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Pulmonary Embolism

Outpatient treatment and risk stratification

Wendy Zondag



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Outpatient treatment and risk stratification

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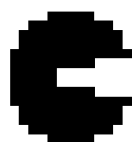
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List of abbreviations

ACCP	American College of Chest Physicians
AUC	area under the curve
BMI	body mass index
BPM	beats per minute
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CPR	cardiopulmonary resuscitation
CT	computed tomography
CTEPH	chronic thromboembolic pulmonary hypertension
CTPA	computed tomography pulmonary angiography
DVT	deep vein thrombosis
ECG	electrocardiography
ED	emergency department
ESC	European Society of Cardiology
GP	general practitioner
HR	hazard ratio
ICU	intensive care unit
INR	international normalized ratio
IRB	institutional review board
ISTH	International Society of Thrombosis and Haemostasis
IU	international units
LMWH	low molecular weight heparin
LV	left ventricle
NA	not applicable
NOACs	new oral anticoagulants
NT-proBNP	N-terminal pro-Brain Natriuretic Peptide
NYHA	New York Heart Association
OAC	oral anticoagulants
OR	odds ratio
PE	pulmonary embolism
PESI	pulmonary embolism severity index
ROC	receiver operating characteristics
RV	right ventricle
RVD	right ventricular dysfunction
SBP	systolic blood pressure
SD	standard deviation
SE	standard error

sPESI	simplified pulmonary embolism severity index
TTE	transthoracic echocardiography
US	ultrasonography
VCF	vena cava filter
VKA	vitamin K antagonists
V/Q scan	ventilation-perfusion scintigraphy
VTE	venous thromboembolism



Chapter 1

General introduction

For more than 100 years it has been recognized that pulmonary embolism (PE), a condition caused by the formation of a thrombus in the pulmonary arteries, could lead to severe dyspnea.¹ However, no effective treatment was available until the first part of the 20th century and the majority of the patients with PE died.²

It was not until 1938 that the first claims of successful anticoagulant treatment with heparin were published.^{3,4} However, there was one disadvantage of the use of heparin: it had to be administered intravenously. Because of the intravenous administration, PE patients had to stay in the hospital and therefore could only be treated for a short period of time. A discovery by two veterinarians in 1920 was the start for the development of the first anticoagulant for long term treatment. They observed that cattle that had eaten spoiled hay suffered from massive hemorrhage.⁵ This led to the discovery of a substance from the sweet clover, named coumarin, which was responsible for the anticoagulant mechanism that caused the bleeding in the cattle. Coumarin was extracted in the laboratory for medicinal use to prevent further thrombus formation in patients with PE. Because coumarin was administered orally, from this point in time patients could be treated out of the hospital and the duration of anticoagulant treatment could be prolonged.

Another breakthrough came in 1960, when the first clinical trial investigating the use of heparin combined with coumarin was published.² This trial demonstrated that the prognosis of patients with PE improved largely upon treatment with the combination of intravenous unfractionated heparin and coumarin. Afterwards, the treatment of PE patients with the combination of heparin and coumarin was considered standard patient care for many decades.³

The next large change in anticoagulant management came with the introduction of low-molecular weight heparin (LMWH), which could be administered subcutaneously and was at least as effective as unfractionated heparin administered intravenously.⁶ Because unfractionated heparin had to be administered intravenously, patients who were diagnosed with PE were admitted to the hospital for at least five days. After the introduction of LMWH, the duration of hospital admission shortened over the years.⁷ In the last decade small observational studies have been published, which gave a first indication towards the safety and efficacy of the outpatient treatment of PE patients.⁸⁻¹⁰ The first systematic review on outpatient treatment of PE patients indicated that the quality of those observational studies was too low to incorporate outpatient treatment of patients with PE in standard patient care.¹¹

Over the last years, more solid evidence on the safety of outpatient treatment in PE patients is accumulating.¹² In the first part of this thesis more recent publications on outpatient treatment of patients with PE are extensively discussed. The results of the Hestia study, a prospective multicenter cohort study on outpatient treatment of PE patients, which we performed in conjunction with 12 hospitals in The Netherlands, are presented in chapter 2 and 3. In chapter 4, the results of all available studies on outpatient treatment of PE patients in the literature are summarized in a meta-analysis.

The second aim of this thesis was to compare methods for risk stratification, which discriminate low from high risk PE patients, in order to treat the low risk patients at home safely.¹³ Several methods for risk stratification are available¹⁴: methods based on clinical signs and symptoms^{15,16}, laboratory values^{17,18} or imaging modalities^{19,20}. In the Hestia study, described in chapter 2, the Hestia criteria were used to select low risk PE patients for outpatient treatment. The Hestia criteria were compared to two other methods for risk stratification, the Pulmonary Embolism Severity Index (PESI) and the assessment of right ventricular dysfunction on computed tomography and the results of these analyses are found in chapters 5 and 6. Chapter 7 describes the potential role of repeated measurements of the laboratory value NT-proBNP in selecting patients with PE for outpatient treatment or early discharge. Finally, in chapters 8 and 9 the prognosis of patients with PE and different baseline characteristics is described: patients with provoked PE versus unprovoked PE and patients presenting to a university hospital versus patients in a non-university hospital.

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Chapter 2

Outpatient treatment in patients with acute pulmonary embolism: the Hestia Study

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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 non-randomized studies suggest that in selected patients with proven PE outpatient treatment is potentially feasible and safe. The objective of this study was to evaluate the efficacy and safety of outpatient treatment according to predefined criteria in patients with acute PE.

Methods

Prospective cohort study of patients with objectively proven acute pulmonary embolism, conducted in 12 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 hemorrhage and total mortality during 3 months follow up.

Results

Of 297 included patients, who all completed follow-up, six patients (2.0%; 95% confidence interval (CI), 0.8-4.3) had recurrent VTE (five PE (1.7%), one DVT (0.3 %)). Three patients (1.0%, 95% CI 0.2-2.9) died during 3 months 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 PE 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 and these patients may potentially be amenable for outpatient treatment.⁴

In patients with deep vein thrombosis (DVT) treatment out of the hospital with low-molecular-weight heparin (LMWH) followed by vitamin K antagonists (VKAs) 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 VKAs for at least 3 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 5 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 months follow-up (e.g. no fixed address, foreign citizen) or life expectancy less than 3 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 unstable?*
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 Cockcroft-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 VKAs (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 5 days and was stopped by the Thrombosis Services if the INR was in the target range for 2 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 1 week and 3 months after initial presentation. After 6 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 3 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 (CI) 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% CI did not exceed the 7%.

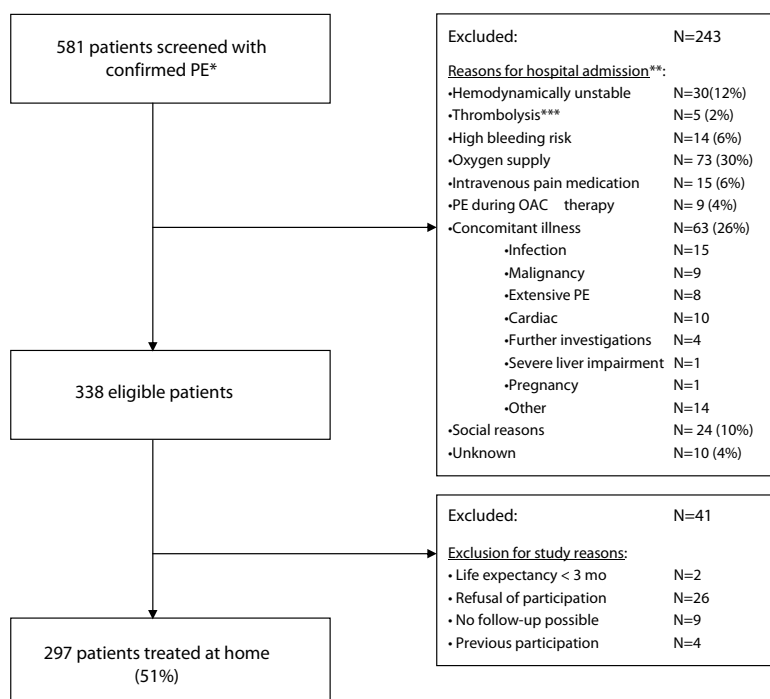
A power calculation was performed assuming an observed VTE recurrence in the study population of 3%.²⁴ To obtain an estimate of the incidence with a CI below 7% a sample size of 257 patients was needed to achieve a power of 0.91 (one-sided binomial test). Allowing for a drop-out rate of 10%, a total of 280 patients with PE eligible for outpatient treatment had to be included. Exact 95% CIs 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 Figure 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 dura-

Figure 1: Flow-chart

* Meeting inclusion criteria: outpatients older than 18 years with acute symptomatic objectively confirmed PE

** Most important exclusion criterion

*** Thrombolysis for other reasons than hemodynamic instability

OAC= oral anticoagulants; PE= pulmonary embolism

tion of hospital admission in these patients was 19 hours. The 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 5 days, except for one patient, who only received 4 days of LMWH treatment because of hemoptysis. In another patient the LMWH treatment protocol was violated. This patient received the first dose of LMWH on the emergency department, but he did not continue the treatment at home. Although he finally received LMWH for at least 5 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). Of the patients, 6.1% were treated with long term LMWH treatment alone because of malignancies or known allergy to VKA. For three patients (1.0%) information about the type and duration of anticoagulant treatment was missing. The 3-month follow-up was completed for all patients.

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

Age (years)	55 (15)
Age $\geq$ 65 yr	78 (26)
Male gender	172 (58)
BMI (kg/m ²)	27 (5)
Duration of complaints (days)	4 (3)
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)
LMWH + VKA**	276 (93)
Duration of LMWH usage (days)	9 (4)
LMWH continued	18 (6.1)

Categorical data are displayed as No (%). 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%)

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 3 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 LMWH and VKAs (Table 4). None of the patients, receiving adequate anticoagulant treatment, experienced a recurrent VTE event within 7 days of the initial event. No patient died of fatal PE during this period.

Efficacy during further follow-up

Between the second week and 3 months 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 months follow-up six patients (2.0 %; 95% CI 0.8-4.3%) had a recurrent VTE, one of whom (0.3 %; 95% CI 0.008.-1.9%) had an objectively proven recurrent DVT, and five of whom (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

Table 3. Adverse clinical outcome during three months 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, CI=confidence interval

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	Recurrent PE, diagnosed clinically without objective testing	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	Recurrent PE, diagnosed clinically without objective testing	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	Recurrent PE, diagnosed clinically without objective testing	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	Recurrent PE, diagnosed clinically without objective testing	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	Recurrent PE, diagnosed clinically without objective testing	Recurrent PE during inadequate VKA therapy (INR 1.4), LMWH therapy until INR was in target range

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

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 sheath (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
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; n=number; 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"

treatment was altered. The details are given in Table 4. None of the recurrent VTE events was 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 7. 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 1 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 hemoglobin. In three patients with clinically relevant non-major bleeding anticoagulant treatment was interrupted for 1 day: in one patient with hemoptysis, in one patient with a large skin hematoma and in the patient with the ovary 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 7, 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 CI reaching 4.3%, which is lower than the predefined limit of 7%. None of the recurrences was fatal. None of the patients in the present study receiving adequate anticoagulant treatment experienced a recurrent VTE event within 7 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 hospital²⁴ 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 review²², a recently performed prospective cohort study⁸ and results of a large retrospective cohort¹³ 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%-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, quick 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 NT-proBNP.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 PE 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 (PE) 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 inpatient or outpatient treatment, but concluded this was not feasible, owing 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-use criteria, on the basis of 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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Chapter 3

Hestia criteria can discriminate high from low risk patients with pulmonary embolism

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Abstract

Background

We investigated whether the clinical criteria, used in the Hestia study for selection of pulmonary embolism (PE) patients for outpatient treatment, could discriminate PE patients with high and low risk for adverse clinical outcome.

Methods

We performed a cohort study with PE patients who were triaged with 11 criteria for outpatient treatment. Patients not eligible for outpatient treatment were treated in-hospital. Study outcomes were recurrent venous thromboembolism, major bleeding and all-cause mortality during 3 months.

Results

In total 530 patients were included, of whom 297 were treated at home. In the outpatient group six patients (2.0%, confidence interval [CI], 0.7-4.3) had recurrent venous thromboembolism versus nine inpatients (3.9%; CI 1.9-7.0). Three patients (1.0%, CI 0.2-2.9) died during 3 months follow-up in the outpatient group versus 22 patients (9.6%, CI 6.3-14) in the inpatient group ($p < 0.05$). In the outpatients none died as a result of fatal pulmonary embolism versus five inpatients (2.2%; $p < 0.05$). In outpatients 0.7% (CI 0.08-2.4) had major bleeding events versus 4.8% (CI 2.4-8.4) of inpatients ($p < 0.05$).

Conclusion

This study showed that the Hestia criteria can discriminate PE patients with low risk from patients with high risk for adverse clinical outcome. The low risk patients can safely be treated at home. (Dutch Trial Register No1319)

Introduction

Nowadays, most patients with acute pulmonary embolism (PE) start anticoagulant treatment in the hospital, but evidence on the safety of initial outpatient treatment in patients with PE is accumulating.¹ Two systematic reviews summarized the results of a few small observational studies on outpatient treatment in patients with PE.^{2,3} These reviews concluded that although the evidence is not of high quality, it indicates that certain subgroups of patients with PE could be eligible for outpatient treatment. In 2010 two large retrospective studies on outpatient treatment of PE patients were published.^{4,5} In these studies low rates of adverse clinical outcome were reported, suggesting safety of outpatient treatment in PE; in both articles prospective validation of the results is recommended.

We have recently published the results of a large prospective study in which clinical signs and symptoms were used to select patients with PE for outpatient treatment.⁶ The Hestia criteria consist of 11 clinical criteria that can be used as a bedside test. The purpose of the Hestia study was to evaluate the safety of outpatient treatment in patients with acute PE triaged by simple and easily performed Hestia criteria. However, in the Hestia Study these selection criteria for outpatient treatment were used for the first time. The criteria have not been validated in other cohorts yet. In order to underline the discriminative power of the Hestia criteria, we wanted to show the contrast between the rates of adverse events in the patients treated at home versus the patients treated in the hospital. Therefore, the aim of the present extension of the Hestia study was to show the difference in adverse clinical outcome between high risk patients, initially treated as inpatients and low risk patients, initially treated at home.

Patients and methods

Overview

The Hestia study was a multicenter prospective cohort study in patients with acute PE who were selected for outpatient treatment with the Hestia criteria. The methods of this study are described elsewhere.⁶

In the Hestia study we prospectively registered all patients that were excluded from outpatient treatment and the reasons why they were excluded. The excluded patients were not study patients because they were not eligible for the intervention of outpatient treatment nor were they followed prospectively.

For the analysis described in this manuscript we retrospectively reviewed the medical charts of the patients excluded from home treatment to investigate whether they had a recurrent VTE, bleeding or died 3 months following the PE. All suspected outcome events

were classified by an independent central adjudication committee, whose members were not participating in the study. This was the same committee as for the initial Hestia study. The Hestia study protocol was approved by the institutional review board of each participating hospital.

Patients

Consecutive patients were included according to the following inclusion criteria: >18 years with proven acute PE presenting to the Emergency Department. Patients with asymptomatic or chronic PE were not included.

Patients were admitted to the hospital if one of the following exclusion criteria for outpatient treatment (Hestia criteria) were fulfilled: hemodynamic instability, thrombolytic treatment or embolectomy, high bleeding risk, oxygen therapy, intravenous pain medication, diagnosis of PE while on therapeutic anticoagulant treatment, medical or social condition necessitating hospital admission, renal or liver impairment, pregnancy or history of heparin induced thrombocytopenia.

This checklist with 11 items can be used as bedside test and can be completed within 5 minutes. If none of the items were present the patient was treated at home. All patients were treated with standard anticoagulant therapy according to international guidelines.⁷

Outcome events

Symptomatic recurrent VTE was the main efficacy parameter and was considered present if recurrent PE or DVT were documented objectively, or in case of death in which PE was demonstrated by autopsy or could not be confidently ruled out as contributing cause. Major bleeding was the main safety outcome and was defined according to international guidelines.⁸ 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 an autopsy report or from a clinical report.

Statistical analysis

The power calculation of the Hestia study is described elsewhere.⁶ In the initial Hestia study we screened patients for eligibility for outpatient treatment until we reached our calculated sample size of patients treated at home. The group of PE patients treated in the hospital, described in this article, consists of consecutive patients who could not be treated at home. These patients were prospectively collected in all 12 hospitals participating in the Hestia study from May 2008 till April 2010.

Differences in baseline characteristics and outcome between the in- and outpatient groups were measured with Fisher's Exact Test for categorical variables and with a *T*-test for continuous variables. SPSS software version 17.0 (SPSS Inc, Chicago, IL) was used for all analyses.

Results

From 2008 to 2010, 581 patients with acute, symptomatic PE presented to 12 Dutch hospitals. Of these patients, 338 patients were potentially eligible for outpatient treatment, however 41 patients were excluded for study reasons (e.g. refusal of participation, previous participation), leaving 297 patients for home treatment. In total 243 patients were admitted to the hospital, for the following reasons: hemodynamic instability (n=30), thrombolytic treatment for massive PE (n=5), high bleeding risk (n=14), requirement of oxygen therapy (n=73), severe pain requiring intravenous medication (n=15), diagnosis of PE during anticoagulant treatment (n=9), medical (n=63) or social (n=24) condition necessitating admission to the hospital. In ten patients, the reason for exclusion from outpatient treatment was not specified. Ten of 243 patients treated in the hospital had to be excluded from this analysis, because the chart review revealed that pulmonary embolism was not objectively proven by imaging. This resulted in a total of 530 PE patients: 297 patients treated as outpatients and 233 patients treated in the hospital. The baseline characteristics of the outpatient and inpatient groups are shown in Table 1. Patients treated in the hospital were significantly older, were more often immobilized and had more co-morbidities (cancer, heart failure and chronic obstructive pulmonary disease (COPD)) than patients treated at home. Four patients were lost to follow-up after hospital admission because they lived abroad.

