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Triaging acute pulmonary embolism for home treatment by Hestia or simplified PESI criteria: the HOME-PE randomized trial

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‡A list of the investigators and collaborator members of the HOME-PE study group is provided in the Acknowledgements section.

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Aims

The aim of this study is to compare the Hestia rule vs. the simplified Pulmonary Embolism Severity Index (sPESI) for triaging patients with acute pulmonary embolism (PE) for home treatment.

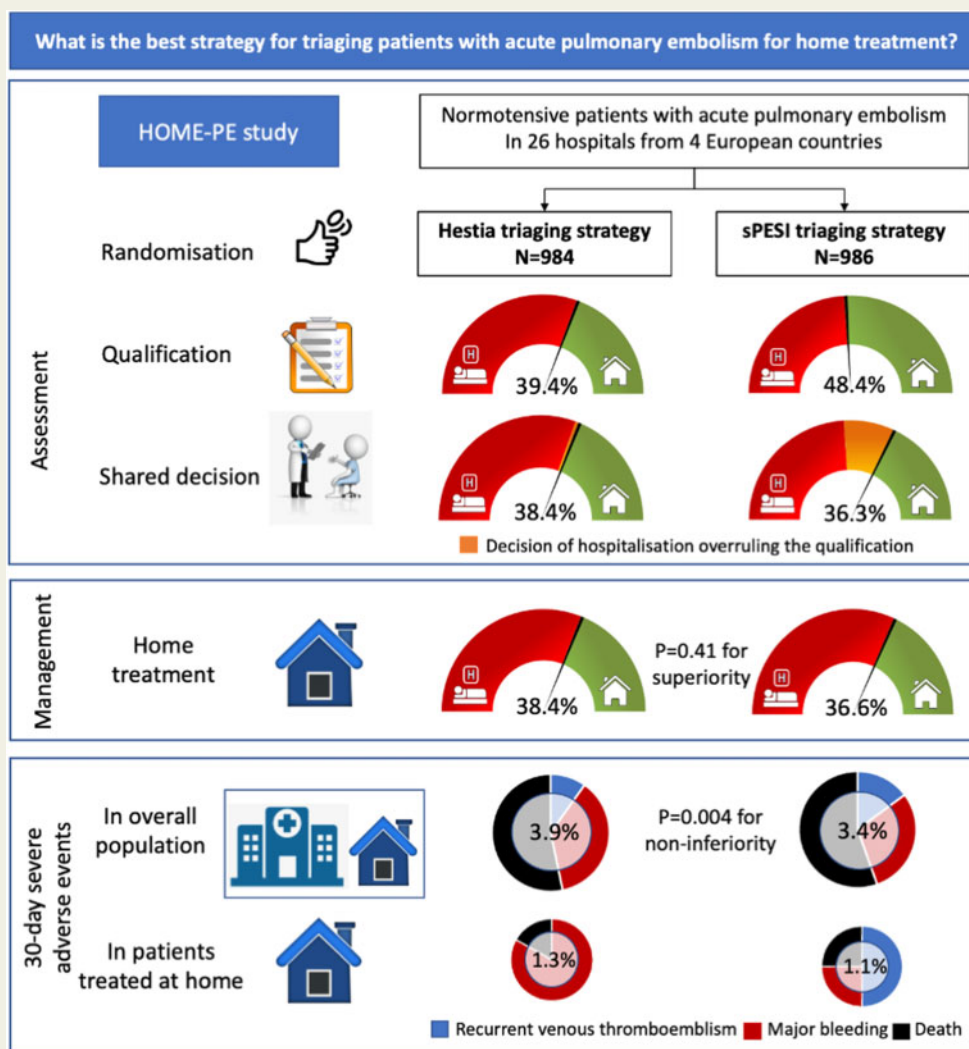
Methods and results

Normotensive patients with PE of 26 hospitals from France, Belgium, the Netherlands, and Switzerland were randomized to either triaging with Hestia or sPESI. They were designated for home treatment if the triaging tool was negative and if the physician-in-charge, taking into account the patient's opinion, did not consider that hospitalization was required. The main outcomes were the 30-day composite of recurrent venous thrombo-embolism, major bleeding or all-cause death (non-inferiority analysis with 2.5% absolute risk difference as margin), and the rate of patients discharged home within 24 h after randomization (NCT02811237). From January 2017 through July 2019, 1975 patients were included. In the per-protocol population, the primary outcome occurred in 3.82% (34/891) in the Hestia arm and 3.57% (32/896) in the sPESI arm ($P=0.004$ for non-inferiority). In the intention-to-treat population, 38.4% of the Hestia patients (378/984) were treated at home vs. 36.6% (361/986) of the sPESI patients ($P=0.41$ for superiority), with a 30-day composite outcome rate of 1.33% (5/375) and 1.11% (4/359), respectively. No recurrent or fatal PE occurred in either home treatment arm.

Conclusions

For triaging PE patients, the strategy based on the Hestia rule and the strategy based on sPESI had similar safety and effectiveness. With either tool complemented by the overruling of the physician-in-charge, more than a third of patients were treated at home with a low incidence of complications.

Graphical Abstract



The international randomized HOME-PE study demonstrates that, for triaging patients with acute pulmonary embolism for home treatment, the Hestia rule and the simplified Pulmonary Embolism Severity Index, complemented by the physician's overruling, are equally safe and efficient.

Keywords

Pulmonary embolism • Emergency department • Home treatment • Randomized controlled trial • Clinical decision-making • Risk assessment

Introduction

International guidelines suggest home treatment in patients with low-risk acute pulmonary embolism (PE), when home circumstances are adequate.^{1,2} However, current evidence is mainly based on cohort studies using different sets of eligibility criteria.^{3,4} Therefore, controversy persists about the optimal triaging strategy and eligibility criteria for home treatment.³

The approach proposed by the European Society of Cardiology firstly refers to a 30-day all-cause mortality risk assessment using the Pulmonary Embolism Severity Index (PESI) or the simplified PESI (sPESI)^{1,5,6} (Table 1). The Hestia rule, a checklist of medical and social criteria precluding home treatment, is proposed as an alternative^{1,7} (Table 2). Although the Hestia rule was not primarily designed as a risk assessment model, the rate of complications in patients treated at home on the basis of a negative Hestia rule was low in prospective cohort studies, the 3-month mortality rate ranging from 0.5% to 1%.⁷⁻⁹ Moreover, the strategy based on the Hestia rule may lead to a higher proportion of PE patients treated at home than the strategy based on the sPESI.¹⁰ Indeed, around 50% of normotensive PE patients were discharged home within 24 h of diagnosis in studies applying the Hestia rule alone.⁷⁻⁹ Conversely, in studies using the PESI or the sPESI, medical or social exclusion criteria complemented the index, leading to a proportion of patients treated at home of <30%.^{11,12} However, the two strategies had never been prospectively compared head-to-head.

