Risk stratification of outpatient management in acute venous thromboembolism

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Right Ventricle-to-Left Ventricle Diameter Ratio Measurement Seems to Have No Role in Low-Risk Patients with Pulmonary Embolism Treated at Home Triaged by Hestia Criteria

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ABSTRACT

Background: There is a continuing debate on the relevance of right ventricular (RV) dilatation in normotensive pulmonary embolism (PE) patients as a tool to identify low-risk patients eligible for outpatient treatment. Formal assessment of RV function is not part of the Hestia clinical decision rule, which has been shown to safely select patients for home treatment.

Aim: To assess the incidence of CT-measured RV dilatation and centrally located PE in patients treated at home based on the application of the Hestia clinical decision rule, and its impact on clinical outcome.

Methods: Patient-level post-hoc analysis of two multicenter prospective outcome studies evaluating the safety of outpatient treatment for PE based on the Hestia criteria. Primary outcome was the combined 3-month incidence of recurrent VTE, major bleeding and mortality in patients with CT measured RV/LV ratio >1 versus those with RV/LV <1.0.

Results: Of 1627 consecutive patients eligible for the two studies, 752 were treated at home (46%); 225/752 (30%) had a RV/LV diameter ratio >1.0 (range 0.74-2.4). The incidence of adverse events was 3.1% in patients with an RV/LV ratio of >1.0 and 3.0% in those with an RV/LV ratio ≤1.0, for an Odds Ratio of 1.1 (95%CI0.44-2.7).

Conclusions: In this study, RV/LV ratio >1 alone as measured on CT does not add to the Hestia criteria to predict poor outcome in patients selected for outpatient treatment. This challenges the concept that CT measured RV function should always be used to guide or change management decisions in these low risk patients.

INTRODUCTION

Current guidelines emphasize the importance of early risk stratification of patients with acute pulmonary embolism (PE) to facilitate assessment of prognosis and guide therapeutic decision-making.[1-3] There is a continuous debate on the relevance of measuring right ventricular (RV) dysfunction in normotensive PE patients as a tool to identify low-risk patients eligible for home treatment. To date, three studies have demonstrated that patients with acute PE can be safely selected for outpatient treatment on a clinical basis alone, with either use of the PESI score or Hestia clinical decision rule.[4-6] In contrast, the 2019 ESC guidelines recommend objective assessment of RV dysfunction in combination with clinical risk assessment based on either the Pulmonary Embolism Severity Index (PESI) score or its simplified sPESI version, to select patients suitable for home treatment.

In a relatively small sample size of 95 patients as part of a post-hoc analysis of the Hestia study, it was shown that patients treated as outpatients based on the Hestia criteria but with (retrospectively assessed) right ventricular dysfunction had an uncomplicated clinical course.[7] However, a recent systematic review of the literature showed a different point of view demonstrating a higher all-cause mortality in low-risk PE patients with RV dysfunction than in those with a normal RV.[8]

Several methods to determine RV dysfunction on computed tomographic pulmonary angiography (CTPA) have been proposed and validated; abnormal position of the interventricular septum, backflow of contrast in the vena cava, enlargement of the pulmonary truncus and right to left ventricle volumes. According to the latest ESC guideline the right ventricle to left ventricle (LV) diameter ratio >1.0 may be the most appropriate to indicate poor prognosis on CTPA.[3-9] This measurement has also been shown to be reproducible, even for (non-radiologist) clinicians.[10]

Notably, besides RV/LV ratio, additional CT parameters such as a higher degree of embolus load have been proposed as predictors of PE severity, although these have never been evaluated in the setting of selecting patients for home treatment, and guidelines do not consider these in initial risk assessment.[11-13]

Considering the above, it remains challenging for the clinician to determine which patients may qualify for outpatient treatment. In an attempt to solve the issue on relevance of CT parameters of RV function and thrombus location for selection of candidates for home treatment, we assessed the incidence of CT-measured RV dilatation and central PE localization in patients treated at home solely selected on the application of the Hestia criteria, and their impact on clinical outcome.

METHODS

Design

This is a patient-level post-hoc analysis of the combined Hestia and Vesta studies, both multicenter prospective outcome studies evaluating the safety of outpatient treatment for PE based on the Hestia criteria.[4,5] These two studies included consecutive normotensive patients with confirmed PE from 3 academic and 11 non-academic Dutch hospitals.

