Risk stratification of outpatient management in acute venous thromboembolism

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Uncertain Value of High-sensitive Troponin T for Selecting Patients With Acute Pulmonary Embolism for Outpatient Treatment by Hestia Criteria

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ABSTRACT

Background: In a randomized trial, the incremental prognostic value of normal NT-proBNP to the Hestia criteria for selecting patients with pulmonary embolism (PE) for outpatient treatment could not be established, due to low prevalence of elevated NT-proBNP. The potential role of highly sensitive troponin T (hsTnT) for this purpose has not been studied.

Aim: To investigate the added prognostic value of hsTnT measurement to the Hestia criteria in patients with acute PE treated at home, and to assess whether hospitalization because of elevated hsTnT would have prevented adverse events.

Methods: In this post-hoc analysis of the Vesta study, we assessed a 30-day adverse outcome in normotensive patients with confirmed PE managed according to the Hestia criteria with normal versus elevated hsTnT levels.

Results: Of all 550 patients included in the original Vesta study, hsTnT was measured in 347 (63%) and elevated in 58 patients (17%). The adverse 30-day composite adverse outcome occurred in 1/58 patients (1.7%) with elevated hsTnT versus 2/289 patients (0.70%) with normal hsTnT (OR 2.5, 95%CI 0.22-28). One patient (1.7%) with elevated hsTnT died compared to five with low hsTnT (1.7%; OR 1.0; 95%CI 0.11-8.7), including the only PE-related death (on day 15).

Conclusion: Although we observed a trend for elevated hsTnT towards a 2.5- fold higher 30-day adverse outcome, we could not establish an incremental value of hsTnT to the Hestia criteria due a very low overall rate of adverse events resulting in wide confidence intervals. Moreover, normal hsTnT levels did not exclude PE-associated adverse events.

INTRODUCTION

Current guidelines emphasize the importance of early risk stratification of patients with acute pulmonary embolism (PE) to facilitate assessment of the prognosis and guide therapeutic decision-making.[1,2] The Hestia criteria have been shown to select patients with PE at low risk of adverse events, who can be managed safely at home.[3-5] It has been suggested that by combining cardiac biomarkers with clinical risk stratification rules, the risk stratification could be further improved.[1,6-8] Specifically, patients with no Hestia criteria and normal cardiac biomarker levels might have an even lower risk of adverse events than patients with no Hestia criteria but an abnormal biomarker indicating right ventricular dysfunction or myocardial injury.[9,10] In a randomized controlled study, the additional incremental value of N-terminal pro brain natriuretic peptide (NT-proBNP) testing to the assessment of the Hestia criteria could not be established due, among others to a lower than expected number of Hestia criteria negative patients with elevated NT-proBNP.[4]

Several other biomarkers have been suggested to aid in the risk stratification for management of acute PE, e.g. elevated circulating levels of cardiac troponin (troponin I or T, by "conventional" or highly sensitive assays). Of those, low troponin T values have been associated with a high sensitivity and negative predictive value (NPV) in predicting an adverse 30-day outcome.[10] Also, it has been shown that troponin T values measured with a highly sensitive assay (hsTnT) provide superior prognostic information compared to the "conventional" fourth generation assay in normotensive patients with acute PE. In a subsequent multicentre observational study, these findings could be confirmed in 526 normotensive patients with acute PE.[10] None of the 127 patients (24.1%) with both hsTnT <14 pg/ml and simplified Pulmonary Embolism Severity Index (sPESI) of 0 points had an adverse outcome (NPV and sensitivity 100% each).[8]

Whether a combination of the Hestia criteria and hsTnT might provide an additional prognostic information in acute PE has not been investigated. We therefore set out to evaluate whether hsTnT measured on admission could provide additional prognostic information on top of the absence of any Hestia criteria for safe(r) outpatient management. Furthermore, we aimed to evaluate whether hospitalization of patients selected for outpatient treatment based on elevated hsTnT levels could have prevented adverse events.

METHODS

Design and patients

This is a post-hoc analysis of the Vesta study. 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 NT-proBNP measurement in patients with acute symptomatic PE.[4] This study included consecutive normotensive

patients with confirmed PE from two academic and 15 non-academic Dutch hospitals.[4] 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 recurrent venous thromboembolism (VTE), major bleeding, all-cause mortality and for 30-day adverse outcome, i.e. a composite of haemodynamic instability, intensive care unit (ICU) admission and death related to PE or major bleeding.

