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FASTTRACK CLINICAL RESEARCH
Pulmonary circulation

Early discharge and home treatment of patients with low-risk pulmonary embolism with the oral factor Xa inhibitor rivaroxaban: an international multicentre single-arm clinical trial

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Aims To investigate the efficacy and safety of early transition from hospital to ambulatory treatment in low-risk acute PE, using the oral factor Xa inhibitor rivaroxaban.

Methods and results We conducted a prospective multicentre single-arm investigator initiated and academically sponsored management trial in patients with acute low-risk PE (EudraCT Identifier 2013-001657-28). Eligibility criteria included absence of (i) haemodynamic instability, (ii) right ventricular dysfunction or intracardiac thrombi, and (iii) serious comorbidities. Up to two nights of hospital stay were permitted. Rivaroxaban was given at the approved dose for PE for ≥3 months. The primary outcome was symptomatic recurrent venous thromboembolism (VTE) or PE-related death within 3 months of enrolment. An interim analysis was planned after the first 525 patients, with prespecified early termination of the study if the null hypothesis could be rejected at the level of $\alpha = 0.004$ (<6 primary outcome events). From May 2014 through June 2018, consecutive patients were enrolled in seven countries. Of the 525 patients included in the interim analysis, three (0.6%; one-sided upper 99.6% confidence interval 2.1%) suffered symptomatic non-fatal VTE recurrence, a number sufficiently low to fulfil the condition for early termination of the trial. Major bleeding occurred in 6 (1.2%) of the 519 patients comprising the safety population. There were two cancer-related deaths (0.4%).

Conclusion Early discharge and home treatment with rivaroxaban is effective and safe in carefully selected patients with acute low-risk PE. The results of the present trial support the selection of appropriate patients for ambulatory treatment of PE.

Keywords Pulmonary embolism • Home treatment • Right ventricular dysfunction • Management trial • Rivaroxaban • Risk stratification

Introduction

Acute pulmonary embolism (PE) is a frequent cause of cardiovascular mortality worldwide[1] and represents a major threat for ageing populations. As PE is characterized by a wide spectrum of severity, risk assessment is mandatory to define the appropriate management strategy.[2] The current guidelines of the European Society of Cardiology (ESC) propose a stepwise risk stratification approach, using a combination of clinical findings, imaging, and biochemical markers, to distinguish between patients with high, intermediate, and low risk of an early adverse outcome.[3] In this regard, one of the most challenging tasks is to identify, within the large group of normotensive and apparently stable patients,[4] those whose risk is 'sufficiently low' to permit early discharge and ambulatory treatment. Such an approach, if shown to be safe, may minimize early complications related to hospitalization[5] and have an impact on healthcare costs[6] as well as on patient satisfaction and quality of life.[7,8]

In the era of the vitamin K antagonists (VKAs), a number of cohort studies and two randomized controlled trials investigated whether ambulatory treatment of acute PE might be feasible and safe.[8–12] These studies, most of which included rather small patient populations and were conducted in single countries, used different sets of clinical, laboratory, and social criteria to define eligibility for early discharge. As a consequence of these limitations, the optimal criteria and treatment regimen to support early discharge strategies for patients with PE have remained controversial. In a recently published real-life European study, as few as 7% of patients with acute low-risk PE were discharged 'immediately' after diagnosis and more than 50% stayed in hospital for more than 5 days.[13]

Recent developments may help to revisit this attitude. Non-vitamin K antagonist oral anticoagulants (NOACs) are increasingly becoming the standard of care for treatment of acute PE. Two of these agents, the factor Xa inhibitors apixaban and rivaroxaban, can be administered as a single oral drug regimen, obviating the need for initial parenteral treatment with low-molecular-weight heparin (LMWH) and thus facilitating the early transition from hospital to ambulatory care.[14] In parallel, risk-adapted management strategies continue to evolve. In this latter context, the results of a recent meta-analysis including 21 studies with more than 3000 patients indicated that the presence of right ventricular (RV) dysfunction on admission may be associated with an increased risk of early PE-related adverse events and death in patients classified into the low-risk category solely on the basis of clinical parameters.[15] These results reinforce the concept that the functional status of the RV should be integrated into the process of patient selection.[3,16]

The Home Treatment of Patients with Low-Risk Pulmonary Embolism with the Oral Factor Xa Inhibitor Rivaroxaban (HoT-PE) trial was designed to address the ongoing change of paradigm in PE care. Specifically, we investigated whether early discharge and ambulatory treatment with the oral factor Xa inhibitor rivaroxaban is effective and safe in patients with acute low-risk PE selected on the basis of clinical criteria as well as the absence of RV dysfunction on

admission. The present report focuses on the results of the prespecified interim analysis, which was performed after recruitment and 3-month evaluation of 525 patients corresponding to 50% of the initially planned intention-to-treat (ITT) trial population.