Table 1. Baseline characteristics

Characteristics	Patients treated at home (n=297)	Patients treated in the hospital (n=233)	p-value
Age (years)	55 ± 15	62 ± 17	<0.001
Male gender	172 (58)	116 (50)	0.066
Immobilization or surgery	27 (9)	71 (31)	<0.001
Paralysis or plaster	10 (3.4)	13 (6)	0.205
Estrogen use	47 (16)	15 (6)	0.001
History of VTE	74 (25)	54 (23)	0.683
Heart failure	1 (0.3)	14 (6)	<0.001
COPD	11 (3.7)	24 (10)	0.003
Active malignancy	28 (9)	48 (21)	<0.001
Hospitalization (days)*	0.3 ± 0.4	7.4 ± 6.9	<0.001

Categorical data are displayed as No (%). Numerical data are displayed as means ± standard deviation. VTE= venous thromboembolism, COPD = chronic obstructive pulmonary disease

* Data were missing in 126 (23%) patients

Outcome events

Recurrent VTE

In patients treated at home six (2.0%; 0.7-4.3) had recurrent VTE; five patients had non-fatal recurrent PE and one patient had recurrent DVT. In patients treated in the hospital nine (3.9%; 1.9-7.0) had recurrent VTE; all patients had recurrent PE. More than half of all recurrent VTE happened in the first 2 weeks after the initial PE (Figure 1). None of the outpatients had fatal PE, while five patients (2.2%; 0.8-4.8) treated in the hospital died of fatal PE on day 1, 3, 6, 33 and 66 ($p<0.05$; Table 2). All three patients with fatal PE during the first week after the initial PE died during hospital admission. None of the fatal recurrences underwent autopsy to prove cause of death.

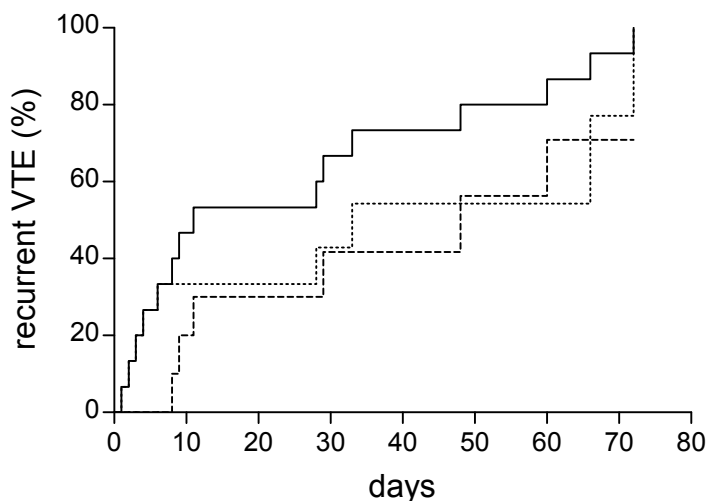


Figure 1: Timing of recurrent venous thromboembolism

— All patients
 Inpatients
 ----- Outpatients

Major bleeding

Two outpatients had a major bleeding event (0.7%; 0.082-2.4; Table 2) versus 11 inpatients (4.8%; 2.4-8.4; $p<0.05$). The two major bleedings in the outpatients consisted of one fatal intracranial bleeding at day 7 and one large abdominal muscle hematoma at day 14. Seven (64%) of the major bleedings in the inpatient group happened during the first week of treatment (Figure 2). The locations of the eleven major bleedings in the inpatient group were: intracranial hemorrhage (fatal), two intra-abdominal bleedings, gastrointestinal bleeding,

Table 2. Adverse clinical outcome in 3 months follow-up period

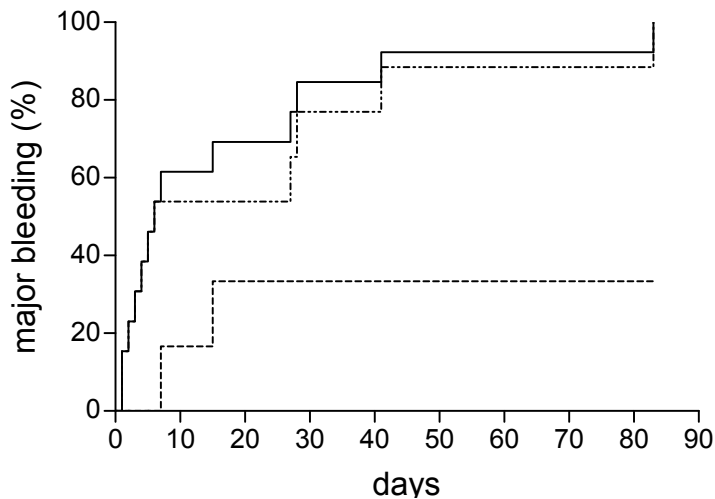
Clinical outcome	All PE patients (n=526)*	PE patients treated as outpatients (n=297)	PE patients treated as inpatients (n=229)*	P-value inpatients versus outpatients
Total recurrences	15 (2.9)	6 (2.0)	9 (3.9)	0.290
Fatal recurrent PE	5 (1.0)	0	5 (2.2)	0.015
Non-fatal recurrent PE	9 (1.7)	5 (1.7)	4 (1.7)	1.000
Non-fatal recurrent DVT	1 (0.2)	1 (0.3)	0	1.000
Major bleeding	13 (2.5)	2 (0.7)	11 (4.8)	0.003
Fatal bleeding	2 (0.4)	1 (0.3)	1 (0.4)	1.000
All-cause mortality	25 (4.8)	3 (1.0)	22 (9.6)	<0.001

Data are displayed as No (%).

PE = pulmonary embolism, DVT = deep vein thrombosis, NS=non-significant

* 4 inpatients were lost-to-follow-up

pericardial bleeding, bleeding in a pacemaker pocket, hemarthros, hematuria, large subcutaneous hematoma of arm and breast, intravenous catheter related bleeding and a muscle hematoma of the upper leg. Five of eleven (45%) major bleedings in the inpatient group happened during thrombolytic treatment, but none of these were fatal.

**Figure 2:** Timing of major bleeding

— All patients
 Inpatients
 ----- Outpatients

Mortality

During 3 months follow-up 25 patients (4.8%; 2.6-8.2) died. Seven patients (28%) died of causes related to PE or bleeding, as described above. Other causes of death were mostly malignancies (9; 36%), respiratory insufficiency (5; 20%) or myocardial infarction (2; 8%). In the patients treated at home three patients (1.0%; 0.21-2.9) died versus 22 patients (9.6%; 6.3-14) treated in the hospital ($p < 0.05$; Table 2). None of the patients treated at home died within the first week versus four patients treated in the hospital ($p < 0.05$). Three of these inpatients died of fatal progression of PE and one inpatient had a fatal bleeding. Active malignancy was present in 16 patients (64%) when they died. When patients with malignancies were excluded, 3-month mortality was 0.4% (95% CI 0.009-2.1) in the outpatients and 4.4% (95% CI 1.9-8.5) in the inpatients.

Discussion

Our study demonstrates that when patients were selected for out- or inpatient treatment with the Hestia criteria, outpatients had less clinical adverse events than patients treated in the hospital. None of the outpatients died of fatal PE, versus five of the inpatients and inpatients also had a higher overall mortality within the first week; this period equals the average duration of hospital admission.⁹ From this we can conclude that the Hestia criteria discriminate well between PE patients at high and low risk for adverse events and adequately select low risk patients for outpatient treatment.

In 2010 two retrospective studies on outpatient treatment of PE have been published.^{4,5} The Hestia Study is an important prospective validation of these retrospective studies. Our results provide a firm validation and an extension of the results of the retrospective studies regarding the safety of outpatient treatment. In both the study presented here and the study of Erkens *et al* the rate of fatal PE was 0% in the outpatient and 2% in the inpatient group.⁴ Overall recurrent VTE rates, major bleeding rates and mortality are higher in the retrospective study than in the Hestia Study, although not statistically, because the confidence intervals overlap. In the Hestia study we found recurrent VTE rates of 2.0% in the outpatients and 3.9% in the inpatients versus 3.8% in outpatients and 4.7% in inpatients in the retrospective study. Major bleeding rates were 0.7% in outpatients and 4.8% in inpatients in the Hestia Study and 1.5% and 6.1% in the other study. In the study of Erkens *et al* mortality was 5% in outpatients and 26% in inpatients, which is higher than in the 1.0% and 9.6% in the Hestia Study. The explanation for the higher rates of adverse outcome in the retrospective study could be that their study population contained a higher proportion of patients with malignancies compared to the Hestia population (36% versus 14%). The proportion of malignancies of 14% we found in the Hestia Study is more comparable to proportions of malignancies observed in

other large studies on anticoagulant treatment in patients with PE.^{10,11} In our view this adds to the generalisability of our results.

The other retrospective study by Kovacs *et al* did not give clinical outcomes of patients treated in the hospital.⁵ The rates of adverse clinical outcome in the outpatient group are comparable to the rates in the Hestia Study: in the patients treated at home none died of fatal PE.

Recently the first randomized controlled trial on outpatient treatment in patients with PE was published.¹² They concluded that outpatient treatment was non-inferior to inpatient treatment regarding recurrent VTE and mortality, but the major bleeding rate was a little higher in the outpatient group. The recurrent VTE and mortality rates in the outpatient group of the randomized trial were lower than the rates in the Hestia study, but this could be due to a highly selected population of young and healthy PE patients: mortality 0.6% and recurrent VTE 0.6%. Despite the selection of young patients with a low proportion of co-morbidities the major bleeding rate of 1.8% was higher than in our study, although the confidence intervals overlap.

The strength of the Hestia Study is that, it is the largest study on outpatient treatment, but there are some limitations to our study: because we did chart review and no prospective study follow-up of the inpatients, some events could have been missed. Because almost all patients had a complete follow-up, it is not likely that we missed important events like fatal PE or fatal bleeding. Within the setting of the Hestia study, PE patients who were treated at home were closely followed. Before outpatient treatment can become a standard of care, it is essential that close follow-up of PE patients treated at home can be guaranteed in every day patient care, especially during the first week.

Another limitation is that one patient in the home treatment group died of fatal intracranial bleeding. The exclusion of patients with high bleeding with the Hestia criteria led to a significantly lower bleeding rate in patients treated at home versus patients treated in the hospital (0.7% vs. 4.8%; $p=0.003$). Despite this careful triaging procedure, one patient in the home treatment group died of major bleeding. That patient had poorly controlled hypertension as an additional risk factor for bleeding in retrospect. Therefore physicians should be very careful in selecting patients for outpatient treatment, especially those with risk factors for major bleeding.

In the study presented here, the Hestia criteria have been used to select patients with PE for outpatient or inpatient treatment. Comparable criteria have been used in other studies abroad, but Dutch doctors used these criteria for the first time. In the Hestia Study the criteria were used by doctors with different specialties and levels of experience. Taken together with the favorable findings, this reinforces the feasibility of these criteria to be used by all kinds of specialists without restriction to thrombosis experts. However, because it was the first time the Hestia criteria were used these results have to be confirmed in future studies.

In conclusion, evidence on the safety of outpatient treatment in low risk patients with PE is accumulating. The Hestia criteria can be used to discriminate PE patients with low risk for adverse clinical outcome from patients with high risk for adverse clinical outcome. The low risk patients can be safely treated at home.

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Chapter 4

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

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Submitted



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 assess 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}

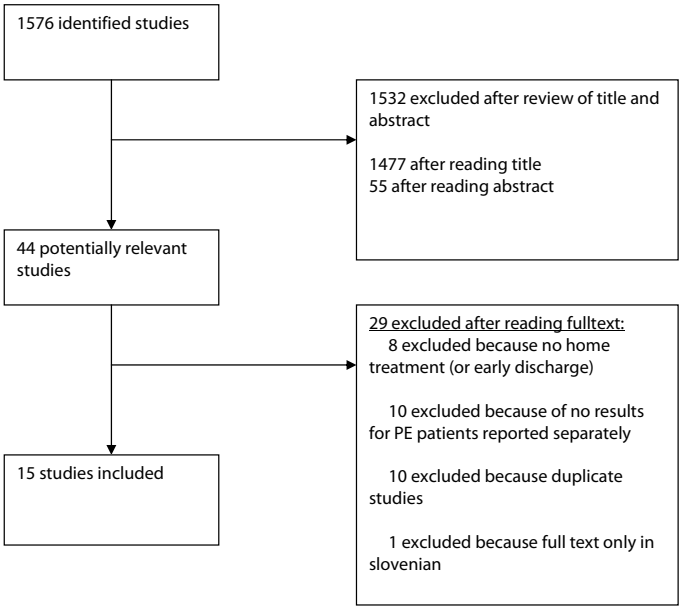


Figure 1: Flow chart: selection of studies

All were published in the English language. All but two studies reported outcome measures at 3 months; one study reported outcomes at 6 months³² 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 only²⁵ 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 generalizability 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	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	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 Aujesky Lui Olsson Otero Rodriguez	NT-proBNP>500 ng/mL Pulmonary Embolism Severity Index>85* Massive pulmonary embolism Large PE (affecting >40% longperfusion on V/Qscan) Clinical score >2, Troponin T>0.1 ng/mL, RV dysfunction on TTE 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 instability	Agterof, Aujesky, Davies, Erkens, Kovacs 2000, Kovacs 2010, Lui, Ong, Otero, Rodriguez, 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, Rodriguez, 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 test²³ 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 days²⁵ 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} dalteparin 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 0.02-1.1). 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%

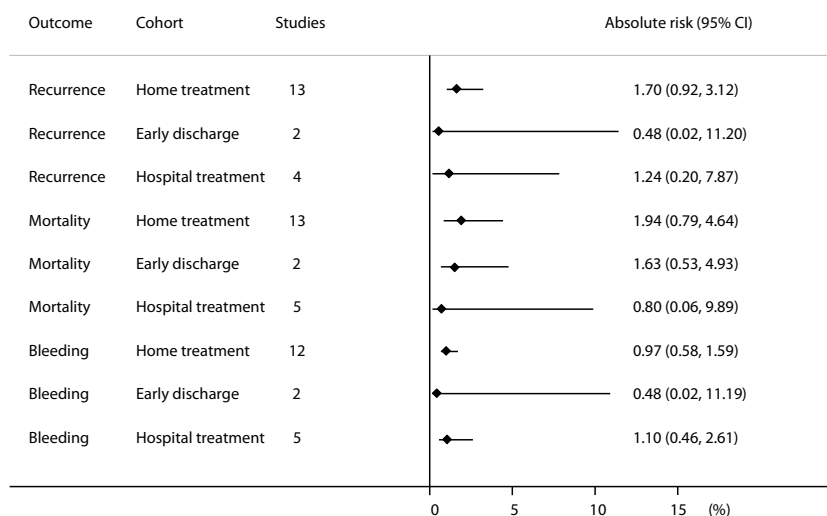


Figure 2: Pooled incidences of clinical outcome after pulmonary embolism in patients treated at home, discharged early or treated as inpatients

(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 statistically 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 from 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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Chapter 5

Comparison of two methods for selection of out of hospital treatment in patients with acute pulmonary embolism

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Abstract

Background

The aim of this study is to compare the performance of two clinical decision rules to select patients with acute pulmonary embolism (PE) for outpatient treatment: the Hestia criteria and the simplified Pulmonary Embolism Severity Index (sPESI).

Methods

From 2008 to 2010, 468 patients with PE were triaged with the Hestia criteria for outpatient treatment: 247 PE patients were treated at home and 221 were treated as inpatients. The outcome of interest was all-cause 30-day mortality. In a post-hoc fashion, the sPESI items were scored and patients were classified according to the sPESI in low and high risk groups.

Results

Of the 247 patients treated at home, 189 (77%) patients were classified as low risk according to the sPESI and 58 patients (23%) as high risk. In total, 11 patients died during the first month; two patients treated at home and nine patients treated in-hospital. None of the patients treated at home died of fatal PE. Both the Hestia criteria and sPESI selected >50% of patients as low risk, with good sensitivity and negative predictive values for 30-day mortality: 82% and 99% for the Hestia criteria and 91% and 100% for the sPESI, respectively.

Conclusions

The Hestia criteria and the sPESI perform equally well in predicting short-term mortality in patients with acute PE. However, this study demonstrates that the Hestia criteria are able to identify a significant proportion of patients classified as high risk by sPESI who can be safely treated at home.

Introduction

Evidence on the safety of outpatient treatment or early discharge of selected low-risk patients with acute pulmonary embolism (PE) is accumulating. The recent American College of Chest Physicians guidelines give a grade 2B recommendation on the safety of early discharge of selected PE patients and the European Society of Cardiology guidelines suggest that low risk PE patients, with negative markers for right ventricular dysfunction or myocardial ischemia, could be treated at home.^{1,2}

When considering outpatient treatment for patients with acute PE, the crucial step is to select those patients who are at low risk of adverse outcome. For this purpose, several methods to aid in the selection of low risk patients have been investigated: clinical signs and symptoms,^{3,4} laboratory values⁵ or imaging techniques.⁶ The most widely validated method for selection of low-risk patients with PE, is the Pulmonary Embolism Severity Index (PESI)^{7,8}; a clinical decision rule, containing 11 items based on signs and symptoms of the patient. The PESI has been prospectively tested in a randomized controlled trial,⁹ in which low risk patients, with <85 points on the PESI, were randomized between home or hospital treatment. Patients treated at home demonstrated equally low rates (<1%) of recurrent venous thromboembolism and all-cause mortality compared to patients treated in-hospital.

Recently, a simplified version of the PESI has been developed.¹⁰ This simple rule, with only six items, is much more useful in the busy emergency department.

Our study group recently published the Hestia study: a multicenter study on outpatient treatment, which used 11 practical clinical exclusion criteria (Hestia criteria) to select patients for outpatient treatment.⁴ The present study is a post-hoc comparison of the data of the Hestia study, in which we applied the simplified PESI (sPESI) to our patients. In this article we compare the performance of the Hestia criteria and the sPESI in selecting low-risk PE patients eligible for outpatient treatment and the relation of both clinical prediction models to clinical outcome.