As part of the Vesta study, venous plasma and serum samples were obtained, processed following standard operating procedures and immediately stored at -80 °C. For the present analysis, these stored samples were used to measure concentrations of hsTnT after a single thaw. Main exclusion criterion for the current analysis was the absence of available blood samples for post-hoc hsTnT measurement, which was performed with the use of a quantitative electrochemiluminescence immunoassay (Elecsys/E170; Roche Diagnostics). The assay is specific for troponin T without relevant interferences and has an analytic range from 3 to 10,000 pg/ml. A concentration of 14 pg/ml has been identified as the 99th percentile of a healthy reference population with a coefficient of variation of less than 10%, and therefore served as the predefined threshold for an abnormal test result.

Study objective

The primary aim of this study was to compare the incidence of a composite 30-day adverse outcome in PE patients with no Hestia criteria present with a normal versus elevated hsTnT. This adverse outcome included a composite of haemodynamic instability, ICU admission and death related to either PE or major bleeding. Furthermore, we aimed to evaluate the PE-related adverse events that occurred in patients treated at home with normal versus elevated hsTnT. For this latter study aim, we only considered patients whose management was based on the Hestia criteria alone, i.e. patients who were not subjected to NT-proBNP testing in the original Vesta study.

Secondary objectives of this study were occurrence of recurrent VTE, major bleeding and all-cause mortality during the 3-month follow-up period in patients treated at home with normal versus elevated hsTnT.

Study definitions

Recurrent VTE was defined as a new intraluminal filling defect on computed tomographic pulmonary angiography (CTPA) or confirmation of a new PE at autopsy. Recurrent lower extremity DVT was defined as new non-compressibility 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).[11]

Major bleeding was defined according to the ISTH criteria and included: any bleeding resulting in death; symptomatic bleeding in a critical organ (intracranial, intra spinal, intraocular, retro-

peritoneal, intra articular and pericardial bleeding and muscle bleeding resulting in compartment syndrome) or symptomatic bleeding resulting in a decrease in the haemoglobin concentration of at least 2 g/dl or resulting in the transfusion of at least two packs of red blood cells.[12]

The cause of death among patients who died within the study period was evaluated by autopsy or based on a clinical report indicating the likely cause of death. An independent adjudication committee evaluated all relevant suspected adverse events.

Statistical analysis

Descriptive statistics tables were provided for all relevant demographic characteristics, comorbidities, risk factors for VTE, clinical findings and symptoms on admission, diagnostics procedures and biomarker measurements. 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 of patients with hsTnT <14 pg/ml compared to patients with hsTnT ≥14 pg/ml, Odds Ratios were provided with corresponding 95% confidence intervals (95%CI). Kaplan Meier analyses of patients stratified according to the hsTnT cut-off value of 14 pg/ml with regard to the primary outcomes were performed. SPSS version 25.0.0 (SPSS, IBM) was used to perform all analyses.

RESULTS

Study patients

A total of 550 patients were included in the original Vesta study, of whom 347 patients (63%) had stored blood samples for hsTnT measurement. **Table 1** summarizes the baseline characteristics of these 347 study patients.

Table 1: Baseline characteristics of study patients

	all study patients (n=347)	hsTnT <14 pg/ml (n=289)	hsTnT ≥14 pg/ml (n=58)	OR (95%CI)
Demographics				
Male, n (%)	183 (52.7%)	146 (50.5%)	37 (63.8%)	1.7 (0.96-3.1)
Female, n (%)	164 (47.3%)	143 (49.5%)	21 (36.2%)	
Age (years), mean (SD)	54.5 (15.3)	51.9 (15.6)	60.3 (13.0)	
Age >60 years, n (%)	136 (39.2%)	99 (34.3%)	37 (63.8%)	3.4 (1.9-6.1)
BMI, kg/m², mean (SD)	27.5 (4.9)	27.4 (4.8)	28.1 (5.0)	
Risk factors for VTE				
Immobilization or recent surgery, n (%)	46 (13.5%)	40 (14.1%)	6 (10.3%)	
Previous VTE, n (%)	84 (24.6%)	67 (23.6%)	17 (29.3%)	

