Risk stratification of outpatient management in acute venous thromboembolism

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Reasons for Hospitalization of Patients with Acute Pulmonary Embolism Based on the Hestia Decision Rule

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ABSTRACT

Background: The Hestia criteria can be used to select pulmonary embolism (PE) patients for outpatient treatment. The subjective Hestia criterion "medical/social reason for admission" allows the treating physician to consider any patient-specific circumstances in the final management decision. It is unknown how often and why this criterion is scored.

Method: This is a patient-level post-hoc analysis of the combined Hestia and Vesta studies. The main outcomes were the frequency of all scored Hestia items in hospitalized patients and the explicit reason for scoring the subjective criterion. Hemodynamic parameters and CT-assessed RV/LV ratio of those only awarded with the subjective criterion were compared with patients treated at home.

Results: From the 1166 patients screened, data were available for all 600 who were hospitalized. Most were hospitalized to receive oxygen therapy (45%); 227 (38%) were only awarded with the subjective criterion, of whom 51 because of 'intermediate to intermediate-high risk PE'. Compared to patients with intermediate risk PE (RV/LV ratio >1.0) treated at home (179/566, 32%), hospitalized patients with only the subjective criterion had a higher mean RV/LV ratio (mean difference +0.30, 95%CI 0.19-0.41) and a higher heart rate (+18/min, 95%CI 10-25). No relevant differences were observed for other hemodynamic parameters.

Conclusion: The most frequent reason for hospital admission was oxygen therapy. In the decision to award the subjective criterion as sole argument for admission, the severity of the RV overload and resulting hemodynamic response of the patient was taken into account rather than just abnormal RV/LV ratio.

INTRODUCTION

The majority of patients diagnosed with acute pulmonary embolism (PE) are hospitalized during the initiation of anticoagulant treatment.[1-7] The main benefit of hospitalization of patients with acute PE is close monitoring for early detection and treatment of adverse events. It may however also expose patients to a higher risk of iatrogenic complications, especially in the elderly, and is associated with higher healthcare costs than home treatment.

According to the 2019 ESC guidelines, all high or intermediate risk PE patients are advised to start initial treatment in hospital.[8] Intermediate risk is defined as normotensive PE patients with either a PESI class III–V, a sPESI ≥1 or those with signs of right ventricular (RV) dysfunction. Notably and in contrast, the Hestia rule is the most widely validated clinical decision tool in the literature for selecting PE patients eligible for home treatment.[6] These pragmatic criteria contain among others objective parameters of risk of mortality such as shock or hypoxaemia, but not explicit parameters of RV function (**Table 1**). Of all 11 score items, one however is subjective, i.e. "medical or social reason for treatment in the hospital for more than 24 hours", allowing the treating physician to consider all patient-specific circumstances in the final management decision, including RV function.[9] It is unknown how often and why this subjective criterion of the Hestia criteria is scored and used as the main argument to hospitalize the patient.

Table 1: Hestia Criteria

Is the patient hemodynamically unstable? [a]	Yes/No
Is thrombolysis or embolectomy necessary?	Yes/No
Active bleeding or high risk of bleeding? [b]	Yes/No
More than 24h of oxygen supply to maintain oxygen saturation > 90%?	Yes/No
Is pulmonary embolism diagnosed during anticoagulant treatment?	Yes/No
Severe pain needing intravenous pain medication for more than 24h?	Yes/No
Medical or social reason for treatment in the hospital for more than 24h?	Yes/No
Does the patient have a creatinine clearance of < 30 ml/min? [c]	Yes/No
Does the patient have severe liver impairment? [d]	Yes/No
Is the patient pregnant?	Yes/No
Does the patient have a documented history of heparin-induced thrombocytopenia?	Yes/No
If the answer to one of the questions is 'yes', the patient cannot be treated at home in the Hestia study	

a) Include the following criteria, but are left to the discretion of the investigator: systolic blood pressure <100mmHg with heart rate >100 beats per minute; condition requiring admission to an intensive care unit.

b) 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* 10^9/L), uncontrolled hypertension (systolic blood pressure > 180mm Hg or diastolic blood pressure > 110mm Hg).

c) Calculated creatinine clearance according to the Cockcroft-Gault formula.

d) Left to the discretion of the physician.

