A more granular view on pulmonary embolism

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CHAPTER 9

Efficacy and safety of outpatient treatment with LMWH in patients with acute pulmonary embolism: The Hestia Study

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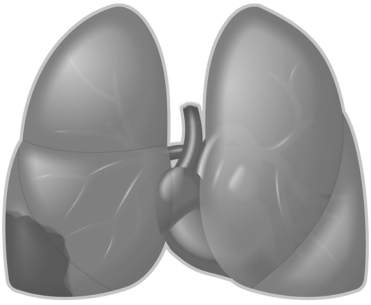
J Thromb Haemost. 2011;9:1500-7



ABSTRACT

Background

Traditionally, patients with pulmonary embolism (PE) are initially treated in the hospital with low molecular weight heparin (LMWH). The results of a few small nonrandomized studies suggest that in selected patients with proven PE outpatient treatment is potentially feasible and safe.

Objective

To evaluate the efficacy and safety of outpatient treatment according to predefined criteria in patients with acute PE.

Patients and Methods

Prospective cohort study of patients with objectively proven acute pulmonary embolism, conducted in twelve hospitals in the Netherlands between 2008 and 2010. Patients with acute PE were triaged with the predefined criteria for eligibility for outpatient treatment starting with LMWH (Nadroparin), followed by vitamin K antagonists. All patients eligible for outpatient treatment were sent home either immediately or within 24 hours after PE was objectively diagnosed. Outpatient treatment was evaluated with respect to recurrent venous thromboembolism (VTE), including PE or deep venous thrombosis (DVT), major haemorrhage and total mortality during 3-month follow up.

Results

Of 297 included patients, who all completed follow-up, 6 patients (2.0%; 95% confidence interval [CI], 0.8-4.3) had recurrent VTE (5 PE (1.7%), 1 DVT (0.3%)).

Three patients (1.0%, 95% CI 0.2-2.9) died during 3-month follow-up, none of fatal PE. Two patients had a major bleeding event, of which one fatal intracranial bleeding (0.7%, 95% CI 0.08%-2.4%).

Conclusion

Patients with pulmonary embolism selected for outpatient treatment with predefined criteria can be treated with anticoagulants on outpatient basis.

INTRODUCTION

Pulmonary embolism (PE) is a common condition with a variable clinical presentation ranging from patients with minor thoracic pain to patients with fatal PE.[1] The risk for mortality and other serious events differs. Patients presenting with symptoms of shock have a high risk for short-term mortality of approximately 30%, while patients who maintain a normal blood pressure have a risk of PE-attributable mortality of 2-6%.[2-4] Patients with a risk of short-term mortality of less than 1% are typically considered to be low-risk patients[4] and these patients may potentially be amenable for outpatient treatment. In patients with deep vein thrombosis (DVT) treatment out of the hospital with lowmolecular-weight heparin (LMWH) followed by vitamin K antagonists (VKA) is commonly accepted.[5,6] Since these patients have a low risk of developing (fatal) PE, outpatient treatment of patients with DVT has become worldwide standard of care.[7] In the last decade, several small observational studies on outpatient treatment in PE have been published.[8-21] These studies on outpatient treatment include 9 prospective and 5 retrospective studies with the largest prospective study containing 152 patients entirely treated at home. The majority of the prospective studies used simple bedside criteria for selection of patients for outpatient treatment.[9,10,12,19-21] In these studies no PE related mortality occurred, only one patient died of major bleeding and non-fatal recurrence rates of venous thromboembolism (VTE) varied from 0% - 6.2%.[22] The objective of the Hestia Study was to confirm the results of these small cohort studies in a large study and provide proof that incidences of VTE recurrence, major bleeding and mortality are very low in patients selected by a simple set of exclusion criteria.