The aim of the present trial was to compare the safety and effectiveness of the Hestia rule vs. the sPESI for triaging PE patients for home treatment, in the way they are applied in routine practice, i.e. with the possibility of the physician to overrule the triaging tool result and to take into account the patient's opinion in a shared decision-making. Our research hypothesis was that the 30-day rate of complications of a triaging strategy based on the Hestia rule would be non-inferior to a strategy based on the sPESI and that the Hestia strategy would lead to a higher rate of patients treated at home than the sPESI strategy.

Methods**Trial design**

HOME-PE study was an international randomized open-label non-inferiority trial, to compare a triaging strategy based on the Hestia rule with a strategy based on the sPESI for home treatment of patients with acute PE. The detailed trial protocol is available in the [Supplementary material](#) online. The trial was conducted in 26 hospitals from France ($n = 15$), Belgium ($n = 5$), the Netherlands ($n = 5$), and Switzerland ($n = 1$). Among them, 18 (69%) were university hospitals and 8 (31%) general hospitals. Prior to study initiation, 9 (35%) centres had a very-low level, 8 (31%) a low level, 5 (19%) an intermediate level and 4 (15%) a high level of experience in home treatment of patients with PE according to local investigators. There was no difference between university hospitals and general hospitals, 12/18 (67%) and 5/8 (62%) having a low or very-low level of

experience, respectively. The study was approved by the relevant regulatory authorities and by the ethics committee *CPP—Ouest II (France)* for all the hospitals in France and by the ethics committee of the participating hospitals for Belgium, Switzerland, and the Netherlands. An independent Data and Safety Monitoring Board provided a timely review of data quality and safety of the clinical trial.

Patients

Patients presenting to the emergency department or just admitted in a clinical observation unit were eligible if they were 18 years or older, had objectively confirmed acute symptomatic PE [either by (i) a high-probability ventilation/perfusion lung scan, (ii) a new contrast segmental or more proximal filling defect on spiral computed tomography or on pulmonary angiography, or (iii) a new proximal deep vein thrombosis (DVT), i.e. thrombus in the popliteal vein or above, on venous compression ultrasonography along with clinical signs of PE]¹³ and provided oral and written informed consent. Patients were excluded if PE had been diagnosed more than 24 h prior to enrolment, if they had been admitted for more than 48 h, had shock or hypotension (defined as a systolic blood pressure <90 mmHg or a systolic blood pressure drop by ≥ 40 mmHg for more than 15 min, and not caused by a new-onset arrhythmia, hypovolaemia, or sepsis), or had conditions precluding 30-day follow-up (e.g. short life expectancy or geographical inaccessibility).

Randomization

Included patients were centrally randomized via a secure interactive web response system in a 1:1 ratio to one of the two triaging arms, with variable-size block stratification according to the hospital.

Procedures

In patients randomized to the Hestia group, the physician assessed the 11 criteria of the rule (Table 2) and patients qualified for home treatment if all criteria were negative. Patients in whom a positive criterion with a 24-h time window improved within 24 h, also qualified for home treatment. All other patients qualified for hospitalization. As per-protocol, the physician-in-charge could overrule the Hestia qualification. They assessed if there was a major reason requiring an overruling of the result of the Hestia rule and took into account the patient's preference in a shared decision-making. A justification explaining the cause of overruling was required.

In the patients randomized to the sPESI group, the physician assessed the six criteria of the index and patients qualified for home treatment if the sPESI was 0 points. They qualified otherwise for hospitalization. As per-protocol, the physician-in-charge could overrule the sPESI qualification in the same way as performed in the Hestia arm. They assessed if there was a major reason requiring an overruling of the result of sPESI and took into account the patient's preference in a shared decision-making. A justification explaining the cause of overruling was required.

In both groups, patients designated for home treatment were to be discharged home within 24 h following randomization.

In all participating hospitals, a specific patient pathway was set up prior to study initiation to organize home treatment. A dedicated clinical team, consisting of physicians who normally were responsible for the treatment and follow-up of PE patients in each hospital, conducted the follow-up of patients and offered a telephone service in case of suspected complications. The patients received therapeutic anticoagulation according to

Table 1 The simplified Pulmonary Embolism Severity Index

sPESI criteria	Points
Age >80 years	1
History of cancer	1
Chronic cardiopulmonary disease	1
Systolic blood pressure <100 mmHg	1
Heart rate \geq 110 b.p.m.	1
Arterial oxygen saturation <90%	1

The sPESI score is the sum of the assigned points for each criterion. If the sPESI score is 0 points, i.e. the patient classified as low 30-day risk of death, patient qualification is home treatment. If the sPESI score is >0, i.e. the patient classified as high 30-day risk of death, patient qualification is in-hospital treatment. sPESI, simplified Pulmonary Embolism Severity Index.

international guidelines, the choice of which was left to the discretion of the physician-in-charge.^{2,13} All patients were followed for 90 days. They were contacted within 3 days following randomization and at 14 ± 3 , 30 ± 5 , and 90 ± 15 days.

Outcomes

The primary outcome of the study was the composite rate of recurrent venous thrombo-embolism (VTE), major bleeding or all-cause death within 30 days after randomization. Recurrent VTE was defined as symptomatic, objectively confirmed DVT, non-fatal or fatal PE. Major bleeding was defined according to the criteria proposed by the International Society on Thrombosis and Hemostasis.¹⁴ All clinical events were adjudicated by an independent event adjudication committee, whose members were unaware of group assignments.

The first secondary outcome was home treatment, strictly defined as patients discharged home within 24 h following randomization. The exact times of discharge were extracted from the patients' administrative report forms, independently of patient allocation and whether the patient qualified for home treatment. The second secondary outcome was qualification for home treatment according to the allocated rule, i.e. patients meeting no criteria of the Hestia rule, or patients with an sPESI of 0 points.

We further assessed and compared the rate of the 30-day composite outcome in patients treated at home. Lastly, we determined and compared the applicability of both triaging tools defined as the proportion of patients who left the hospital in the first 24 h after randomization among those who qualified for home treatment.