Methods

Design

This is a post-hoc analysis on data from the Hestia study, which was a multicenter

prospective cohort study performed in 12 hospitals in The Netherlands. For this analysis we selected consecutive patients with acute PE treated as in- or outpatients with anticoagulants between 2008 and 2010. Inclusion criteria were: over 18 years of age with proven acute PE presenting to the Emergency Department or outpatient clinic. Patients with asymptomatic or chronic PE, defined as symptoms > 14 days, without acute worsening, were not included. All patients were treated at home with anticoagulants, unless one of the Hestia criteria was

present (Table 1). If one of the Hestia criteria was present, the patient was admitted to the hospital. The complete methods of this study are described elsewhere.⁴ The Hestia study was approved by the Institutional Review Board of all participating hospitals and patients gave informed consent. The patients treated in-hospital were not study patients because they were not eligible for the intervention of outpatient treatment. After the study we thoroughly reviewed the medical charts of the patients treated in the hospital to investigate whether they had had predefined adverse clinical outcome within 3 months after the initial PE, as described below.

Table 1. Items in the Hestia criteria and the simplified Pulmonary Embolism Severity Index

Hestia criteria	Simplified Pulmonary Embolism Severity Index
1. Hemodynamically unstable?*	1. Age > 80 years?
2. Thrombolysis or embolectomy necessary?	2. Cardiopulmonary co-morbidity?
3. High risk for bleeding?**	3. History of cancer?
4. Oxygen supply to maintain oxygen saturation >90% >24 h.?	4. Arterial oxyhemoglobin saturation level <90%?
5. Pulmonary embolism diagnosed during anticoagulant treatment?	5. Systolic blood pressure <100 mmHg?
6. Intravenous pain medication >24 h.?	6. Pulse frequency ≥110 beats/min?
7. Medical or social reason for treatment in the hospital >24 h.?	
8. Creatinine clearance of less than 30 ml/min?***	
9. Severe liver impairment****	
10. Pregnant?	
11. Documented history of heparin induced thrombocytopenia?	
If one of the questions is answered with YES, the patient can not be treated at home	If one of the items is present the patient cannot be treated at home

* 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 Cockcroft-Gault formula

**** Left to the discretion of the physician

Endpoints

All patients were followed for 3 months. Follow-up in the patients treated as outpatients was done according to the Hestia study protocol; patients visited the outpatient clinic at 1 week, 6 weeks and 12 weeks after the initial PE. In the patients treated as inpatients, the endpoints were collected by chart review. The primary outcome was recurrent venous thromboembolism during 3 months following the diagnosis of PE. The secondary outcomes were: major bleeding and all-cause mortality during 7 days and 3 months. The 30-day all-cause mortality endpoint was added after the study was finished, to compare our data with the literature. An

independent adjudication committee adjudicated all outcomes. They also assessed whether death was likely to be PE related based on autopsy reports and clinical reports.

Simplified Pulmonary Embolism Severity Index

In this post-hoc analysis, the sPESI was applied on the data of the Hestia study.¹⁰ The sPESI consists of six items and if one of the items is present, the patient is considered at high risk for 30-day mortality and cannot be treated at home (Table 1). The age, cardiopulmonary co-morbidity and history of cancer were prospectively registered in out- and inpatients during the Hestia study. The pulse frequency, blood pressure and oxygen saturation were collected in all patients by chart review. We calculated the proportion of patients who were treated at home according to the Hestia criteria, but could not be treated at home according to the sPESI and vice versa.

Statistics

Differences between categorical variables were studied using the Fisher's Exact test and continuous variables were compared using an independent samples T-test. A two-sided p-value was considered to indicate a significant difference if <0.05 . The discriminatory abilities of the Hestia criteria and the sPESI were investigated by measuring the area under the curve (AUC) in receiver operating characteristics (ROC) analyses. SPSS version 17 (SPSS Inc, Chicago, IL) was used for all analysis.

Results

Patient selection and characteristics

From 2008 to 2010 530 patients were selected; 297 were treated at home in the Hestia Study and 243 were excluded from outpatient treatment by the Hestia criteria and treated in-hospital. In 468 of 530 patients all items of the sPESI score could be collected from the medical charts. This resulted in the inclusion of 247 patients treated at home and 221 patients treated in the hospital according to the Hestia criteria in this post-hoc analysis.

The patients treated in the hospital were excluded from outpatient treatment by the following Hestia criteria: medical or social reasons 82 (37%), hypoxia 67 (30%), hemodynamic instability 28 (13%), high bleeding risk 14 (6%), intravenous narcotics 11(5%), use of therapeutic anticoagulants 7 (3%) and indication for thrombolysis 5 (3%). The reason for hospital admission was not specified in 7 patients.

Overall, the patients had a mean age of 58 years and 55% were male. Fifteen percent of patients had a history of cancer and 10% had a cardiopulmonary co-morbidity, for example heart failure or chronic obstructive pulmonary disease (Table 2).

Table 2. sPESI items in patients at home versus patients treated in the hospital

Characteristics of sPESI	All patients N=468	Home treatment N=247*	Hospital treatment N=221**
Age >80	43 (9)	9 (4)	34 (15)
History of cancer	69 (15)	21 (9)	48 (22)
Cardiopulmonary co-morbidity	47 (10)	12 (5)	35 (16)
Heart rate ≥ 110 bpm	76 (16)	22 (9)	54 (24)
Systolic blood pressure <100 mmHg	18 (4)	0	18 (8)
Oxygloblin saturation <90%	33 (7)	2 (0.8)	31 (14)
sPESI low risk	275 (59)	189 (77)	86 (39)
sPESI high risk	193 (41)	58 (23)	135 (61)

Data are displayed as N(%). Bpm=beats per minute; sPESI= simplified Pulmonary Embolism Severity Index

* 50 patients were excluded because one or more items of the sPESI score were missing

** 12 patients were excluded because one or more items of the PESI score were missing

Simplified Pulmonary Embolism Severity Index

The distribution of the items of the sPESI in all patients and the patients treated at home or in the hospital is displayed in Table 2. Overall, 275 of 468 patients (59%) were classified as low risk according to the sPESI and 193 of 468 patients (41%) were classified into the high risk sPESI group. Patients with low risk according to sPESI had significantly lower 30-day mortality of 0.4% versus 5.3% in the high risk sPESI patients ($p=0.001$).

Of the 247 patients treated at home, 189 (77%) of patients would have been in the low risk sPESI group and 58 patients (23%) would have been in the high risk sPESI group. Of the 221 patients treated in the hospital, 86 (39%) would have been in the low risk sPESI group and 135 (61%) would have been in the high risk sPESI group.

Patients with cardiopulmonary co-morbidity, malignancy or age >80 years are defined as high risk patients according to the sPESI. In the Hestia study 26% of patients with cardiopulmonary co-morbidities, 21% of patients with malignancies and 30% of patients >80 years could be treated at home, with only one adverse event. One of the patients with pancreatic cancer died of end-stage cancer within 30 days (day 29) and the other patients had uncomplicated clinical courses. Nine patients died within 30 days in the high-risk sPESI patients treated in the hospital (6.8%; 95%CI 3.2-13) versus one in the high-risk sPESI patients treated at home (1.7%; 95%CI 0.04-9.2; Table 3).

Test characteristics Hestia criteria versus sPESI

Eleven patients (2.4%) died within 30 days, nine patients treated in-hospital and two patients treated at home. None of the patients treated at home died of fatal PE. Of the 11 patients that died within 30 days, ten would be classified as high risk according to the sPESI and one would have been classified as sPESI low risk. The Hestia criteria had a sensitivity for 30-day mortality of 82% and a negative predictive value of 99% (Table 4). The sensitivity of the sPESI was 91% and the negative predictive value was almost 100%. Because of the low incidence

Table 3. Distribution of adverse clinical events of low and high risk sPESI groups in the patients treated at home or in the hospital in the Hestia study

	All patients	Home treatment	Hospital treatment*	p-value
sPESI low risk	N=275	N=189	N=86	
All-cause mortality				
7 days	0	0	0	1.0
30 days	1 (0.4)	1 (0.5)	0	1.0
3 months	1 (0.4)	1 (0.5)	0	1.0
Major bleeding	3 (1.1)	1 (0.5)	2 (2.3)	0.231
Recurrent VTE	4 (1.5)	3 (1.6)	1 (1.2)	1.0
sPESI high risk	N=190	N=58	N=132	
All-cause mortality				
7 days	4 (2.1)	0	4 (3.0)	0.315
30 days	10 (5.3)	1 (1.7)	9 (6.8)	0.288
3 months	23 (12.1)	2 (3.4)	21 (16)	0.015
Major bleeding	9 (4.7)	0	9 (6.8)	0.059
Recurrent VTE	10 (5.3)	2 (3.4)	8 (6.1)	0.726

sPESI= simplified Pulmonary Embolism Severity Index

* 3 patients lost to follow-up

Table 4. Test characteristics Hestia criteria versus sPESI on 30-day mortality

	Hestia criteria	sPESI
Sensitivity	82 (48-97)	91 (57-100)
Specificity	54 (49-59)	60 (56-65)
Proportion identified as high risk	47 (42-51)	41 (36-45)
Proportion identified as low risk	53 (48-58)	59 (54-64)
Negative predictive value	99 (97-100)	100 (98-100)
Positive predictive value	4 (2-8)	5 (3-10)

Data displayed as percentage (95% confidence interval). sPESI= simplified Pulmonary Embolism Severity Index

of 30-day mortality, the specificity and positive predictive value were low for both clinical decision rules: 54% and 4% for the Hestia criteria and 62% and 5% for the sPESI, respectively (Table 4). The ROC-curve demonstrated an AUC of 0.756 (95% CI 0.642-0.871) for the sPESI and 0.679 (95% CI 0.536-0.822) for the Hestia criteria.

The Hestia criteria identified 53% as low risk and the sPESI would have identified 59% of PE patients as low risk. The Hestia low risk patients were all treated at home. Of the patients identified as low risk by the sPESI, 86 of 275 (31%) had an indication for hospital admission according to the Hestia criteria. The main reasons for hospital admission were: medical or social reasons in 34 patients (40%), hypoxia in 24 patients (28%), high bleeding risk in 7 patients (8%), intravenous narcotics in 7 patients (8%).

Discussion

Our study demonstrated that the Hestia criteria and the sPESI perform equally well in predicting 30-day mortality in patients with acute PE. Both methods safely identified more than half of the PE patients as low risk. However, there were also several discrepancies. Most importantly, a fourth of the patients treated at home safely in the Hestia study would have been classified as high risk by the sPESI and therefore would not have been eligible for outpatient treatment according to the sPESI. Of importance, none of the patients with a high risk sPESI score treated at home in the Hestia study died of fatal PE and two patients died of end-stage cancer. On the other hand, 39% of patients identified as low risk by sPESI could not be treated at home in the Hestia Study, because of medical or social reasons for hospital admission.

In our study, 59% of PE patients were identified as low risk by the sPESI. This is a high proportion of low-risk patients when compared to the 31-46% reported in the literature.¹⁰⁻¹³ This is mainly due to the lower proportion of patients with malignancies in our study. Two recent studies have reported low 30-day mortality rates of 0-0.6% of both low risk (s)PESI patients treated at home and low risk patients treated in the hospital.^{9,11} This is well comparable to the mortality of 0.5% in low risk patients treated at home and to the 0% mortality in low risk patients treated in the hospital in our study. Our study and the study of Erkens *et al.* are the only studies that describe clinical outcome in PE patients with high sPESI scores treated at home. The patients with high PESI scores, selected for home treatment, had markedly lower 30-day mortality rates than patients with high PESI scores treated in the hospital: 0-2% in patients treated at home versus 7-11% in patients treated in the hospital.¹¹ In the majority of the patients with high risk sPESI, who were safely treated at home, malignancy was the only sPESI risk item present. This suggests that with the use of the clinical criteria like the Hestia criteria, a selected group of patients with one of the sPESI risk items, mainly patients with cancer, can be safely treated at home. From a clinical perspective this is very important. Patients with malignancy already have many intensive oncology therapies in the hospital and often have a short life expectancy; therefore every day that can be spent at home is of great value to the patient. Moreover, although oncology patients with PE are indeed at increased risk of mortality¹⁴ and therefore considered as high risk patients by (s)PESI, most of this mortality is not directly related to the PE event but rather to progression of the underlying malignancy. It is, in our view, unlikely that this mortality could be prevented by treating these patients as inpatients.

Our study had some limitations that should be acknowledged. In 62 of 530 patients (12%) some of the items of the sPESI score were not recorded and therefore these patients were excluded from the analyses. However, follow-up was complete in all of these patients, except for one patient living abroad. During follow-up only one of 62 patients died of a pulmonary infection. This patient would have been in the high risk sPESI group because of preexisting COPD and was admitted to the hospital in the Hestia study because of the need of intra-

venous antibiotics. The test characteristics of the Hestia criteria and the sPESI in predicting 30-day mortality would not alter significantly by adding this one case in the high risk sPESI group that was treated in-hospital.

Another limitation is that the sPESI was not tested prospectively in our cohort in selecting patients for outpatient treatment. Future studies should focus on that.

The PESI is currently the best validated method for risk stratification for PE outpatient treatment; however this score has some practical disadvantages. First, before PESI can be used in clinical practice, some practical exclusion criteria for hospital treatment have to be added to the PESI. In the randomized trial by Aujesky *et al.* the 11 items of the PESI scored after 14 practical exclusion criteria for outpatient treatment were applied, because a part of the PESI low risk patients could not be treated as outpatients, because of medical or social conditions.⁹ In this trial physicians had to check 25 items before the patient could be selected for outpatient treatment. This triaging is too complicated and time consuming for use in busy emergency departments.¹⁵ The introduction of the sPESI, with only six risk items, partly solves this problem, but still this score cannot directly select patients eligible for outpatient treatment; several practical exclusion criteria have to be added.

Second, due to the many exclusion criteria for outpatient treatment that had to be added to the PESI, only 30% of patients with PE could be selected for outpatient treatment.⁹ When using the sPESI instead of the original PESI, the proportion of PE patients eligible for outpatient treatment could be even lower.^{10,11}

The advantage of using the Hestia criteria for selecting patients for outpatient treatment is that more than 50% of PE patients can be treated at home, with equally low mortality rates compared to the PESI.^{4,9} The sPESI generally excludes patients with co-morbidities or advanced age on forehand from outpatient treatment. Our study demonstrated that 20-30% of all patients with malignancies, cardiopulmonary co-morbidities or elderly patients can be safely treated at home, without PE-related mortality. Therefore, we conclude that the Hestia criteria appear to offer a more individualized and simple approach in selecting patients for outpatient treatment, with close-to-practice, clinical criteria.

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Chapter 6

Hestia criteria can safely select patients with pulmonary embolism for outpatient treatment irrespective of right ventricular function

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Abstract

Background

The aim was to compare the Hestia criteria to the European Society of Cardiology (ESC) criteria for selecting low risk patients with pulmonary embolism (PE) for outpatient treatment.

Methods and results

From 2008 to 2010, 496 patients with acute, symptomatic PE presented to 12 Dutch hospitals, of which 275 were treated at home and 221 were treated in the hospital according to the Hestia study protocol. The Hestia criteria were used to select patients for outpatient treatment. Right and left ventricular (RV, LV) diameters were measured on computed tomography images. RV dysfunction was defined as a RV/LV ratio >1.0 . Patients were classified according to the ESC criteria in low, intermediate and high risk groups, based on blood pressure and RV dysfunction. During 3 months follow-up adverse events were scored.

Adverse events occurred in 22 patients (4.5%) treated in the hospital versus none of the patients treated at home ($p<0.001$). Sensitivity and negative predictive value for adverse outcome were 100% for the Hestia criteria and 83% and 98% for the ESC criteria, respectively. Of the patients treated at home according to the Hestia criteria, 34% were normotensive, but had RV dysfunction and were classified as intermediate risk according to the ESC criteria. No adverse events happened in these patients treated at home.

Conclusion

Clinical criteria, like the Hestia criteria, could be helpful in selecting patients including those with RV dysfunction who have low risk for adverse clinical outcome and could be candidates for outpatient treatment.

Introduction

The presence of right ventricular (RV) dysfunction is an important predictor for short term mortality in patients with pulmonary embolism (PE).¹ A substantial proportion of normotensive patients with PE have signs of RV dysfunction; proportions up to 60% have been reported.^{2,3} These patients with PE and RV dysfunction have a two to five times higher risk for short term mortality than patients without RV dysfunction.^{2,4-6}

The latest European Society of Cardiology (ESC) guidelines advise to perform initial risk stratification in patients with PE to distinguish patients with high risk for short term mortality from those with non-high risk (Grade IB recommendation).⁷ High risk patients are defined as having cardiovascular shock or persisting hypotension and they have a mortality risk >30%.⁸ Normotensive patients are considered as non-high risk patients, with a lower risk for short term mortality of 2-15%.⁹⁻¹¹ In non-high risk patients further risk stratification to intermediate and low risk groups can be performed. Imaging (e.g. computed tomography (CT) or echocardiography) or laboratory markers ((NT-pro)BNP or troponins) have been proposed in distinguishing low from intermediate risk patients.⁶ Low risk patients are defined by the absence of any signs of right ventricular (RV) dysfunction or myocardial ischemia on imaging and/or laboratory tests. These patients have a very low risk for short term mortality of less than 1%.⁴ The ESC guidelines recommend the restriction of PE outpatient treatment to patients with low risk, determined by laboratory or imaging parameters.⁷ Importantly, these criteria are based on consensus and lack prospective validation in clinical practice.

From 2008-2010 we performed the Hestia study: a study on the safety of initial outpatient treatment in patients with PE.¹² PE patients were selected for outpatient treatment with the Hestia criteria, a set of 11 clinical criteria (Table 1). The present study compared two methods for selection of patients for outpatient treatment: the Hestia Criteria and the ESC criteria. Our hypothesis was that a part of the intermediate risk patients, as defined by the ESC criteria, with the advice to be hospitalized, could be safely treated at home in the Hestia study. Therefore, the aim of this study was to describe the distribution of low, intermediate and high risk patients (according to the ESC criteria), assessed with blood pressure combined with RV dysfunction measured on CT, and the clinical outcome among the patients treated at home or in the hospital, according to the Hestia criteria.