METHODS

Design Overview

The Hestia study was a multicenter prospective cohort study in patients with acute PE who were selected for outpatient treatment if they did not apply to a predefined set of exclusion criteria. We evaluated the efficacy and safety of out of hospital anticoagulant treatment with LMWH followed by vitamin K antagonists for at least three months. The protocol was approved by the institutional review board of each participating hospital. The data were collected and stored in the database by the investigators. All suspected outcome events were classified by an independent central adjudication committee, whose members were not participating in the study. It was predefined that an independent data and safety monitoring board periodically reviewed the studies' outcomes after every 50 included patients and advised the investigators. The manuscript was written by the investigators and they vouch for the accuracy and completeness of the reported data.

Setting and Participants

Patients were recruited from 12 hospitals in the Netherlands (three academic and nine non-academic hospitals). Consecutive patients, applying to the following inclusion criteria, were potentially eligible: over 18 years of age with objectively proven acute PE presenting to the Emergency Department or outpatient clinic. Patients with asymptomatic or chronic PE, defined as duration of symptoms existing longer than 14 days and no acute worsening within the last 14 days, were not included. Patients were triaged according to predefined exclusion criteria (Exclusion criteria; Table 1). This checklist with 11 items can be used as a bedside test and can be completed within five minutes. Patients could not be treated at home if one of the exclusion criteria (Table 1) were fulfilled; otherwise patients were eligible for outpatient treatment. For study reasons additional exclusion criteria were the following: impossibility for the required 3-month follow-up (e.g. no fixed address, foreign citizen) or life expectancy less than three months. After giving written informed consent and starting treatment with LMWH, patients were sent home either immediately, or within 24 hours after the diagnosis of PE for out-of-hospital treatment.

Table 1. Exclusion criteria for outpatient treatment.

Is the patient hemodynamically instable?*
Is thrombolysis or embolectomy necessary?
Active bleeding or high risk for bleeding?**
More than 24 hours of oxygen supply to maintain oxygen saturation > 90%?
Is pulmonary embolism diagnosed during anticoagulant treatment?
Severe pain needing intravenous pain medication for more than 24 hours?
Medical or social reason for treatment in the hospital for more than 24 hours? (infection, malignancy, no support system ie)
Does the patient have a creatinine clearance of less than 30 ml/min?***
Does the patient have severe liver impairment?****
Is the patient pregnant?
Does the patient have a documented history of heparin-induced thrombocytopenia?

*Include the following criteria, but are left to the discretion of the investigator: systolic blood pressure < 100 mmHg with heart rate > 100 beats per minute; condition requiring admission to an intensive care unit.
**Gastrointestinal bleeding in the preceding 14 days, recent stroke (less than 4 weeks ago), recent operation (less than 2 weeks ago), bleeding disorder or thrombocytopenia (platelet count < 75 x 109/L), uncontrolled hypertension (systolic blood pressure > 180 mm Hg or diastolic blood pressure > 110 mm Hg).
*** Calculated creatinine clearance according to the Cockroft-Gault formula.
****Left to the discretion of the physician.

Interventions

Patients were treated with standard anticoagulant therapy according to international guidelines.[7] Initial treatment consisted of once daily subcutaneous LMWH Nadroparin

corrected for body weight (11400 IU for body weight < 70 kg.; 15200 IU for body weight ≥ 70 kg). The first dose of LMWH was given at the emergency department under supervision of a nurse. The patient or a family member was instructed how to administer LMWH at home. On the same day vitamin K antagonists (phenprocoumon or acenocoumarol) were started and titrated to an INR between 2.0 and 3.0. The INR was monitored and VKA was titrated by the Dutch Thrombosis Services. LMWH was continued for at least five days and was stopped by the Thrombosis Services if the INR was in the target range for two consecutive days. Patients with active malignancy could be treated with LMWH alone during a 6-month period, according to the guidelines.[7] This treatment decision was left to the treating physician.

