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 values[5] 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 instable?*	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 Cockroft-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 mortality[14] 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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