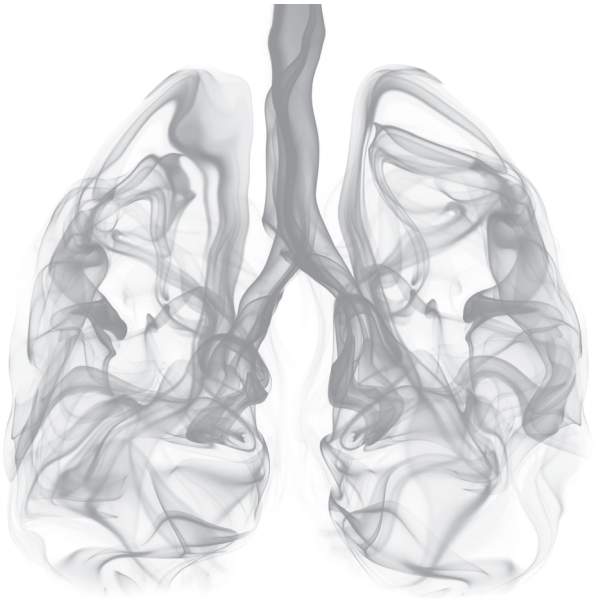
CHAPTER 7

Efficacy and safety of outpatient treatment based on the Hestia clinical decision rule with or without NT-proBNP testing in patients with acute pulmonary embolism: a randomized clinical trial



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ABSTRACT

Rationale

Outpatient treatment of pulmonary embolism (PE) may lead to improved patient satisfaction and reduced health care costs. However, trials to assess its safety and the optimal method for patient selection are scarce.

Objectives

To validate the utility and safety of selecting PE patients for outpatient treatment by the Hestia criteria, and to compare the safety of the Hestia criteria alone with the Hestia criteria combined with NT-proBNP testing.

Methods

We performed a randomized non-inferiority trial in 17 Dutch hospitals. PE patients without any of the Hestia criteria were randomized to direct discharge or additional NT-proBNP testing. The latter patients were discharged as well if NT-proBNP was ≤500ng/L or admitted if NT-proBNP was >500ng/L. Primary endpoint was 30-day adverse outcome defined as PE- or bleeding-related mortality, cardiopulmonary resuscitation or intensive care admission. The non-inferiority margin for the primary endpoint was 3.4%.

Measurements main results

550 patients were randomized. In the NT-proBNP group, 34/275 (12%) had elevated NT-proBNP values and were managed as inpatients. No patient (0/34) with elevated NT-proBNP level treated in hospital (0%; 95% CI: 0-10.2%), versus no patient (0/23) with a post-hoc determined elevated NT-proBNP from the direct discharge group (0%; 95% CI: 0-14.8%), experienced the primary endpoint. In the total trial cohorts, the primary endpoint occurred in none of the 275 patients (0%; 95%CI: 0-1.3%) subjected to NT-proBNP testing, versus in 3/275 patients (1.1%; 95%CI 0.2-3.2%) in the direct discharge group (p=0.25). During 3-month follow-up, recurrent VTE occurred in 2 patients (0.73%; 95%CI 0.1-2.6%) in the NT-proBNP group versus 3 patients (1.1%; 95%CI: 0.2-3.2%) in the direct discharge group (p=0.65).

Conclusions

Outpatient treatment of PE patients selected by the Hestia criteria alone was associated with a low risk of adverse events. Given the low number of patient with elevated NT-proBNP levels, this trial was unable to draw definite conclusions upon the incremental value of NT-proBNP testing in patients who fulfil the Hestia criteria.

INTRODUCTION

Acute pulmonary embolism (PE) is a relatively common and potentially fatal vascular disease.[1]Traditionally, patients with acute PE are hospitalized for initial treatment with parenteral anticoagulant agents. However, the introduction of low-molecular-weight heparins (LMWH), and more recently non-vitamin K dependent oral anticoagulants (NOACs), has enabled early discharge or even complete out-of-hospital treatment. For deep vein thrombosis (DVT), this strategy has become widely accepted and practiced as a result of high level evidence demonstrating equivalent efficacy and safety compared to inpatient treatment.[2,3] More recently, accumulating evidence has indicated that outpatient treatment is feasible and safe for selected, hemodynamic stable PE patients as well.[4-10] A shift from in-hospital to outpatient care may not only avoid potentially unnecessary admission but also be associated with substantial cost savings and improved patient satisfaction.[6,11]