We therefore aimed to evaluate reasons for hospitalization according to the Hestia criteria. We aimed specifically to explore the reasons for the application of the subjective Hestia criterion "medical/social reason for admission", and additionally set out to evaluate whether assessment of PE severity is relevant in awarding the subjective Hestia criterion as sole argument for hospitalization in daily clinical practice in the Netherlands.

METHODS

Design

This is a patient-level post-hoc analysis of the combined Hestia and Vesta studies.[9,10] The Hestia Study was a multicenter prospective cohort study aimed to evaluate the efficacy and safety of outpatient treatment in PE patients in the absence of all Hestia criteria (**Table 1**). Patients were selected to start anticoagulant treatment at home (discharge within 24 hours after diagnosis) if none of the Hestia criteria were present. The remainder of screened patients was hospitalized.

The Vesta study was a multicentre, randomised, interventional study investigating whether outpatient treatment based on the Hestia criteria alone is as safe as a strategy based on the Hestia criteria combined with N-terminal pro brain natriuretic peptide (NT-proBNP) measurement in patients with acute symptomatic PE.[10] Patients were eligible for randomization if none of the items of the Hestia criteria were present. Patients were hospitalized in the presence of at least one Hestia criterion or an abnormal NT-proBNP test (if randomized to the NT-proBNP arm).

For the present analysis, all patients screened for either of the studies hospitalized because of the presence of one or more Hestia criteria were included. Patients randomized to the intervention arm of the Vesta study were excluded because cardiac function was routinely assessed at baseline. Further exclusion criteria were the inability to measure the right ventricular to left ventricular diameter ratio (RV/LV ratio) on CT images post-hoc due to 1) the use of ventilation-perfusion scan for the initial diagnosis or 2) insufficient quality of CT images for valid assessment.

Study objectives and outcomes

The primary aims of this study were to evaluate reasons for hospitalization and specifically, the reasons for the application of the subjective Hestia criterion "medical/social reason for admission". We additionally aimed to evaluate whether PE severity, i.e. RV/LV ratio, centrally located PE and/or hemodynamic status of the patient, were relevant in awarding this subjective Hestia criterion. Our hypothesis was that the hemodynamic impact of the PE is intrinsically weighted in the decision to award the subjective Hestia criterion and treat the patient at home or in hospital. We therefore expected a higher prevalence of RV overload, more severe RV overload, higher prevalence of centrally located PE and less favorable hemodynamic profile (e.g. higher

heart rate and lower blood pressure) in patients admitted solely because of the subjective Hestia criterion than in patients discharged within 24 hours after diagnosis.

The primary outcomes of this analysis were the frequency of all scored Hestia items in hospitalized patients, and the explicit reason for scoring the subjective Hestia criterion as noted in the patient chart. Our secondary outcomes were the proportion of 1) post-hoc assessed RV/LV ratio >1.0 and 2) centrally located PE in patients admitted to the hospital solely because of the subjective Hestia criterion and in those treated at home. Also, we evaluated the mean RV/LV ratio and clinical hemodynamic parameters, e.g. blood pressure and heart rate, in patients with RV/LV ratio >1.0 admitted because of the subjective Hestia criterion awarded due to 'intermediate or intermediate-high risk PE' versus those with RV/LV ratio >1.0 treated at home.

Study definitions

The definition of acute PE was an intraluminal filling defect of the subsegmental or more proximal pulmonary arteries confirmed by computed tomographic pulmonary angiography.[11] RV/LV ratio was measured in the transverse plane at the widest points between the inner surface of the free wall and the surface of the interventricular septum.[12,13] Centrally located pulmonary emboli were defined as clots involving the pulmonary truncus, right or left main pulmonary or lobar arteries.