Outcomes and Follow-up

All patients were seen at the outpatient clinic at one week and three months after initial presentation. After six weeks follow-up an additional telephone contact was planned. At each contact the presence of clinical signs and symptoms suggestive of recurrent VTE or bleeding were assessed. Patients were instructed to contact their specialist before the fixed appointments for objective testing whenever clinical signs or symptoms suggestive of recurrent PE, DVT or if a bleeding complication occurred. The primary endpoint was objectively proven recurrent VTE during 3-months follow-up. Major bleeding and death within three months were defined as secondary endpoints. Symptomatic recurrent VTE was the main efficacy parameter. 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 intraluminal filling defect on spiral CT or pulmonary angiography; cut-off of contrast material in a vessel > 2.5 mm in diameter on pulmonary angiography; a new perfusion defect involving at least 75% of a segment, with corresponding normal ventilation (i.e. a high probability lung scan); a new non-diagnostic lung scan accompanied by documentation of DVT by ultrasonography or venography; or confirmation of a new PE at autopsy. The objective criterion of a new DVT was a –new-, non-compressible venous segment or a substantial increase (≥ 4 mm) in the diameter of the thrombus during full compression in a previously abnormal segment on ultrasonography or a new intraluminal filling defect on contrast venography. Major bleeding was the main safety outcome and 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.[23] Clinically relevant bleeding episodes, not qualifying as major bleeding, were classified as clinically relevant non-major bleeding (e.g. epistaxis that required intervention,

large hematoma visible on the skin, or spontaneous macroscopic hematuria). Mortality was defined as death due to recurrent PE (fatal PE), fatal bleeding, cancer, or another established diagnosis. Information about the cause of death was obtained from autopsy reports or from a clinical report. An independent adjudication committee consisting of two physicians not involved in the study evaluated all possible endpoints i.e. recurrent VTE, major bleeding or death. Any dispute was resolved by a third opinion. If no objective imaging of a suspected event was obtained, the event was evaluated on clinical grounds by the adjudication committee.

Statistical analysis

The primary endpoint is symptomatic recurrent VTE during 3 months of follow-up. We considered outpatient treatment to be effective if the upper limit of the 95% confidence interval of the incidence of recurrent VTE did not exceed a predefined margin. This predefined margin was based on incidences reported in literature.[6,24] It was stated that VTE recurrence rates of patients treated at home should not be higher than rates found in patients treated in the hospital. Incidences of recurrent VTE in the literature are reported up to 7%.[6,25] We therefore defined outpatient treatment according to the predefined criteria to be effective if the upper limit of the 95% confidence interval did not exceed the 7%. A power calculation was performed assuming an observed VTE recurrence in the study population of 3%.[24] To obtain an estimate of the incidence with a confidence interval below 7% a sample size of 257 patients was needed to achieve a power of 0.91 (one-sided binomial test). Allowing for a drop-out rate of 10%, a total of 280 patients with PE eligible for outpatient treatment had to be included. Exact 95% confidence intervals (CI) were calculated around the observed incidences with Fisher's Exact Test. SPSS software version 17.0 (SPSS Inc, Chicago, IL) was used for all analysis. The analysis was performed according to the intention to treat principle.

RESULTS

Study patients

Between May 2008 and April 2010 a total of 581 consecutive patients with acute PE were screened with the exclusion criteria for outpatient treatment, of which 243 were not eligible for outpatient treatment according to the criteria described in Table 1.

A total of 338 patients were eligible for outpatient treatment, of which 41 patients were excluded for study reasons. This resulted in a total study population of 297 (51%) patients treated as outpatients (Figure 1). Some of the patients (23%) were admitted to the hospital for less than 24 hours, mainly because CT scanning was not available at night. The mean duration of hospital admission in these patients was 19 hours. The