As the short-term outcome of acute PE is associated with serious, potentially life threatening complications, it is of vital importance that careful risk stratification takes place when considering outpatient treatment.[12] Such stratification can be based on clinical criteria, biochemical measurements or radiological findings. To date, one prospective cohort study and one randomized trial have been conducted that identified low-risk PE patients for outpatient treatment solely on the basis of clinical criteria, i.e. the Hestia clinical decision rule criteria and a combination of a set of clinical criteria and the Pulmonary Embolism Severity Index (PESI) respectively, and both studies yielded promising results.[6,10] Accumulating evidence, however, suggests that adding biomarkers to clinical or radiological assessment of PE severity may improve the risk stratification process.[13,14] N-terminal pro-brain natriuretic peptide (NT-proBNP), a marker of myocardial stretch, has been most extensively studied in this setting and is the only biomarker that has been evaluated in an outcome study with outpatient treatment of acute PE. In that study, none of the PE patients selected for outpatient treatment on the basis of a combination of ad hoc defined clinical criteria and a normal NT-proBNP test result (<500ng/L) experienced an adverse clinical course.[5]

Even so, it remains unanswered whether NT-proBNP offers additional safety on top of clinical criteria in the selection of patients for home treatment, since a head-to-head comparison is still lacking to date. The present randomized clinical trial investigated whether selecting patients for home treatment on a clinical basis alone, with the use of the Hestia clinical decision rule, was as safe as combining the Hestia clinical decision rule with NT-proBNP testing. Second, we aimed to prospectively validate the utility and safety of the Hestia clinical decision rule.

METHODS

Study design

We performed an investigator initiated, randomized, non-inferiority open label clinical trial (Netherlands Trial Register identifier NTR2603), in two academic and 15 non-academic hospitals in the Netherlands.

Patients

Patients aged 18 years or older with objectively proven acute PE were screened for eligibility. Diagnostic criteria for acute PE were defined as: 1) (New) intraluminal filling defect on computed tomography pulmonary angiography (CTPA); 2) (New) high probability finding on a ventilation/perfusion (V/Q) scan; 3) (New) constant intraluminal filling defect or an abrupt cutoff of vessels greater than 2.5 mm in diameter on contrast dye pulmonary angiography or 4) Combination of a non-high probability V/Q scintigraphy with objectively documented DVT (compression ultrasonography or venography). Patients with asymptomatic or chronic (symptoms present > 14 days) PE were excluded. Patients with acute PE were eligible for randomization in case none of the items of the previously defined Hestia clinical decision rule were present (table 1).[10] For study reasons, additional exclusion criteria included a life expectancy <3 months or inability to achieve the required 3-month follow-up (e.g. foreign citizen, no fixed address). The

Table 1. Hestia clinical decision rule

Hemodynamically instable?*
Thrombolysis or embolectomy necessary?
High risk for bleeding?**
Oxygen supply to maintain oxygen saturation >90% >24 h.?
Pulmonary embolism diagnosed during anticoagulant treatment?
Severe pain needing intravenous pain medication >24 h.?
Medical or social reason for treatment in the hospital >24 h.?
Creatinine clearance of less than 30 ml/min?***
Severe liver impairment****
Pregnant?
Documented history of heparin induced thrombocytopenia?

If at least one of the above 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 109/L), uncontrolled hypertension (systolic blood pressure > 180 mm Hg or diastolic blood pressure > 110 mm Hg)

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

**** Left to the discretion of the physician

institutional review board of all participating hospitals approved the study protocol and written informed consent was obtained from all patients before randomization.

Randomization

Eligible patients were randomly allocated to undergo NT-proBNP testing or to direct discharge in a 1:1 ratio with the use of a password protected, web-based database management system.