The Hestia Study was a multicenter prospective cohort study in patients with acute PE who were selected to start anticoagulant treatment at home according to the Hestia criteria, which are 11 simple and readily available clinical selection criteria (**Table 1**). If none of the criteria were present, the patient was treated at home, i.e. discharged within 24 hours after diagnosis of PE. The efficacy and safety of this practice was assessed during a 3-month follow-up period.[4]

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 24 hour 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 24 h?	Yes/No
Medical or social reason for treatment in the hospital for more than 24 h (infection, malignancy, no support system)?	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	

[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 9 109/L), uncontrolled hypertension (systolic blood pressure > 180mm Hg or diastolic blood pressure > 110mm Hg).*

[c] *Calculated creatinine clearance according to the Cockroft-Gault formula.*

[d] *Left to the discretion of the physician.*

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.[5] Patients were eligible for randomization if none of the items of the Hestia criteria were present, with the main exclusion criteria of a life expectancy less than 3 months or an expected inability to attend the required 3-month follow-up. Patients were followed for three months to assess the occurrence of a composite outcome

of haemodynamic instability, intensive care unit (ICU) admission and death related to PE or major bleeding. In addition, occurrence of recurrent venous thromboembolism (VTE), major bleeding and all-cause mortality were monitored.

For the present analysis, all patients diagnosed with acute PE at baseline and treated at home were eligible for inclusion. The main exclusion criteria was the inability to measure the RV/LV ratio due to either the use of ventilation-perfusion scan for initial diagnosis or insufficient quality of CT images for valid post-hoc RV/LV ratio measurement. Furthermore, all patients with routinely assessed NT-proBNP as part of the intervention arm of the Vesta study were excluded irrespective of the NT-proBNP level, as they had been managed based on the outcome of the NT-proBNP.

Hypothesis

In this cohort of acute PE patients managed according to risk stratification by the Hestia criteria, we hypothesized that patients with RV dilatation and/or centrally located PE selected by the treating physician for outpatient treatment, did not have a higher incidence of PE-associated adverse outcomes than those selected for outpatient treatment with normal RV function and/or more peripheral PE localization.

Study objectives

The primary aim of this study was to assess the incidence of CT-measured RV dilatation in patients treated at home based on the application of the Hestia criteria, and its impact on clinical outcome. Additionally, we set out to assess the prevalence of centrally located PE and its association with clinical outcome.

The primary outcomes were 1) the proportion of patients treated at home with a RV/LV ratio >1.0, and 2) the combined 3-month incidence of recurrent VTE, major bleeding and mortality ('adverse events') in patients with versus those without RV dilatation. The secondary outcomes of this study were the combined 3-month adverse events in 1) patients with versus those without severe RV dilatation and 2) patients with centrally located PE versus those with peripheral PE.

Study definitions

Home treatment was defined as discharge from the hospital within 24 hours after diagnosis. The definition of acute PE was an intraluminal filling defect of the subsegmental or more proximal pulmonary arteries confirmed by computed tomography pulmonary angiography. Right ventricular dilatation was defined as a RV/LV diameter ratio greater than 1.0 with ventricular diameters measured in the transverse plane at the widest points between the inner surface of the free wall and the surface of the interventricular septum.[14] Severe right ventricular dilatation was defined as a RV/LV ratio greater than 1.5.[7,15] Centrally located PE was defined as a clot involving the main pulmonary artery, the left or right pulmonary arteries or the interlobar

arteries. Clot location was scored by the most proximal embolus. Peripheral located PE was defined as a clot involving the segmental or subsegmental arteries.

Recurrent VTE was defined as a new intraluminal filling defect on CTPA or confirmation of a new PE at autopsy. Recurrent lower extremity DVT was defined as new non-compressibility in a previously affected segment by ultrasonography or as an increase in vein diameter under maximal compression, as measured in the abnormal venous segment, indicating an increase in thrombus diameter (≥ 4 mm).[16]

Major bleeding was defined in accordance to the ISTH criteria.[17] The cause of death among patients who died within the study period was evaluated by autopsy or based on a clinical report indicating the most likely cause of death. An independent adjudication committee evaluated relevant suspected adverse events as part of the original Hestia and Vesta studies.