Statistical analysis

The analyses were performed in compliance with the CONSORT statement. The analyses for the primary outcome and the two main secondary outcomes followed a hierarchical approach in three steps. The 1st step was a non-inferiority analysis of the primary outcome for the Hestia vs. the sPESI strategy and was performed in the per-protocol population by logistic regression adjusted for hospital organization regarding PE.¹⁵ The 2nd and 3rd steps were two-sided difference superiority analyses, with an alpha level set at 5% and were performed in the randomized population with application of the intention-to-treat principle, using the same model as for the primary outcome.

Protocol deviations were defined as disregarding of an inclusion and/or exclusion criterion and/or of the recommended delay for home discharge (patients designated for home treatment but discharged home more than

Table 2 The Hestia rule

Checklist questions of the Hestia rule

- Is the patient haemodynamically unstable?^a
- Is thrombolysis or embolectomy necessary?
- Active bleeding or high risk of bleeding?^b
- More than 24 h of oxygen supply to maintain oxygen saturation >90%?
- Is pulmonary embolism diagnosed during anticoagulant treatment?
- Severe pain needing intravenous pain medication for more than 24 h?
- Medical or social reason for treatment in the hospital for more than 24 h (infection, malignancy, no support system)?
- Does the patient have a creatinine clearance of <30 mL/min? ^c
- Does the patient have severe liver impairment?^d
- Is the patient pregnant?
- Does the patient have a documented history of heparin-induced thrombocytopenia?

If the answer to all the questions is no, i.e. the Hestia rule is negative, patient qualification is home treatment. If the answer to one of the questions is yes, i.e. the Hestia rule is positive, patient qualification is in-hospital treatment.

^aInclude the following criteria but leave these to the discretion of the clinician: systolic blood pressure <100 mmHg with heart rate >100 b.p.m.; condition requiring admission to an intensive care unit.

^bGastrointestinal bleeding in the preceding 14 days, recent stroke (<4 weeks ago), recent operation (<2 weeks ago), bleeding disorder or thrombocytopenia (platelet count < $75 \times 10^9/L$), uncontrolled hypertension (systolic blood pressure >180 mmHg or diastolic blood pressure >110 mmHg).

^cCalculated creatinine clearance according to the Cockcroft–Gault formula.

^dLeft to the discretion of the physician.

24 h after the randomization or patients designated for hospitalization but discharged within 24 h following randomization).

The absolute risk difference of the primary outcome was calculated and the upper limit of the one-sided 95% confidence interval (CI), i.e. two-sided 90% CI, was compared with the pre-specified non-inferiority margin of 2.5%. This non-inferiority margin is consistent with the International Conference on Harmonization Guidelines and lower than those used in previous studies of home treatment in acute PE.^{8,11} Considering this non-inferiority margin, a 5% rate of the primary outcome in each study arm,^{16,17} and a dropout rate of 5%, 1975 patients were needed to achieve an 80% power using a one-sided alpha level at 5%.

For all outcomes based on categorical variables, results are presented as the adjusted absolute difference in rates between the two strategies and their 95% CI. Missing data were not imputed and no adjustment for competing risk of death was performed for the secondary outcomes, recurrent VTE, and major bleeding, when assessed as binary variables at 14, 30, or 90 days of follow-up.

All statistical analyses were performed with SAS software (SAS Institute, Cary, NC, USA) and R software (R Core Team, R Foundation for Statistical Computing, Vienna, Austria). Details including patients' recruitment, definition of the populations, and other pre-specified subgroup analyses are provided in the protocol and the statistical analysis plan of the trial ([Supplementary material online](#)).

Role of the funding source

The trial was funded by a grant from the French Health Ministry (PHRC-N-15-0480) and by an unrestricted grant of the participating hospitals in the Netherlands. Angers University Hospital sponsored the participating hospitals in France, Belgium, and Switzerland, and the Leiden University