Interventions

In patients randomized to the intervention cohort, NT-proBNP levels were assessed with a quantitative electrochemiluminescence immunoassay (Elecsys or cobas e analyzer, Roche Diagnostics, Mannheim, Germany). The cut-off value for outpatient treatment was predefined at 500 ng/L, consistent with previous studies.[5,15] To put this threshold into perspective, the mean NT-proBNP level is estimated to be 70 pg/L in the general population.[16, 17] Patients with an elevated NT-proBNP were admitted to the hospital and patients with an NT-proBNP level < 500 pg/mL were discharged within 24h of diagnosis. All patients randomized to the direct discharge cohort were discharged within 24h of diagnosis without additional biochemical tests. In these patients, venous plasma and the serum samples preferably taken at arrival on the Emergency Department were obtained and stored immediately at minus 80°C, for post-hoc NT-proBNP measurement. This was performed after a single thaw with use of a quantitative electrochemiluminescence immunoassay (Elecsys/E170, Roche Diagnostics, Mannheim).

All patients were treated with LMWH and vitamin K antagonists (VKA) according to the standard care for patients with PE recommended by international guidelines.[18] This consisted of weight-adjusted doses of LMWH for at least five days and concomitant start of vitamin K antagonists. LMWH was discontinued when the international normalized ratio (INR) was 2.0 or more for two consecutive days. In patients with active cancer, LMWH was continued at therapeutic doses as mono-therapy for at least three months. Patients selected for outpatient treatment received an emergency contact number on a pocket card outlining the symptoms suggestive of a recurrent PE or DVT. Patients were evaluated at the outpatient department after 5-9 days from discharge. For patients selected for inpatient treatment, the duration of in hospital treatment was determined by the local physician. After seven days patients were contacted either in the hospital or by telephone (if they had already been discharged). For all patients, two additional study visits were planned after 4-6 weeks and after three months. The final study visit was allowed to be either at the outpatient clinic or by telephone.

Endpoints

The primary endpoint was a 30-day adverse outcome defined as PE related mortality, major bleeding related mortality, cardiopulmonary resuscitation, admission to an Intensive Care Unit, or requirement of thrombolytic therapy or surgical embolectomy.

Secondary endpoints were symptomatic recurrent venous thromboembolism (VTE), major bleeding and all-cause mortality during three months of follow-up. Recurrent VTE was defined as recurrent PE if demonstrated by new defects on CTPA, perfusion-ventilation lung scan, pulmonary angiography, PE demonstrated at autopsy or a clinical report indicating PE as the (likely) cause of death; recurrent VTE was defined as recurrent DVT if demonstrated by compression ultrasonography or contrast venography showing a thrombus in a new area or in the same area after a normal echo in the past. Bleeding was defined as major if it was clinically overt combined with at least one of the following situations: 1) Critical site involvement e.g. intracranial, retroperitoneal, intraocular, intraspinal, pericardial or non-traumatic intra-articular; 2) Bleeding associated with a decrease in hemoglobin level of 1.3 mmol/L (2.0 gr/dl) or more; 3) Bleeding leading to transfusion of ≥ 2 units of whole blood or packed red cells; 4) Fatal bleeding.[19] The cause of death in patients who died within the study period was assessed by autopsy or a clinical report indicating the -likely- cause of death.

An independent adjudication committee consisting of two experts not involved in the study evaluated all possible endpoints, i.e. adverse outcome, recurrent VTE, major bleeding, or death. Any dispute was resolved by a third opinion.

Monitoring and judging of the plausibility of serious adverse events (death, adverse outcome, recurrent PE, DVT, bleeding, hospitalization) of study patients was carried out by a data safety monitoring board The independent DSMB reviewed safety data at regular intervals. The DSMB assessed the category classification and seriousness of reported adverse events and their possible relation to the study drug. Serious adverse events were also transmitted to the study investigators as well as institutional review boards as per local regulations.

Statistical analysis

The primary and secondary endpoint analyses were based on all events that occurred in the intention-to-treat population.

Our hypothesis was that patients with high NT-proBNP levels treated at home at least did not have a higher rate of adverse outcome than patients with high NT-proBNP who were initially hospitalized. To prove our hypothesis, we aimed to compare the proportion of adverse events between the group with high NT-proBNP treated in the hospital and the group with post-hoc determined high NT-proBNP from the direct discharge group. The non-inferiority margin for our primary endpoint was 3.4%, meaning that the maximum difference in the rate of adverse outcomes between the two study arms is

3.4%. The risk of 30-day adverse outcome in both treatment groups was assumed to be 1%.[5, 10] The test statistic used was the one-sided Z test (pooled). With a targeted significance level of 0.0500 and a power of 80%, 106 patients in each study cohort were needed to prove our hypothesis. Based on previous results, it was estimated that 40% of patients would have elevated NT-proBNP levels.[5, 15] Therefore a total of 530 patients would have to be randomized to achieve the sample size of 106 patients in each high NT-proBNP group.