Table 1: Hestia criteria

HESTIA CRITERIA
1. Hemodynamically instable?*
2. Thrombolysis or embolectomy necessary?
3. Active bleeding or high risk for bleeding?**
4. Oxygen supply to maintain oxygen saturation >90% >24 h.?
5. Pulmonary embolism diagnosed during anticoagulant treatment?
6. Intravenous pain medication >24 h.?
7. Medical or social reason for treatment in the hospital >24 h.?
8. Creatinine clearance of less than 30 ml/min?***
9. Severe liver impairment?****
10. Pregnant?
11. Documented history of heparin induced thrombocytopenia?

If one of the questions is answered with **YES**, the patient can NOT be treated at home

* 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 Cockcroft-Gault formula

**** Left to the discretion of the physician

Methods

Design

This study was a post-hoc analysis on data from the Hestia study, a multicenter prospective cohort study performed in twelve Dutch hospitals from May 2008 till April 2010.¹² In this study patients with acute PE were selected for anticoagulant treatment at home according to the Hestia criteria, which are 11 clinical selection criteria based on signs and symptoms. Patients who were not eligible for outpatient treatment were admitted to the hospital for treatment with anticoagulants. The complete methods of the Hestia study are described elsewhere.¹² The Hestia study was approved by the Institutional Review Board of all participating hospitals and patients gave informed consent. The patients treated in the hospital were not study patients because they were not eligible for the intervention of outpatient treatment. After the study we reviewed the medical charts of the patients treated in the hospital to investigate whether they had had adverse clinical outcome within 3 months after the initial PE.

Patients

Consecutive patients with acute PE treated as in- or outpatients with anticoagulants were selected for this post-hoc analysis. Inclusion criteria were: over 18 years of age with proven acute PE presenting to the Emergency Department or outpatient clinic. Patients with asymptomatic or chronic PE, the latter defined as duration of symptoms existing longer than 14

days and no acute worsening within the last 14 days, were not included. If patients had a proven PE on CT and none of the Hestia criteria (Table 1) were present, informed consent was asked for participation in the outpatient study. If one of the Hestia criteria was present or informed consent was refused, the patient was admitted to the hospital for anticoagulant treatment.

Endpoints

All patients were followed for 3 months. Follow-up in the patients treated as outpatients was done according to the Hestia study protocol; patients visited the outpatient clinic at 1 week, 6 weeks and 3 months after the initial PE. In the patients treated as inpatients, the endpoints were collected by chart review. The outcomes of interest were the occurrence of one of the following clinical adverse events: PE related mortality, resuscitation after respiratory or cardiac arrest, need for mechanical ventilation or use of inotropic agents, administration of thrombolytic drugs or surgical embolectomy.¹³ An independent adjudication committee assessed whether death was likely to be PE related based on autopsy reports and clinical reports. All-cause mortality was reported at 1 week and 3 months according to the initial Hestia study protocol. The 30-day mortality was added to the outcomes to compare our data to the ESC guidelines.⁷

Procedures

Most of the patients underwent computed tomography pulmonary angiography (CTPA) to confirm the diagnosis of PE, but other imaging modalities were also allowed in the Hestia study protocol. CTPA was performed by the CT equipment of the local hospitals. CT scanners of various vendors were used (Toshiba, Philips, Siemens, GE). Multi-slice non-ECG-gated helical CT with 4, 16, and 64-slice scanners were used with a slice thickness of 1 mm (64-slice scanners) or 2 mm (4 and 16-slice scanners). Tube voltage was 120-140 kV and tube current was 150-400 mA.

Left and right ventricle diameters were measured for calculation of the RV/LV ratios. The ventricular diameters were measured in the transverse plane at the widest points between the inner surface of the free wall and the surface of the interventricular septum (Figure 1).³ The maximum diameters could be found at different levels in the right and the left ventricle.

Right ventricular dysfunction was considered absent if the RV/LV ratio was 1.0 or less, modest RV dysfunction was defined as a ratio greater than 1.0, but less or equal to 1.5 and severe RV dysfunction was defined as a ratio greater than 1.5.³



Figure 1: Right and left ventricular diameters measured on transversal CT-image
A: right ventricle diameter **B:** left ventricle diameter

Ventricular diameter measures and reproducibility

The measuring of the ventricular diameters was performed on different post-processing workstations in standard axial views by one observer (WZ). This observer was trained and supervised by a radiologist with 11 years of experience on thoracic/cardiac CT imaging (LK). The observers were blinded for the clinical conditions of the patients and for information regarding treatment at home or in the hospital. For logistic reasons, one observer (WZ) visited all 12 hospitals for measuring LV and RV diameters on the CT-images. As to determine reproducibility for ventricular diameter measurements, a pilot study was performed to assess interobserver agreement. In addition intraobserver agreement of both observers was assessed to show the consistency of the LV and RV measurements. To calculate the intra- and interobserver agreement, a random sample of the CT scans ($n=86$) was measured by the two observers and the correlation coefficient was calculated. Intra- and interobserver agreement were classified based on the magnitude of the correlation coefficient: <0.2 poor agreement, $0.21-0.40$ fair agreement, $0.41-0.60$ moderate agreement, $0.61-0.80$ good agreement, $0.81-1.0$ very good agreement. Only if the correlation coefficient showed at least a good agreement (0.61), the pilot study would be extended with the measurements of CT-scans in the other hospitals. When comparing the observations between both observers, the interobserver agreement, the correlation coefficients were 0.899 for the LV diameter, 0.944 for the RV diam-

eter and 0.682 for the RV/LV ratio ($p < 0.001$ for all correlations). This corresponds with good (>0.61) to very good (>0.81) agreement.

When comparing both measurements of observer WZ, the correlation coefficients were 0.941 for LV diameter, 0.891 for RV diameter and 0.902 for RV/LV ratio ($p < 0.001$ for all). For observer LK, the correlation coefficients were 0.933 for LV diameter, 0.928 for RV diameter and 0.768 for RV/LV ratio ($p < 0.001$ for all correlations). The intraobserver agreement calculations showed good to very good agreement in both observers.

Risk classification

Patients were divided in three risk groups according to the ESC guidelines.⁷ Patients were considered to have low risk for mortality if they were hemodynamically stable and had no signs of RV dysfunction (RV/LV ratio < 1.0). Patients were considered to be of intermediate risk if they were normotensive, but had signs of RV dysfunction on the CT-scan (RV/LV ratio > 1.0). Patients were considered as high risk patients if they presented to the Emergency Department in cardiovascular shock or had a systolic blood pressure lower than 100 mmHg or were classified as being hemodynamically unstable by the local physician, irrespective of RV/LV ratio.

Statistics

Pearson correlation was used to calculate the correlation coefficient to determine the intra- and interobserver agreement in the pilot study. We evaluated the clinical utility of the Hestia criteria and the ESC criteria by assessing the specific test characteristics for predicting adverse events. Differences between categorical variables were studied using the Fisher's Exact test when comparing two groups and Chi Squared test when comparing three groups. Continuous variables were compared using an independent samples T-test. The association between RV dysfunction/ESC risk groups and adverse clinical outcome was studied by calculating odds ratios (OR) by logistic regression, adjusted for age, gender and cardiopulmonary co-morbidity. A two-sided p -value < 0.05 was considered to indicate a significant difference. SPSS version 17 (SPSS Inc, Chicago, IL) was used for all analyses.

Results

Patients

From 2008 to 2010, 530 patients with acute, symptomatic PE presented to 12 Dutch hospitals. Of these patients 297 were treated at home and 233 were admitted to the hospital. In 34 patients (6%) the CT parameters could not be measured, because ventilation/perfusion scan was used to diagnose PE ($n=18$) or due to technical problems ($n=16$). This resulted in 496 patients with CT-scans available for evaluation, 275 patients treated at home and 221 treated

Table 2: Baseline characteristics of patients with pulmonary embolism treated at home versus patients treated in the hospital

	All patients n=496	Home treated patients n=275	In-hospital patients n=221**	P-value home vs hospital treatment
Age (years)	58 ± 17	55 ± 16	62 ± 17	<0.001
Male sex	268 (54%)	159 (58%)	109 (49%)	0.07
Heart failure	13 (2.6%)	1 (0.4%)	12 (5.5%)	<0.001
COPD	32 (6.5%)	10 (3.6%)	22 (10%)	0.005
Systolic blood pressure (mmHg)	138 ± 24	143 ± 21	134 ± 26	<0.001
Diastolic blood pressure (mmHg)	82 ± 15	85 ± 14	80 ± 16	<0.001
Heart rate (bpm)	91 ± 19	87 ± 15	95 ± 22	<0.001
RV/LV ratio	1.1 ± 0.3	0.99 ± 0.2	1.2 ± 0.4	<0.001
No RV dysfunction	271 (55%)	180 (66%)	91 (41%)	<0.001
RV/LV ratio > 1	225 (45%)	95 (35%)	130 (59%)	<0.001
Modest RV dysfunction	169 (34%)	84 (31%)	85 (39%)	0.070
Severe RV dysfunction	56 (11%)	11 (4%)	45 (20%)	<0.001
All cause mortality				
< 7 days	4 (0.8%)	0	4 (1.8%)	0.038
< 30 days	11 (2.2%)	2 (0.7%)	9 (4.1%)	0.014
< 90 days	23 (4.7%)	3 (1.1%)	20 (9.2%)	<0.001
PE related mortality	5 (0.9%)	0	5 (2.3%)	0.016
Adverse events	22 (4.5%)	0	22 (10%)	<0.001
Treatment escalation				
Mechanical ventilation	6	0	6	0.006
CPR	6	0	6	0.006
Thrombolysis	16	0	16	<0.001
Inotropic medication	6	0	6	0.006

Continuous variables are displayed as mean (standard deviation(sd)) and categorical variables are displayed as number (percentage); bpm= beats per minute; COPD= chronic obstructive pulmonary disease; LV = left ventricle; RV= right ventricle; CPR=cardiopulmonary resuscitation **3 patients lost-to-follow-up

in the hospital. Three patients treated in the hospital were lost to follow-up during the 3 months of follow-up, because they lived abroad.

Patients had a mean age of 58 years and 54% of patients were male, 7% of patients had COPD and 3% of patients had heart failure. Patients treated in the hospital were older and had a higher percentage of co-morbidity (Table 2). Patients treated at home had a higher systolic blood pressure (143 vs. 134 mmHg, $p<0.001$) and a lower heart rate (87 vs. 95 beats per minute, $p<0.001$) at presentation. The mean duration of hospital admission was 7 days in the patients who were treated in the hospital.

Adverse clinical outcome

All-cause mortality during 3 months following the diagnosis of PE was 4.7% and 47% of mortality happened within the first month (Table 2). All of the 22 (4.5%) patients who had

one or more adverse events during 3 months follow-up, were patients treated in the hospital: six patients were ventilated mechanically, six patients underwent cardiopulmonary resuscitation (CPR), 16 had thrombolysis and six needed inotropic medication for hemodynamic problems caused by the pulmonary embolism (Table 2).

Right ventricular dysfunction in patients treated at home or in the hospital

In Table 2 RV and LV parameters are presented. RV/LV ratio was lower in patients treated at home than in patients treated in the hospital (0.99 vs. 1.2, $p<0.001$). In the total group of 496 patients, 225 (45%) had right ventricular dysfunction defined as a RV/LV ratio >1.0 : 34% had modest RV dysfunction (RV/LV ratio 1.0-1.5) and 11% had a severe RV dysfunction (RV/LV ratio >1.5). A significant lower proportion of patients treated at home had RV dysfunction compared to patients treated in the hospital (35% vs. 59%, $p<0.001$). Patients treated in the hospital had a higher proportion of patients with severe RV dysfunction (20% vs. 4%, $p<0.001$). None of the patients with a severe RV dysfunction who were treated at home had an adverse event.

RV dysfunction was significantly associated with adverse events. Patients with modest RV dysfunction had a six times higher risk for adverse events compared to patients without RV dysfunction (OR 5.8, 95%CI 1.1-29; $p=0.03$) and patients with a severe RV dysfunction had a 47 times higher risk for adverse events compared to patients with no RV dysfunction (OR 47, 95%CI 9-238; $p<0.001$). RV dysfunction was not significantly associated with all-cause mortality nor with PE related mortality.

Test characteristics of Hestia criteria versus ESC criteria

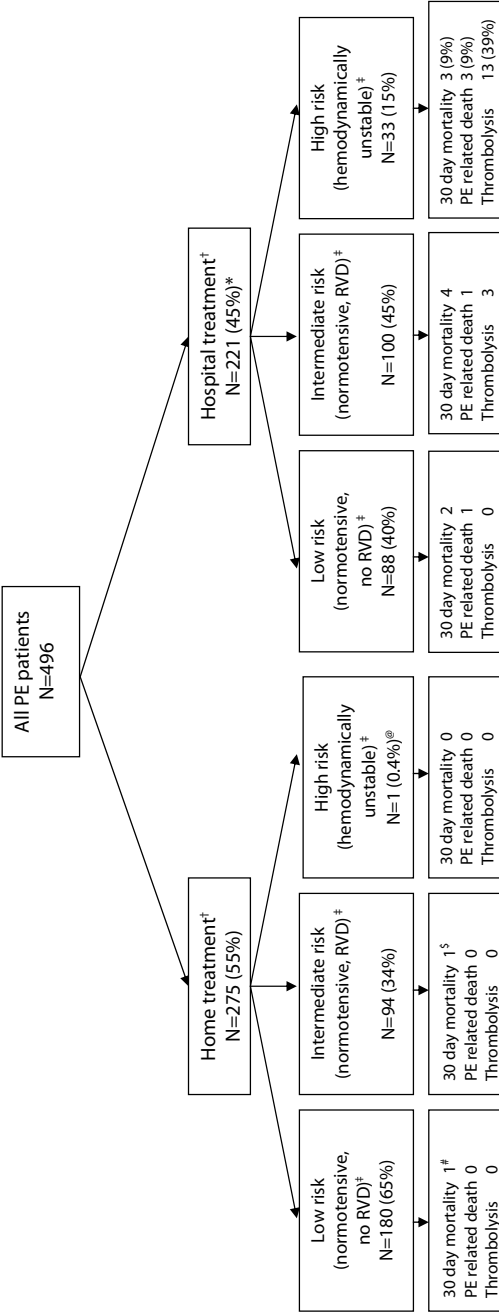
The discriminative power of both selection methods are underlined by a high sensitivity for adverse events: 100% (95% CI 82-100) in the Hestia criteria and 83% (95% CI 64-93) in the ESC criteria. Both methods also had a high negative predictive value: Hestia criteria 100% (95% CI 98-100) and ESC criteria 98% (95% CI 95-99). The specificity and positive predictive values were 58% (95% CI 54-63) and 10% (95% CI 7-15) for the Hestia criteria and 56% (95% CI 52-61) and 11% (95% CI 7-16) for the ESC criteria. Both the Hestia criteria and the ESC criteria selected more than half of patients as low risk and potentially eligible for outpatient treatment (55% and 54%).

Comparison of patients selected as low risk by Hestia or ESC criteria

Overall, 54% of patients were normotensive and had no RV dysfunction and could therefore be classified in the ESC low risk group. In addition, 39% of patients were normotensive with RV dysfunction and classified as intermediate risk and 7% of patients were hemodynamically unstable and classified as high risk

Of the 275 patients treated at home according to the Hestia criteria, 180 (65%) belonged to the low risk ESC group, 94 (34%) belonged to the intermediate risk ESC group and only

Figure 2: Distribution of ESC risk classes and clinical outcome in patients with pulmonary embolism treated at home or in the hospital according to Hestia criteria



RVD = right ventricular dysfunction measured on CT according to Hestia criteria; [‡]according to ESC criteria; ^{*}3 hospital patients were lost to follow-up (1 low risk and 2 intermediate risk); [#]patient with fatal intracranial bleeding; [§]patient died of end-stage pancreatic cancer; [@]patient with persisting hypotension because of vomiting with suboptimal hydration, but no symptoms of shock

one (0.4%) to the high risk ESC group (Figure 2). None of the outpatients had an adverse event. Three outpatients died during 3 months of non-PE related causes: one of intracranial bleeding (day 8) and two of end-stage pancreatic cancer (day 29, 59).

Of the 221 patients treated in the hospital according to the Hestia criteria, 88 (40%) belonged to the low risk ESC group, 100 (45%) belonged to the intermediate risk group and 33 (15%) to the high risk group. The main reasons for hospital admission due to the Hestia criteria in patients selected as low risk, according to the ESC criteria, were medical (mainly co-morbidities) or social reasons for hospital admission (51%) and need for oxygen supply to maintain adequate oxygen saturation (24%). The risks for adverse events were higher in all three risk groups treated in the hospital versus the risks of adverse events of the patients treated at home (Figure 2).

Discussion

Our study shows that the Hestia criteria and the ESC criteria had both good discriminative power to select patients with low risk for adverse events for outpatient treatment (negative predictive values of 100% and 98%). Of note, 34% of patients treated at home in the Hestia study had RV dysfunction, demonstrated by an increased RV/LV ratio at CTPA. These patients would have been excluded from outpatient treatment by the ESC criteria, but were treated at home safely in the Hestia study, without PE related adverse events. This study is the first to describe a group of patients with RV dysfunction, who have been safely treated at home.

Both the Hestia criteria and the ESC criteria safely selected more than 50% of PE patients as low risk and potentially eligible for initial outpatient treatment. The Hestia criteria consist of risk markers for adverse outcome (e.g. hemodynamic status, hypoxia) combined with practical criteria to select PE patients for outpatient treatment. The Hestia criteria can be implemented in clinical care without changes. The ESC criteria, however, only consist of risk markers for adverse clinical outcome. Some patients with PE can not be treated at home for medical or social reasons unrelated to PE. Before the ESC criteria can be used in clinical practice for selection of PE patients for outpatient treatment, practical exclusion criteria have to be added. This would decline the proportion of patients with PE treated at home to less than 50%.

Both echocardiography and CT can be used to establish RV dysfunction, since both methods have a high negative predictive value of 92-99%, which is important in selecting low risk PE patients.¹⁴ In this study CT was used to establish RV dysfunction. The advantage of CT over echocardiography is that it can be used as a diagnostic and prognostic method in the same procedure and is generally available.