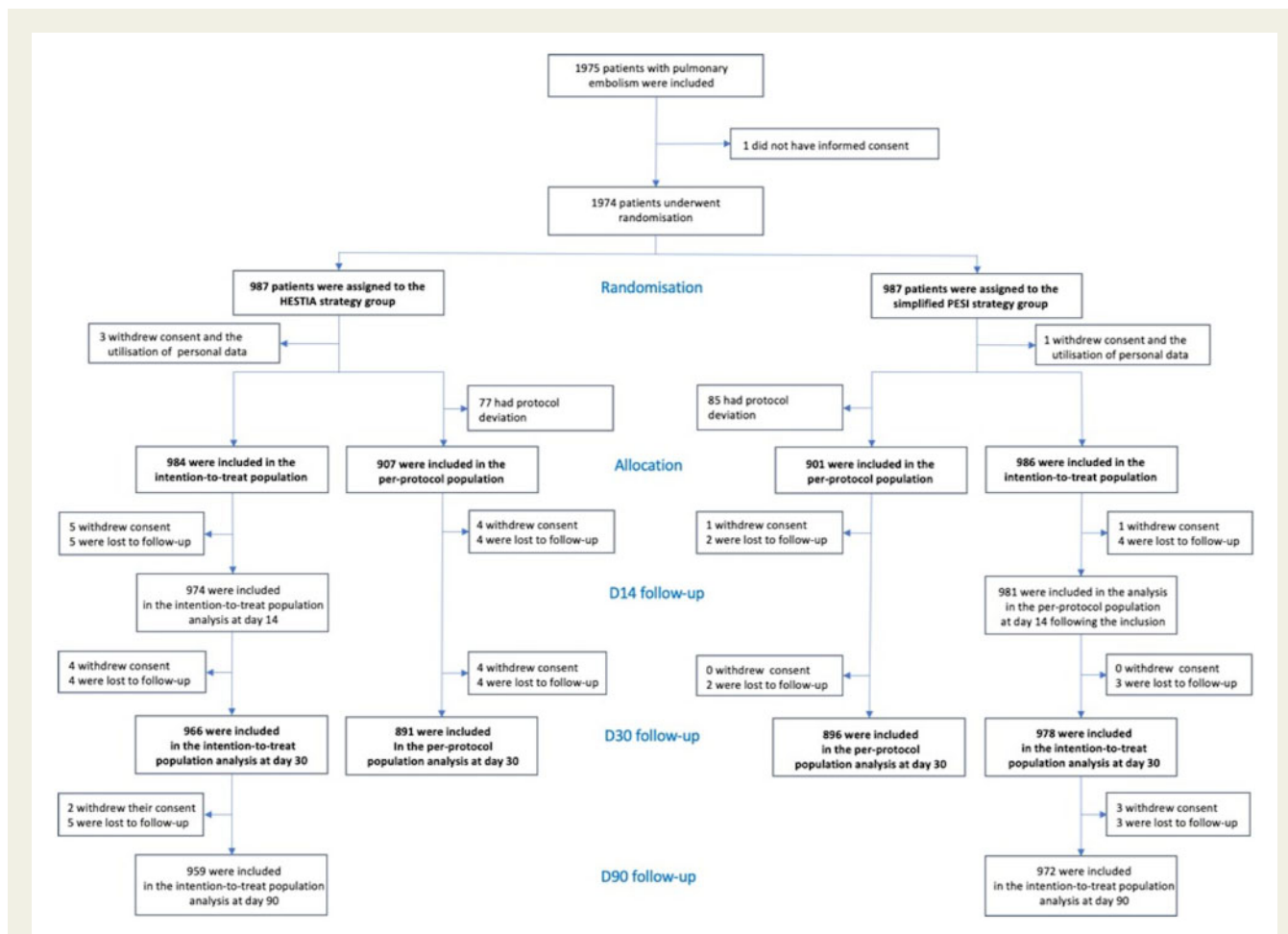


Figure 1 Enrolment, randomization, and follow-up. Among randomized patients, three subsequently withdrew consent in the Hestia arm and one in the sPESI arm; 77 patients were excluded from the per-protocol population in the Hestia arm: 13 for disregard of the inclusion or exclusion criteria (for 6 patients the initial diagnosis of acute pulmonary embolism was subsequently refuted, 2 patients had systolic blood pressure <90 mmHg at baseline, 2 had a time interval between emergency department presentation and inclusion >48 h, and 3 patients had a time interval between pulmonary embolism diagnosis and inclusion >24 h), 63 for disregard of the protocol strategy (32 were designated for home treatment but discharged home more than 24 h after randomization and 31 were designated for hospitalization but discharged within 24 h following randomization), and 1 for both protocol deviations (unconfirmed pulmonary embolism diagnosis and designated for hospitalization but discharged within 24 h following randomization); 85 patients were excluded from the per-protocol population in the sPESI arm: 18 for disregard of the inclusion or exclusion criteria (for 12 patients, the initial diagnosis of acute pulmonary embolism was subsequently refuted, 3 had a time interval between emergency department presentation and inclusion >48 h, and 3 patients had a time interval between pulmonary embolism diagnosis and inclusion >24 h), 64 for disregard of the protocol strategy (31 were designated for home treatment but discharged home more than 24 h after randomization and 33 were designated for hospitalization but discharged within 24 h following randomization), and 3 for both protocol deviations (2 with unconfirmed pulmonary embolism diagnosis and designated for hospitalization but discharged within 24 h following randomization, and 1 with a time interval between emergency department presentation and inclusion >48 h, and designated for home treatment but discharged home more than 24 h after randomization).

Medical Center was the sponsor for the participating hospitals in the Netherlands. The sponsors had no role in the study design, analysis of the data or in the preparation of the manuscript.

Results

Patients

Between 2 January 2017 and 7 July 2019, 1974 patients were randomized. Four patients withdrew their consent after randomization, leaving 984 patients in the Hestia arm and 986 in the sPESI

arm (Figure 1). The baseline characteristics of the randomized patients are presented in Table 3. A total of 72.6% of patients in the Hestia arm and 74.1% in the sPESI arm were treated with a direct oral anticoagulant.

Primary outcome and clinical events

In the overall randomized population, a protocol deviation occurred in 162 patients, 9 patients opted out of the study and 12 patients were lost to follow-up at Day 30, leaving 891 patients in the Hestia arm and 896 in the sPESI arm for the per-protocol main analysis (Figure 1). The 30-day primary composite outcome occurred in

Table 3 Demographic and clinical characteristics of the randomized patients at baseline

	Hestia strategy (N = 984)	sPESI strategy (N = 986)
Characteristics		
Age, years, median ± IQ	63.5 ± 17.7	62.3 ± 17.5
>80 years, n (%)	185 (18.8)	161 (16.3)
Female sex, n (%)	475 (48.3)	473 (48.0)
ED presentation to randomization, h, median ± IQ	15.7 ± 16.2	14.5 ± 16.2
Medical history, n (%)		
Previous venous thrombo-embolism	253 (25.9)	257 (26.3)
Current oestrogen therapy	54 (5.5)	55 (5.6)
Bed rest >72 h within past 3 months	122 (12.5)	110 (11.2)
Surgery within past 3 months	94 (9.6)	86 (8.8)
Current pregnancy	4 (0.8)	2 (0.4)
Active cancer or remission <1 year	148 (15.1)	101 (10.3)
History of cancer or active cancer	217 (22.2)	183 (18.7)
Chronic heart failure	42 (4.3)	38 (3.9)
Chronic lung disease	101 (10.3)	92 (9.4)
PE diagnosed during anticoagulation	44 (4.5)	40 (4.1)
Signs and symptoms, n (%)		
Syncope	59 (6.0)	42 (4.3)
Systolic blood pressure <100 mmHg	23 (2.4)	10 (1.0)
Heart rate ≥110 b.p.m.	178 (18.2)	157 (16.0)
Oxygen saturation <90%	57 (5.9)	87 (8.9)
Right ventricular dilatation ^a	221 (22.4)	225 (22.8)
High level of troponin ^b	294 (29.9)	268 (27.2)
High level of BNP or NT-proBNP ^c	190 (19.3)	187 (18.8)
Anticoagulant treatment ^d , n (%)		
Direct oral anticoagulant	714 (72.6)	731 (74.1)
Vitamin K antagonist	50 (5.1)	52 (5.3)
Low molecular weight or unfractionated heparin	180 (18.3)	154 (15.6)
Miscellaneous	40 (4.1)	49 (5.0)

^aRight ventricle/left ventricle >1 on computed tomography pulmonary angiography or on transthoracic echocardiography; assessed in 819 (83%) patients in the Hestia group and (84%) patients in the sPESI group.

^bTroponin level >99th percentile according to local technique; assessed in 729 (74%) patients in the Hestia group and 719 (73%) patients in the sPESI group.