Methods

Study design and participants

The rationale and study design of HoT-PE have been published previously.[17] HoT-PE (EudraCT Nr. 2013-001657-28) is a prospective multicentre single-arm investigator-initiated Phase 4 interventional trial sponsored by the University Medical Centre Mainz, Germany, and supported by public funding. In addition, the sponsor obtained the study drug and a grant from the market authorization holder of rivaroxaban (Bayer AG). The authors were entirely responsible for the design and conduct of the study, statistical analysis, interpretation of results, and drafting of the manuscript. The sponsor's academic research organization was responsible for data collection and monitoring at the participating sites in Germany; in the other participating countries, this task was performed by an international clinical research organization appointed by the sponsor. The institutional ethics review board of each participating site approved the study protocol and two amendments, all of which are available as Supplementary online material. All patients provided written informed consent for participation in the study. An independent Data and Safety Monitoring Board periodically reviewed the study.

The inclusion and exclusion criteria are listed in the Supplementary online material; their rationale has been explained previously.[6] Briefly, patients were eligible for inclusion if they were 18 years of age or older and had objectively confirmed acute PE; in addition, evidence of *absence* of RV enlargement or dysfunction [RV/left ventricle (RV/LV) ratio $\geq$ 1.0], and of free-floating thrombi in the right atrium or ventricle, was required by echocardiography or computed tomographic pulmonary angiography (CTPA). The majority of the exclusion criteria corresponded to items adapted from the Hestia management study.[11] More specifically, patients were excluded if they had haemodynamic instability at presentation; mechanical or pharmacological reperfusion, or placement of a cava filter; active bleeding or known significant bleeding risk; need for supplemental oxygen administration; chronic treatment with anticoagulant drugs; pain requiring parenteral administration of analgesic agents; other medical conditions requiring hospitalization; non-compliance or inability to adhere to the treatment or the follow-up visits, or lack of a family environment or support system; and contraindications to rivaroxaban as defined in the summary of product characteristics of the drug.

Treatment

Treatment with an approved parenteral or oral anticoagulant [unfractionated heparin (UFH), LMWH, fondaparinux, rivaroxaban, or apixaban] was allowed before enrolment, but should have been started no later than 3 h after confirmation of PE. After enrolment in the study, patients received the first dose of rivaroxaban 2 h or less before the time that the next subcutaneous injection of LMWH or fondaparinux (or oral dose of rivaroxaban or apixaban) would have been due, or at the time of discontinuation of intravenous UFH.

The rivaroxaban dosage scheme was based on the label of the marketed product for the treatment of acute PE; it consisted of 15 mg twice daily for the first three weeks followed by 20 mg once daily for at least three months. Reduction of the maintenance dose to 15 mg once daily was possible at the discretion of the treating physician for patients with creatinine clearance below 50 mL/min, if the individual risk for bleeding was deemed to outweigh the risk for recurrent venous thromboembolism (VTE). The trial protocol mandated that patients be discharged from the hospital within 48 h of initial presentation for PE; it tolerated up to two nights of hospital stay.

Follow-up and study outcomes

All patients were followed for 3 months with a final on-site visit scheduled 90 (±7) days after enrolment. A 24-h emergency telephone number was provided, and patients received instructions on how to behave if they noticed symptoms suggestive of VTE recurrence or bleeding.