In a secondary analysis, we aimed to assess whether selecting PE patients for outpatient therapy based on the Hestia clinical decision rule alone would be non-inferior to performing additional NT-proBNP testing, by comparing the two total study arms with respect to the risk of the primary endpoint, again using the non-inferiority margin of 3.4%. In addition, the groups were compared for all secondary endpoints separately, with use of the two-sided chi-square test of proportions, or the Fisher's exact test.

To validate the safety of the Hestia clinical decision rule, the upper limit of the 95% CI interval of the risk of recurrent VTE in patients assigned to the direct discharge group had to be below 7% with a point estimate of 3%, as defined in the original Hestia study, which would require a total of 257 patients in each arm (power 0.91; one-sided binomial test).[10]

SPSS version 20 (SPSS Inc, Chicago, IL) was used to perform all analyses.

RESULTS

Patients

Between December 2010 and February 2014, a total of 1102 patients were screened for eligibility in the participating hospitals. Of those, 544 (49%) were ineligible for randomization according to the reasons specified in figure 1. The most frequent reasons for ineligibility included requirement for oxygen therapy (33.5%) and other medical or social reasons that required inpatient treatment (23.7%). The most frequent medical or social reasons included: Twenty-one patients were admitted because of committed pneumonia. Sixteen patients were admitted because analysis was required for a suspected malignancy or another medical disease. In eleven patients, the attending physician decided to hospitalize the patient because of the extend of the thrombus load at CTPA. Ten patients were found to have elevated troponins, EKG changes or heart rhythm disorders and were admitted to a cardiology department or coronary care unit. Seven patients suffered of delirium or cognitive dysfunction. In nine patients, outpatient treatment was not possible due to complaints caused by malignant disease. In another nine patients, other acute medical conditions required hospitalization (e.g. hyponatremia, COPD exacerbation). In seven patients the home situation was deemed unsafe for outpatient treatment. Finally, six patients were anxious and refused being treated at home.

