

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

**Running head:** Pulmonary embolism treating at home or in-hospital

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## **Abstract**

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.

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 three months.

In total 530 patients were included, of which 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%; CI1.9-7.0). Three patients (1.0%, CI0.2-2.9) died during three months follow-up in the outpatient group versus 22 patients (9.6%, CI6.3-14) 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% (CI0.08-2.4) had major bleeding events versus 4.8% (CI2.4-8.4) of inpatients ( $p<0.05$ ).

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 eleven 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 three 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 five 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 twelve 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 till 2010, 581 patients with acute, symptomatic PE presented to twelve 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.

### 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 two 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.

### *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 seven 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, pericardial bleeding, bleeding in a pacemaker pocket, haemarthros, haematuria, 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.

### *Mortality*

During three 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, three 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 risk 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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Menno V Huisman reports having received research grants from GSK and Actelion; has given presentations and has been consulting for Bayer, Boehringer Ingelheim and Pfizer. Other authors do not report any disclosures.

## References

1. Kearon C, Akl EA, Comerota AJ, Prandoni P, Bounameaux H, Goldhaber SZ, Nelson ME, Wells PS, Gould MK, Dentali F, Crowther M, Kahn SR. Antithrombotic Therapy for VTE Disease: Antithrombotic Therapy and Prevention of Thrombosis, 9<sup>th</sup> ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; 141: e419S-e494S.
2. Janjua M, Badshah A, Matta F, Danescu LG, Yaekoub AY, Stein PD. Treatment of acute pulmonary embolism as outpatients or following early discharge. A systematic review. *Thromb Haemost* 2008; 100: 756-761.
3. Squizzato A, Galli M, Dentali F, Ageno W. Outpatient treatment and early discharge of symptomatic pulmonary embolism: a systematic review. *Eur Respir J* 2009; 33: 1148-1155.
4. Erkens PM, Gandara E, Wells P, Shen AY, Bose G, Le GG, Rodger M, Prins MH, Carrier M. Safety of outpatient treatment in acute pulmonary embolism. *J Thromb Haemost* 2010; 8: 2412-2417.
5. Kovacs MJ, Hawel JD, Rekman JF, Lazo-Langner A. Ambulatory management of pulmonary embolism: a pragmatic evaluation. *J Thromb Haemost* 2010; 8: 2406-2411.
6. Zondag W, Mos IC, Creemers-Schild D, Hoogerbrugge AD, Dekkers OM, Dolsma J, Eijsvogel M, Faber LM, Hofstee HM, Hovens MM, Jonkers GJ, van Kralingen KW, Kruip MJ, Vlasveld T, de Vreede MJ, Huisman MV. Outpatient treatment in

- patients with acute pulmonary embolism: the Hestia Study. *J Thromb Haemost* 2011; 9: 1500-1507.
7. Kearon C, Kahn SR, Agnelli G, Goldhaber S, Raskob GE, Comerota AJ. Antithrombotic therapy for venous thromboembolic disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008; 133: 454S-545S.
  8. Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost* 2005; 3: 692-694.
  9. Aujesky D, Stone RA, Kim S, Crick EJ, Fine MJ. Length of hospital stay and postdischarge mortality in patients with pulmonary embolism: a statewide perspective. *Arch Intern Med* 2008; 168: 706-712.
  10. van BA, Buller HR, Huisman MV, Huisman PM, Kaasjager K, Kamphuisen PW, Kramer MH, Kruip MJ, Kwakkel-van Erp JM, Leebeek FW, Nijkeuter M, Prins MH, Sohne M, Tick LW. Effectiveness of managing suspected pulmonary embolism using an algorithm combining clinical probability, D-dimer testing, and computed tomography. *JAMA* 2006; 295: 172-179.
  11. Simonneau G, Sors H, Charbonnier B, Page Y, Laaban JP, Azarian R, Laurent M, Hirsch JL, Ferrari E, Bosson JL, Mottier D, Beau B. A comparison of low-molecular-weight heparin with unfractionated heparin for acute pulmonary

embolism. The THESEE Study Group. Tinzaparine ou Heparine Standard: Evaluations dans l'Embolie Pulmonaire. *N Engl J Med* 1997; 337: 663-669.