Reasons for awarding the subjective Hestia criterion 'social or medical reason for admission' were scored as noted in the patient chart and classified in the following categories: concomitant infection, malignancy related admission, concomitant other acute condition (e.g. electrolyte disorders), intermediate to intermediate-high risk PE (including syncope as presenting symptom and/or cardiac arrhythmias), outpatient treatment not feasible because of comorbidities or social reasons, need for non-intravenous pain medication, contrast allergy, or other. For example, concomitant infection was scored if the patient was treated with intravenous antibiotics because of a proven or suspected infection, 'Outpatient treatment not feasible because of comorbidities or social reasons' was scored when the patient needed treatment for acute delirium and 'malignancy related admission' was for example noted if duration of admission was extended for administration of chemotherapy. Importantly, intermediate to intermediate-high risk PE was scored when extensiveness of clot burden, severity of RV overload and/or the presence of abnormal cardiac biomarkers was explicitly noted as reason for admission in the patient chart.

For assessment of the hemodynamic profile of the patients, we extracted the first registered measurement of blood pressure, heart rate and oxygen saturation of the presentation that lead to the PE diagnosis from the electronic patient charts.

Statistical analysis

Descriptive statistics were provided for all relevant demographic characteristics, comorbidities, risk factors for VTE, clinical findings and symptoms on admission. Categorical data are presented as percentages and continuous variables as means ± standard deviation (SD).

For the primary outcome frequencies and percentages for every reason for scoring the subjective Hestia were provided. For the secondary outcomes, the proportion of patients with a RV/LV ratio >1.0 and with embolus localization in the central arteries in those admitted because of the subjective Hestia criterion and those treated at home were compared by crude odds ratios with corresponding 95% confidence intervals (95%CI). In the same two groups but limited to those patients with RV/LV ratio >1.0 and when admitted because of the subjective Hestia criterion limited to those with signs of 'intermediate to intermediate-high risk PE', we calculated the absolute difference with corresponding 95%CI for the mean RV/LV ratio and for relevant hemodynamic parameters. Lastly, frequencies and percentages were provided for all scored Hestia criteria in hospitalized patients. SPSS version 25.0.0 (SPSS, IBM) was used to perform all analyses.

RESULTS

Study patients

Of 1166 consecutive PE patients eligible for either of the two studies without routinely assessed cardiac function, complete data were available for all 600 initially hospitalized patients. The remaining 566 patients were treated initially at home. **Table 2** summarizes the relevant baseline characteristics of the study patients. Their mean age was 64 years (SD 16), 17% had active malignancy, 4.8% had a history of heart failure and 8.5% suffered from chronic obstructive pulmonary disease. Centrally located PE was present in 57% of the admitted PE patients, while 55% had RV/LV ratio >1.0.

Table 2: Baseline characteristics of hospitalized patients with acute PE

	Total N=600
Age, mean (SD)	64 (16)
Male sex, no (%)	309 (50)
Weight in kg, mean (SD)	85 (19)
Body Mass Index, mean (SD)	27.9 (5.6)
Comorbidities	
COPD (%)	51 (8.5)
Heart failure (%)	29 (4.8)
VTE Risk factors	
Previous VTE — no. (%)	166 (27)

Table 2: Baseline characteristics of hospitalized patients with acute PE (continued)

	Total N=600
DVT	65 (11)
PE +/- DVT	96 (16)
Estrogen Use (%)	30 (5.0)
Active malignancy no. (%)	99 (17)
Immobilisation no. (%)	121 (20)
Clinical symptoms	
Systolic blood pressure in mmHg (mean, SD)	135 (45)
Proportion SBP < 100 mmHg (%)	36 (6.0)
Heart rate (mean, SD)	93 (22)
Proportion Heart rate > 110/min (%)	128 (21)
Median time from symptom onset (mean, SD)	6.5 (14)
Admission details	
Mean time of admission in days (SD)	6.5 (14)
Central located PE* (%)	344 (57)
RV/LV ratio >1 (%)	329 (55)

Abbreviations: PE, pulmonary embolism; SD, standard deviation; COPD, chronic obstructive pulmonary embolism; VTE, venous thromboembolism; DVT, deep venous thrombosis; SBP, systolic blood pressure; RV, right ventricle; LV, left ventricle
*Central located PE: clots involving the following arteries: the pulmonary truncus, right or left main pulmonary or lobar arteries

Primary outcome

The overall most frequent reason for admission according to the Hestia criteria was the need for oxygen supply (45%). Sixty out of six-hundred (10%) of the admitted patients were hemodynamically instable (i.e. high-risk PE), of whom 26 received reperfusion therapy. The need for intravenous pain medication was present in 6.3% whereas 4.7% had a high bleeding risk or were bleeding actively. Less frequently observed reasons for hospital admission were renal insufficiency (0.50%), severe liver impairment (0.16%), pregnancy (0.50%) and a history of heparin induced thrombocytopenia (0.33%). **Table 3** summarizes the number and percentages of the individual Hestia criteria.