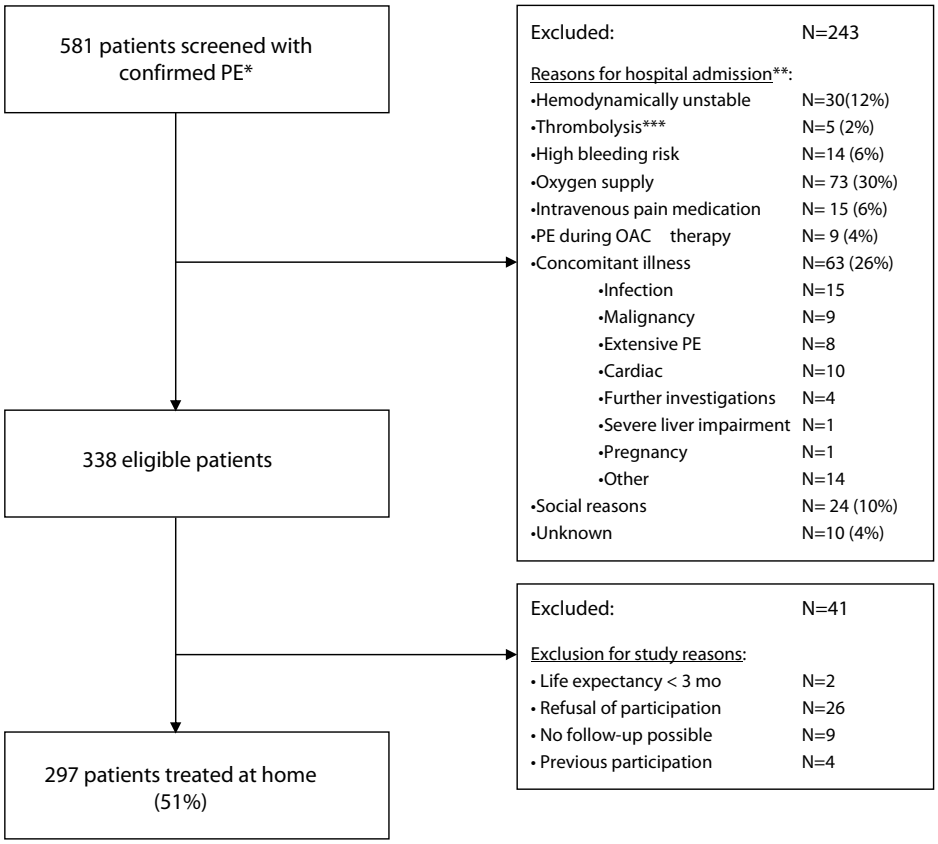


Figure 1. Flow-chart. *Meeting inclusion criteria: outpatients older than 18 years with acute symptomatic objectively confirmed pulmonary embolism (PE). **Most important exclusion criterion. ***Thrombolysis for other reasons than hemodynamic instability. OAC: oral anticoagulants.

clinical baseline characteristics of these patients are shown in Table 2. The mean age was 55 years and 26% of patients were older than 65 years, 58% of the patients were male and 9% had an active malignancy.

Treatment and follow-up

All patients were treated with LMWH for at least five days, except for one patient, who only received four days of LMWH treatment because of hemoptysis. In another patient the LMWH treatment protocol was violated. This patient received the first dose of LWMH on the emergency department, but he did not continue the treatment at home. Although he finally received LMWH for at least five days, the LMWH treatment was interrupted for 48 hours during the second and third day after the index event. In the majority of patients, initial LMWH therapy was followed by VKA treatment (Table 2). 6.1% of patients were treated with long term LMWH treatment alone because of malignancies or known

Table 2. Baseline characteristics of study patients (n=297).

Characteristics	
Age (years)	55 (15)
Age ≥ 65 yr	78 (26)
Male gender	172 (58)
BMI (kg/m^2)	27 (5)
Duration of complaints (days)	4 (3)
Risk factors for VTE	
Immobilization > 3 days or surgery < 4 weeks	27 (9.1)
Paralysis, paresis or plaster cast lower limbs	10 (3.4)
Estrogen use	47 (16)
Active malignancy	28 (9.4)
Heart failure with therapy	1 (0.3)
COPD with therapy	11 (3.7)
History of VTE	74 (25)
Unprovoked VTE*	207 (70)
Treatment**	
LMWH + VKA	276 (93)
Duration of LMWH usage (days)	9 (3)
LMWH continued	18 (6.1)

Categorical data are displayed as N° (%). Numerical data are displayed as means (standard deviation). *Unprovoked VTE is defined as venous thromboembolism without presence of one of the following provoking factors: estrogen use, immobilization more than 3 days or operation in the last month or active malignancy. No thrombophilia testing was done. LMWH: low molecular weight heparin; VKA: vitamin K antagonists; VTE: venous thromboembolism; COPD: chronic obstructive pulmonary disease. **Data on treatment were missing in N=3 (1.0%).

allergy to VKA. In 3 patients (1.0%) information about the type and duration of anticoagulant treatment was missing. The 3-month follow-up period was completed in all patients.