^cBNP (B-type natriuretic peptide) >100 ng/L or NT-proBNP (N-terminal proBNP) >600 ng/L; assessed in 562 (57%) patients in the Hestia group and 539 (55%) patients in the sPESI group.

^dMain anticoagulant treatment, i.e. drug prescribed ≥90% of the time, within 30 days following inclusion.

3.82% (34/891) in the Hestia arm and in 3.57% (32/896) in the sPESI arm, for an adjusted absolute difference of 0.20% (upper limit of the one-sided 95% CI 1.43%; $P=0.004$ for non-inferiority; *Table 4*). Similar results were observed in the overall intention-to-treat population: 3.93% (38/966) in the Hestia arm and 3.37% (33/978) in the sPESI arm, for an adjusted absolute difference of 0.49% (upper limit of the one-sided 95% CI 1.68%; $P=0.0076$ for non-inferiority) (*Table 4*). The rate of the primary composite outcome and each of its components, i.e. recurrent VTE, major bleeding, and all-cause death, was comparable between the study arms at Days 14, 30, and 90 (*Table 4*). Likewise, the time-to-event curves were comparable (*Supplementary material online, eFigures S1–4*).

First secondary outcome

In the Hestia arm, 38.4% (378/984) of the patients were treated at home vs. 36.6% (361/986) in the sPESI arm, for an adjusted absolute

difference of 1.78% (95% CI -2.40 to 5.96; $P=0.41$ for superiority; *Table 4*). Similar results between the study arms were observed in the per-protocol population (*Supplementary material online, eTable S1*).

Second secondary outcome and selection for home treatment

The Hestia rule was negative in 39.4% (388/984) of patients and the sPESI was 0 points in 48.4% of patients (477/986), for an adjusted absolute difference of -8.91% (95% CI: -13.3 to -4.56; *Table 4* and *Figure 2*).

The negative Hestia rule was overruled in 3.4% of patients (13/388): 10 patients refused home treatment and 3 had a contra-indication to a low molecular weight heparin and a direct oral anti-coagulant. A positive Hestia rule was overruled in 0.5% of patients (3/596): all those patients refused to be hospitalized. The sPESI of 0

Table 4 Outcomes in per-protocol and intention-to-treat populations

	Hestia strategy (N = 984)	sPESI strategy (N = 986)	
Main outcome	<i>n</i> ^o of patients with event/total <i>n</i> ^o of patients (%)		Adjusted absolute difference ^a (90% CI)
In the per-protocol population			
Composite of recurrent VTE, major bleeding and all-cause death at Day 30	34/891 (3.82)	32/896 (3.57)	+0.20% (-1.03 to 1.43) <i>P</i> = 0.004 ^b
In the intention-to-treat population			
Composite of recurrent VTE, major bleeding and all-cause death at Day 30	38/966 (3.93)	33/978 (3.37)	+0.49% (-0.71 to 1.68) <i>P</i> = 0.008 ^b
Major secondary outcomes	<i>n</i> ^o of patients with event/total <i>n</i> ^o of patients (%)		Adjusted absolute difference ^a (95%CI)
In the intention-to-treat population			
Rate of patients actually treated at home	378/984 (38.4)	361/986 (36.6)	+1.78% (-2.40 to 5.96) <i>P</i> = 0.41 ^c
Rate of patients qualified for home treatment according to the rule	388/984 (39.4)	477/986 (48.4)	-8.91% (-13.3 to -4.56) –
Applicability of the triaging strategy			
Patients treated at home among qualified patients according to the rule	343/388 (88.4)	309/477 (64.8)	+25.3 % (19.5 to 31.1)
Clinical events at Day 14			
Composite of recurrent VTE, major bleeding and all-cause death	18/974 (1.85)	24/981 (2.45)	-0.47% (-1.50 to 0.55)
Recurrent VTE	3/967 (0.31)	4/969 (0.41)	+0.07% (-0.47 to 0.32)
Major bleeding	9/967 (0.93)	8/960 (0.83)	+0.10% (-0.67 to 0.86)
All-cause death	8/974 (0.82)	13/981 (1.33)	-0.37% (-1.05 to 0.31)
Clinical events at Day 30			
Composite of recurrent VTE, major bleeding and all-cause death	38/966 (3.93)	33/978 (3.37)	+0.49% (-0.94 to 1.92)
Recurrent VTE	4/946 (0.42)	5/959 (0.52)	+0.07% (-0.50 to 0.36)
Major bleeding	15/947 (1.58)	10/960 (1.04)	+0.54% (-0.48 to 1.56)
All-cause death	22/966 (2.28)	19/978 (1.94)	+0.28% (-0.78 to 1.35)
Clinical events at Day 90			
Composite of recurrent VTE, major bleeding and all-cause death	74/959 (7.72)	61/972 (6.28)	+1.34% (-0.77 to 3.45)
Recurrent VTE	8/910 (0.88)	13/934 (1.39)	-0.49% (-1.43 to 0.44)
Major bleeding	24/912 (2.63)	15/937 (1.60)	+1.05% (-0.30 to 2.40)
All-cause death	51/959 (5.32)	38/972 (3.91)	+1.24% (-0.40 to 2.90)

The total number of patients (denominator) corresponds to the number of patients in the subgroup minus the number of patients who had withdrawn their consent or who were lost to follow-up.

VTE, venous thrombo-embolism.

^aDifferences are expressed as absolute rate differences adjusted for hospital organization regarding PE.

^b*P*-value of one-sided non-inferiority analysis with a non-inferiority limit fixed to 2.5% in absolute risk difference.

^c*P*-value of two-sided superiority analysis.

