criteria for outpatient treatment (table 2), which predominantly contained items on haemodynamic or respiratory compromise, high bleeding risk, comorbidity 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 randomised controlled trial used the pulmonary embolism severity (PES) index, a clinical prognostic score based on signs and symptoms [5]. Patients in the low risk PES index classes have a risk for 90-day all-cause mortality of $\leqslant$1% [33]. Other studies used different clinical risk scores [20, 26, 34], the laboratory value N-terminal pro-brain natriuretic peptide [4], or imaging parameters, such as the size of the embolus [23, 27] or the size of the perfusion defect [24]. 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 h) and patients discharged early (24–72 h). 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 that made them potentially eligible for outpatient treatment, is relevant because it enhances comparability of baseline risk factors for adverse outcome, such as comorbidity and severity of PE, 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 randomised controlled trial on outpatient treatment of PE patients has been completed [5]. The trial by OTERO *et al.* [26] was stopped early because of two deaths within 14 days in the early discharge group *versus* none in the standard hospitalisation group, which was too high for their pre-defined margins, but this proportion had wide confidence intervals and was not statistically significant. The lack of more high-quality randomised controlled trials means that our conclusions cannot be supported by grade 1A evidence yet. However, well-designed cohort studies can also

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provide reliable evidence. This meta-analysis included five high quality observational studies with many patients and no serious sources of bias (appendix II of online supplementary material) (table 1). Therefore, we conclude that the estimates of incidences of adverse outcome are reliable.

Another drawback of our study is that one of three treatment groups was small: only three studies described patients discharged early. Therefore, the confidence intervals of the incidences in this group were wide. Conversely, the incidences of recurrence, bleeding and mortality in the outpatients groups are representative, because they were based on 1657 patients from 13 studies. Additionally, the autopsy rates in all studies were low, giving some uncertainty as to whether PE-related mortality was really absent. Finally, 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 PE. This conclusion is also supported by the latest ACCP guidelines with a grade 2B recommendation [2]. More randomised controlled trials on outpatient treatment of PE patients are needed for outpatient treatment to be graded with a 1A recommendation. Heterogeneous criteria were used for the selection of patients in the studies included in this meta-analysis. Therefore, it is of utmost importance to define ''low-risk patients'' in a uniform manner in future studies.

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