The primary efficacy outcome was symptomatic recurrent VTE, or PE-related death within 3 months of enrolment. Recurrent PE was confirmed using the same diagnostic procedure(s) as the initial event, and defined as at least one of the following: (i) a new intraluminal filling defect on CTPA or pulmonary angiography; (ii) a new perfusion defect involving at least 75% of a segment with normal ventilation on lung scan; (iii) a non-diagnostic lung scan accompanied by evidence of (new) deep vein thrombosis on ultrasonography; new PE (fresh thrombi) at autopsy. The safety outcomes included major bleeding (defined by the criteria of the International Society on Thrombosis and Haemostasis),[18] clinically relevant non-major bleeding, and serious adverse events. Secondary efficacy outcomes included all-cause mortality and the number of rehospitalizations due to PE or to a bleeding event within three months. All efficacy and safety outcomes were adjudicated by an independent clinical events committee; a detailed description of all outcome measures has been published before.[17]

Sample size calculation and criteria for early study termination

The null hypothesis (H_0) that $P \geq 0.03$ (P being the probability of recurrent VTE or PE-related death within 3 months) was tested against the alternative hypothesis (H_1) that $P < 0.03$, using a binomial test (two-stage adaptive design based on an O'Brien Fleming design) and assuming a 3-month symptomatic VTE recurrence rate of 1.7%. A total of 1050 patients were required to provide 80% power to reject H_0 at an overall significance level $\alpha \leq 0.05$. The point estimate (1.7%) and the upper margin (3%) of the 3-month symptomatic VTE recurrence rate were chosen based on studies dating back to the VKA era.[19] Moreover, the rate of 1.7% is also similar to the 3-month rate observed in the EINSTEIN-PE trial which compared rivaroxaban to VKA anticoagulation for the treatment of acute PE.[20] An interim analysis was planned after enrolment and 3-month evaluation of the first 525 patients in the ITT population, with the objective of early termination of the study if H_0 could be rejected at the level of $\alpha = 0.004$; this corresponded to less than six symptomatic or fatal recurrent VTE events.

Statistical analysis

The primary and secondary outcome analyses were performed in the ITT population, which included all patients who signed the informed consent. Safety analysis was conducted in the safety population, including all patients who received at least one dose of study drug. Per-protocol analysis was carried out as a sensitivity analysis for the primary outcome, including all patients who received at least one dose of study drug and fulfilled the protocol requirements for early discharge from the hospital. A sensitivity analysis was planned by imputing missing data for the primary outcome according to the worst-case principle assuming that the primary outcome had occurred. Details regarding the Statistical Analysis Plan and the interim analysis have been published previously[17] and are provided in the study protocol available in the Supplementary online material.

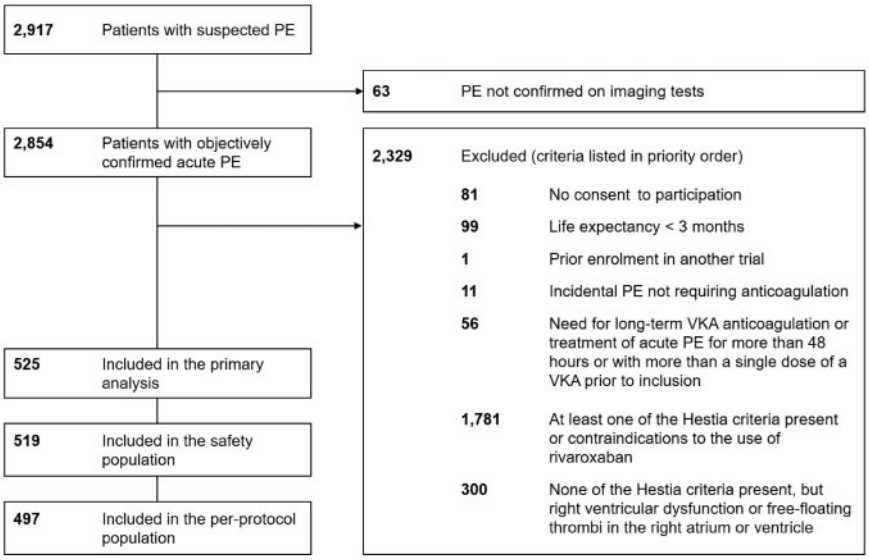

Figure 1 Flow diagram of the screening, selection, and enrolment process. PE, pulmonary embolism; VKA, vitamin K antagonist.

Results

From May 2014 through June 2018, a total of 2854 patients diagnosed with acute PE were screened for enrolment at 49 centres in seven countries. Sites in Germany were initiated in 2014 and 2015, whereas centres in other European countries were initiated starting in 2016.