Table 1: Baseline characteristics of study patients (continued)

	all study patients (n=347)	hsTnT <14 pg/ml (n=289)	hsTnT ≥14 pg/ml (n=58)	OR (95%CI)
Active malignancy, n (%)	23 (6.7%)	19 (6.7%)	4 (6.9%)	
Estrogen use, n (%)	54 (15.8%)	48 (16.9%)	6 (10.3%)	
Comorbidities				
Chronic heart failure, n (%)	3 (0.9%)	2 (0.7%)	1 (1.7%)	
COPD, n (%)	15 (4.4%)	12 (4.2%)	3 (5.2%)	
Clinical status and symptoms on admission				
Systolic blood pressure (mmHg), mean (SD)	138 (18.3)	137 (17.8)	140 (20.7)	
Heart rate (bpm), mean (SD)	82 (15.7)	81 (15.5)	87 (16.1)	
Oxygen saturation (%), mean (SD)	97.0 (1.9)	97.3 (1.9)	96.2 (2.2)	

Abbreviation: hsTnT, highly sensitive troponin T; OR, Odds Ratio; SD, standard deviation; VTE, venous thromboembolism; COPD, chronic obstructive pulmonary disease; bpm, beats per minute

Results of troponin testing

HsTnT levels were elevated in 58 of 347 patients (17%). Patients with elevated hsTnT were older than those with normal values (mean difference 10.7%; 95%CI 6.5 – 14.8%) and more male (64%) than female patients (36%; OR 1.7, 95%CI 0.96-3.1) had elevated hsTnT levels.

Primary outcome

The adverse 30-day composite outcome occurred in one of 58 patients (1.7%) with elevated hsTnT levels compared to two of 289 patients (0.70%) with normal hsTnT; associated with an OR of 2.5 (95%CI 0.22-28; **Table 2**).

The adverse 30-day composite outcome in the elevated hsTnT group consisted of an ICU admission because of respiratory insufficiency due to pneumonia in the right lower lobe which was temporarily treated with mechanical ventilation on day 2 after inclusion, whereas the adverse events in patients with normal hsTnT consisted of one ICU admission on day 12 because of respiratory insufficiency secondary to pneumonia, and one PE-related death on day 15. Of note, all three adverse events occurred in the direct discharge group not subjected to initial NT-proBNP testing.

Secondary outcome

All-cause death occurred in one patient with elevated hsTnT (1.7%) versus five patients with normal hsTnT (1.7%; OR 1.0; 95%CI 0.11-8.7; **Table 2**). The cumulative 3-month incidence of recurrent VTE was 1.7% (95%CI 0.0-9.2) in patients with elevated hsTnT versus 1.0% in the normal hsTnT group (95%CI 0.2-3.0) associated with an OR of 1.7 (95%CI 0.17-16; **Table 2**).

During the study period, major bleeding was observed in two patients with elevated hsTnT (3.4%) at baseline versus one with normal hsTnT (0.35%, OR 10.3; 95%CI 0.91-115).

Table 2: Outcomes of study patients stratified according to post-hoc assessed hsTnT level.

	all study patients (n=347)	hsTnT <14 pg/ml (n=289)	hsTnT ≥14 pg/ml (n=58)	OR	95% CI
30-day adverse outcome	N=3 (0.9%)	N=2 (0.7%)	N=1 (1.7%)	2.5	(0.22-28)
-PE-related mortality	N=1 (0.29%)	N=1 (0.3%)			
-ICU admission	N=2 (0.58%)	N=1 (0.3%)	N=1 (1.7%)		
3-month all-cause death	N=6 (1.7%)	N=5 (1.7%)	N=1 (1.7%)	1.0	(0.11-8.7)
Recurrent VTE at 3 months	N=4 (1.2%)	N=3 (1.0%)	N=1 (1.7%)	1.7	(0.17-16)
- DVT	N=2 (0.58%)	N=1 (0.3%)	N=1 (1.7%)		
- PE	N=2 (0.58%)	N=2 (0.7%)			
Major bleeding at 3 months	N=3 (0.9%)	N=1 (0.3%)	N=2 (3.4%)	10.3	(0.91-115)

Abbreviation: hsTnT, highly sensitive troponin T; OR, Odds Ratio; CI confidence interval; PE, pulmonary embolism; ICU, intensive care unit; VTE, venous thromboembolism;

DISCUSSION

In this analysis, in patients with PE treated at home based on Hestia criteria, we observed a 2.5 fold higher incidence of 30-day adverse outcome in those with elevated hs-TnT, with wide confidence intervals due to overall low rate of adverse events. Of note, only one of 58 patients in the elevated hsTnT group had an adverse outcome which consisted of a pneumonia necessitating mechanical ventilation at the ICU. These low adverse event rates were also observed in the original Vesta study for patients with abnormal NT-proBNP levels, because of which we were unable to draw definite conclusions on the incremental value of NT-proBNP testing in patients with PE and none of the Hestia criteria. We assume that the Hestia rule preselects patients with normal NT-proBNP and hsTnT levels, and thus low rates of PE-associated adverse events.