Statistical analysis

Descriptive statistics were provided for all relevant demographic characteristics, comorbidities, risk factors for VTE, clinical findings and symptoms on admission. Continuous variables were summarised (number, mean, standard deviation). Frequency and percentage of subjects within each category were provided for categorical data.

In order to describe differences with regard to the primary and secondary outcomes, odds ratios (OR) were provided with corresponding 95% confidence intervals (95%CI). The proportion of patients treated at home with an RV/LV ratio >1.0 was provided as frequency with corresponding 95%CI. SPSS version 25.0.0 (SPSS, IBM) was used to perform all analyses.

RESULTS

Study patients

Of 1627 consecutive patients eligible for the Hestia and Vesta studies, RV/LV ratio were available for 1474 patients, of whom 752 were treated at home (51%). The baseline characteristics of these 752 study patients are summarized in **Table 2**. Their mean age was 54 years (standard deviation (SD) 15), 44% was female and 9% had active malignancy at time of diagnosis. In this cohort 4.8% suffered from chronic obstructive pulmonary disease, while heart failure was present in 0.8% of all patients.

Primary outcome

Of the 752 patients diagnosed with acute PE and treated at home, 225 (30%) had a RV/LV diameter ratio >1.0 (range 0.74-2.4). A larger proportion of male than female patients treated at home was diagnosed with RV dilatation (OR 1.9, 95%CI 1.5-2.5). The mean age was also higher in patients treated at home who had RV dilatation, and the proportion of patients aged >60

years was higher (OR 2.6, 95%CI 1.9-3.6). At baseline no relevant differences were found in vital parameters in patients with versus those without RV dilatation.

Table 2: Baseline characteristics of PE patients treated at home

	RV/LV ratio > 1.0 (n=224)	RV/LV ratio ≤ 1.0 (n=527)
Demographics		
Male, n (%)	161 (71.6)	263 (49.9)
Female, n (%)	64 (28.4)	264 (50.1)
Age (years), mean (SD)	60.4 (13.2)	51.3 (14.8)
Age >60 years, n (%)	117 (52)	154 (29.2)
Length (cm), mean (SD)	178 (10)	175 (13)
Weight (kg), mean (SD)	88 (18)	85 (18)
BMI, kg/m², mean (SD)	27.6 (5.0)	27.1 (5.0)
Risk factors for VTE		
Immobilization or recent surgery, n (%)	21 (9.3%)	69 (13.1%)
Previous VTE, n (%)	68 (30.2%)	126 (23.9%)
Active malignancy, n (%)	26 (11.6%)	40 (7.6%)
Estrogen use, n (%)	13 (5.8%)	105 (19.9%)
Comorbidities		
Chronic heart failure, n (%)	4 (1.8%)	2 (0.4%)
COPD, n (%)	7 (3.1%)	29 (5,5%)
Clinical status and symptoms on admission		
Systolic blood pressure (mmHg), mean (SD)	140 (18)	139 (19)
Heart rate (bpm), mean (SD)	84 (17)	84 (15)
Oxygen saturation (%), mean (SD)	97 (2)	97 (2)

Abbreviation: PE, pulmonary embolism; RV, right ventricular; LV, left ventricular; OR, Odds ratio; SD, standard deviation; BMI, body mass index; VTE, venous thromboembolism; COPD, chronic obstructive lung disease;

The incidence of adverse events was seven of 225 patients (3.1%) with a RV/LV diameter ratio >1.0 treated at home compared to 15 of 527 (3.0%) patients with a normal RV/LV ratio treated at home, for an Odds Ratio of 1.1 (95% CI 0.44-2.7; **Table 3**). In the group treated at home with a RV/LV diameter ratio >1.0 the following adverse events were observed: four out of five patients died during the 3-month follow up in the presence of metastasized carcinoma with all deaths occurring beyond the first 14 days after diagnosis (**Figure 1**); one major bleeding occurred on day 14, consisting of a large hematoma in the abdominal muscle sheath with a drop in hemoglobin of 2,5 mmol/l; and lastly, one event was adjudicated as recurrent VTE, consisting of an episode of chest pain on day 8 in the presence of unstable INR levels, diagnosed clinically without objective testing.