Figure 1 displays the screening, selection, and enrolment process. Of 525 patients included in the interim analysis of the ITT population, 240 (45.7%) were women and the mean age was 57 (range 18–90) years. Their baseline characteristics are shown in *Table 1*. The median duration between the onset of symptoms and PE diagnosis was 4 [interquartile range (IQR) 2–9] days. The most frequent symptom was dyspnoea (61.0% of patients), followed by pleuritic pain (38.5%), cough (21.1%), retrosternal pain (21.0%), fever (7.6%), haemoptysis (5.1%), and syncope (2.7%). Unilateral leg pain was present in 24.2% and unilateral oedema in 15.1% of patients.

The diagnosis of acute PE was confirmed based on the results of CTPA in 463 (88.2%) patients, ventilation-perfusion lung scan in 55 (10.5%), and pulmonary angiography in 33 (6.3%) patients, alone or in combination. Echocardiography was performed in 447 (85.1%) patients. A total of 388 patients underwent both CTPA and echocardiography; of 137 patients in whom the RV/LV ratio was assessed and reported by both methods, four (2.9%) had a ratio of ≥1.0 on CTPA but were included in the trial because all echocardiographic parameters (including the RV/LV ratio) were normal. Compression ultrasound of the lower extremities (not mandated by the protocol) was performed in 415 (79.0%) patients, and deep vein thrombosis was detected in 214 (40.8% of the total study population).

Anticoagulation during and after hospitalization for index PE

Before enrolment, initial anticoagulation was given to 505 (96.2%) patients and consisted of LMWH in 344 (65.5%) patients (*Table 2*). As already mentioned, the trial protocol mandated discharge from the hospital within 48 h of presentation, permitting up to two nights of hospital stay for patients who had been admitted early after midnight. In compliance with the protocol, 502 (96.0%; 2 missing values) patients were hospitalized for up to two nights; of these, 61 (11.7%) were discharged directly and 219 (41.9%) were hospitalized for one night. The median length of hospitalization was 34 (IQR 23–47) h, and the median time from PE diagnosis to discharge 31 h. Eleven (2.1%) patients required prolonged hospitalization due to early adverse events. These included acute infection ($n = 5$), elevation of troponin ($n = 2$), cancer-related complications ($n = 2$), fever ($n = 1$), and removal of an external bone fixator ($n = 1$).

After enrolment, 519 (98.9%) patients received at least one dose of rivaroxaban (safety population). Initial anticoagulation with rivaroxaban 15 mg twice daily was given over a mean period of 21 [standard deviation (SD) 3] days. Rivaroxaban was given at the standard maintenance dosage of 20 mg once daily over a mean period of 68 (SD 13) days; the reduced dosage of 15 mg once daily was given to four patients. Three patients unintentionally received supratherapeutic doses of rivaroxaban for 4, 11, and 32 days, respectively.

Primary efficacy outcome

The primary efficacy outcome of symptomatic recurrent VTE or PE-related death within three months occurred in three [0.6%; one-sided upper 99.6% confidence interval (CI) 2.1%; one-sided *P*-value <0.0001] of the 525 patients of the ITT population (*Table 3*). All three recurrent events presented as non-fatal PE (*Table 4*). *Figure 2* depicts the early stopping boundaries along with subject-by-subject accounting of the event rate, thus visually providing the justification for early termination of the study after 50% of the initially planned patient population based on the predefined interim analysis. According to the prespecified worst case scenario analysis, the primary efficacy outcome might have occurred in two further patients with

