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

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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] Improved risk stratification in non–high-risk PE patients has already been shown for the combination of the simplified Pulmonary Embolism

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Severity Index (sPESI) score combined with troponin T values measured with a high-sensitive assay (hsTnT).[7]

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.

In this post hoc analysis of the Vesta study, we included consecutive normotensive patients with confirmed PE if none of the items of the Hestia criteria were present. The Vesta study was a multicenter, randomized, 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] As part of the Vesta study, venous plasma and serum samples were obtained. The main exclusion criterion for the current analysis was the absence of available blood samples for post hoc hsTnT measurement. A concentration of 14 pg/mL has been identified as the 99th percentile of a healthy reference population with a coefficient of variation of <10% and therefore served as the predefined threshold for an abnormal test result.

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 hemodynamic instability, intensive care unit admission, and death related to either PE or major bleeding. Major bleeding was defined according to the International Society on Thrombosis and Haemostasis criteria.[8] 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. The secondary objective of this study was the occurrence of all-cause mortality during the 3-month follow-up period in patients treated at home with normal versus elevated hsTnT.

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 (ORs) were provided with corresponding 95% confidence intervals (95% CI). SPSS version 25.0.0 was used to perform all analyses.

In this analysis, 347 patients (63%) had stored blood samples for hsTnT measurement of the original 550 patients who were included in the Vesta study. 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 to 14.8) and more male (64%) than female patients (36%; OR = 1.7, 95% CI = 0.96 to 3.1) had elevated hsTnT levels.

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 to 28; Table 1). 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 to 8.7; Table 1).

In this analysis, in patients with PE treated at home based on Hestia criteria, we observed a 2.5-fold higher odds of 30-day adverse outcome in those with elevated hsTnT, with wide CIs due to overall low rate of adverse events. These low adverse event rates were also observed in the original Vesta study for patients with abnormal NT-proBNP levels.

For optimal selection of hemodynamically stable patients with acute PE who qualify for outpatient

Table 1
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	3 (0.9%)	2 (0.7%)	1 (1.7%)	2.5 (0.22–28)
PE-related mortality	1 (0.29%)	1 (0.3%)		
ICU admission	2 (0.58%)	1 (0.3%)	1 (1.7%)	
3-month all-cause death	6 (1.7%)	5 (1.7%)	1 (1.7%)	1.0 (0.11–8.7)

Data are reported as *n* (%).
hsTnT = high-sensitive troponin T; ICU = intensive care unit; PE = pulmonary embolism.

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 to 20).[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; that is, 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. 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.

The main question to be answered is how hsTnT could be included as part of the decision-making process to optimize risk stratification for outpatient treatment. Currently, a prospective outcome study on that topic is lacking. Moreover, the optimal cutoff value of hsTnT in combination with a clinical decision rule to consider acute PE patients eligible for outpatient treatment is yet unknown. In this analysis we could not establish an incremental prognostic value of hsTnT with a cutoff value of 14 pg/mL, the conventional cutoff value. However, an age-adjusted hsTnT cutoff point has previously been proposed to improve the identification of elderly PE patients (age > 75 years); this increased cutoff value of 45 pg/mL seemed to be superior in predicting an adverse 30-day endpoint.[9] Secondly, and of interest is sequential assessment of troponin, like in the diagnosis of myocardial infarction, which may yield increased prognostic value. In a study assessing the kinetics of troponin I, the highest levels of that cardiac biomarker were reached 8 hours after initial presentation, leading to misclassification in 15% of patients at the time of admission.[10] Thus, the addition of hsTnT combined with the Hestia criteria could potentially be of value in the risk stratification of outpatient treatment, although this remains to be studied.

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; that is, 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 health care 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. 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, we observed an absolute higher proportion of 30-day composite outcomes in those with elevated hsTnT relative to those with normal values. This difference was not significant due to a very low overall rate of adverse events overall and resultant wide confidence intervals. Hence, we could not establish an incremental value of hsTnT measurement in patients with no Hestia criteria for selecting PE patients for outpatient treatment.

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