Of all 600 study patients, 227 (38%; **Table 3**) were admitted solely because the subjective Hestia criterion was awarded. Of those, the criterion was awarded because of 'intermediate or intermediate-high risk PE' in 51 patients (8.5% of total population; **Table 4**). Other reasons for awarding the subjective Hestia criterion as explicitly noted in the chart were concomitant infection (6.5% of total population) and the need for inpatient treatment due to extensive comorbidities or social reasons (13% of total population).

Secondary outcome

The proportion of right ventricular dysfunction (RV/LV ratio >1.0) in patients only awarded with the subjective Hestia criterion because of 'intermediate to intermediate-risk PE was 57%

(29/51) versus 32% (179/565) in those without any Hestia criteria who were treated at home (OR 2.8, 95%CI 1.6-5.1). Centrally located PE was found in 73% (37/51) compared to 32% (176/546) in those treated at home (OR 5.6, 95%CI 2.9-11).

Table 3: Reasons for hospitalization according to the Hestia criteria (N=600)

Reasons for hospital admission	Frequency	Proportion
1. Hemodynamically unstable	60	10%
2. Need for thrombolysis of embolectomy	26	4.3%
3. Active bleeding or high bleeding risk	28	4.7%
4. > 24 hours oxygen supply	272	45%
5. Need for intravenous pain medication > 24 hours	38	6.3%
6. Subjective Hestia criterion: medical or social reasons	227	38%
7. Renal insufficiency (< 30 ml/min)	3	0.5%
8. Severe liver impairment	1	0.16%
9. Pregnancy	3	0.5%
10. Heparin induced thrombocytopenia	2	0.33%

Abbreviations: hr, Hour

Table 4: Reasons for awarding the subjective Hestia criterion 'social or medical reason for admission'

Reasons for hospital admission	Frequency n=227	Proportion 100 %
1. Concomitant infection	39	17%
2. Malignancy	9	4.0%
3. Concomitant acute condition, e.g. electrolyte disorders	32	14%
4. Intermediate to intermediate-high risk PE	51	22%
5. Outpatient treatment not feasible because of comorbidities or social reasons	76	34%
6. Need for pain medication (not i.v.)	13	5.7%
7. Contrast allergy	4	1.8%
8. Other	3	1.3%

Abbreviations: PE. Pulmonary embolism; i.v., intravenously

Of all patients with signs of RV dysfunction, the mean RV/LV ratio in patients admitted due to the subjective Hestia criterion because of `intermediate to intermediate-high risk PE' was 1.5 (SD 0.52) versus 1.2 (SD 0.21) in those treated at home, for a mean difference of +0.30 (95% CI 0.19-0.41). Also, a notable higher mean heart rate was observed in patients with RV/LV ratio >1.0 admitted due to the subjective Hestia criteria because of `intermediate to intermediate-high risk PE' than those treated at home with RV/LV ratio >1.0: 103/minute versus 85/minute, with a mean difference of +18 (95% CI 10-25). No relevant differences were observed for other hemodynamic parameters (**Table 5**).

Table 5: Differences in hemodynamic parameters in patients awarded with only the subjective criterion because of intermediate to intermediate-high risk PE and those threated at home with RV/LV ratio >1.0.