This study also has some limitations. First, while the Hestia criteria were applied prospectively in the Hestia study, the ESC criteria were determined in a post-hoc fashion. As

a consequence, only hemodynamic status and the presence of RV dysfunction on CT scan were used to classify patients to the low, intermediate or high risk ESC groups. In the ESC consensus document it is suggested to add biomarkers of myocardial ischemia, including troponins. It is stated in the literature that the addition of troponin testing improves test characteristics.¹⁵ Troponins were not measured in the Hestia study. However, because no PE related adverse events happened in the patients treated at home, adding troponins to the selection of patients for outpatient treatment could not have increased the high negative predictive value of 100%.

Second, right and left ventricle diameters were measured by one investigator. However, the interobserver agreement in a subset of patients was good. In addition, the 45% proportion of PE patients with RV/LV ratio >1.0 is well comparable to previous reported proportions of 38-58%.^{3,16}

Third, although RV dysfunction was significantly associated with the occurrence of adverse events, we were unable to repeat the association between RV dysfunction and PE related mortality described in the literature.³ The lack of a significant association between RV dysfunction and fatal PE is probably due to the low number of fatal PE in our study.

What are the implications of our findings? The ESC guidelines recommend restriction of PE outpatient treatment to patients with low risk, determined by laboratory or imaging parameters and to hospitalize those with signs of RV dysfunction. As none of the hemodynamically stable patients, with or without RV dysfunction, treated at home in the Hestia study had a PE related adverse event, our results strongly suggest that a proportion of patients with RV dysfunction can be pre-identified, who could be treated at home safely. Clinical criteria, like the Hestia criteria, could be helpful in selecting patients with RV dysfunction who have a very low risk for adverse clinical outcome and could be candidates for outpatient treatment. Ideally prospective studies comparing the ESC criteria and the Hestia criteria are needed to corroborate our findings.

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Chapter 7

Repeated NT-proBNP testing and risk for adverse outcome after acute pulmonary embolism

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Abstract

Introduction

Many studies show that NT-proBNP at diagnosis of pulmonary embolism (PE) can be used to discriminate patients at low risk for adverse outcome after PE. The first aim of this study was to describe the course of NT-proBNP one week after PE. The second aim was to investigate whether adding a NT-proBNP test at day 2 to the test at day 1 would increase the predictive value for adverse events after pulmonary embolism.

Methods

Prospective cohort study with patients admitted for PE. NT-proBNP levels were measured daily. Primary outcome was adverse events during the first week, defined as PE-related mortality or clinical deterioration.

Results

Of 67 patients, nine patients (13%) had adverse events: seven on day 1, two on day 2. The median NT-proBNP level of patients with an event was higher during the first 3 days than of patients without an event. A proBNP cut-off >500 pg/mL on day 1 selected 41% of patients as low risk. A proBNP cut-off >1800 pg/mL on day 2 selected 62% of patients as low risk.

Conclusion

Repeated NT-proBNP testing within 48 hours after presentation with PE can identify 20% extra patients with PE as low risk than when using a single measurement at day 1. These patients could be possible candidates for outpatient treatment. It remains to be seen how these results translate into clinical practice, since all adverse events occurred within 48 hours.

Introduction

NT-proBNP (N-terminal brain natriuretic peptide) has been extensively investigated in the literature as a prognostic factor for an adverse outcome in pulmonary embolism (PE)¹⁻⁶. Patients with an elevated NT-proBNP at the time of diagnosis of PE have a seven times higher risk for an adverse outcome than patients with a low NT-proBNP.

A recently published prospective cohort study has shown that outpatient treatment in patients presenting with acute hemodynamically stable PE and NT-proBNP levels <500 pg/mL is safe with regard to short-term mortality.⁷ None of the 152 patients with PE and NT-proBNP levels <500 pg/mL died within 10 days (negative predictive value (NPV) 100%). This high NPV has also been observed in other studies.²⁻⁴ However, when using the cut-off of 500 pg/mL only 43% of PE patients can be treated at home.⁷ The first aim of the present study was to describe the course of NT-proBNP levels within one week after the diagnosis of PE. The second aim was to investigate whether adding a NT-proBNP test at day 2 to the test at day 1 would increase the predictive value for adverse events after PE.

Methods

We conducted a cohort study in a large teaching hospital in the Netherlands from April 2006 to June 2008. Patients with objectively proven, acute PE admitted to the hospital were included. Patients who died before the diagnosis of PE was established and patients transferred for treatment to another hospital were excluded. PE was demonstrated by imaging according to the local diagnostic guidelines (high probability ventilation-perfusion scan or abnormal CT-scan). Patients were treated with anticoagulants according to the current international guidelines.⁸ NT-proBNP levels were measured every morning using the Elecsys proBNP electrochemiluminescence immunoassay (Roche Diagnostics, Mannheim, Germany). Adverse events (defined as PE or major bleeding related mortality, cardiopulmonary resuscitation, mechanical ventilation, use of vasopressors, thrombolytic therapy, thrombosuction, open surgical embolectomy and PE or major bleeding related admission to Intensive Care (IC) unit) were collected during the first week.³

For the first aim of the study, to describe the course of NT-proBNP levels after the diagnosis of PE, all patients with acute PE were included. For the second aim of the study patients who had an adverse event during the first day were excluded. In order to find the NT-proBNP cut-off on the second day that would be most predictive for adverse events, we calculated test characteristics (sensitivity and specificity) of various absolute cut-off levels of NT-proBNP on day 2.

Differences in baseline characteristics and course of NT-proBNP levels between groups were examined by Mann-Whitney U statistics for continuous variables and χ^2 statistics for

categorical variables. The Fisher's Exact test was used if the count was less than five. SPSS version 17.0 (SPSS Inc., Chigago, IL, USA) was used for all analyses. The study was approved by the local review board and all patients gave informed consent.

Results

In total 67 patients with acute PE were included. The median age was 63 years and 43% were male (Table 1). None of the patients had a history of heart failure.

Nine patients (13%; 95% CI 6.9-25.4%) had adverse events during the first week, seven (78%) on day 1 and two (22%) on day 2. More than 48 hours after presentation with PE no further events happened. Eight patients with an adverse event were treated with thrombolytics, and in one patient surgical embolectomy was performed, because of high bleeding risk. All patients with an adverse event recovered completely.

Patients with adverse events during follow-up had significant lower systolic blood pressure (117 vs. 137 mmHg, $p=0.01$) and oxygen saturation (84% vs. 95%, $p=0.003$) at presentation than patients without adverse events. The difference in the course of NT-proBNP in PE patients with and without an adverse event is described in Table 2. The median NT-proBNP level of patients with an event was higher during the first three days than of patients without an event, but after the third day these differences in the median NT-proBNP levels disappeared (Figure 1). The median peak NT-proBNP levels of patients with an adverse event were higher than of patients without an adverse event (3181 vs. 1399 pg/mL, $p=0.01$). Most of the patients (85%) had reached the highest level of NT-proBNP within 48 hours after the diagnosis of PE.

Of the total of 67 patients, four patients were already hemodynamically unstable or had clinical deterioration before the first measurement of NT-proBNP. When these four patients

Table 1: Baseline characteristics of patients

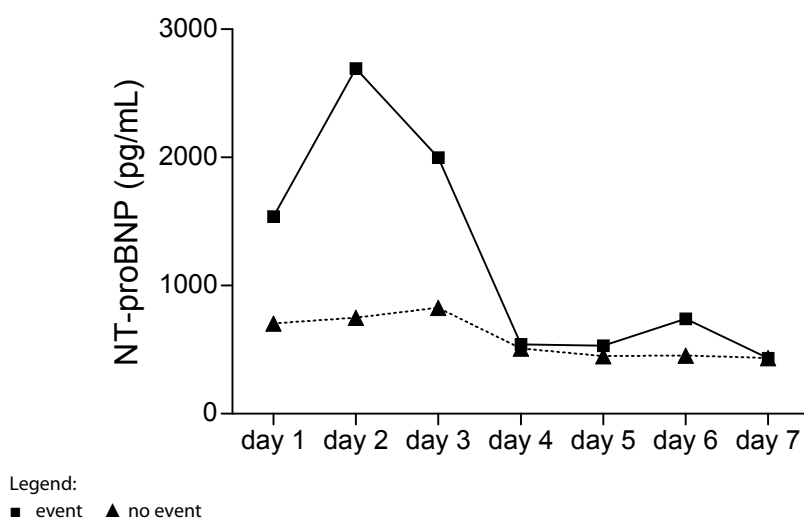
	All patients N=67		Events N=9		No event N=58		P-value
Age (year)	63	(50-73)	52	(42-62)	65	(51-74)	P=0.081
Male sex n(%)	29	(43)	2	(22)	27	(47)	P=0.280
SBP (mmHg)	134	(125-151)	117	(93-132)	137	(128-153)	P=0.014
Heart Rate (bpm)	88	(74-105)	92	(82-116)	88	(70-105)	P=0.130
Oxygen saturation* (%)	94	(89-97)	84	(79-90)	95	(90-97)	P=0.003
Heart Failure n(%)	0	(0)	0	(0)	0	(0)	-
COPD n(%)	6	(9)	0	(0)	6	(10)	P=0.587
Cancer n(%)	11	(16)	0	(0)	11	(19)	P=0.336

SBP=systolic blood pressure, bpm= beats per minute, n=number. Continuous data are displayed as median (25th percentile-75th percentile). *Patients in whom oxygen saturation was measured while on oxygen suppletion were removed from this analysis (N=10).

Table 2. Course of NT-proBNP

	All patients N=67		Events N=9		No event N=58		P-value
NT proBNP at diagnosis of PE (N=66)	910	(195-2367)	1823	(617-3456)	703	(178-2187)	P=0.153
NT proBNP day 2 (N=63)	1016	(195-3181)	2953	(2301-6600)	749	(160-2215)	P=0.004
NT-proBNP day 3 (N=48)	889	(221-2799)	2632	(1009-3557)	769	(186-2545)	P=0.088
NT-proBNP day 4 (N=40)	508	(243-1121)	512	(264-1574)	508	(177-1121)	P=0.892
NT-proBNP day 5 (N=34)	448	(186-853)	214	(117-1271)	459	(191-819)	P=0.738
NT-proBNP day 6 (N=28)	460	(128-794)	484	(100-867)	460	(177-767)	P=1.000
NT-proBNP day 7 (N=25)	433	(159-768)	101	(60-1437)	478	(237-768)	P=0.231
Peak NT-proBNP	1897	(297-3397)	3181	(2421-5876)	1399	(259-3163)	P=0.011
Proportion patients with peak NT-proBNP < 48 hours	55	(85)	8	(89)	47	(84)	P=1.000
Proportion patients with increase in NT- proBNP from day 1 to day 2	32	(51)	7	(88)	25	(46)	P=0.053
Proportion patients with increase NT- proBNP >50% from day 1 to day 2	18	(29)	5	(63)	13	(24)	P=0.039

NT-proBNP levels are given in pg/mL. Continuous data are displayed as median (25th percentile-75th percentile) and categorical data are displayed as number (percentage).

Figure 1. Course of NT-proBNP

were excluded from the analysis, 63 patients remained, of which five patients (7.9%; 95%CI 3.0-17.6%) had an adverse event. Of the 36 patients with NT-proBNP >500 at day 1 (57%), five patients got adverse events during hospital admission versus none in the patients with NT-proBNP <500 pg/mL (14% vs. 0%; $p=0.06$).

NT-proBNP cut-off of 1800 pg/mL at day 2 showed the highest sensitivity and specificity for adverse events at day 2 (sensitivity 100% (95% CI 46-100%), specificity 65% (95% CI 51-77%)). When adding the cut-off of 1800 pg/mL at day 2 to the cut-off of 500 pg/mL at day 1, an extra 13 patients (21%) at low risk for adverse events could be added to the 26 (41%) patients already selected as low risk at day 1. When combining two different NT-proBNP cut-off levels at day 1 and 2, 39 of 63 patients (62%; 95% CI 50-73%) could be selected as low risk patients within two days after the diagnosis of PE.

Discussion

In this study the course of NT-proBNP levels within one week after the diagnosis of PE was studied. We investigated whether patients with low proBNP on day 1 or day 2 could be candidates for outpatient treatment. Some hypothesis generating observations could be made: patients with upcoming adverse events have higher NT-proBNP levels during the first three days after PE and have a higher median peak NT-proBNP level than patients with an uneventful clinical course. This study is the first to describe the course of NT-proBNP more than 24 hours after diagnosis of PE. Only one other study has reported on repeated NT-proBNP testing after PE, but only within 24 hours and concluded that persistent elevation in NT-proBNP levels within 24 hours after PE has a high positive predictive value for mortality.⁹ Our results show that repeated NT-proBNP testing, as compared to single testing, could play a role in the further selection of low risk patients, who could be candidates for early discharge: when combining two cut-off levels for NT-proBNP on day one and day two, 62% (95% CI 50-73%) of patients could be classified as being low risk for adverse events. This is higher than the average proportions of 42-43% of patients with low risk described in the literature with single testing.^{3,7}

The small population is a limitation of this study. Because of this the cut-off on day 2 was based on only two adverse events. In larger populations the cut-off with the highest sensitivity and specificity could be different. The limited availability of NT-proBNP tests in some hospitals may reduce generalisability of our results.

Our results generated the hypothesis that with an extra NT-proBNP test on day 2, a larger proportion of low-risk PE patients (62%) can be selected as possible candidates for early discharge within 48 hours after the diagnosis of PE. However, since in our study all adverse events in this small population of PE patients happened within 48 hours after the diagnosis of PE, we cannot decide on whether two day-testing is sufficient to exclude adverse outcome

occurring later on. Therefore, the usefulness of repeated NT-proBNP testing for clinical practice has to be proven in a larger cohort of patients.

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Chapter 8

Patient outcomes after acute pulmonary embolism: a pooled survival analysis of different adverse events

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Abstract

Background

The aim of this study was to assess the long term risk for adverse events after acute pulmonary embolism (PE).

Methods

Consecutive patients diagnosed with PE between January 2001 and July 2007, and patients in whom PE was ruled out from a previous study were followed until July 2008 for the occurrence of adverse clinical events: mortality, symptomatic recurrent venous thromboembolism (VTE), cancer, arterial cardiovascular events and chronic thromboembolic pulmonary hypertension (CTEPH). Hazard ratios (HR) for all endpoints and a combined endpoint were calculated and adjusted for potential confounders.

Results

308 patients with unprovoked, 558 with provoked and 334 without PE were studied with a median follow-up period of 3.3 years. Patients with unprovoked PE had lower overall risk for mortality than patients with provoked PE (HR 0.59, 95% CI 0.43-0.82), but higher risk for non-malignancy related mortality (HR 1.8, 95% CI 1.3-2.5), recurrent VTE (HR 2.1, 95% CI 1.3-3.1), cancer (HR 4.4, 95% CI 2.0-10), cardiovascular events (HR 2.6, 1.5-3.8) and CTEPH (1.5% vs. 0%). The risk for the combined endpoint did not differ between both groups (HR 0.98, 95% CI 0.82-1.1). Patients without PE had similar risks for malignancy and cardiovascular events than patients with provoked PE, but lower risks for the remaining outcomes. The fraction of both patients with provoked and unprovoked PE without events after 1 year was only 70%, and decreased to fewer than 60% after 2 years and fewer than 50% after 4 years, whereas this latter was 84% for the control patients.

Conclusion

The clinical course of acute PE is complicated by high rates of serious adverse events, which occur in half of the patients within 4 years.

Introduction

Acute pulmonary embolism (PE) is a common and potentially serious medical condition.¹ The interaction of an extensive pulmonary artery obstruction rate and presence of cardio-pulmonary comorbidity may lead to right ventricular dysfunction, which is associated with hemodynamic instability and, in severe cases, with death.² This PE attributable mortality occurs in approximately 2-6% of patients with hemodynamically stable PE and in 30% or more of patients with PE presenting with hemodynamic instability or in shock.²⁻⁴ Of note, 25% of the patients do not survive the first year after diagnosis, although the majority of deaths during this time are related to underlying conditions, such as cancer or chronic heart disease, rather than to PE itself.^{3,4} Even after surviving the acute episode, the clinical course of acute PE can be complicated by several thrombotic and non-thrombotic adverse events. Bleeding complications and recurrent episodes of venous thromboembolism (VTE) are common and chronic obstruction of the pulmonary vessels with organized blood clots may lead to chronic thromboembolic pulmonary hypertension (CTEPH).^{3,5-8} This latter disease is further characterized by pulmonary arteriopathy and progressive right heart failure.⁶ Furthermore, it has been well established that patients with acute PE are at higher risk of being subsequently diagnosed with cancer as well as with arterial cardiovascular events than population controls.^{9,10} The prognosis of patients diagnosed with unprovoked PE, i.e. PE occurring in the absence of established risk factors or predisposing illnesses, might be less favourable than that of patients suffering from provoked PE. Several studies have shown that patients with unprovoked PE are at particular risk for recurrent PE, CTEPH, arterial cardiovascular events and the detection of cancer.^{9,11-18}

Although all individual complications of PE have been studied extensively, the combined risk for all adverse clinical events has not been reported yet. Knowledge of this short and long term prognosis after acute PE is of great importance since this should guide clinical decision making regarding treatment regimes, specific preventive screening programs and follow-up duration. Accordingly, we have performed a prospective cohort study evaluating the overall occurrence of complications in the clinical follow-up of patients diagnosed with acute PE. We contrasted the studied complication rate in patients with unprovoked PE to patients with provoked PE and to a control group of patients in whom PE was suspected but ruled out.