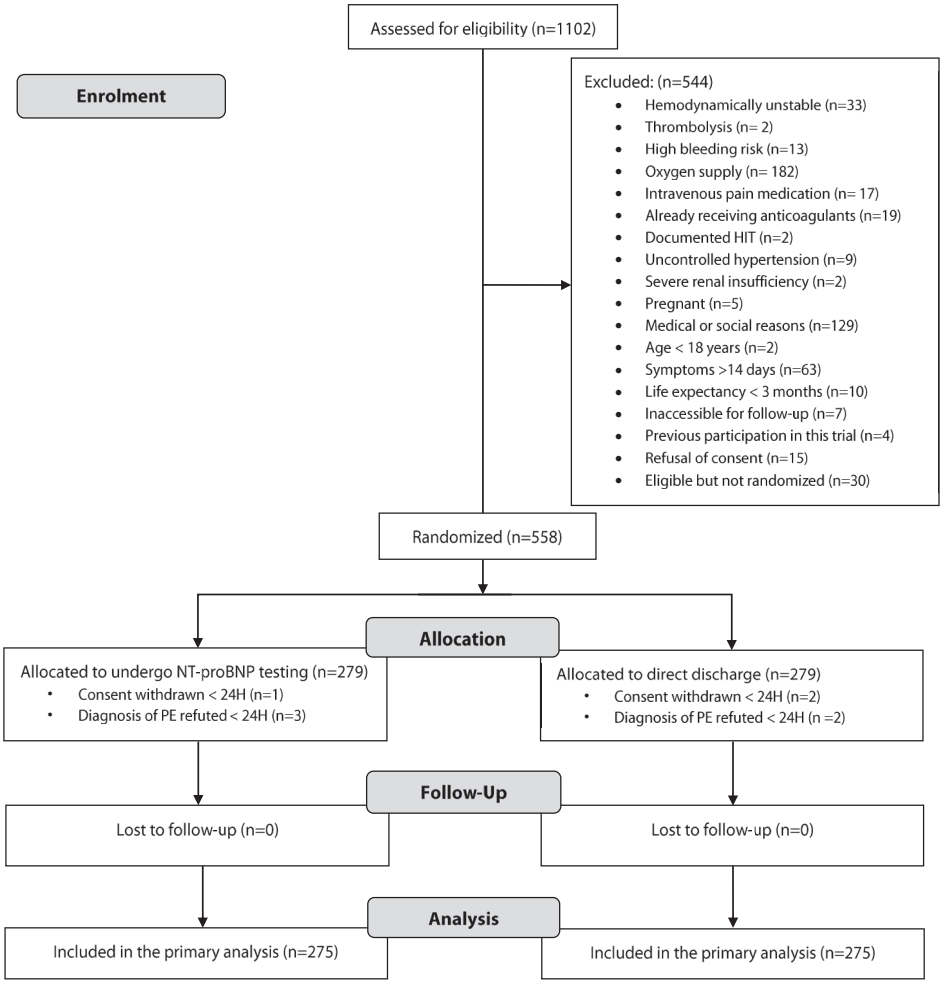

Figure 1. Flow of patients through the study

Of the 558 eligible patients, in both groups four patients were excluded from all analyses because of withdrawal of consent (n=4) or because the diagnosis of PE was rejected at second evaluation of the images (n=4) after randomization.

The demographic criteria, medical history and clinical characteristics of the 550 randomized patients included in the analysis are shown in table 2. A total of 297 male patients were included (54%). Two-hundred-and-seventy-five patients were randomized to be subjected to NT-proBNP testing. Of those patients, 34 (12.4%) had a NT-proBNP level >500ng/L and were treated as inpatients. Mean duration of their hospitalization was 3.5 days. There were three protocol violations: two patients from the NT-proBNP group were hospitalized even though NT-proBNP levels were normal, and one patient

Table 2. Baseline Characteristics

Characteristic	NT-proBNP (N=275)	Direct discharge (N=275)
Age (mean ± SD)	55 (15)	53 (15)
Age > 60 (n, %)	108 (39.3)	99 (36.0)
Male sex (n, %)	145 (52.7)	152 (55.3)
BMI (kg/m2, mean ± SD)	27.0 (4.6)	27.7 (5.2)
VTE Risk factors		
Immobilization or recent surgery (n, %)	33 (12.2)	39 (14.4)
Previous PE (n, %)	41 (15.1)	45 (16.6)
Previous DVT (n, %)	30 (11.0)	28 (10.3)
Active Malignancy (n, %)	23 (8.5)	14 (5.2)
Estrogen use (n, %)	50 (18.4)	45 (16.6)
Clinical signs and symptoms		
Duration of complaints, days (mean ± SD)	4 (3.2)	4 (3.5)
Suspected DVT (n, %)	38 (13.8)	41 (14.9)
Heartrate(mean ± SD)	83 (15.2)	82 (15.7)
Systolic blood pressure mmHg(mean ± SD)	137 (17.1)	139 (19.3)
D-dimer (mean± SD)	2960 (3159)	2878 (4275)
Comorbidities		
COPD with therapy (n, %)	9 (3.3)	14 (5.2)
Heart failure with therapy (n, %)	3 (1.1)	2 (0.7)

N, number; SD, standard deviation; VTE, venous thromboembolism; DVT, deep vein thrombosis; COPD, chronic obstructive pulmonary disease; NT-proBNP, N-terminal pro-brain natriuretic peptide

assigned to the direct discharge group was initially hospitalized for four days. All other patients were discharged within 24 hours of diagnosis. Mean duration of stay in the hospital was 18 hours for patients randomized to undergo NT-proBNP testing, and 10 hours for patients randomized to direct discharge. Of the 275 patients in the direct discharge group, post-hoc NT-proBNP measurement was possible in 240 (87%). Of those patients, 23 (9.6%) had elevated NT-proBNP levels. No patient was lost to follow-up.

Primary endpoint

No patient (0/34) with an elevated NT-proBNP level treated in hospital (0%; 95% CI: 0-10.2%), versus no patient (0/23) with a post-hoc determined elevated NT-proBNP from the direct discharge group (0%; 95% CI: 0-14.8%), experienced the primary endpoint.