12. Aujesky D, Roy PM, Verschuren F, Righini M, Osterwalder J, Egloff M, Renaud B, Verhamme P, Stone RA, Legall C, Sanchez O, Pugh NA, N'gako A, Cornuz J, Hugli O, Beer HJ, Perrier A, Fine MJ, Yealy DM. Outpatient versus inpatient treatment for patients with acute pulmonary embolism: an international, open-label, randomised, non-inferiority trial. *Lancet* 2011; 378: 41-48.

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Wendy Zondag and Menno V. Huisman had full access to all of the data in this study and take complete responsibility for the integrity of the data and the accuracy of the data analysis.

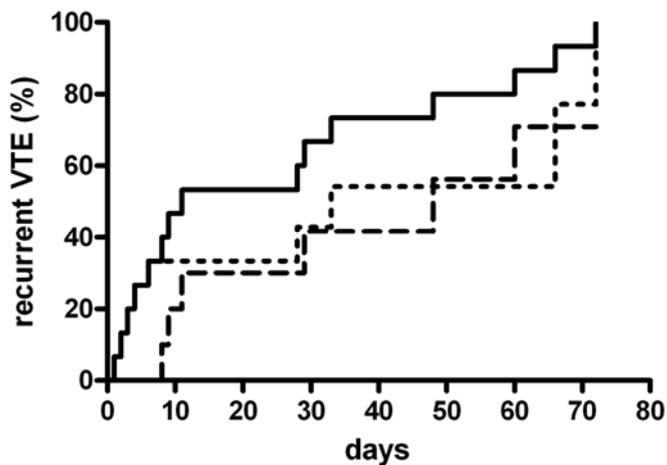
*Study concept and design, acquisition, analysis and interpretation of data, drafting of the manuscript:* MVH, WZ;

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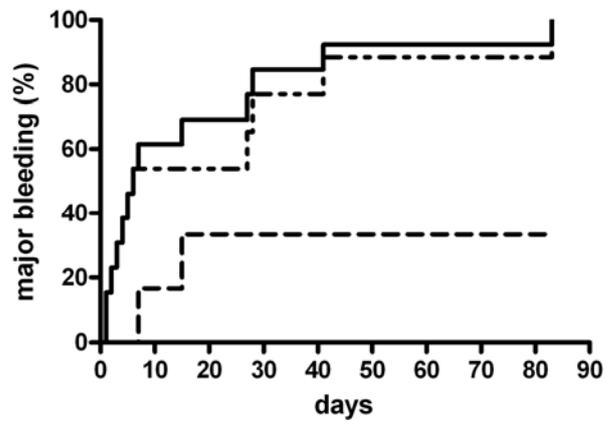
**Figure 1:** Timing of recurrent venous thromboembolism

Legend:

— All patients

..... Inpatients

- - Outpatients



**Figure 2:** Timing of major bleeding

Legend:

- All patients
- ..... Inpatients
- - Outpatients

**Table 1.** Baseline characteristics

<b>Characteristics</b>	<b>Patients treated at home (n=297)</b>	<b>Patients treated in the hospital (n=233)</b>	<b>p-value</b>
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 N<sup>o</sup> (%). Numerical data are displayed as means ± standard deviation. VTE= venous thromboembolism, COPD = chronic obstructive pulmonary disease

\* Data were missing in 126 (23%) patients

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

<b>Clinical outcome</b>	<b>All PE patients (n=526)*</b>	<b>PE patients treated as outpatients (n=297)</b>	<b>PE patients treated as inpatients (n=229)*</b>	<b>P-value inpatients versus outpatients</b>
<b>Total recurrences</b>	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
<b>Major bleeding</b>	13 (2.5)	2 (0.7)	11 (4.8)	0.003
Fatal bleeding	2 (0.4)	1 (0.3)	1 (0.4)	1.000
<b>All cause mortality</b>	25 (4.8)	3 (1.0)	22 (9.6)	<0.001

Data are displayed as N<sup>o</sup> (%).

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

\* 4 inpatients were lost-to-follow-up