Methods

Patients

The original admission charts of all consecutive in- and outpatients diagnosed with acute PE between January 1st 2001 and July 1st 2007 in an academic (LUMC, Leiden, the Netherlands) and affiliated teaching hospital (Medical Center Haaglanden, The Hague, the Netherlands)

were systematically reviewed using predefined criteria for the diagnosis of acute PE, i.e. intraluminal filling defects on pulmonary angiography or computed tomography pulmonary angiography (CTPA), high probability ventilation perfusion scintigraphy (V/Q-scan) or intermediate probability V/Q-scan in combination with objectively diagnosed deep vein thrombosis (DVT).^{14,19} All patients fulfilling these criteria were included in this analysis. Patients were initially treated with at least 5 days of either unfractionated heparin or weight based therapeutic doses of low molecular weight heparin, followed by vitamin K antagonists for a period of at least 6 months with a target international normalized ratio (INR) of 2.0 to 3.0.²⁰ In patients with severe acute PE presenting with hemodynamic instability, anticoagulant treatment was preceded by administration of thrombolytic drugs, thrombosuction or surgical embolectomy according to the judgment of the attending clinician. The control cohort consisted of patients in whom PE was clinically suspected but ruled out by either an unlikely probability (Wells rule ≤ 4 points) in combination with a normal high sensitive D-dimer test or a CT scan without signs of PE. These patients were recruited for participation in a previous outcome study between November 2002 and September 2004.²¹

Procedures

Detailed information regarding diagnostic management, cause, treatment and documented clinical course of the index PE were extracted from the medical charts of the included patients with and without PE. When a patient had died, the pathology report was scrutinized to establish the cause of death. In case autopsy was not performed, the likely cause of death was verified with the treating physician or general practitioner. All surviving patients were contacted by mail or phone and were asked to complete our data with the latest information regarding their medical history and clinical condition. Patients living abroad or for whom up-to-date contact specifications were not available were excluded. This study was approved by the Institutional Review Board of both participating hospitals and all patients provided informed consent.

Outcome

Unprovoked PE was defined as PE occurring in the absence of the following risk factors: active malignancy, immobility more than 3 days or recent long flight, recent surgery or fracture of extremity, pregnancy or peri-partum period and use of oral contraception or hormone replacement therapy.¹ All-cause mortality, symptomatic recurrent VTE, i.e. acute PE as well as deep vein thrombosis, CTEPH, arterial cardiovascular events or detection of a previously unknown malignancy were considered to be adverse events in the clinical course of acute PE. Only information on anticoagulant related fatal bleeding was available. Recurrent PE was defined as 1) a new filling defect revealed by pulmonary angiography or spiral CTPA or 2) a new high probability perfusion defect revealed by VQ-scan or 3) any new defects after earlier normalizing of the scan.^{5,7} Criteria for the diagnosis of CTEPH were mean pulmonary

artery pressures assessed by right heart catheterization exceeding 25 mmHg respectively and normal pulmonary capillary wedge pressure in combination with an abnormal perfusion scintigram and signs for CTEPH on pulmonary angiography.⁶ Arterial cardiovascular events were defined as clinically adjudicated acute myocardial infarction, stroke or transient ischemic attack, claudication, unstable angina, carotid endarterectomy, coronary artery bypass graft, peripheral arterial bypass or angioplasty.^{13,22} Apart from standard clinical work-up for expected acute PE, the included patients were not systematically screened for occult cancer in neither of the two participating hospitals. Thus, the patients in whom cancer was detected had developed symptomatic malignant disease or the cancer was an accidental finding during regular clinical care.

Statistical analysis

All patients were followed from the index event to the date of death or July 1st 2008, whichever came first. The Kaplan-Meier life table method was used to estimate the event free survival for all individual study endpoints and for the combined endpoint of adverse outcome in patients with unprovoked, provoked and without PE. For this latter analysis, the adverse event that occurred first was accounted for. The Log-Rank test was used for comparing the three study groups for statistical differences. A Cox proportional hazard model was used to calculate hazard ratios (HR) for adverse clinical events. HRs were adjusted for age, sex and in addition all further relevant patient demographics; recurrent VTE and CTEPH for initial treatment; malignancy for active smoking; cardiovascular events for active smoking, diabetes and use of anti-platelet, lipid-lowering or blood pressure-lowering medication; mortality for left sided heart failure, COPD and active malignancy; and overall adverse events for all above mentioned potential confounders. SPSS version 14.02 (SPSS Inc, Chicago, IL) was used for all analyses.

Results

Patients

The diagnosis of acute PE had been established in 877 patients between January 1st 2001 and July 1st 2007 in the two participating hospitals. Eleven patients were excluded because of geographical inaccessibility (1.3%), leaving 866 patients for analysis. In addition, 334 patients without PE were included. The final diagnosis in the 334 patients in whom acute PE was suspected but ruled out was infectious disease in 84 (25%), non infectious or malignancy associated pulmonary disease in 43 (13%), complications of an active malignancy in 47 (14%), musculoskeletal disease in 37 patients (11%), cardiovascular disease in 33 (9.9%), gastrointestinal disease in 17 (5.1%) and other/unknown in 73 patients (22%). General characteristics of the study patients are presented in Table 1: the patients without PE were

Table 1: Patient demographics.

	Unprovoked PE (n=308)	Provoked PE (n=558)	No PE (n=334)
Age at index event (years $\pm$ SD)	59 $\pm$ 17*¶	55 $\pm$ 18¶	48 $\pm$ 17
Male sex (n, %)	149 (48)¶	261 (47)¶	123 (37)
Initial treatment†			
Low molecular/unfractionated heparin (n, %)	285 (93)	523 (94)	NA
Thrombolysis (n, %)	14 (4.5)	24 (4.3)	NA
Surgery, VCF or both (n, %)	9 (2.9)	11 (2.0)	NA
COPD‡ (n, %)	26 (8.4)	57 (10)	33 (9.9)
Left sided heart failure‡ (n, %)	16 (5.2)	26 (4.7)	11 (3.3)
Active malignancy‡ (n, %)	0 (0)*¶	201 (36)¶	46 (14)
Diabetest (n, %)	18 (5.8)	27 (4.8)	17 (5.1)
Active smoking‡ (n, %)	102 (33)	172 (31)	110 (33)
Anti-platelet/lipid-lowering/blood pressure-lowering medication‡ (n, %)	151 (49)	240 (43)	147 (44)

PE=Pulmonary embolism, SD=standard deviation, n=number, VCF=vena cava filter; COPD=chronic obstructive pulmonary disease; NA=not applicable; †at index event; ‡at hospital discharge after index event; *p<0.05 vs. provoked PE; ¶p<0.05 vs. no PE. Continuous parameters were compared using ANOVA with Bonferroni post hoc testing; bivariate variables were compared by the Chi-Square test.

significantly younger than the patients with provoked and unprovoked PE (48 $\pm$ 17 vs. 55 $\pm$ 18 and 59 $\pm$ 17 years respectively). In addition, the fraction of male patients was lowest in the patients without PE (37% vs. 47% and 48% respectively). Further, the presence of comorbidity and cardiovascular risk factors was similar between the three study groups, except for active malignancy, which was most frequently present in patients with provoked PE. Lastly, the patients with unprovoked and provoked PE received comparable anticoagulant treatment. The median follow-up period for the complete study population was 3.3 years.

Risk for recurrent VTE and CTEPH

Symptomatic recurrent VTE was diagnosed in 64 (21%) patients with unprovoked PE and in 54 (9.7%) patients with provoked PE (Table 2, Figure 1) during follow-up. The adjusted HR for recurrent VTE was increased for patients with unprovoked versus provoked PE (2.1, 95% CI 1.3- 3.1) and versus patients without PE (10, 95% CI 4.9-28). Patients with provoked PE had higher risk on recurrences than the control patients as well (adjusted HR 6.0, 95% CI 2.8-13). Recurrent PE was fatal in 22 of the 118 patients initially diagnosed with PE (19%, 95% CI 12-27%), and in 1 of the 4 (25%, 95% CI 0.06-81%) VTE diagnoses in the control patients. Recurrences within the first 3 weeks after the index diagnosis were associated with significantly higher mortality (Odds Ratio 7.9, 95% CI 1.2-51). CTEPH was only diagnosed in four patients after unprovoked acute PE (cumulative incidence 1.5%), and not in the patients with provoked PE or without PE (Table 2). The four patients diagnosed with CTEPH were all in stable clinical condition at the end of the follow-up period.

Table 2: Event free survival and hazard ratios for patients with provoked and unprovoked acute PE.

Adverse event	Unprovoked PE			Provoked PE			No PE			HR† (95%CI)			HR† (95%CI)			HR† (95%CI)		
	N (%)	Event free survival§ (±SE)	N (%)	Event free survival§ (±SE)	N (%)	Event free survival§ (±SE)	N (%)	Event free survival§ (±SE)	N (%)	HR† (95%CI) unprovoked vs provoked PE	HR† (95%CI) unprovoked vs no PE	HR† (95%CI) provoked vs no PE	HR† (95%CI) unprovoked vs no PE	HR† (95%CI) unprovoked vs no PE	HR† (95%CI) provoked vs no PE	HR† (95%CI) unprovoked vs no PE	HR† (95%CI) unprovoked vs no PE	HR† (95%CI) provoked vs no PE
Recurrent VTE	64 (21)	0.75±0.029	54 (9.7)	0.84±0.024	8 (2.4)	0.96±0.015	8 (2.4)	0.96±0.015	8 (2.4)	2.1 (1.3-3.1)			10 (4.9-28)			6.0 (2.8-13)		
CTEPH	4 (1.3)	0.99±0.007	0 (0)	*	0 (0)	*	0 (0)	*	0 (0)	*			*			*		*
Malignancy	23 (7.5)	0.91±0.017	8 (1.4)	0.98±0.007	8 (2.4)	0.97±0.010	8 (2.4)	0.97±0.010	8 (2.4)	4.4 (2.0-10)			2.5 (1.1-2.7)			0.78 (0.26-1.4)		
Cardiovascular event	41 (13)	0.82±0.029	30 (5.4)	0.90±0.024	26 (7.8)	0.91±0.018	26 (7.8)	0.91±0.018	26 (7.8)	2.6 (1.5-3.8)			2.4 (1.2-3.7)			1.1 (0.72-1.5)		
Mortality	67 (22)	0.72±0.038	193 (35)	0.60±0.026	29 (8.7)	0.87±0.037	29 (8.7)	0.87±0.037	29 (8.7)	0.59 (0.43-0.82)			1.4 (1.1-1.8)			3.0 (2.0-4.5)		
Adverse outcome‡	155 (50)	0.42±0.038	252 (45)	0.47±0.028	58 (17)	0.76±0.041	58 (17)	0.76±0.041	58 (17)	0.98 (0.82-1.1)			2.6 (1.9-3.6)			2.9 (2.1-3.8)		

PE=pulmonary embolism, VTE=venous thromboembolism, CTEPH=chronic thromboembolic pulmonary hypertension, SE=standard error, n=number, CI=confidence interval.

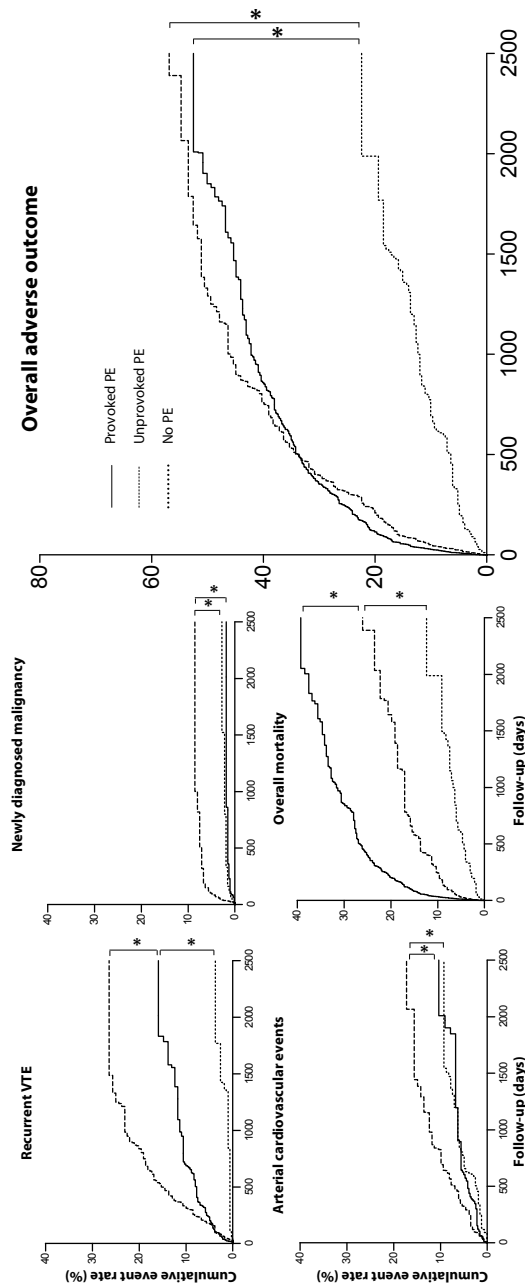
§Estimated by Kaplan-Meier life table method after 2500 days; †Hazard Ratio's were adjusted for age, sex and in addition all further relevant patient demographics; recurrent

VTE and CTEPH for initial treatment, malignancy for active smoking, cardiovascular events for active smoking, diabetes and use of anti-platelet/lipid-lowering/blood pressure-

lowering medication, mortality for left sided heart failure, COPD and active malignancy, and overall adverse events for all above mentioned; *could not be calculated due to

0-value, ‡ combined endpoint.

Figure 1: Cumulative adverse event rates by Kaplan-Meier life table method for recurrent VTE, diagnosis of malignancy, arterial cardiovascular events, mortality and the occurrence of any adverse event in patients with provoked, unprovoked or no PE.



VTE=venous thromboembolism, PE=pulmonary embolism, * =p<0.05.

Risk for malignancy and arterial cardiovascular events

The risk for cancer was higher for the patients after unprovoked PE than for the patients with provoked (adjusted HR 4.4, 95% CI 2.0-10) and without PE (adjusted HR 2.5, 95% CI 1.1-2.7; Table 2, Figure 1). There was no difference in the rate of newly diagnosed malignancies between patients with provoked and without PE (adjusted HR 0.78, 95% CI 0.26-1.4). In 27 of the 31 patients with PE (87%, 95% CI 70-96%) who were diagnosed with cancer, this malignancy was detected within the first year after the index PE. Patients with unprovoked PE suffered severe cardiovascular disease two to three times more often than the patients from the other two study cohorts (adjusted HR 2.6, 95% CI 1.5-3.8 and 2.4, 1.2-3.7 respectively; Table 2, Figure 1). Patients with PE, who suffered arterial cardiovascular events or were diagnosed with cancer had case fatality rates of 14% (95% CI 7.0-24) and 19% (95% CI 7.5-37) respectively.

Risk for mortality

In total, 259 (30%) patients with PE died, mainly as a result of a malignancy (110 patients,

Table 3: Yearly overall event free survival for patients with unprovoked, provoked and without acute PE.

Follow-up period	Unprovoked PE (n=308)		Provoked PE (n=558)		Overall PE (n=866)	No PE (n=334)	
	NLFA	Event free survival\$ (±SE)	NLFA	Event free survival\$ (±SE)	Event free survival\$ (±SE)	NLFA	Event free survival\$ (±SE)
1 year	212	0.70±0.026	379	0.68±0.020	0.69±0.016	298	0.94±0.014
2 years	151	0.59±0.028	280	0.61±0.021	0.60±0.017	275	0.90±0.017
3 years	108	0.52±0.030	195	0.56±0.022	0.54±0.018	265	0.87±0.019
4 years	78	0.48±0.031	122	0.54±0.023	0.51±0.018	203	0.84±0.021
5 years	52	0.45±0.032	76	0.50±0.025	0.48±0.019	78	0.80±0.024
6 years	31	0.44±0.034	37	0.48±0.027	0.46±0.021	26	0.77±0.038
7 years	14	0.42±0.038	16	0.47±0.028	0.45±0.024	9	0.76±0.041

PE=pulmonary embolism, SE=standard error, n=number, NLFA=number left for analysis. \$Estimated by Kaplan-Meier life table method.

13%). Furthermore, 67 (7.7%) patients died of (recurrent) PE, 6 (0.69%) because of severe bleeding from anticoagulant therapy, 30 (3.5%) of cardiovascular disease, 11 (1.3%) of non-malignant pulmonary disease and 35 (4.2%) of other causes. Twenty-nine patients without PE died during the study period (8.7%): 1 of acute PE (0.30%), 1 of myocardial infarction (0.30%),

4 of non-ischemic heart diseases (1.2%), 3 of non-malignant pulmonary disease (1.2%), 12 of malignancies (3.6%) and 8 by other causes (2.4%). Risk for overall mortality in patients after unprovoked PE was lower than in patients after provoked PE (adjusted HR 0.59, 95% CI 0.43-0.82; Table 2, Figure 1). Intriguingly, the patients with unprovoked PE who by definition did not suffer from active malignancies at time of the index event, were at higher risk for dying than the non-cancer patients with provoked PE (adjusted HR 1.8, 95% CI 1.3-2.5). Patients with unprovoked as well as with provoked PE had higher risks for death than the control patients (adjusted HR 1.4, 95% CI 1.1-1.8 and 2.9, 95% CI 2.1-3.8 respectively).

Risk for overall adverse outcome

The prognostic differences between patients with unprovoked and provoked PE disappeared after combining all adverse events to one pooled endpoint of adverse outcome (adjusted HR 0.98, 95% CI 0.82-1.1; Table 2, Figure 1). Nonetheless, both groups had significantly worse prognosis than the control patients without PE (adjusted HR 2.6, 95% CI 1.9-3.6 and 2.9, 2.1-3.8 respectively). Importantly, the fraction of PE patients without any event after 1 year was only 69% and decreased to 60% after 2 years and 50% after 4 years (Table 3, Figure 1). These numbers were applicable to both patients with unprovoked as well as with provoked PE. The patients without PE had significant higher event free survival with 84% of the patients surviving without any of the adverse events after a follow-up period of 4 years.

Discussion

We aimed to evaluate the long term overall prognosis of patients after acute PE. Two important conclusions can be drawn from this analysis. First, we have demonstrated that after 1 year of follow-up, only 70% of the patients are free of adverse outcome and notably, after a period of 4 years, half of the patients developed one or more serious clinical complications. A control cohort consisting of patients in whom PE was suspected but ruled out had significantly higher event free survival. Second, although risks for the occurrence of specific adverse events differed significantly between patients with unprovoked and provoked PE, the risk of the combined endpoint of adverse outcome was similar between the two patient groups, both higher than for the control patients without PE.

