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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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Submitted
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 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). A substantial proportion of normotensive patients with PE have signs of RV dysfunction; proportions up to 60% have been reported. These patients with PE and RV dysfunction have a two to five times higher risk for short term mortality than patients without RV dysfunction.

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). High risk patients are defined as having cardiovascular shock or persisting hypotension and they have a mortality risk >30%. Normotensive patients are considered as non-high risk patients, with a lower risk for short term mortality of 2-15%. 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. 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%. The ESC guidelines recommend the restriction of PE outpatient treatment to patients with low risk, determined by laboratory or imaging parameters. 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. 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.
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. 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.

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 were excluded. Patients with severe liver impairment, chronic renal failure, and pregnant women were also excluded.

Table 1: Hestia criteria

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

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

*** Calculated creatinine clearance according to the Cockroft-Gault formula

**** Left to the discretion of the physician
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. 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.

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). 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.
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-

Figure 1: Right and left ventricular diameters measured on transversal CT-image
A: right ventricle diameter  B: left ventricle diameter
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. 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
Chapter 6

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

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

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

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
Risk stratification based on right ventricular function

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. 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. 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%.

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. 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.
References

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