Clinical findings	Only subjective criterion because of intermediate-risk PE n=29	Treated at home with RV/LV ratio >1.0 n=179	Mean difference (95% CI)
Mean RV/LV ratio (SD)	1.50 (0.52)	1.20 (0.22)	0.3 (0.2-0.4)
Heart rate (SD)	103 (21)	86 (19)	18 (10-25)
Systolic blood pressure (SD)	133 (20)	140 (19)	-7.0 (-14 to 0.7)
Diastolic blood pressure (SD)	83 (15)	85 (14)	-1.6 (-7.4 to 4.2)
Oxygen saturation (SD)	95 (7.5)	97 (2.0)	-2.0 (-3.3 to -0.6)

Abbreviations: RV: right ventricular; CI: confidence interval; SD: standard deviation, LV: left ventricular

DISCUSSION

In this study, the overall most frequent reason for hospital admission according to the Hestia criteria was the need for oxygen supply (45%), while 10% of all PE patients had high-risk PE. Interestingly, a large group of 38% was admitted solely based on the subjective Hestia criterion. In the further exploration of the reason for awarding PE patients solely with the subjective Hestia criterion, 22% (8.5% of the overall population) were judged to have too severe PE to consider home treatment even despite the fact that by definition they were hemodynamically stable and did not require oxygen therapy. The main reasons for in hospital treatment of these patients awarded with only the subjective Hestia criterion however were concomitant infection and the need for inpatient treatment due to extensive comorbidities or social reasons requiring hospitalization.

The majority of patients with acute PE are treated in hospital.[1-7] Notably, over the last decades, due to the increased diagnostic sensitivity and frequency of computed tomographic pulmonary angiography testing, the incidence of PE and hospitalization rates have increased.[14-16] Partly because of this, overall outcomes for hospitalized PE patients have improved, with a decrease in average hospital admission from 8 to 4 days and a decreased inpatient mortality from 7.1% to 3.2% even despite an increasing age and prevalence of comorbidities in hospitalized patients with PE.[14-17] The threshold for treating patients at home has been lowered after the introduction of DOACs, which are more safe than conventional treatment with vitamin-k antagonists and have practical advantages.[18] Consequently, patient characteristics of inpatients with PE will very likely continue to change over the next years, as patients are not required to start with parenteral anticoagulants in hospital. As a proportion of low-risk PE patients will be discharged early or even treated at home, the population that requires hospitalisation will likely have more severe PE and/or comorbidities than those admitted in the past years, and thus is at higher risk of adverse events. This has important consequences for daily clinical practice, i.e.

health care utilization for the individual patient, and therefore is highly relevant for guideline and policy makers.

It remains challenging to select patients for initial in-hospital treatment or treatment at home. According to the 2019 ESC guidelines, hospitalization is recommended for all patients with intermediate risk PE.[8] In the Hestia and Vesta studies, RV function evaluation (which is critical to the risk stratification as recommended by the ESC) was not part of standard baseline assessment. As a consequence, 32% of all patients treated at home had a RV/LV diameter ratio >1.0, without a higher incidence of adverse outcome.[19] Our current study provides important insight in the ongoing debate on the relevance of RV dilatation in normotensive PE patients: we found relevant differences between patients with RV overload that were treated at home or were hospitalized. Those latter patients had a considerably higher RV/LV ratio as well as (and consequently) a higher heart rate. This observation suggests that the hemodynamic profile of a patient, i.e. the severity of RV overload and the resulting hemodynamic response rather than just an abnormal RV/LV ratio, is intrinsically taken into account in the decision to treat patients at hospital or at home when applying the Hestia criteria. Furthermore, and of interest, we also observed a larger proportion of patients with centrally located PE in hospitalized patients than those treated at home. Thrombus location is not part of standard risk assessment according to either the Hestia criteria or the 2019 ESC guidelines, whereas for the clinician, it seems to be important in clinical decision making when selecting the initial therapy.

Strengths of this analysis include the novelty and completeness of our data and the use of data of two large high-quality prospective studies. All baseline characteristics, vital parameters and Hestia criteria were collected prospectively. The main limitation of this study is its post-hoc design. Therefore, reasons for scoring the subjective Hestia criterion were collected retrospectively. Also, we could not adjust the hemodynamic parameters for initial fluid resuscitation or oxygen therapy.

In conclusion, after diagnosing PE the most frequent reason for hospital admission was oxygen therapy. The subjective Hestia criterion is used in 38% as sole reason to hospitalize patients and mostly involves patients with comorbidities or social circumstances precluding immediate discharge, or patients with concomitant infections. Based on our observations, management decisions were made based on the severity of RV overload and resulting hemodynamic profile of the patients rather than solely on assessment of the RV/LV ratio. This observation provides an explanation for the good prognosis of patients with dilated RV selected to be treated at home.

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