Further, in the total study cohorts, no patient assigned to NT-proBNP testing (0%; 95% CI: 0-1.3%) experienced the primary endpoint versus three of the patients assigned to direct discharge (1.1%; 95% CI: 0.2-3.2%) (p=0.25): absolute difference 1.1% (95% CI: -0.46% - 3.2%). All these three patients had an NT-proBNP level below 500ng/L, as

measured post-hoc. A clinical description of these cases is provided in table 3. In all three patients, the adjudication committee concluded that the predefined definitions of the primary endpoint had been fulfilled.

After 10 days of follow-up, the primary endpoint had occurred in no patient assigned to NT-proBNP testing (0/275, 0%) and in one patient assigned to direct discharge (1/275, 0.4%).

Recurrent venous thromboembolism

A total of five patients developed recurrent VTE during follow-up; two patients (0.73%; 95% CI: 0.09 – 2.6%) who were assigned to NT-proBNP testing versus three patients (1.1%; 95% CI: 0.2-3.2%) assigned to direct discharge (p=0.65). In both groups, none of the patients with recurrent VTE had elevated levels of NT-proBNP at baseline. In the NT-proBNP testing group, one patient with lung cancer developed DVT of both the lower and upper extremity during follow-up. Another patient was diagnosed with CTPA proven recurrent PE, whilst the INR was adequate. In the direct discharge group, one patient developed DVT two months after randomization. INR levels were suboptimal at time of the recurrent event and LMWH was re-started. Another patient in the direct discharge group was readmitted during follow-up with new thoracic pain whilst the INR was inadequate. Anticoagulant treatment was intensified. Although no new imaging tests were performed, this patient was adjudicated to have recurrent PE on clinical grounds. Finally, one patient in the direct discharge group experienced sudden death after 15 days, adjudicated as possibly due to recurrent PE (case 1, table 3).

Major bleeding

One patient (0.4%; 95% CI: 0.01-2.0%) in the NT-proBNP group versus three patients (1.1%; 95% CI: 0.2-3.2%) in the direct discharge group experienced major bleeding (p=0.62). In the NT-proBNP group, one patient experienced traumatic bleeding of the lower extremity whilst INR was 7.6, leading to a significant drop in haemoglobin. In the direct discharge group, one patient developed an intra-abdominal bleeding one month after randomization after laparoscopic cystectomy which she had undergone two days before randomization. The second patient developed pericardial bleeding which was likely related to a pacemaker implantation one month before randomization. Finally, the third patient developed gastrointestinal bleeding requiring blood transfusion. All four patients fully recovered.

Mortality

During the 3 months follow-up period, four patients died (1.5%) in the NT-proBNP group versus three (1.1%) in the direct discharge group (p=0.70). In the NT-proBNP group, two patients died because of progressive lung cancer and one patient because of metas-

Table 3. Case descriptions of primary endpoint events

Gender, age	Case description	Vital signs and biochemical markers at initial diagnosis of PE	Conclusion	Outcome
Female, 69yrs	Patient was assigned to the direct discharge group. She was seen at the outpatient clinic 4 days later according to study protocol. At that time she was still using LMWH and VKA. Two weeks later she suddenly felt unwell after dinner and complained of severe flank pain. She went to bed were she collapsed. At time of arrival of the ambulance the patient had already died. She used LMWH as well as VKA until the day she died because INR levels were still inadequate. Permission for autopsy was not obtained.	Heart rate: 76/min RR: 138/89 mmHg D-dimer 2560 ng/mL NT-proBNP: 232 pg/mL	Death because of possible recurrent PE	Death
Female, 47yrs	Patient was assigned to the direct discharge group. One week later the patient was readmitted because of dyspnoea and coughing, which was diagnosed as a respiratory tract infection. Because of progressive dyspnoea, patient was admitted to the IC 5 days later. She responded well to high flow oxygen therapy and returned to the general ward 3 days later. Because of progressive alveolar consolidations, unresponsive to antibiotic treatment, patient was transferred to an academic hospital and admitted to the Intensive Care because of respiratory insufficiency. Bronchoalveolar lavage fluid was positive for Serratia, influenza B virus, and Aspergillus. Although these conditions were all treated, her medical condition worsened. She developed several episodes of pneumothorax due to high pressure ventilation. At last, oxygenation was no longer possible and it was decided to stop treatment after which the patient died.	Heart rate: 80/min RR: 140/84 D-dimer: not determined NT-proBNP: 64 pg/mL	Death because of respiratory insufficiency due to a combination initial PE, pulmonary infection and ARDS with complicated pneumothorax.	Death
Male, 54yrs	Patient was assigned to direct discharge group. Two days later he returned to the emergency department because of progressive dyspnea and thoracic pain. A chest X-ray was suggestive for pneumonia in the right lower lobe. Because of respiratory insufficiency not responding to CPAP, patient was admitted to the IC where he temporary was treated with mechanical ventilation. Eventually the patient responded well to antibiotic treatment after which he was discharged to a general ward.	Heart rate: 92/min RR: 116/98 mmHg D-dimer: 1833 ng/mL NT-proBNP: 390 pg/mL	Respiratory insufficiency due to a combination of initial pulmonary embolism and respiratory tract infection	Fully recovered