Table 1 Baseline characteristics of the study population

Variables	Value	Missing or not tested
Patient demographics		
Age (years), mean (SD; range)	56.7 (16.6; 18–90)	0
Age >80 years, *n*/*N* (%)	24/525 (4.6)	0
Women, *n*/*N* (%)	240/525 (45.7)	0
Caucasian, *n*/*N* (%)	517/525 (98.5)	0
Functional parameters and biochemical markers		
Body mass index (kg/m^2), median (IQR)	27.1 (24.2–30.5)	15
Systolic/diastolic blood pressure (mmHg), mean (SD)	137 (19)/80 (12)	1
Heart rate (b.p.m.), mean (SD)	78 (13)	0
Oxygen saturation (%), median (IQR)	97 (96–98)	18
Body temperature (°C), mean (SD)	36.6 (0.6)	28
Respiratory rate (breaths per minute), median (IQR)	16 (15–18)	57
Creatinine clearance <50 mL/min, *n*/*N* (%)	29/525 (5.5)	0
Risk factors for pulmonary embolism and comorbidities		
Oestrogen use, *n*/*N* (%)	81/520 (15.6)	5
Immobilization (for at least 3 days), *n*/*N* (%)	54/520 (10.4)	5
Previous deep vein thrombosis, *n*/*N* (%)	82/515 (15.9)	10
Previous pulmonary embolism, *n*/*N* (%)	39/521 (7.5)	4
Recent major surgery (past 30 days), *n*/*N* (%)	37/523 (7.1)	2
Recent major trauma (past 30 days), *n*/*N* (%)	23/524 (4.4)	1
Recent stroke (past 30 days), *n*/*N* (%)	0/524 (0)	1
Long travel (>4 h, past 30 days), *n*/*N* (%)	66/517 (12.8)	8
Active cancer, *n*/*N* (%)	32/518 (6.2)	7
Chronic obstructive pulmonary disease, *n*/*N* (%)	26/518 (5.0)	7
Chronic heart failure, *n*/*N* (%)	7/524 (1.3)	1
Coronary artery disease, *n*/*N* (%)	40/519 (7.7)	6
Arterial hypertension, *n*/*N* (%)	211/522 (40.4)	3
Simplified pulmonary embolism severity index ≥1, *n*/*N* (%)	107/506 (21.1)	19

IQR, interquartile range; SD, standard deviation.

incomplete follow-up, amounting to a theoretical rate of 0.95% (one-sided upper 95% CI 2.0%; one-sided *P*-value = 0.0015).

Of the 497 patients included in the per-protocol population, the primary outcome occurred in two (0.4%; one-sided upper 95% CI 1.3%; one-sided *P*-value < 0.0001). A similar rate (0.4%) was observed in patients who were discharged early and received a complete 3-month treatment of rivaroxaban (*n* = 482).

Safety and secondary efficacy outcomes

The safety and secondary efficacy outcomes are shown in *Table 3*. Six (1.2%, two-sided 95% CI 0.4–2.5%) of 519 patients in the safety population had a major bleeding episode. *Table 4* summarizes the time to occurrence and the characteristics of these events. Clinically relevant non-major bleeding occurred in 31 (6.0%; two-sided 95% CI 4.1–8.4%) of 519 patients included in the safety population. Serious adverse events occurred in 58 (11.2%; two-sided 95% CI 8.6–14.2%) patients; a complete overview of the type and time of onset of these events is provided in the Supplementary material online.

A total of 54 (10.3%) of 525 patients required either prolongation of the initial hospital stay (*n* = 11) or rehospitalization (*n* = 43) due to serious adverse events, which occurred a median of 14 (IQR 4–54) days after the initial presentation. The median additional length of hospital stay (including rehospitalizations) was 6 (IQR 3–9) days. Twelve (2.3%) patients required rehospitalization due to suspected VTE recurrence or bleeding, which was subsequently confirmed in 7 (1.3%) cases; *Tables 3 and 4*.

Two patients (0.4%; 95% CI 0.1–1.4%) died 46 days and 89 days after enrolment due to complications of metastatic gynaecological cancer and advanced mesothelioma, respectively. One further patient who had intracranial haemorrhage (*Table 4*) on Day 72 survived the 3-month follow-up period but died 10 weeks after the event.

Discussion

We conducted an international multicentre single-arm Phase 4 management trial, designed to test whether early discharge and ambulatory treatment of patients with acute low-risk PE with rivaroxaban is effective and safe. The study was terminated for efficacy after the predefined interim analysis, which was performed after enrolment and