Outcome events

Efficacy during the first week of treatment

One patient had recurrent PE during the first week (0.3% 95% CI 0.008-1.9%; Table 3). In this patient the LMWH treatment protocol had been violated (described above), because he did not use LMWH at home. He returned to the hospital at day three with increasing dyspnea; although no repeat CT scan was performed, it was adjudicated as an extension of the initial PE. He was admitted to the hospital for adequate anticoagulant therapy with therapeutic doses of LWMH and vitamin K antagonists (Table 4). None of the patients, receiving adequate anticoagulant treatment, experienced a recurrent VTE event within seven days of the initial event. No patient died of fatal PE during this period.

Table 3. Adverse clinical outcome during 3-month follow-up (N=297).

Clinical outcome	Number	Percentage (95% CI)
Total recurrences	6	2.0 (0.75 – 4.3)
Fatal recurrent PE	0	0 (0-1.2)
Non-fatal recurrent PE	5	1.7 (0.55-3.9)
Non-fatal recurrent DVT	1	0.34 (0.0082-1.9)
Major bleeding complications	2	0.67 (0.082-2.4)
Fatal bleeding	1	0.34 (0.0082-1.9)
Non-fatal major bleeding	1	0.34 (0.0082-1.9)
Clinically relevant non-major bleeding	15	5.1 (2.9-8.2)
All cause mortality	3	1.0 (0.21-2.9)

PE: pulmonary embolism; DVT: deep vein thrombosis.

Efficacy during further follow-up

Between the second week and 3-month follow-up, another five patients had recurrent VTE: recurrent PE in four patients and DVT in one patient (Table 3).

During the whole study period of 3-month follow-up six patients (2.0%; 95% CI 0.8-4.3%) had a recurrent VTE of which one patient (0.3%; 95% CI 0.008.-1.9%) had an objectively proven recurrent DVT and five patients (1.7%; 95% CI 0.5-3.9%) had recurrent PE, adjudicated on clinical grounds. In five of six patients adjudicated as having recurrent VTE anticoagulant treatment was altered. Details are described in Table 4. None of the recurrent VTE events were fatal and all patients recovered completely (Table 4).

Safety

Two patients (0.7%; 95% CI 0.08-2.4%) had a major bleeding episode (Table 3). One patient had a fatal intracranial bleeding at day seven. This intracranial bleeding started while she was in the outpatient clinic for a predefined appointment; she died within 24 hours. The second patient had a large abdominal muscle hematoma accompanied with a drop in hemoglobin level of 2.5 mmol/L at day 14, for which a short observation on the intensive care unit was needed; this patient recovered completely. Clinically relevant non-major bleeding occurred in 15 patients (5.1%; 95% CI 2.9-8.2%). These non–major clinically relevant bleeds occurred between day one and day 66 (median day 24) and consisted of five patients with large skin hematomas, six patients with macroscopic hematuria, three patients with hemoptysis and one patient with an ovary bleeding without significant drop in haemoglobin. In three patients with clinically relevant non-major bleeding anticoagulant treatment was interrupted for one day: in one patient with hemoptysis, in one patient with a large skin hematoma and in the patient with the ovary bleeding.

Table 4. Description of adverse clinical outcome during 3 months of follow-up.