PE, pulmonary embolism; LMWH, low-molecular-weight heparins; VKA, vitamin K antagonists; INR, international normalized ratio; CPAP, continuous positive airway pressure.

Table 4. Primary and secondary endpoints

Outcome	NT-proBNP (n=275)	Direct discharge (n=275)
Primary endpoint* at day 30	0	3 (1.1%)
PE related mortality	0	1 (0.36%)
ICU admission	0	2 (0.73%)
Recurrent VTE at 3 months	2 (0.73%)	3 (1.1%)
DVT	1 (0.36%)	1 (0.46%)
Recurrent PE	1 (0.36%)	2 (0.73%)
Major bleeding at 3 months	1 (0.36%)	3 (1.1%)
All-cause mortality at 3 months	4 (1.5%)	3 (1.1%)

N, number; PE, pulmonary embolism; VTE, venous thromboembolism; DVT, deep vein thrombosis; ICU, intensive care unit.
*defined as the occurrence of defined as PE or major bleeding related mortality, cardiopulmonary resuscitation, admission to an Intensive Care Unit, or requirement of thrombolytic therapy or surgical embolectomy.

tasized cholangiocarcinoma. The fourth patient was diagnosed with recurrent B-cell lymphoma at time of PE diagnosis. During follow-up she died in a nursing home because of suspected sepsis of unknown origin. In the direct discharge group, one patient died because of progressive lung cancer. The last two patients who died have been described in table 3 (case 1 and 2).

DISCUSSION

The Hestia clinical decision rule was constructed to provide a simple set of readily available clinical criteria to triage possible candidates for outpatient treatment. The safety of this decision rule has thus far only been assessed in one prospective, single-arm management study.[10] In the present trial, we observed that in patients who were sent home on the basis of the Hestia clinical decision rule alone, the 3-month risk of recurrent VTE was 1.1% with an upper limit of the 95% CI reaching 3.2%. This was well within the predefined safety limit of 7%. Hence, this study serves as an external validation of the Hestia clinical decision rule. Further evidence for the safety of outpatient treatment based on clinical criteria alone comes from the recently published Outpatient Treatment of PE (OTPE) trial.[6] In this trial, a set of clinical criteria combined with the PESI score was used to select outpatient treatment candidates. No difference was observed in the 3-month rate of recurrent VTE for patients with a low PESI score treated at home (0.6%) versus those treated in hospital (0%). These rates of recurrent VTE compare well to the risk observed in both study arms in our trial.

There are several differences between the Hestia clinical decision rule and the PESI rule or its simplified version (sPESI).[20,21] First, the (s) PESI rule was constructed to assess 30-day all-cause mortality instead of providing an estimation of the risk of complications directly related to PE or its treatment. Second, a great practical advantage of the Hestia rule over the (s) PESI score is that the Hestia rule doesn't by definition exclude patients with cancer or patients of older age. The Hestia rule is therefore able to select a larger proportion of outpatient candidates out of the total PE population, underlined by the fact that both in the original Hestia study and the present trial, approximately 50% of all patients screened for eligibility could be treated at home, compared to only 30% in the OTPE trial. Finally and importantly, the (s) PESI score has never been prospectively evaluated to be used as a sole decision tool to treat patients with acute PE at home directly.