Table 2 Initial hospitalization and anticoagulant treatment

Variables	Value	Missing
Anticoagulant treatment before enrolment		
Low-molecular-weight heparin, *n*/*N* (%)	344/525 (65.5)	0
Enoxaparin, *n*	234	0
Dalteparin, *n*	20	0
Nadroparin, *n*	17	0
Tinzaparin, *n*	39	0
Certoparin, *n*	30	0
Other or not specified, *n*	4	0
Unfractionated heparin, *n*/*N* (%)	43/525 (8.2)	0
Fondaparinux, *n*/*N* (%)	19/525 (3.6)	0
Rivaroxaban, *n*/*N* (%)	96/525 (18.3)	0
Apixaban, *n*/*N* (%)	3/525 (0.6)	0
No initial anticoagulation, *n*/*N* (%)	20/525 (3.8)	0
Hospitalization for index pulmonary embolism		
Duration of hospitalization (h), median (IQR)	34 (23–47)	27 (exact time of admission or discharge not stated)
Two nights or less in hospital	502/523 (96.0)	2
Prolonged initial hospitalization due to adverse events	11	—
Anticoagulant treatment after enrolment		
Received the study medication, *n*	519	0
Rivaroxaban 15 mg twice daily for the initial therapy, mean duration (SD)	21 (3)	1
Rivaroxaban 20 mg once daily for the maintenance therapy, mean duration (SD)	68 (13)	1
Treatment not completed, *n*/*N* (%)	30/519 (5.8)	2

IQR, interquartile range; SD, standard deviation.

3-month follow-up of 50% of the initially planned patient population. The rate of symptomatic recurrent VTE or PE-related death within 3 months was 0.6% (one-sided upper 99.6% CI 2.1%), thus permitting the early rejection of the null hypothesis. Besides criteria including the lack of serious comorbidities or conditions mandating hospitalization, and the presence of a familial/social environment able to support ambulatory treatment, HoT-PE is the first management trial to implement recent advances in our knowledge by defining the absence of RV enlargement or dysfunction (reviewed and meta-analysed in Ref. 15), and of free-floating thrombi in the right atrium or ventricle on imaging, as a key exclusion criterion.

Acute PE is a potentially life-threatening acute cardiovascular syndrome. Therefore, the decision to discharge a patient within the first hours following presentation may raise medical, ethical, and legal concerns, which underline the importance of relying on validated criteria for patient selection. Current guidelines[3] support the use of two clinical scores, the Pulmonary Embolism Severity Index (PESI) and its simplified version (sPESI), for the identification of patients with low-risk PE. In addition, the so-called Hestia criteria were proposed, aiming to select candidates for early discharge by taking into account general medical factors along with the patients' social and family supporting environment.[11,12] Clinical criteria alone, however, may not suffice to safely select patients with acute low-risk PE, since the risk of early mortality and PE-related complications may be elevated, despite a low clinical severity score, if RV dysfunction or intracardiac thrombi are present.[9,15] Today, assessment of the right ventricle by imaging is a fast, uncomplicated process in most emergency departments.[21] The HoT-PE trial therefore confirms that simple and easily obtainable clinical and imaging parameters of severity can identify patients at truly low risk of early PE-related complications.

The rates of efficacy and safety outcomes documented in HoT-PE are generally in line with those reported in previous trials. Recurrent symptomatic (non-fatal) VTE occurred within the first three months in 0.6% of the patients enrolled in HoT-PE, compared with 2.0% of those in the Hestia study and 0.6% in the Outpatient Treatment of Pulmonary Embolism (OTPE) trial; both latter trials had used VKA treatment.[8] The incidence of major bleeding was 1.2% in HoT-PE vs. 0.7–1.8% in previous studies.[8,11] In two large post-marketing studies investigating the use of rivaroxaban in VTE, the rate of major bleeding at three months ranged from 0.5% in a prospective Phase 4 study, which included mostly patients with deep vein thrombosis, to ~2.0% in the Dresden registry.[22,23] The most frequent sites of major bleeding in HoT-PE, notably gastrointestinal and uterine bleeding, are in line with the results of previous trials on coagulation factor Xa inhibitors.[20,24] Clearly, any comparisons between the results of this and previous studies should be interpreted with caution in view of the differences in the patients' characteristics and the anticoagulation strategy followed.

HoT-PE is the first management study using a direct, NOAC which does not require initial parenteral heparin anticoagulation and thus offers the advantage of facilitated early discharge of patients at low risk. The results of HoT-PE support the feasibility of this strategy,