Recurrent VTE (n=6)						
Gender	**Age**	**Complaints**	**Day**	**Imaging**	**Adverse event**	**Brief description**
Male	80	Increasing dyspnea	3	No extra CT scanning performed	Clinically adjudicated recurrent PE	Patient did not administer LMWH at home, complaints of dyspnea increased and he was admitted for administration of LMWH until INR was in target range
Male	78	Chest pain	8	No extra CT scanning performed	Clinically adjudicated recurrent PE	Admission for observation. Acenocoumarol was switched to Phenprocoumon to achieve increased stability of INR levels.
Female	38	New thoracic pain	10	No extra CT scanning performed	Clinically adjudicated recurrent PE	LMWH dosage was increased from 15200 IU once daily to 22800 IU once daily (BMI 40 kg/m^2). Admission until INR was stable in target range.
Female	37	Increasing dyspnea	28	No extra CT scanning performed	Clinically adjudicated recurrent PE	Admission for recurrent PE during inadequate INR level (1.5), LMWH treatment until INR was in target range
Female	55	Recurrent DVT	48	US: extension of thrombus from calf vein to iliac vein level	Objectively proven recurrent DVT	Admission for recurrent DVT in patient with malignancy, increasing dosage of LMWH from 11400 IU once daily to 19000 IU once daily.
Male	45	New thoracic pain	60	No extra CT scanning performed	Clinically adjudicated recurrent PE	Recurrent PE during inadequate VKA therapy (INR 1.4), LMWH therapy until INR was in target range
Major bleeding (n=2)						
Gender	**Age**	**Adverse event**	**Day**	**Imaging**	**Brief description**	
Female	54	Fatal intracranial bleeding	7	Cerebral CT scan: central bleeding right basal ganglion area	Admission for intracranial bleeding in patient treated with Nadroparin combined with VKA, INR of 4.0 and concomitant uncontrolled hypertension, died the same day, autopsy confirmed diagnosis. Hypertension existed at index PE event, but was controlled by medication before discharge.	
Female	74	Abdominal hematoma	14	Large hematoma in abdominal muscle sheet (volume 1.7 L)	One day ICU admission for large hematoma of abdominal rectal sheet, INR of 5.3 while still on Nadroparin therapy with hypotension, drop in hemoglobin of 2.5 mmol/L, fully recovered	

Table 4. (continued)

Mortality (n=3*)					
Gender	**Age**	**Adverse event**	**Day**	**Autopsy**	**Brief description**
Male	67	Died	29	No	Died of metastatic pancreatic cancer, diagnosed before index PE
Female	59	Died	59	No	Died of metastatic pancreatic cancer, diagnosed before index PE

CT: computed tomography; DVT: deep vein thrombosis; ICU: intensive care unit; IU: international units; LMWH: low molecular weight heparin; PE: pulmonary embolism; US: ultrasonography; VKA: vitamin K antagonist; VTE: venous thromboembolism

*Including one patient that died of fatal intracranial bleeding, mentioned in section "major bleeding".

Mortality

Three patients (1.0%; 95% CI 0.2-2.9%) died during the study (Table 3). One patient died of fatal intracranial bleeding at day seven, confirmed by autopsy. The cause of mortality in the two other patients was progressive metastatic pancreatic cancer (at day 29 and 59). The cause of death in the two patients with malignancy was clinically adjudicated by the treating physician. None of the patients died of fatal PE.

DISCUSSION

This study evaluated the efficacy and safety of outpatient treatment of patients presenting with acute PE. Patients with acute PE were triaged in a standardized way and eligible patients were treated as outpatients. The present study shows that outpatient anticoagulant treatment of patients selected by the exclusion criteria has a low risk for recurrent VTE: VTE recurred in 2% of patients, with the upper limit of the confidence interval reaching 4.3%, which is lower than the predefined limit of 7%. None of the recurrences were fatal. None of the patients in the present study, receiving adequate anticoagulant treatment, experienced a recurrent VTE event within seven days of the initial event, a period which equals the average duration of hospital admission for PE.[26] Comparison of the recurrence rate of 2.0% (95% CI 0.8 – 4.3%) found in the present study to the VTE recurrence rate of 3.0% (95% CI 1.8-4.6%) in a historical cohort of patients with PE treated in the hospital[24] demonstrates almost identical rates, suggesting the efficacy of the LMWH treatment at home may be at least as good as the efficacy in the hospital. Moreover, our results are similar to outcomes in small prospective studies summarized in a systematic review,[22] a recently performed prospective cohort study[8] and results of a large retrospective cohort[13] on outpatient treatment of PE. Of note, our rate is considerably lower than the 6.2% found in the study of Kovacs et al.[12] This discrepancy might be explained by the higher proportion of patients with malignancies