The importance of our findings is underlined by the complication specific prognosis, which is poor for all adverse events studied in this analysis. First, the index PE itself had a mortality rate of 5.2%, which compares well to the existing literature.¹⁻⁴ Second, recurrent VTE was diagnosed in 118 patients. Previous studies have shown that thrombotic recurrences are associated with increased mortality.^{5,7} The case fatality rate in our study was 19% in the complete study period and even 60% within the first 3 weeks after the index diagnosis. This 3 weeks mortality rate is comparable to the range of 51-79% that was reported in earlier stud-

ies.^{5,7,23} In addition, according to the latest ACCP guidelines, recurrent VTE should be treated with long term anticoagulant therapy (Grade 1A), which is associated with an increased risk of often severe bleeding complications.²⁰ Third, cancer diagnosed at the same time as or shortly after the diagnosis of VTE is a bad prognostic sign, as this is associated with more advanced stages of cancer and a poor prognosis.¹⁸ Sørensen *et al* have shown that patients in whom cancer was diagnosed within 1 year after the diagnosis of VTE had an increased risk of distant metastasis at the time of diagnosis and a relatively low rate of survival compared to patients with cancer without a history of VTE.¹⁸ In our population, cancer diagnosed after the index PE proved to be fatal in 19% of the cases within the follow-up period. The association between unprovoked PE and the subsequent development of clinically overt cancer is most likely explained by the fact that these cancers are already present at the time of, and may even be causally related to the PE, although not yet detected.¹⁷ Fourth, although the exact mechanism underlying the association between arterial cardiovascular events and VTE is unknown, evidence exists that both diseases are closely linked.^{10,13} The observation that control patients without PE and patients with provoked PE have the same risk for arterial cardiovascular events, which is significantly lower than for patients after unprovoked PE, supports the hypothesis that a shared but yet unidentified mechanism causes events in both the venous and the arterial system.¹³

Arterial events such as myocardial infarction or stroke have great implications for the patients' health and lead to high morbidity and mortality rates and decreased quality of life.¹⁵ Lastly, four patients were diagnosed with CTEPH (cumulative incidence in patients with unprovoked PE 1.5%). This percentage is relatively low compared to some recent studies reporting incidences of 3.8% and even 8.8% in patients after PE.^{12,16} This discrepancy might very well be explained by different selection criteria than in previous studies, or by underdiagnosis of CTEPH in our cohort, although the included patients with PE were systematically screened for the presence of pulmonary hypertension.¹⁴ Even though none of our four patients with CTEPH died during the study period, it has previously been shown in larger cohorts that the prognosis of patients with CTEPH is rather poor, unless a successful pulmonary endarterectomy is achievable.⁶

Thus, we have combined four very serious complications of PE as well as all-cause mortality in this analysis. The pooled endpoint of adverse outcome was reached by 50% or more of the patients with PE after 4 years of follow-up, which is significantly more than for the control patients. Remarkably, this overall prognosis is comparable for patients with unprovoked and patients with provoked PE. This latter observation was mainly driven by the malignancy related high mortality rates in the patients with provoked PE. Further analysis showed that patients with unprovoked PE have in fact the highest risk on non-malignancy related mortality and all the other included endpoints. These findings emphasize that acute PE is an important clinical problem with poor prognosis for short and long term survival and the occurrence of serious thrombotic or non-thrombotic adverse events.

Many risk stratification and screening strategies including intensified or prolonged anti-thrombotic therapy regimes to identify and treat patients with high risk for PE-related mortality, recurrent VTE or detection of cancer have been proposed, but all remain insufficient or controversial.^{20,24-27} An earlier study concluded that treatment of heparin and anticoagulants is not enough for all PE patients.²⁸ Our results, although almost 30 years later, confirm this conclusion and once more emphasize the poor overall prognosis of patients with acute PE. In current clinical practice and despite the increased risk for serious clinical complications, patients with a first episode of acute PE stop their anticoagulant therapy usually after 3-6 months.²⁰ From then on, they are usually no longer subject to clinical supervision by a medical specialist. Importantly, by lack of scientific based evidence and proven cost-efficacy, standard screening for classic cardiovascular risk factors, hidden cancer or CTEPH is at this moment not part of routine clinical work-up of patients with PE. Our results underline the importance of close clinical surveillance in the first months after PE, especially in those patients with unprovoked PE, to evaluate the basic risks for future adverse events and in addition, treat patients accordingly. Therefore, future outcome studies should focus on 1) better individual assessment of the risk for recurrent venous thromboembolism and CTEPH to enable the physician to identify those patients who could benefit from prolonged anticoagulant therapy or specific screening for pulmonary hypertension; 2) effectiveness of cardiovascular risk factor evaluation and proper treatment measures to prevent arterial cardiovascular events; and 3) effect of specific screening programs for underlying malignancies, to achieve very early identification of hidden malignancies thereby potentially improving the patients' prognosis.

Our study has strengths and limitations. Our findings are likely to be generalizable to most patients with PE since we have included all consecutive patients diagnosed with this disease in an academic and non-academic teaching hospital independently of their clinical condition or comorbidity. Even though our study endpoints are severe clinical events that are likely to be recorded in detail, we have additionally verified the accuracy and completeness of the data from the medical charts with the surviving patients. Only 11 patients with PE (1.3%) who could not be reached due to geographical inaccessibility, were excluded. Furthermore, our findings are in accordance with the extensive literature on this subject, although we are the first to combine all adverse events into one pooled endpoint. We acknowledge that we were not able to report on all bleeding events, which are important complications in the clinical course of acute PE. Nonetheless, the adverse effect of bleeding is often transient and the period at risk is limited to the first 6 months after diagnosis in the majority of patients. Moreover, the most severe bleedings that resulted in mortality could in fact be accounted for.

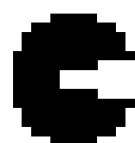
We conclude that acute PE remains a very serious clinical condition with high mortality and high risk on PE associated severe complications. Remarkably, there was no difference in the pooled risk for adverse outcome of patients with unprovoked and provoked PE, although the risk on all separate endpoints except for overall mortality was markedly higher for the patients with unprovoked PE. Physicians should be well aware of the fact that in 4 years time,

half of the patients diagnosed with acute PE has died or is diagnosed with cancer, recurrent VTE, CTEPH or arterial cardiovascular disease. The challenge of future trials remains to enable the treating physician to use accurate prediction tools for adjusting treatment regimes and clinical surveillance to the personalized prognosis of the individual patient.

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Chapter 9

Comparison of risk profile and clinical outcome of patients after acute pulmonary embolism in university and non-university hospitals

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Abstract

Background

Current knowledge on diagnostic management and treatment of patients with acute pulmonary embolism (PE) is partly derived from outcome studies including patients from university hospitals alone. It is debatable whether these data are applicable to patients in non-university hospitals. The aim of this study was to compare baseline characteristics and clinical outcome of patients with PE treated in university hospitals versus patients treated in non-university hospitals.

Methods

Post-hoc analysis on data derived from Christopher study, a prospective multicenter management study.

Results

A total of 399 (59%) patients with PE presented to a university hospital and 275 (41%) to a non-university teaching hospital. The characteristics of patients from the university and non-university hospitals were different with respect to female ratio (46% vs. 56%, Odds Ratio [OR] 0.65, 95% confidence interval [CI] 0.47-0.88), outpatient ratio (73% vs. 84%, OR 0.53, 95%CI 0.36-0.79), presence of immobilization (37% vs. 23%, OR 2.0, 95%CI 1.4-2.8) and the presence of active malignancy (19% vs. 12%, OR 1.6, 95%CI 1.1-2.5). Risk on venous thromboembolic recurrence (3.3% vs. 2.6% OR 1.3, 95%CI 0.50-3.3) and mortality (9.0% vs 6.9% OR 1.3, 95%CI 0.75-2.4) were higher for patients in university than in non-university hospitals. Bleedings occurred twice more often in patients from university hospitals (4.3% vs 2.2% OR 2.0, 95%CI 0.77-5.1).

Conclusion

Physicians should be aware of differences in patient characteristics and outcome between university and non-university hospitals when interpreting results from large clinical trials and applying these to their everyday medical practice.

Introduction

Current knowledge regarding diagnostic management and treatment of patients with acute pulmonary embolism (PE) is mainly derived from large outcome studies including patients from university and non-university hospitals or university hospitals alone.¹⁻⁴ A common perception of university hospitals is that they treat more severely ill patients than non-university hospitals.⁵ Therefore, it must be debated whether data on the diagnostic management and treatment of patients with acute PE derived from university hospitals are relevant and applicable to everyday patient care in non-university hospitals, and vice-versa. We hypothesized that patients from university hospitals would be a population with more comorbidity than in non-university hospitals. Accordingly, we investigated differences between baseline risk factors predicting adverse clinical outcome (e.g. higher age, immobilization, cancer and cardiopulmonary comorbidity) in patients with established acute PE in university and non-university hospitals. In addition, the clinical outcome of these patient groups was compared.

Methods

We performed a post-hoc analysis on data obtained from a large multicenter prospective cohort follow-up study.² In this study, executed from November 2002 until September 2004, consecutive hemodynamic stable patients with computed tomography proven acute PE were followed for a period of 3 months to document the occurrence of recurrent symptomatic venous thromboembolic events. All patients were treated according to the previously followed guidelines.⁶ Furthermore, all patients were treated as inpatients and hemodynamically instable patients were excluded from the study. Therefore, no patient was treated with fibrinolytic drugs or vena cava filter. Secondary endpoints were all-cause mortality and bleeding complications. Follow-up consisted of a hospital visit or telephone interview with the patient after 3 months. Patients were instructed to contact the study center immediately in case of complaints suggestive of PE, deep vein thrombosis (DVT) or bleeding. In case of clinically suspected DVT, PE or bleeding objective tests were performed to confirm the diagnosis. Symptomatic recurrent VTE was considered to have occurred if recurrent PE or DVT were documented objectively, or if there was a 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 venography. 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. Hemorrhagic complications were the composite of major bleeding and clinically relevant bleeding. 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 or pericardial, or intramuscular with compartment syndrome, and/or bleeding causing a fall in hemoglobin level of ≥ 20 g/L (1.24 mmol/L), or leading to transfusion of ≥ 2 U of whole blood or red cells. Bleeding was considered clinically relevant when the episode did not qualify as a major bleeding but included one of the following: epistaxis requiring intervention, formation of a large hematoma visible on the skin or spontaneous macroscopic hematuria.⁷ All patients were treated with therapeutic doses of unfractionated or low molecular weight heparin followed by vitamin K antagonist for a period of at least 6 months. Patients diagnosed as outpatients as well as inpatients were eligible. The study was executed in 12 hospitals in the Netherlands, of which five were university hospitals. Non-university hospitals differed in size from 330 to 1386 patient beds and university hospitals from 715 to 1100 patient beds. All participating centers had comparable services including emergency units, intensive care units and 24-hour access to a CT scan. A total of 673 patients with acute PE completed 3 months follow-up with one patient lost to follow-up (0.15%).

Results

The baseline characteristics of the included patients are shown in Table 1. A total of 399 (59%) patients attended a university hospital and 275 (41%) a non-university teaching hospital. The characteristics of patients from the university and non-university hospitals were different with respect to female ratio (46% vs. 56%, Odds Ratio [OR] 0.65, 95% confidence interval [CI] 0.47-0.88), outpatient ratio (73% vs. 84%, OR 0.53, 95% CI 0.36-0.79), presence of immobilization (37% vs. 23%, OR 2.0, 95% CI 1.4-2.8) and the presence of active malignancy (19% vs. 12%, OR 1.6, 95% CI 1.1-2.5). The rates of adverse clinical events are presented in Table 2. Overall 55 patients died; of these, 11 patients died because of fatal recurrent PE and two died because of fatal hemorrhage. The cause of death in the remaining patients was mainly malignancy or cardiovascular disease. The time of death ranged from 1 to 90 days, with a median of 22 days. Risk of venous thromboembolic recurrence (3.3% vs. 2.6% OR 1.3, 95% CI 0.50-3.3) and mortality (9.0% vs. 6.9% OR 1.3, 95% CI 0.75-2.4) was higher for patients in university than in non-university hospitals. Furthermore, bleeding occurred in 23 patients, and was fatal in two of these. Both fatal bleeding events occurred out of hospital, while seven of the eight non-fatal major bleedings occurred in the hospital and 7 of 13 clinically relevant

Table 1. Baseline characteristics

Characteristics	University hospital (n=399)	Non-university teaching hospital (n=275)	OR
Age (years)	56± 18	59±18	NS
Female gender	183 (46)	156 (56)	0.65 (0.47-0.88)
Duration of complaints (days)	5.9±11	6.4±10	NS
Outpatients	294 (73)	231 (84)	0.53 (0.36-0.79)
Risk factors for VTE			
Paralysis	23 (5.8)	15 (5.5)	NS
Immobilization	151 (37)	65 (23)	2.0 (1.4-2.8)
Recent surgery	33 (8.3)	34 (12)	NS
History of VTE	69 (17)	48 (17)	NS
Heart failure	26 (6.5)	14 (5.1)	NS
COPD	34 (8.5)	28 (10)	NS
Active malignancy	89 (19)	41 (12)	1.6 (1.1-2.5)
Clinical findings			
Hemoptysis	37 (9.3)	19 (6.9)	NS
Tachycardia	143 (35)	104 (37)	NS

Categorical data are displayed as No (%). Numerical data are displayed as means ± standard deviation. VTE= venous thromboembolism, COPD = chronic obstructive pulmonary disease, OR = Odds Ratio

Table 2. Adverse clinical outcome in a three months follow-up period

	University hospital (n=399)	Non-university teaching hospital (n=274)
Total recurrences	13 (3.3)	7 (2.6)
Fatal recurrent PE	6 (1.5)	5 (1.8)
Non-fatal recurrent PE	2 (0.5)	1 (0.4)
Non-fatal recurrent DVT	5 (1.3)	1 (0.4)
All bleeding complications	17 (4.3)	6 (2.2)
Fatal bleeding	1 (0.3)	1 (0.4)
Major bleeding	7 (1.8)	1 (0.4)
Clinically relevant bleeding	9 (2.3)	4 (1.5)
All cause mortality	36 (9.0)	19 (6.9)

Data are displayed as No (%).

PE = pulmonary embolism, DVT = deep vein thrombosis

bleedings occurred in the hospital. Hemorrhagic complications occurred twice more often in patients from university hospitals (4.3% vs. 2.2% OR 2.0, 95% CI 0.77-5.1). These bleeding complications were strongly associated with the baseline presence of active malignancy (OR 3.4, 95% CI 1.5-7.9).

Discussion

Our data demonstrate that patients with acute PE presenting to university hospitals are different from patients presenting to non-university hospitals regarding gender, proportion of outpatients and malignancy. Especially the latter two are established risk factors for adverse events and mortality in the first 3 months following acute PE.⁸ To our best knowledge, there were no different characteristics between the hospitals other than being a university hospital, which could have biased these study observations. According to our hypothesis we identified differences in baseline characteristics and observed a higher rate of adverse clinical events in patients from university hospitals than in patients from non-university hospitals. Of note, we found a significant association between bleeding and malignant comorbidity. This association has been described previously and thus underlines the validity of our study results.⁹ Of note, correlations between additional patient demographics were not studied. A limitation of our study is that although we have performed a post hoc analysis of a reasonable large patient cohort, the study might have included too few patients to detect a significant difference between the patient cohorts.

In summary, we have identified important differences in demographics, comorbidity and clinical outcome between patients diagnosed with PE in university and in non-university hospitals. Physicians should be aware of these differences when interpreting results from large clinical trials and applying these to their everyday medical practice.

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Chapter 10

General discussion and summary

The aims of this thesis were to investigate the efficacy and safety of outpatient treatment of patients with pulmonary embolism (PE) and to identify the best method for selection of PE patients for outpatient treatment. Therefore, we performed the Hestia study and compared the selection of patients with the Hestia criteria to other methods for risk stratification, for example the simplified Pulmonary Embolism Severity Index and the method described in the European Society of Cardiology guidelines. **Chapter 1** provides a general introduction to the history of treatment of patients with PE and an overview of risk stratification methods.

A recent systematic review on outpatient treatment in PE patients concluded that outpatient treatment could not be implemented in clinical practice yet, because only a few small observational studies could be included. High quality evidence on the safety of outpatient PE treatment was lacking.¹ In recent years large studies have been published on the subject, including the Hestia study.²⁻⁴ The results of the large, multicenter Hestia study are described in **chapter 2**. This study was performed in 12 Dutch hospitals from 2008 to 2010. Patients with acute and symptomatic PE were screened for eligibility for outpatient treatment with the Hestia criteria: 11 clinical criteria based on signs and symptoms. We concluded that outpatient treatment following the Hestia criteria is safe, because patients had a low incidence of recurrent venous thromboembolism (VTE) of 2.0% (95% confidence interval (CI) 0.8-4.3), a low incidence of major bleeding of 0.7% (95% CI 0.08-2.4) and a low incidence of all-cause mortality of 1.0% (95% CI 0.2-2.9). None of the patients treated at home died of fatal PE. These favorable clinical outcomes in patients treated as outpatients are contrasted by the more severe clinical outcomes in patients selected for hospital treatment by the Hestia criteria, as discussed in **chapter 3**. Patients treated in-hospital had marked higher incidences of recurrent VTE of 3.9%, major bleeding of 4.8% and all-cause mortality of 9.6%. Five patients treated as inpatients died of PE-related causes in contrast to none of the patients treated at home. Therefore, we concluded that the Hestia criteria can be used to discriminate PE patients with low risk for adverse clinical outcome from patients with high risk for adverse clinical outcome. Low-risk patients with PE can be safely treated at home.

Because a few large studies investigating outpatient treatment of patients with PE had been published recently, we performed a meta-analysis on this subject (**chapter 4**). In this meta-analysis we pooled incidences of recurrent VTE, major bleeding and all-cause mortality of three groups of patients: patients treated as outpatients, patients admitted initially to the hospital, but discharged early within 3 days and patients treated in the hospital for 3 days or more. Patients treated as outpatients had equally low pooled incidences of recurrent VTE 1.7%, major bleeding 1.0% and all-cause mortality 1.9% as patients discharged early or treated as inpatients. We concluded that home treatment or early discharge of selected low-risk patients with acute PE is as safe as inpatient treatment.