NT-proBNP plasma levels, reflecting myocardial stress and thereby the severity of hemodynamic compromise in acute PE, have been extensively studied as a biomarker to optimize risk stratification in PE patients.[15,22,23] Low NT-proBNP levels are associated with a low risk for adverse outcome.[24] This was also observed in a single-arm outcome study in which PE patients selected for outpatient treatment on the basis of clinical criteria and low NT-proBNP levels did not experience any adverse events during follow-up.[5] However, in the most recent guidelines of the European Society of Cardiology (ESC) on the diagnosis and management of acute pulmonary embolism, further risk stratification with cardiac biomarkers is not advocated in patients classified as low-risk with use of the (s)PESI score and those patients could be considered for outpatient therapy.[25] Nevertheless, these guidelines still state that, if NT-proBNP levels are known and are elevated in patients with a low (s)PESI score, patients should be regarded as intermediate-low risk and therefore not suitable for outpatient management. The present trial provides proof for the concept that the assessment of outpatient eligibility could be based on a clinical decision rule alone, irrespective of NT-proBNP levels. This approach based on clinical factors alone would facilitate efficiency and cost-savings in the busy emergency department.

This trial has some aspects that warrant comment. First, the proportion of patients with elevated NT-proBNP levels was considerably lower than anticipated from previous studies. Consequently, we were unable to include the number of patients with elevated NT-proBNP levels as calculated in the power analysis. Increasing the sample size would have led to a vast increase in the number of patients to be included, that was not feasible within our resource capabilities. Therefore, we are unable to definitively conclude whether treating patients selected with the Hestia clinical decision rule with elevated NT-proBNP levels at home is non-inferior to treating them in an inpatient setting. Even so, the most likely explanation for the low number of patients with an elevated NT-proBNP is that the Hestia rule is able to pre-select patients with normal NT-proBNP levels. To further explore this hypothesis, we chose to include an additional

analysis, which compared the total study groups with respect to all primary and secondary endpoints. Although this analysis was not included in the original study protocol, it used identical statistical conditions as was predefined for the primary and secondary endpoints: i.e. a non-inferiority margin difference between the group proportions of 3.4% for the primary endpoint. The very low and non-significant risks of adverse outcome between the two study groups, supports our conclusion that NT-proBNP testing does not clearly provide incremental safety when selecting patients with acute PE for outpatient treatment. Of note, a recent study identified a NT-proBNP cut-off level of 600 pg/mL as the optimal cut-off for distinguishing low-risk from intermediate risk patients with acute PE.[23] This less strict cut-off would have identified even less patients with elevated NT-proBNP levels in our study sample, further supporting the hypothesis that risk stratification can take place on a clinical basis alone. Second, our study had an open-label design, which could have enhanced the risk of bias in the assessment of outcome events. To decrease this risk, all patients were instructed to contact the hospital in case of symptoms suggestive of recurrent VTE and all endpoints were adjudicated by an independent committee unaware of the study intervention assignment. Third, since NOACs were not yet registered for the treatment of VTE during the inclusion period of this trial, we were unable to assess the performance of these agents in the specific setting of outpatient PE treatment. As NOACs do not require laboratory monitoring and continuous dose-adjustment, these agents may further facilitate the management of acute PE on an outpatient basis. Beam et al. reported promising results for the use of the NOAC rivaroxaban in an outpatient setting.[26] In a small observational study including 106 VTE patients, of whom 35 had PE, patients triaged for outpatient treatment based on the Hestia criteria and subsequently treated with rivaroxaban had a favourable outcome without any VTE recurrences or major bleeding complications during treatment. At present, a single-arm management trial aims to confirm these findings, aiming at a total of 1100 PE patients who fulfil the Hestia criteria treated on an outpatient basis with rivaroxaban (EudraCT No.: 2013-001657-28).

This trial confirms that outpatient treatment of patients presenting with acute PE selected by the Hestia clinical decision rule alone is feasible and associated with a very low risk of adverse events. This is important since it reaffirms findings of an earlier study.[10] Given the low number of patient with elevated NT-proBNP levels, this trial was unable to draw definite conclusions upon the incremental value of NT-proBNP testing in patients who fulfil the Hestia criteria. Larger trials will be required to answer this question.

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