For optimal selection of haemodynamically stable patients with acute PE who qualify for outpatient management, proper and simple risk stratification is of utmost importance. Currently two different approaches have been applied for risk stratification: the sPESI, which predicts the 30-day mortality rate in hospitalized patients with acute PE and the Hestia criteria, which directly selects patients who may be treated at home.

In a recent systematic review of the literature, a higher all-cause mortality rate (3.8%) was observed in low-risk PE patients (according to the PESI, sPESI or Hestia criteria) with abnormal levels of cardiac troponin I or T compared to those with normal troponin levels (0.5%; OR 6.3,

95% CI 2.0–20). Furthermore, in this same analysis, PE patients with BNP/NT-proBNP values above the cut-off value had an increased risk of early PE-related adverse outcomes (OR 3.6; 95% CI 1.7–7.8), despite being "low-risk" according to clinical criteria. The authors concluded that the prognostic value of abnormal cardiac biomarkers appeared to be comparable to that of signs of right ventricular dysfunction on imaging.[6] These results, if validated by prospective management studies, are of importance for clinical decision making. Of note, most of the studies selected for this meta-analysis were observational and the results were retrospectively collected, i.e. a predefined algorithm to select patients for home treatment was not applied. Because of that, they may not be representative of the clinical setting where management decisions are taken based on one or sequential prognostic tests.

In our cohort, we found that patients with elevated hsTnT indeed had a higher incidence of 30-day adverse outcome, but not of all-cause mortality. Moreover, the rate of adverse events was generally low, and the very only adverse event that occurred in patients randomized to direct outpatient treatment but with elevated hsTnT levels was non-PE related (respiratory insufficiency due to pneumonia). Notably, the incidence of adverse events in patients with normal hsTnT was not zero. Hence, as for NT-proBNP in the original study, we could not establish an incremental prognostic value of hsTnT to the Hestia criteria for the purpose of selecting PE patients for outpatient treatment.

In general, the addition of biomarkers and/or the assessment of right ventricle dysfunction to clinical criteria will likely increase sensitivity of risk stratification in acute PE at cost of lower specificity, i.e. more patients would need to be hospitalized. The main question to be answered is which incidence as well as type of adverse events would be considered acceptable to consider outpatient management of PE 'safe'. Importantly, the decision to treat PE patients at home depends not only on PE-specific circumstances or the presence of comorbidities, but also on the healthcare system and the infrastructure in a given country as well as on local culture and patient preferences. Thus, international guidelines cannot mandate that patients with certain characteristics be treated at home, but only indicate what patient categories could be treated at home at a certain risk. The acceptability of that risk level is not necessarily the same in each different situation. In this light, although it has been established that cardiac biomarker measurements and assessment of right ventricular function improve risk stratification in patients with a sPESI of 0 points, our data do not appear to support the same conclusion for the Hestia criteria, which well may be the result of the strong preselection of low-risk PE patients by applying the Hestia criteria.

Strong points of this post-hoc analysis include the use of predefined and adjudicated outcomes of a large randomized controlled trial. The main limitation of this study is the low proportion of patients with elevated hsTnT levels, probably due to preselection by the Hestia criteria, which has led to limited statistical power for the performed analyses. Furthermore, the absence of hsTnT measurements in some study patients may cause selection bias, although samples were missing at random.

In conclusion, our data suggest that elevated hsTnT levels are associated with a 2,5 fold higher incidence of 30-day adverse outcome in patients with none of the Hestia criteria, although confidence intervals were wide and the rate of adverse events was overall low. While PE-associated death occurred in patients with normal hsTnT levels, adverse events in patients with elevated hsTnT levels were not PE-related. Hence, we could not establish an incremental value of hsTnT measurement on top of assessment of the Hestia criteria for selecting PE patients for outpatient treatment.

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