Table 3 Adverse outcomes in patients with acute pulmonary embolism treated out-of-hospital stratified by RV/LV ratio

	RV/LV ratio > 1.0 (n=224)	RV/LV ratio ≤ 1.0 (n=527)	OR	95% CI
1. All-cause mortality within 3 months	5 (2.2%)	5 (0.9%)	2.4	(0.7-8.3)
2. Major bleeding within 3 months	1 (0.45%)	3 (0.6%)	0.78	(0.1-7.6)
3. Recurrent VTE within 3 months	1 (0.45%)	7 (1.3%)	0.33	(0.0-2.7)
4. Total adverse events	7 (3.1%)	15 (3.0%)	1.1	(0.4 -2.7)

Abbreviation: RV, right ventricular; LV, left ventricular; OR, Odds ratio; VTE, venous thromboembolism;

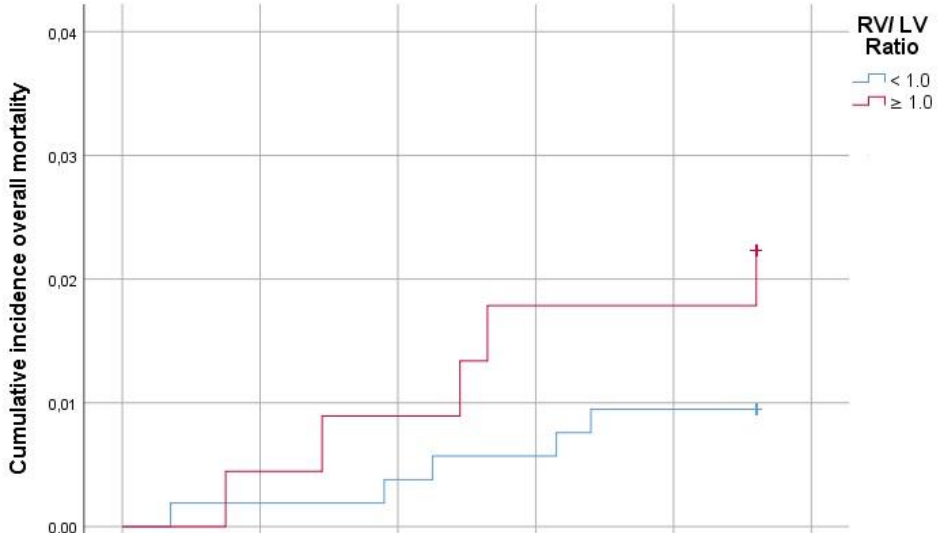

Figure 1 Cumulative incidence of overall mortality in time in patients with acute pulmonary embolism treated out-of-hospital stratified by RV/LV ratio

Secondary outcome

RV dilatation with a RV/LV diameter ratio >1.5, was present in 19 patients treated at home (2.5%). No adverse events occurred in these patients. The location of the PE involved a central pulmonary artery in 250 patients (34%). The remaining patients had segmental (n=268, 50%) or subsegmental (n=115, 16%) PE. The incidence of adverse events was 4.1% in patients with central PE and 2.3% in those with peripheral PE on CTPA (OR 1.8; 95%CI 0.75 -4.3; **Table 4**).

Table 4: Adverse outcomes in patients with acute pulmonary embolism treated out-of-hospital stratified by embolic burden

	Central PE (n=246)	Peripheral PE (n=477)	OR	95% CI
1. All-cause mortality within 3 months	3 (1.2%)	6 (1.2%)	1.0	(0.3-4.2)
2. Major bleeding within 3 months	3 (1.2%)	1 (0.2%)	2.6	(0.3-0.8)
3. Recurrent VTE within 3 months	4 (1.6%)	4 (0.8%)	1.3	(0.7-2.6)
4. Total adverse events	10 (4.1%)	11 (2.3%)	1.8	(0.8-4.3)

Abbreviation: RV, right ventricular; LV, left ventricular; OR, Odds ratio; VTE, venous thromboembolism; PE, pulmonary embolism