Table 3 Study outcomes within 3 months of enrolment

Outcomes	
Primary efficacy outcome	
Recurrent venous thromboembolism or fatal PE, *n/N* (%; one-sided upper 99.6% CI)	3/525 (0.6; 2.1)
Recurrent PE, *n* (%; 95% CI)	3/525 (0.6; 0.1–1.7)
Recurrent deep vein thrombosis, *n*	0
Death related to PE, *n*	0
Safety outcomes	
Major bleeding,[a] *n/N* (%; 95% CI)	6/519 (1.2; 0.4–2.5)
Clinically relevant bleeding, *n/N* (%; 95% CI)	31/519 (6.0; 4.1–8.4)
At least one serious adverse event, *n/N* (%; 95% CI)	58/519 (11.2; 8.6–14.2)
Secondary efficacy outcomes	
Serious adverse events requiring prolonged initial hospitalization, or rehospitalization, *n/N* (%)	54/525 (10.3)
Time between initial presentation and first rehospitalization (days), median (IQR)	29 (7–56)
Duration of hospital stay due to serious adverse events (days), median (IQR, range)	6 (3–8)
Patients rehospitalized due to suspected recurrent PE or bleeding, *n/N* (%)	12/525 (2.3)
Pneumonia, *n/N* (%)	4/525 (0.8)
Recurrent PE, *n/N* (%)	2/525 (0.4)
Major bleeding, *n/N* (%)	4/525 (0.8)
Clinically-relevant-non-major bleeding, *n/N* (%)	1/525 (0.2)
Other, *n/N* (%)	1/525 (0.2)
Death of any cause within 3 months, *n/N* (%; 95% CI)	2/525 (0.4; 0.1–1.4)
Advanced cancer as cause of death, *n*	2

CI, confidence interval; IQR, interquartile range; PE, pulmonary embolism.
[a]As defined by the criteria of the International Society on Thrombosis and Haemostasis.[18]

since more than 95% of the study patients enrolled were hospitalized for two nights or less, and 54% were either discharged immediately or hospitalized for (only) one night after presentation. Long-term follow-up focusing on 1-year survival of the patients included in HoT-PE is still ongoing, and will also provide data on the quality of life, patient satisfaction and, in selected countries, utilization of healthcare resources.

Some limitations of our results need to be mentioned. First, it is not possible to determine from an interventional management trial like HoT-PE how many unselected patients with PE may fulfil our eligibility criteria in clinical practice. The enrolment-to-screening ratio did not represent a pre-defined measure of this trial and there was significant heterogeneity among centres in the reported percentage of screened patients who were ultimately enrolled. For example, in 25 of the 49 study sites, the reported enrolment rates exceeded 40%. Further, we cannot exclude the possibility that some eligible patients may not have been screened for HoT-PE at some of the participating study sites. Notwithstanding, the fact that overall only a minority, ~20%, of the (reportedly) screened unselected patients with acute PE were ultimately included in the trial, highlights the complexity and need for individualization of management decisions concerning early discharge and home treatment of PE. In this context, it can be argued, based on the numbers shown in *Figure 1*, that relying on the Hestia criteria alone might have increased the enrolment rate to ~30% in our study, and that the reported inclusion rates in previous studies using those clinical criteria were even higher, over 50%.[11,12] However, beyond the medical rationale for additionally excluding RV dysfunction or intracardiac thrombi as explained above, it needs to pointed out that HoT-PE was performed in seven European countries with different healthcare systems, social infrastructure, geography, and physicians'/patients' preferences. This important aspect should be taken into account when attempting comparisons of enrolment feasibility with studies performed in a single country.

HoT-PE suggests that neither advanced age nor active cancer, two of the 'high-risk' items included in sPESI, mandate by themselves a prolonged hospital stay. Keeping in mind that the absolute numbers of patients with these sPESI items were small and do not permit definitive conclusions, these results are encouraging news with potential medical and socioeconomic implications for ageing societies. The strategy validated in HoT-PE may therefore be applicable to a large number of patients and countries under real-life conditions, and that it addresses the true medical need to shorten the duration of hospitalization for patients with acute low-risk PE.

Finally, no control arm with 'conventional' care was included in our study. Such an arm might have been defined either as parenteral heparin followed by VKA, or as hospitalization over several days corresponding to current practice in many European countries and hospitals.[13,25] The steering committee of HoT-PE decided against either approach for the following reasons. First, high-quality Phase 3 trial data demonstrating the efficacy and safety of PE treatment with NOAC vs. LMWH followed by VKA had been published short before initiation of HoT-PE,[20,26] and it was deemed unnecessary (and perhaps also unethical) to reproduce existing robust evidence. Second, from a historical perspective, the rapid evolution of care in

Table 4 Patients with the primary efficacy outcome or a major bleeding event within 3 months of enrolment