(25% vs. 9%) in that study. The rate of bleeding with the outpatient treatment was low in comparison to bleeding rates reported in the literature. In the present study major bleeding occurred in 0.7% and 5.1% of patients had non-major clinically relevant bleeding. In studies with comparable groups of patients major bleeding rates in patients with PE treated at home varied between 0 and 2.8%.[22] Moreover, fatal bleeding occurred in only one patient (0.3%) in the present study. This is well comparable to the fatal bleeding rates of 0.3% to 0.6% in unselected patients with PE treated in the hospital.[24,27] In this study a simple set of exclusion criteria was used to select patients for outpatient treatment. The choice for these criteria was reinforced by former research.[12] The criteria are pragmatic, easy to use at the bedside, fast-to-perform and cheap. This study, where predefined exclusion criteria were used, 51% of patients with PE could be treated out of the hospital, which is comparable to the 51-55% found in two large retrospective studies, using comparable criteria.[11,12] In the literature the use of "subjective items" has been criticized.[28] However this study shows that physicians guided by the simple bedside criteria are well able to distinguish low risk patients eligible for outpatient treatment. In addition, comparable sets of criteria have been used safely in different cohorts from different countries.[9,10,12,19-21] Two other approaches have recently been suggested for selecting patients for outpatient treatment: the Pulmonary Embolism Severity Index (PESI)[29] and NTproBNP.[8] The predictive values of PESI and NT-proBNP have been derived from unselected cohorts of patients with PE treated in the hospital.[30,31] A large cohort study with unselected patients treated for PE in the hospital demonstrated that patients with PE and low PESI scores (class I and II) have a risk for 90-day mortality of 1.2%.[29] A recent meta-analysis showed that unselected patients with low NT-proBNP levels have a 30-day mortality of 1.3%.[32] The predictive value of the PESI and NT-proBNP in patients preselected with pragmatic exclusion criteria is currently unknown. In addition, these two selection methods are validated on short term mortality, but our data showed that short term mortality in preselected groups potentially eligible for outpatient treatment is very low (1.0%). This study had strengths and limitations that should be addressed. To our knowledge this is the largest trial in patients with acute pulmonary embolism who were treated as outpatients within 24 hours after the diagnosis of pulmonary embolism. The inclusion of consecutive patients as well as the absence of loss to follow-up make that selection bias is no issue in the present study.[33] One limitation of the study is that the endpoint ascertainment could not be blinded due to the single-arm design of the study. However, ascertainment of both the exposure (pulmonary embolism) and the outcome (recurrent VTE) was performed according to predefined criteria, which minimizes the risk of information bias. The reported recurrence rate of 2% could be an overestimation, because in the five patients who were centrally judged as having recurrent PE, no objective imaging was done. These five patients were centrally adjudicated as recurrent PE because of the clinical signs suggestive of recurrent PE and/or the local decision to

change anticoagulant therapy. The central adjudication committee was conservative on this to avoid an underestimation of the recurrence rate. Another limitation is that 23% of patients had to stay in the hospital for up to 24 hours for logistic reasons. Finally, we initially considered a randomized study design with random allocation to in or outpatient treatment, but concluded this was not feasible due to the very large sample size that would have been needed. Instead, a single-arm clinical trial was performed with predefined triaging of patients and careful standardized follow-up in all patients using predefined criteria for assessing and adjudicating recurrent events and bleeding. Such a single-arm trial is a valid instrument to evaluate treatment in a population provided that consecutive patients are included and all patients get standardized triaging, to avoid investigator bias.

In conclusion, outpatient treatment of acute PE may be effective and safe in patients selected with the predefined and easy-to-perform criteria, based on the observed low recurrence, mortality and bleeding rates. In view of the single arm trial design these results have to be confirmed in a randomized controlled trial.

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