Besides the Hestia criteria, other methods for risk stratification in outpatient PE treatment have been described: methods based on clinical signs and symptoms^{5,6}, laboratory values⁷ and imaging modalities.⁸ In **chapter 5** the performance of the Hestia criteria was compared to the performance of the simplified Pulmonary Embolism Severity Index (sPESI) for prediction of 30-day mortality.⁹ Both methods had a good performance in selecting PE patients with low risk for 30-day mortality; the negative predictive value for the Hestia criteria was 99% and for the sPESI 100%. The advantages of the use of the Hestia criteria are that these criteria can be implemented in clinical practice without modifications, in contrast to the sPESI. With the Hestia criteria more than 50% of PE patients can be selected for outpatient treatment, which is high compared to the sPESI. Although both the Hestia criteria and the sPESI had good test characteristics in predicting 30-day mortality, according to the Hestia criteria 20-30% of patients with cancer, cardiopulmonary co-morbidity or elderly patients can be safely treated at home. These patients would have been excluded from outpatient treatment by the sPESI.

In **chapter 6** we compared the performance of the Hestia criteria to the selection method advised by the European Society of Cardiology (ESC). The ESC method combined hemodynamic status (blood pressure and heart frequency) with right ventricular (RV) function to assess whether patients were eligible for outpatient treatment. Adverse events occurred in 22 patients (4.5%) treated in the hospital versus none in the patients treated at home ($p < 0.001$). Sensitivity and negative predictive value for adverse outcome were 100% for the Hestia criteria and 83% and 98% for the ESC criteria, respectively. Of the patients treated at home according to the Hestia criteria, 34% could not have been treated at home according to the ESC criteria because they had RV dysfunction. When this group of patients with RV dysfunction was treated at home in the Hestia study no adverse events happened. In conclusion clinical criteria, like the Hestia criteria, could be helpful in selecting patients, including those with RV dysfunction, who have low risk for adverse clinical outcome and could be candidates for outpatient treatment.

Elevated NT-proBNP is a known risk factor for adverse outcome after PE.¹⁰ One study previously selected patients with a low NT-proBNP and treated them at home safely.⁷ We hypothesized that repeated measurements of NT-proBNP could potentially select a larger proportion of patients with PE for early discharge from the hospital. The results are presented in **chapter 7**. We demonstrated that repeated NT-proBNP testing within 48 hours after presentation with PE can identify 20% extra patients with PE as low risk than when using a single measurement at day 1.

Patients with PE without a provoking risk factor have a higher risk for various types of adverse clinical outcome, including non-malignancy related mortality, newly diagnosed malignancies and recurrent VTE, than patients with provoked PE. Importantly, **chapter 8** demonstrated that the fraction of all patients without clinical adverse events 1 year after PE was only 70% and decreased to fewer than 60% after 2 years and fewer than 50% after 4 years, whereas this latter was 84% for the control patients without PE.

In **chapter 9** an additional risk factor for adverse outcome after PE is described. Patients admitted to university hospitals had higher risks on venous thromboembolic recurrence (3.3% vs. 2.6%; odds ratio (OR) 1.3, 95% CI 0.50-3.3) and mortality (9.0% vs. 6.9% OR 1.3, 95% CI 0.75-2.4) than patients in non-university hospitals. Furthermore, hemorrhagic complications occurred twice more often in patients from university hospitals (4.3% vs. 2.2% OR 2.0, 95% CI 0.77-5.1). These bleeding complications were strongly associated with the baseline presence of active malignancy (OR 3.4, 95% CI 1.5-7.9). Our data demonstrate that patients with acute PE presenting to university hospitals are different from patients presenting to non-university hospitals regarding baseline characteristics (gender, proportion of outpatients and malignancy) and clinical outcome. Physicians should be aware of these differences when interpreting results from large clinical trials and applying these to their everyday medical practice.

Future perspectives

Evidence on the safety of outpatient treatment of patients with PE is accumulating. The recent American College of Chest Physicians guidelines give a grade 2B recommendation on the safety of early discharge of selected PE patients.¹¹ Before outpatient treatment of patients with PE will be graded with an 1A recommendation, more high quality evidence is needed.

As suggested in this thesis, risk stratification of normotensive patients with PE can be based on clinical criteria, biomarkers or measurements of RV dysfunction. Current evidence from large multicenter studies, including the Hestia study, suggests that patients with a low risk for adverse events can be treated on outpatient basis. However, it is yet to be determined which method of risk stratification most safely selects patients for outpatient treatment. Therefore, trials have to be performed in which different selection methods for outpatient treatment will be compared, preferably in a randomized way.

Another important change in treatment of patients with PE will be the introduction of the new oral anticoagulants (NOACs), for example the factor Xa and thrombin inhibitors. Clinical trials on the efficacy and safety of these drugs in treatment of PE patients are ongoing. Introduction of NOACs will potentially simplify the outpatient treatment of patients with PE, because these medications do not need frequent laboratory monitoring. However, before NOACs can be used in the outpatient treatment of patients with PE, adequate care has to be guaranteed, especially in the first weeks. In the future, prospective trials have to be performed to prove the safety of using these drugs in outpatient PE treatment.

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Chapter 11

Nederlandse samenvatting

Nederlandse samenvatting

De doelen van dit proefschrift waren om de veiligheid en effectiviteit van thuisbehandeling van patiënten met longembolie te onderzoeken en de beste methode te identificeren waarmee patiënten voor thuisbehandeling geselecteerd kunnen worden. Om dit te bereiken hebben we de Hestia Studie uitgevoerd en de criteria die gebruikt zijn in de Hestia studie (Hestia criteria) vergeleken met andere methoden voor risicoselectie die beschikbaar zijn, bijvoorbeeld de gesimplificeerde Pulmonary Embolism Severity Index (sPESI) en de methode zoals beschreven door de European Society of Cardiology. **Hoofdstuk 1** geeft de geschiedenis weer van de behandeling van patiënten met longembolie en dient als een algemene introductie. Tevens wordt een overzicht gegeven van de beschikbare methoden voor risicostratificatie.

In een recent verschenen overzichtsartikel over thuisbehandeling van patiënten met longembolie werd geconcludeerd dat thuisbehandeling nog niet veilig genoeg was voor implementatie in de klinische praktijk, omdat slechts kleine observationele studies beschikbaar waren en kwalitatief hoogstaand bewijs ontbrak. In de afgelopen jaren zijn enkele grote studies verschenen die de thuisbehandeling van longembolie onderzochten, waaronder de Hestia studie. De resultaten van de Hestia studie zijn beschreven in **hoofdstuk 2**. Deze grote multicenter studie is van 2008 tot 2010 uitgevoerd in 12 Nederlandse ziekenhuizen. Patiënten met acute en symptomatische longembolie zijn gescreend met de Hestia criteria (11 klinische criteria) om te bepalen of ze in aanmerking kwamen voor thuisbehandeling. Onze conclusie was dat patiënten met longembolie veilig thuis behandeld konden worden als ze geselecteerd waren met de Hestia criteria, omdat de patiënten uit de Hestia studie een laag percentage recidief veneuze trombo-embolieën (VTE) van 2.0% (95% CI 0.8-4.3), een laag percentage majeure bloedingen van 0.7% (95% CI 0.08-2.4) en een lage mortaliteit van 1.0% (95% CI 0.2-2.9) hadden. Geen van de patiënten die thuis zijn behandeld overleden aan fatale longembolie. Deze gunstige klinische uitkomsten van thuisbehandelde patiënten staan in contrast met de ernstiger klinische uitkomsten van patiënten die geselecteerd waren voor behandeling in het ziekenhuis, zoals besproken wordt in **hoofdstuk 3**. Patiënten die geselecteerd waren voor behandeling in het ziekenhuis hadden hogere incidenties van recidief VTE van 3.9%, majeure bloeding van 4.8% en mortaliteit van 9.6%. Vijf patiënten die behandeld waren in het ziekenhuis zijn overleden aan longembolie gerelateerde oorzaken in tegenstelling tot geen van de patiënten die thuis behandeld zijn. Hierdoor hebben we geconcludeerd dat de Hestia criteria een goed onderscheid kunnen maken tussen patiënten met een laag en hoog risico op negatieve klinische uitkomsten. De longemboliepatiënten met een laag risico op negatieve klinische uitkomsten kunnen thuis behandeld worden.

Omdat recent een aantal grote studies naar thuisbehandeling van patiënten met longembolie is verschenen, hebben we een meta-analyse uitgevoerd (**hoofdstuk 4**). In deze

meta-analyse hebben we gewogen incidenties van recidief VTE, majeure bloeding en mortaliteit bepaald in drie groepen: patiënten die volledig thuis behandeld waren, patiënten die initieel in het ziekenhuis behandeld waren, maar binnen drie dagen naar huis ontslagen zijn en patiënten die drie dagen of meer in het ziekenhuis behandeld waren. Patiënten die thuis behandeld waren, hadden vergelijkbaar lage incidenties van recidief VTE 1.7%, majeure bloeding 1.0% en mortaliteit 1.9% als patiënten die vervroegd ontslagen waren en patiënten die volledig in het ziekenhuis behandeld waren. Onze conclusie luidde dat thuisbehandeling of vervroegd ontslag uit het ziekenhuis van geselecteerde laagrisico patiënten met longembolie tenminste even veilig is als behandeling van patiënten in het ziekenhuis.

In de Hestia studie hebben we 11 klinische criteria, de zogenaamde Hestia criteria, gebruikt om patiënten met longembolie te selecteren voor thuisbehandeling. Er zijn ook andere methoden voor risicostratificatie beschreven, zoals methoden die gebruik maken van klinische symptomen en bevindingen, laboratoriumbepalingen of beeldvormende technieken. In **hoofdstuk 5** hebben we de Hestia criteria vergeleken met de gesimplificeerde PESI wat betreft het voorspellend vermogen voor mortaliteit binnen 30 dagen. Beide methoden voor risicostratificatie presteerden goed in het selecteren van laagrisico patiënten; de negatief voorspellende waarde was 99% voor de Hestia criteria en 100% voor de sPESI. Echter, bij het gebruik van de Hestia criteria kwam een kwart meer patiënten in aanmerking voor thuisbehandeling ten opzichte van de sPESI. Een ander voordeel van het gebruik van de Hestia criteria was dat deze criteria in de klinische praktijk kunnen worden geïmplementeerd zonder aanpassingen, in tegenstelling tot de sPESI.

In hoofdstuk 6 hebben we de prestatie van de Hestia criteria wat betreft voorspellen van negatieve klinische uitkomsten vergeleken met de prestatie van de selectiemethode die geadviseerd wordt door de European Society of Cardiology (ESC). De ESC methode combineert hemodynamische status (bloeddruk en polsfrequentie) met de functie van de rechterventrikel van het hart om te bepalen of een patiënt met longembolie geschikt is voor thuisbehandeling. Tweeëntwintig patiënten (4.5%) die volgens de Hestia criteria in het ziekenhuis zijn behandeld hadden negatieve klinische uitkomsten in tegenstelling tot geen van de patiënten die geselecteerd waren voor thuisbehandeling ($p < 0.001$). Sensitiviteit en negatief voorspellende waarde voor negatieve klinische uitkomsten waren respectievelijk 100% voor de Hestia criteria en 83% en 98% voor de ESC criteria. Van de patiënten die thuis behandeld waren volgens de Hestia criteria, zou 34% niet thuis behandeld kunnen worden volgens de ESC criteria omdat ze rechterventrikeldisfunctie hadden. In de groep patiënten met rechterventrikeldisfunctie die volgens de Hestia criteria thuis zijn behandeld konden in de Hestia studie zijn geen negatieve klinische uitkomsten voorgekomen. Concluderend: klinische criteria als de Hestia criteria zouden gebruikt kunnen worden om patiënten, inclusief patiënten met rechterventrikeldisfunctie, met een laag risico op negatieve klinische uitkomsten te selecteren die in aanmerking komen voor thuisbehandeling.

Verhoogd NT-proBNP is een bekende risicofactor voor het optreden van negatieve klinische uitkomsten bij patiënten met longembolie. Een eerdere studie heeft bewezen dat geselecteerde patiënten met een laag NT-proBNP veilig thuis behandeld kunnen worden. Wij hebben onderzocht of een herhaalde meting van NT-proBNP een groter percentage patiënten zou kunnen selecteren voor vervroegd ontslag of thuisbehandeling. De resultaten hiervan worden besproken in **hoofdstuk 7**. Het herhaald testen NT-proBNP binnen 48 uur leidde tot identificatie van 20% extra patiënten met een laag risico op negatieve uitkomsten, ten opzichte van het verrichten van één NT-proBNP test.

Patiënten met een longembolie zonder een uitlokkende risicofactor hebben een hoger risico op verschillende soorten negatieve klinische uitkomsten, zoals niet-maligniteit gerelateerd overlijden, nieuw ontstane maligniteit en recidief VTE in vergelijking met patiënten die een longembolie uitlokt door een risicofactor hebben. Dit is een van de conclusies die getrokken wordt in **hoofdstuk 8**. In dit hoofdstuk wordt tevens aangetoond dat slechts een deel van de patiënten in de jaren volgend op de longembolie geen negatieve uitkomsten heeft meegemaakt: 70% na één jaar, minder dan 60% na twee jaar en minder dan de helft na vier jaar. Dit in tegenstelling tot de controlepatiënten zonder longembolie, van wie 84% na vier jaar geen negatieve uitkomsten heeft gehad.

In **hoofdstuk 9** wordt een additionele risicofactor voor een slecht klinisch beloop na longembolie besproken. Patiënten uit universitaire ziekenhuizen hadden een hoger risico op recidief VTE (3.3% vs. 2.6%; OR 1.3, 95% CI 0.50 - 3.3) en mortaliteit (9.0% vs. 6.9% OR 1.3, 95% CI 0.75-2.4) dan patiënten uit perifere ziekenhuizen. Tevens hadden patiënten uit universitaire ziekenhuizen een tweemaal hoger risico op majeure bloedingen (4.3% vs. 2.2%; OR 2.0, 95% CI 0.77-5.1). De bloedingen waren sterk geassocieerd met de aanwezigheid van een actieve maligniteit ten tijde van het stellen van de diagnose longembolie (OR 3.4, 95%CI 1.5-7.9). Onze gegevens laten zien dat patiënten met longembolie in universitaire ziekenhuizen verschillen van patiënten in perifere ziekenhuizen wat betreft patiëntkenmerken, zoals leeftijd en comorbiditeit, en klinische uitkomsten. Artsen moeten rekening houden met deze verschillen bij de interpretatie van resultaten van grote klinische studies en de toepassing van deze studies in de klinische praktijk.

Toekomstperspectieven

Er komt steeds meer bewijs over de veiligheid van thuisbehandeling van patiënten met longembolie. De meest recente richtlijnen van het American College of Chest Physicians geven een aanbeveling van het niveau 2B over vervroegd ontslag uit het ziekenhuis van patiënten met longembolie. Voordat thuisbehandeling van patiënten met longembolie een aanbeveling van niveau 1A krijgt, zal meer kwalitatief hoogstaand onderzoek nodig zijn.

Zoals besproken is in dit proefschrift kan risicostratificatie van patiënten met longembolie gedaan worden met klinische criteria, biomarkers of meting van de rechterventrikelfunctie van het hart. Het huidige bewijs dat geleverd is door grote multicenter studies, waaronder

de Hestia studie, laat zien dat een geselecteerde groep laagrisico patiënten met longembolie thuis behandeld zou kunnen worden. Het moet echter nog blijken welke methode van risicostratificatie het meest veilig patiënten voor thuisbehandeling kan selecteren. Daarom moeten nieuwe onderzoeken, bij voorkeur gerandomiseerde studies, gedaan worden waarin verschillende manieren van risicostratificatie met elkaar vergeleken worden.

Een andere belangrijke verandering in de behandeling van patiënten met longembolie zal de introductie van de nieuwe orale anticoagulantia zijn. Voorbeelden van nieuwe orale anticoagulantia zijn de factor Xa- en trombineremmers. Op dit moment worden grote klinische trials uitgevoerd naar de veiligheid en effectiviteit van deze middelen in de behandeling van longembolie. De introductie van de nieuwe anticoagulantia zou de thuisbehandeling van patiënten met longembolie kunnen vereenvoudigen, omdat bij de nieuwe anticoagulantia, in tegenstelling tot vitamine K antagonisten, geen frequente laboratoriumcontroles uitgevoerd moeten te worden. Voordat de nieuwe orale anticoagulantia gebruikt kunnen worden voor thuisbehandeling van patiënten met longembolie, moet gegarandeerd worden dat patiënten, vooral in de eerste weken, goed gecontroleerd worden. In de toekomst moet nieuw prospectief onderzoek uitwijzen of thuisbehandeling van patiënten met longembolie met de nieuwe orale anticoagulantia veilig is.

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Nawoord

Dit proefschrift is tot stand gekomen door de vriendschap en wetenschappelijke toewijding van velen. Ik wil enkelen in het bijzonder noemen, zonder anderen tekort te willen doen.

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Curriculum vitae

Wendy Zondag werd geboren op 29 december 1982 te Delft. In juni 2001 haalde zij cum laude haar VWO diploma aan het Christelijk Lyceum Delft. In datzelfde jaar startte zij met de studie Geneeskunde aan de Universiteit Leiden. In augustus 2005 vingen haar co-schappen aan. In 2007 behaalde zij haar doctoraal examen na een afstudeerproject op de afdeling Endocrinologie van het Leids Universitair Medisch Centrum getiteld: "Myocardial triglyceride accumulation and decreased diastolic heart function induced by metabolic alterations in healthy subjects and patients with diabetes" onder supervisie van prof. J.W.A. Smit. Na een semi-artsstage op de afdeling Interne Geneeskunde van het Lange Land Ziekenhuis in Zoetermeer, behaalde zij haar arts-examen in maart 2008. Aansluitend werkte zij een jaar als arts-assistent niet in opleiding (ANIOS) op de afdeling Interne Geneeskunde van het Lange Land Ziekenhuis in Zoetermeer. In maart 2009 begon zij aan het wetenschappelijk onderzoek op de afdeling Algemene Interne Geneeskunde van het Leids Universitair Medisch Centrum onder leiding van dr. M.V. Huisman, waarvan de resultaten zijn beschreven in dit proefschrift. In mei 2012 is zij begonnen met de opleiding tot internist in het Rijnland Ziekenhuis te Leerdorp (opleiders: dr. M.J.F.M. Janssen, prof. dr. J.T. van Dissel).