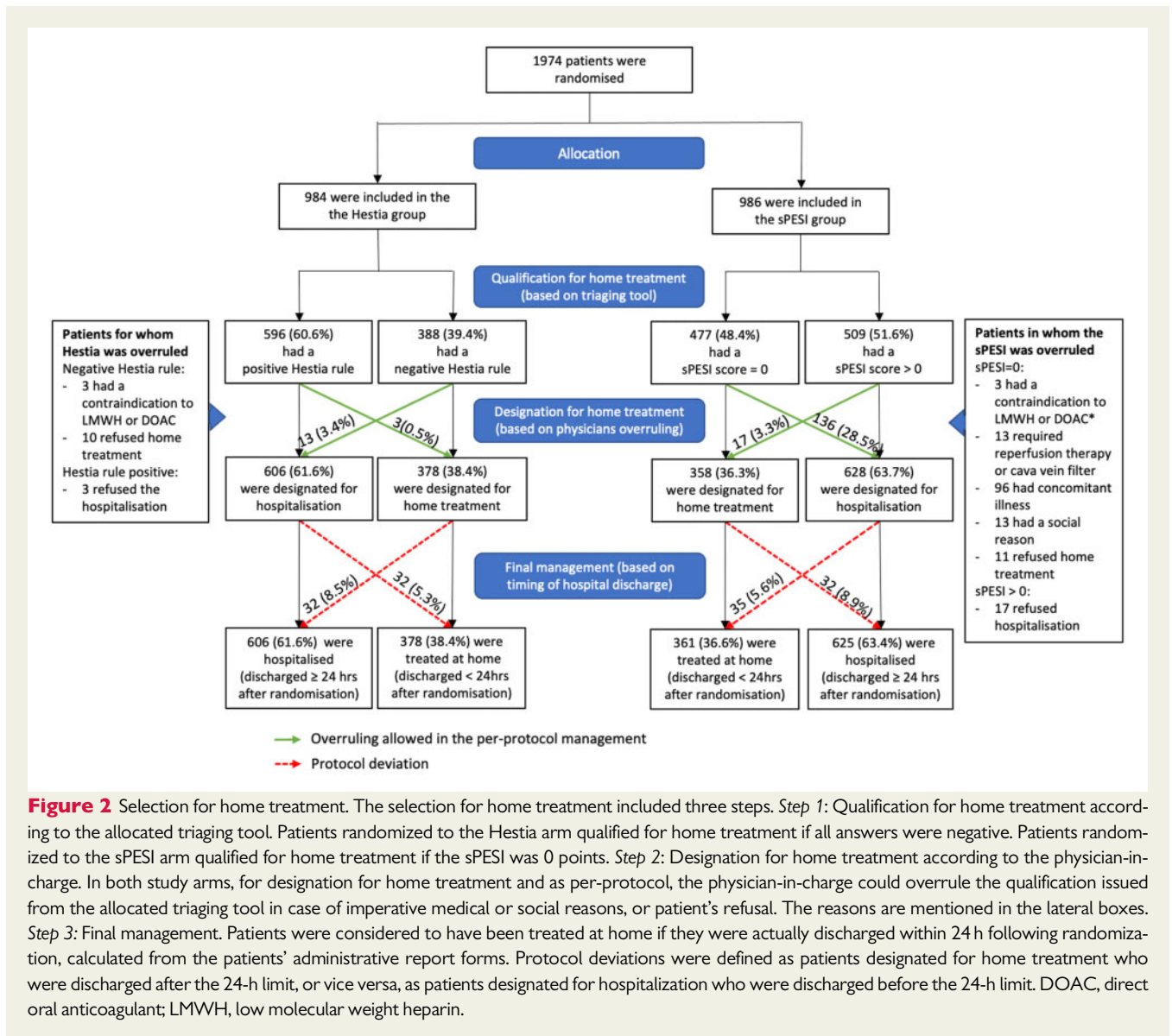
points was overruled in 28.5% of patients (136/477): 96 patients had a concomitant illness necessitating hospitalization and 13 patients a social reason for hospitalization; 13 patients required specific PE treatment, including reperfusion therapy or vena cava filter insertion according to the physician-in-charge; 11 patients refused home treatment; and 3 patients had a contra-indication to low molecular weight heparin or direct oral anticoagulant. An sPESI of 1 point or more was overruled in 3.3% of patients (17/509): all 17 patients refused to be hospitalized. Therefore, 38.4% (378/984) of the patients in the Hestia arm and 36.3% (358/986) in the sPESI arm were designated by the physician-in-charge for home treatment (Figure 2).

Applicability of the triaging tools

The applicability of the triaging tools, i.e. the proportion of patients with a negative Hestia rule or an sPESI of 0 points, who were discharged to home in the first 24 h after randomization, was 88.4% (343/388) for the Hestia rule and 64.8% (309/477) for the sPESI, for an adjusted absolute difference of +25.3% in favour of the Hestia rule (95% CI 19.5 to 31.1; Table 4).

Patients treated at home

The baseline characteristics of the patients treated at home are presented in Table 5. The median in-hospital length of stay



between emergency department presentation and discharge to home was 19.2 h in the Hestia arm and 16.7 h in sPESI arm (Supplementary material online, eTable S2). In the Hestia arm, the proportion of patients older than 80 years (absolute difference +4.72%, 95% CI 1.31 to 8.14), with active cancer (+4.77%, 95% CI 0.66 to 8.87), history of cancer (+8.55%, 95% CI 3.46 to 13.63), chronic lung disease (+3.55%, 95% CI 0.31 to 6.80), and heart rate ≥ 110 b.p.m. (+4.63%, 95% CI 0.38 to 8.89) was higher than in the sPESI arm (Supplementary material online, eTable S3). Within 14 days following home discharge, 9 (2.4%) and 17 (4.7%) patients had an unscheduled hospitalization in the Hestia arm and in the sPESI arm, respectively (Supplementary material online, eTable S2).

Among patients treated at home, the 30-day primary composite outcome occurred in 1.33% (5/375) of patients assigned to the Hestia arm and in 1.11% (4/359) in patients assigned to the sPESI arm

(adjusted absolute difference 0.19%, 95% CI -1.15 to 1.52; Table 6). No patient suffered from fatal PE, recurrent non-fatal PE, or haemodynamic collapse in either study arm. Four out of five non-fatal major bleedings were metro- or menorrhagia, all in women receiving direct oral anticoagulant treatment. Two patients had a symptomatic extension, objectively confirmed by compression ultrasonography, of a pre-existing DVT despite anticoagulation (Supplementary material online, eTable S4).

Further subgroup analysis

Characteristics and outcomes of patients (i) qualified for home treatment by Hestia and sPESI, (ii) designated for home treatment after physician-in-charge overruling, and (iii) treated in hospital are shown in Supplementary material online, eTables S5, S6, eTables S7, S8, and eTables S9, S10, respectively. The outcomes were similar between the two study arms in all of these subgroup analyses.