DISCUSSION

In this study in patients with acute PE treated at home based on absence of all Hestia criteria, our most important finding was that there was no difference in the incidence of adverse events in those with RV/LV diameter ratio >1 on CTPA compared to those without a RV/LV diameter ratio <1. Importantly, and in line with our earlier observations, RV/LV ratio >1 was present in 30% of patients treated at home.[7] Overall, the number of adverse events in patients treated at home were low, independent of RV/LV ratio and independent of the location of the PE, as was observed in the original Hestia and Vesta studies.[4,5]

In the 2019 ESC guideline, the selection of low-risk PE patients, who qualify for home treatment, is based on the PESI score or its simplified version (sPESI) combined with the mandatory absence of RV dysfunction on transthoracic echocardiography or CTPA.[3] Of the latter, the presence of RV enlargement, i.e. RV/LV ratios of > 0.9 or >1.0 measured in the transverse or four-chamber view, was used as indicator of RV dysfunction. If no other reason for hospitalization is present, patients are eligible for early discharge or home treatment. This recommendation is largely based on a recent systematic review of the literature, in which a higher early all-cause mortality was shown in low risk PE patients with abnormal cardiac biomarkers levels or signs of RV dysfunction, on CTPA or transthoracic echocardiography, compared to those with normal biomarker levels or with normal RV function.[8] These results indeed do imply that assessment of RV dysfunction by imaging methods should be considered, even in the presence of a low PESI or a negative sPESI score. However and importantly, the vast majority of studies included in this meta-analysis were observational studies with results collected post-hoc or retrospectively. No management decisions were made based on the (s)PESI. Moreover, all but one study were studies in hospitalised patients with unclear selection criteria. This implies that hospitalization in these patients was unable to prevent the mortality occurring more frequently in those with elevated RV/LV ratio. Finally, the authors could not indicate which percentage of patients had fatal PE among all-cause mortality, leaving it unclear whether there was a true association between RV dysfunction and PE-related mortality in low-risk patients.

In the current analysis, using the Hestia criteria as clinical decision rule for the selection of home treatment, we did not observe a significantly higher all-cause mortality or incidence of adverse events in patients with a RV/LV diameter ratio >1.0 on CTPA. Notably, four out of five patients with signs of RV dilatation who died during the 3-month follow up had metastasized carcinoma and all deaths occurred beyond the first 14 days after diagnosis (**Figure 1**). It is unlikely that these adverse events likely could have been prevented by initial hospital admission, given a mean hospital duration of 3.9 days in the inpatient arm of OTPE study. [6]

In our view and based on the published literature, several risk assessment methods can be used to select for home treatment: 1) the strategy recommend by the ESC, 2) the Hestia criteria, 3) the PESI score and 4) the combination of a clinical decision rule, with the majority of the exclusion criteria correspond to the items of the Hestia criteria, and the mandatory absence of signs of RV dysfunction on echocardiography or CTPA as applied in the HOT-PE trial.[3,4,6,18,19] Because all have been studied in prospective studies and shown safe, and comparative studies are lacking, none of these four strategies can be considered superior. However, efficiency and medical health care costs should also be considered when selecting the optimal approach for selecting outpatient treatment candidates. It is therefore of relevance that our analyses show that RV assessment would have excluded a large proportion of 30% of our cohort from outpatient treatment without affecting their prognosis, making the Hestia model not only less efficient but also more cost-consuming.

The results of the HOME-PE study (Clinicaltrials.gov identifier: NCT02811237), comparing safety of outpatient management in normotensive PE patients stratified by the HESTIA rule or the simplified PESI score without mandatory assessment of RV dysfunction, will shed more light on this issue.

Strengths of this analysis include the use of predefined and adjudicated outcomes of both large prospective studies and also the completeness of follow-up. The main limitation of this study is its post-hoc design. Further, of the Hestia items, one 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.[4] It is likely that this item preselects the patients at low risk of adverse events, even when signs of RV dysfunction are present. Furthermore, likely due to this preselection by the Hestia criteria, the rate of PE-associated adverse events was low leading to wide confidence intervals of our outcomes.

In conclusion, in this study, neither RV/LV ratio >1.0 nor RV/LV ratio >1.5 on CTPA and centrally located PE were associated with less favorable outcome in patients selected for outpatient treatment by the Hestia criteria, challenging the concept that RV function assessment should be used routinely to guide management in all low risk PE patients.

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