Sex, age (years)	sPESI (points)	Type of event	Dosage	Days from enrolment	Length of rehospitalization (days)	Description	Management
Female, 46	0	Recurrent PE	20 mg once daily	29	4	Segmental recurrent PE occurring during rivaroxaban therapy. No haemodynamic decompensation.	Rivaroxaban discontinuation and switch to LMWH. No further complications.
Male, 46	≥ 1	Recurrent PE	15 mg twice daily	7	6	Segmental recurrent PE occurring during rivaroxaban therapy. No haemodynamic decompensation.	The therapy with rivaroxaban (15 mg twice daily) was continued. No further complications.
Female, 47	0	Recurrent PE	20 mg once daily	75	—	Segmental recurrent PE occurring during rivaroxaban therapy. No haemodynamic decompensation.	Rivaroxaban discontinuation and switch to LMWH; no further complications.
Female, 37	0	Major bleeding[a]	15 mg twice daily	12	1	Uterine bleeding.	Rivaroxaban discontinuation and switch to LMWH.
Male, 81	≥1	Major bleeding[a]	20 mg once daily	57	12	Haemorrhagic shock following acute bleeding from intestinal diverticula.	Red blood cell concentrates; rivaroxaban discontinuation and switch to LMWH. Subsequently, the patient suffered one further gastrointestinal major bleeding episode on heparin.
Female, 69	0	Major bleeding[a]	20 mg once daily	70	—	Gastrointestinal bleeding (onset 10 days before) and anaemia.	—
Female, 50	0	Major bleeding[a]	15 mg once daily	72	—	Uterine bleeding (onset 15 days before).	Rivaroxaban discontinuation.
Female, 49	0	Major bleeding[a]	20 mg once daily	57	6	Uterine bleeding (onset 20 days before).	Red blood cell concentrates; rivaroxaban discontinuation and switch to LMWH.
Male, 85	≥1	Major bleeding[a]	20 mg once daily	72	69	Intracranial haemorrhage.	After rivaroxaban discontinuation, the patient received prothrombin complex concentrate. He died 69 days later.

PE, pulmonary embolism; LMWH, low-molecular-weight heparin; sPESI, simplified Pulmonary Embolism Severity Index.
[a]As defined by the criteria of the International Society on Thrombosis and Haemostasis.[18]

the field deep vein thrombosis, which shifted to ambulatory treatment as soon as effective and practical anticoagulation regimens became available,[27] was a strong argument against the feasibility of randomizing patients with low-risk PE 'back' to longer hospitalization periods, also considering that the safety or the approach chosen in HoT-PE was constantly monitored by an independent data safety monitoring board.

In conclusion, early discharge with continuation of anticoagulant treatment at home was effective and safe in carefully selected patients with acute PE. Patients were identified by clinical criteria of low risk and the absence of RV dysfunction and of free-floating thrombi in the right atrium or ventricle on admission, and received the standard approved regimen of rivaroxaban for at least three months. The present trial may have a clinically relevant impact on the selection of PE patients for early discharge and ambulatory management, helping to reduce in-hospital complications and rationalize the use of healthcare resources.

Supplementary material

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

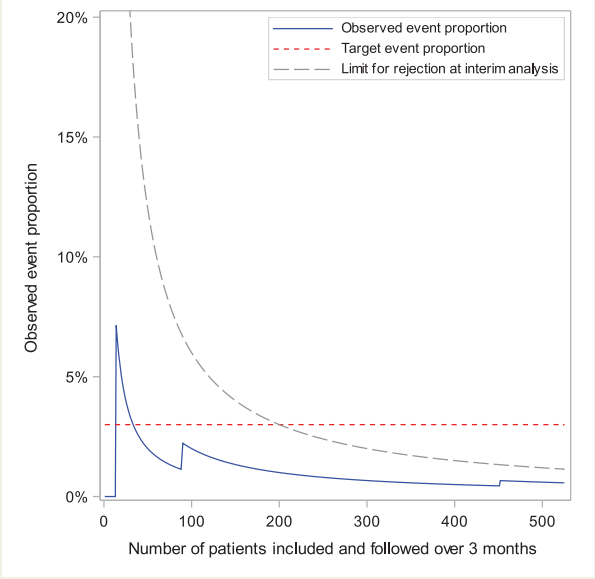

Figure 2 Early stopping boundaries along subject-by-subject accounting of the event rate.

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