Table 5 Demographic and clinical characteristics of patients treated at home

	Hestia strategy (N = 378)	sPESI strategy (N = 361)
Characteristics		
Age, years, mean ± SD	57.9 ± 16.7	55.4 ± 15.5
>80 years, n (%)	26 (6.9)	9 (2.5)
Female sex, n (%)	177 (46.8)	164 (45.4)
ED presentation to randomization, h, median ± IQ	13.1 ± 15.3	10.0 ± 15.1
Medical history, n (%)		
Previous venous thrombo-embolism	83 (22.3)	106 (29.9)
Current oestrogen therapy	32 (8.6)	32 (9.0)
Bed rest >72 h within past 3 months	31 (8.3)	25 (7.0)
Surgery within past 3 months	38 (10.2)	29 (8.2)
Current pregnancy	2 (1.1)	1 (0.6)
Active cancer or remission <1 year	34 (9.1)	17 (4.8)
History of cancer or active cancer	59 (15.9)	28 (7.9)
Chronic heart failure	7 (1.9)	1 (0.3)
Chronic lung disease	26 (7.0)	12 (3.4)
PE diagnosed during anticoagulant treatment	7 (1.9)	10 (2.8)
Signs and symptoms at baseline, n (%)		
Syncope	10 (2.7)	8 (2.2)
Systolic blood pressure <100 mmHg	2 (0.5)	2 (0.6)
Heart rate ≥110 b.p.m.	42 (11.3)	24 (6.7)
Oxygen saturation <90%	1 (0.5)	2 (0.6)
Right ventricular dilatation ^a	46 (12.2)	44 (12.2)
High level of troponin ^b	54 (14.3)	37 (10.2)
High level of BNP or NT-proBNP ^c	19 (5.0)	11 (3.0)
Anticoagulant treatment ^d , n (%)		
Direct oral anticoagulant treatment	321 (84.9)	315 (87.3)
Vitamin K antagonist	7 (1.9)	12 (3.3)
Low molecular weight heparin	37 (9.8)	24 (6.6)
Miscellaneous	13 (3.4)	10 (2.8)

^aRight ventricle/left ventricle >1 on computed tomography pulmonary angiography or on transthoracic echocardiography; assessed in 312 (82%) patients in the Hestia arm and 304 (84%) patients in the sPESI arm of outpatients.

^bTroponin level >99th percentile according to local technique; assessed in 242 (64%) patients in the Hestia subgroup and 218 (60%) in the sPESI subgroup of outpatients.

^cBNP (B-type natriuretic peptide) >100 ng/L or NT-proBNP (N-terminal proBNP) > 600 ng/L; assessed in 185 (49%) patients in the Hestia subgroup and 145 (40%) patients in the sPESI subgroup of outpatients.

^dMain anticoagulant treatment, i.e. drug prescribed ≥90% of the time, within 30 days following inclusion.

Discussion

Principal findings

In the HOME-PE study, the Hestia rule strategy was non-inferior to the sPESI strategy for triaging normotensive PE patients for home treatment, with respect to the 30-day composite complication rate. Compared with the sPESI, the Hestia rule qualified fewer patients as eligible for home treatment but its applicability was higher, because fewer home treatment qualifications were overruled by the physician-in-charge taking into account the patient's preference. Despite differences in the characteristics of patients treated at home, the proportion of patients discharged home within the 24 h following inclusion, did not differ between the two strategies. More than a third of PE patients were treated at home using either the Hestia rule or the sPESI, with a low 30-day rate of complications (*Graphical abstract*).

Meaning of the study and comparison with other studies

Several studies have previously evaluated these two triaging tools, but most of them were single-arm cohort studies precluding direct comparison of their safety, applicability, and effectiveness.^{3,4} To our knowledge, only two studies previously compared the sPESI and the Hestia rule. The first one was retrospective,¹⁸ and the other a single-centre observational prospective study where the investigators did not use the triaging tools for decision-making of home treatment.¹⁹ The aim of the present trial was to compare the two triaging strategies as they would be applied in routine practice, to directly guide clinical decision-making. In light of the 30-day rates of the main primary composite outcome and its individual components, our data demonstrate that, while the patients managed at home differed between the two strategies in several aspects, their safety was comparable in both the per-protocol and intention-to-treat populations. Of note, the rates

Table 6 Outcomes in patients treated at home

	Hestia strategy (N = 378)	sPESI strategy (N = 361)	Adjusted absolute difference (95% CI) ^a
<i>n° of patients with event/total n° of patients (%)</i>			
Clinical events at Day 14			
Composite of recurrent VTE, major bleeding, and all-cause death	3/376 (0.80)	2/360 (0.56)	+0.20% (-0.76 to 1.16)
Recurrent VTE	0/376 (-)	2/360 (0.56)	-0.26% (-0.62 to 0.10)
Major bleeding	3/376 (0.80)	0/360 (-)	+0.81% (-0.34 to 1.96)
All-cause death	1/376 (0.27)	0/360 (-)	+0.13% (-0.12 to 0.37)
Clinical events at Day 30			
Composite of recurrent VTE, major bleeding, and all-cause death	5/375 (1.33)	4/359 (1.11)	+0.19% (-1.15 to 1.52)
Recurrent VTE	0/374 (-)	2/358 (0.56)	-0.26% (-0.63 to 0.10)
Major bleeding	5/375 (1.33)	1/358 (0.28)	+1.07% (-0.38 to 2.53)
All-cause death	1/375 (0.27)	1/359 (0.28)	-0.01% (-0.36 to 0.35)
Clinical events at Day 90			
Composite of recurrent VTE, major bleeding, and all-cause death	11/371 (2.96)	5/357 (1.40)	+1.07% (-0.43 to 2.57)
Recurrent VTE	3/369 (0.81)	3/356 (0.84)	-0.03% (-1.38 to 1.32)
Major bleeding	9/370 (2.43)	2/356 (0.56)	+1.45% (-0.07 to 2.97)
All-cause death	2/371 (0.54)	1/357 (0.28)	+0.12% (-0.31 to 0.56)

The total number of patients (denominator) corresponds to the number of patients in the subgroup minus the number of patients who opted out of the trial or who were lost to follow-up.

VTE, venous thrombo-embolism.

^aDifferences are expressed as absolute rate differences adjusted for hospital organization regarding PE.

of recurrent VTE and all-cause death in the overall HOME-PE population were lower than reported in historical cohorts of normotensive PE patients.^{16,17} Improvement of hospital adherence to evidence-based guidelines, e.g. the introduction of risk stratification-based initial management and direct oral anticoagulants, may have contributed to a clear decrease in PE mortality over time.^{20,21}

Contrary to our hypotheses, a lower proportion of patients was qualified for home treatment with the Hestia rule than with the sPESI and a similar proportion of patients was actually treated at home. The 39.4% rate of patients with a negative Hestia rule was lower in our study than in Dutch hospitals, which first described and used the Hestia rule (51–55%),^{7,8} but higher than in two other studies (27%).^{19,22} Conversely, the 48% rate of patients with an sPESI of 0 points was higher than the 28% rate in two other recent studies.^{19,23} Possible reasons for these discrepancies are differences in hospital settings and patient characteristics as well as the way the triaging tools are used. Indeed, both tools include measurements of three vital signs: systolic blood pressure, pulse rate, and oxygen saturation. Vital signs are dynamic and the use of one or another measurement in the triaging assessment may change the qualification. Moreover, some criteria of the Hestia rule, such as 'high risk for bleeding' and 'medical or social reason for admission', leave some room for the physician's interpretation.¹⁹

One important feature of our trial is its pragmatic design allowing reliable assessment of the effectiveness of the two triaging tools as they are applied in everyday clinical practice.²⁴ Indeed, the physician-in-charge had the possibility to overrule the qualification issued by the triaging tool and to take into account the patient's opinion in the decision-making process. This overruling occurred in 28.5% of patients with an sPESI of 0 points, vs. in 3.4% of patients with a negative Hestia rule. As a result, the applicability of the Hestia rule was higher than that of the sPESI. This difference is likely related to the

divergent original purposes of the two triaging rules, i.e. to predict 30-day mortality for the sPESI⁶ and to identify conditions precluding home treatment for the Hestia rule.⁷ The sPESI cannot be applied as a standalone rule to decide on the feasibility of home treatment. It requires an implicit assessment of medical or social conditions precluding home treatment. The addition of these implicit criteria to the sPESI criteria could have resulted in a lower proportion of patients sent home than when only the explicit Hestia criteria would have been used. For instance, according to sPESI, patients older than 80 years or with cancer or cardiorespiratory disease are precluded from home treatment. The proportion of these patients treated at home was therefore higher in the Hestia arm than in the sPESI arm. The same findings were observed in a retrospective assessment of the Hestia study.¹⁸ However, despite these differences in patients' characteristics, the rate of patients managed at home was not higher with the Hestia strategy than with the sPESI strategy. This unexpected result emphasizes the relevance and importance of physicians' and patients' related factors in the real-world applicability and effectiveness of the two triaging tools.

Importantly, the rate of adverse events in patients treated at home in our study was low and similar between the two triaging strategies. It compares well to that in recent studies on this topic, supporting the external validity of our study.^{12,25,26} Notably, the most commonly occurring complication was major uterine bleeding in women treated with a direct oral anticoagulant.²⁷

Nearly, a quarter of our patients had right ventricular dilatation as assessed by echocardiography or computed tomography pulmonary angiography. How the presence of right ventricular dilatation should influence the decision to treat normotensive PE patients at home is an ongoing debate.²⁸ The HOME-PE study was not designed to solve this issue and assessment of right ventricular function was not compulsory. However, none of the 90 patients, who had right ventricular

dilatation at presentation and were treated at home, returned to the hospital because of haemodynamic deterioration or experienced a PE recurrence or PE-related death. Similar results have been reported in another study.²⁹

Strengths and limitations of this study

HOME-PE is the largest trial of PE home treatment to date, providing robust results with a narrow 95% CI on the rate of adverse events. Several strengths reinforce the generalizability of its results. HOME-PE was performed in four European countries with different health-care organization and in 26 hospitals with, for most of them, a very low or low level of experience in home treatment of PE patients prior to study initiation. Although we had a strict randomization process, the trial was designed and conducted in real-world clinical practice. Especially, the physician-in-charge had the possibility to overrule the qualification issued from the triaging tool in each study arm and could involve the patient's preference in the decision-making, as would occur in daily practice.

Our study also has limitations. First, we chose a pragmatic trial design over an explanatory design, since the goal of HOME-PE was to provide clinicians with robust evidence to safely triage PE patients for home treatment directly transferable into their everyday clinical practice.²⁴ Second, HOME-PE was not formally powered to compare the rate of adverse events in the subgroups of patients treated at home, but the very low rate of complications reinforces the validity of using either triage tool. Third, participating hospitals had to set up a specific patient pathway for home treatment that may be difficult to organize in lack of local expert availability, especially in community hospitals. Finally, as a double-blind study design was not feasible, physicians may have incorporated some criteria of one rule when assessing patients randomized to the other one. Nonetheless, the characteristics of patients treated at home were different between the two study arms, confirming that the physicians made different decisions in patients assigned to the Hestia triaging strategy or to the sPESI triaging strategy.

Implications for policy and practice

Our findings add evidence to current guidelines supporting home treatment with either the Hestia rule or the sPESI. The sPESI consists of fewer and exclusively objective criteria but requires an additional assessment of the suitability of home treatment. The Hestia rule includes medical and social conditions that preclude home treatment. Its applicability is better but certain criteria leave room for the physician's judgement. In our study, both strategies safely led to home treatment in more than one-third of patients. Widespread implementation of either Hestia or sPESI triaging strategy could therefore result in considerable cost savings, as more than 90% of PE patients are currently hospitalized in several European countries and in the USA.^{30,31} One important feature is that all participating hospitals had set up a specific patient pathway based on local experts, to organize home treatment, with timely follow-up and clear instructions for discharged patients. This may have contributed to the low rate of complications. In our view, and in line with current guidelines^{1,2} and with the organization in place in the countries that have a wide experience in home treatment of PE patients,^{9,32,33} such an organization should optimally be in place before home treatment is implemented.

Conclusions

For triaging normotensive PE patients for home treatment, the strategy based on the Hestia rule and the strategy based on the sPESI had similar safety and effectiveness. With either triaging tool complemented by the overruling of the physician-in-charge, more than a third of patients were treated at home, with a low rate of complications.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Ethics

This study complies with the Declaration of Helsinki. It was approved by the ethics committee *CPP—Ouest II (France)* for all the hospitals in France and by the ethic committee of the participating hospitals for Belgium, Switzerland, and the Netherlands.

Copyright

This study has not previously been published and is not currently submitted elsewhere.

Transparency

The corresponding author (P.M.R.) has access to the data and affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Data availability

All anonymized raw data on individual patients on which the analysis, results, and conclusions reported in the paper are based are available to a third-party auditor and to researchers on reasonable request to the corresponding author.

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