Home treatment of patients with low-risk pulmonary embolism with the oral factor Xa inhibitor rivaroxaban

Rationale and design of the HoT-PE Trial

Stefano Barco1; Mareike Lankeit1; Harald Binder2; Sebastian Schellong3; Michael Christ4; Jan Beyer-Westendorf5; Daniel Duerschmied6; Rupert Bauersachs7; Klaus Empen8; Matthias Held9; Martin Schwaiblmair10; Cândida Fonseca11; David Jiménez12; Cecilia Becattini13; Kurt Quitzau1; Stavros Konstantinides1,14

1Center for Thrombosis and Hemostasis (CThH), University Medical Center of the Johannes Gutenberg University, Mainz, Germany; 1Institute of Medical Biostatistics, Epidemiology and Informatics (IMBEI) at the University Medical Center Mainz, Germany; 2 Municipal Hospital of Dresden-Friedrichstadt, Dresden, Germany; 3Department of Emergency and Critical Care Medicine, Paracelsus Medical University, General Hospital, Nuernberg, Germany; 4Center for Vascular Medicine and Department of Medicine III, Division of Angiology, University Hospital ‘Carl Gustav Carus’, Dresden, Germany; 5Heart Center, University of Freiburg, Freiburg, Germany; 6Department of Vascular Medicine, Klinikum Darmstadt GmbH, Darmstadt, Germany; 7Department of Internal Medicine, Ernst Moritz Arndt University, Greifswald, Germany; 8Medical Mission Hospital, Department of Medicine, Academic Teaching Hospital of the Julius-Maximilian University of Wuerzburg, Wuerzburg, Germany; 9Klinikum Augsburg, I. Medizinische Klinik, Augsburg, Germany; 10Hospital S. Francisco Xavier/CHLO, Faculdade de Ciências Médicas, Universidade Nova de Lisboa, Lisbon, Portugal; 11Respiratory Department, Ramón y Cajal Hospital, IRYCIS, Madrid, Spain; 12Internal and Cardiovascular Medicine - Stroke Unit, University of Perugia, Italy; 13Department of Cardiology, Democritus University of Thrace, Alexandroupolis, Greece

Summary

Pulmonary embolism (PE) is a potentially life-threatening acute cardiovascular syndrome. However, more than 95% of patients are haemodynamically stable at presentation, and among them are patients at truly low risk who may qualify for immediate or early discharge. The Home Treatment of Pulmonary Embolism (HoT-PE) study is a prospective international multicentre single-arm phase 4 management (cohort) trial aiming to determine whether home treatment of acute low-risk PE with the oral factor Xa inhibitor rivaroxaban is feasible, effective, and safe. Patients with confirmed PE, who have no right ventricular dysfunction or free floating thrombi in the right atrium or ventricle, are eligible if they meet none of the exclusion criteria indicating haemodynamic instability, serious comorbidity or any condition mandating hospitalisation, or a familial/social environment unable to support home treatment. The first dose of rivaroxaban is given in hospital, and patients are discharged within 48 hours of presentation. Rivaroxaban is taken for at least three months. The primary outcome is symptomatic recurrent venous thromboembolism or PE-related death within three months of enrolment. Secondary outcomes include quality of life and patient satisfaction, and health care resource utilisation compared to existing data on standard-duration hospital treatment. HoT-PE is planned to analyse 1,050 enrolled patients, providing 80% power to reject the null hypothesis that the recurrence rate of venous thromboembolism is >3% with 0.05. If the hypothesis of HoT-PE is confirmed, early discharge and out-of-hospital treatment may become an attractive, potentially cost-saving option for a significant proportion of patients with acute PE.

Keywords

Pulmonary embolism, home treatment, management trial, rivaroxaban, risk stratification

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Accepted after major revision: March 3, 2016
Epub ahead of print: March 24, 2016
http://dx.doi.org/10.1160/TH16-01-0004

Introduction

Acute pulmonary embolism (PE), the most dangerous clinical manifestation of venous thromboembolism (VTE), represents a major threat for the health, the well-being, and occasionally the life of a large number of patients worldwide (1). However, more than 95% of patients are haemodynamically stable at presentation and thus considered not to be at high risk of an adverse early outcome. Within this large group, the challenge for the clinician is to determine which patients are at truly low risk and may qualify for early discharge.
Current guidelines propose a stepwise risk stratification approach, using a combination of clinical findings, imaging parameters, and biochemical markers, to distinguish between ‘low-risk’ and ‘intermediate-risk’ PE (2). However, this classification is mostly based on observational data and does not directly address the eligibility for ambulatory treatment. In fact, a consensus regarding the candidates for home treatment of acute PE and the safety of this approach is still lacking due to the heterogeneous design, relatively small size, and partly conflicting results of the trials performed thus far (3–6). Moreover, previous studies addressing this topic used initial heparin anticoagulation followed by vitamin K antagonists (VKA) (3–6). In the meantime, four non-vitamin K–dependent oral anticoagulants (apixaban, dabigatran, edoxaban, and rivaroxaban) have been approved for the treatment and secondary prophylaxis of VTE, and two of them were successfully tested in a ‘single oral drug’ regimen which may facilitate the early transition from hospital to ambulatory care (7, 8). Consequently, and in light of the substantial but partly preventable VTE-related economic burden for health systems (9, 10), we designed and initiated the Home Treatment of Pulmonary Embolism (HoT-PE) trial in order to determine the place of early discharge and home treatment within the contemporary management of acute PE.

Study overview

HoT-PE (EudraCT Nr. 2013–001657–28) is a prospective international multicentre single-arm phase 4 management trial. An overview of the trial design and study flow is provided in Figure 1. In patients clinically suspected of having acute PE, the diagnostic work-up should be completed within 24 hours (h) of admission. Treatment with an approved parenteral or oral anticoagulant (unfractionated heparin, low-molecular-weight heparin [LMWH], fondaparinux, rivaroxaban, or apixaban) may be started before enrolment upon clinical suspicion of PE and no later than 3 h after confirmation of PE (2). The first dose of the study drug (rivaroxaban) is given in hospital, 2 h or less before the time that the second dose of LMWH, fondaparinux, rivaroxaban, or apixaban would have been due, or at the time of discontinuation of intravenous unfractionated heparin. Echocardiography and compression ultrasonography of the leg veins are recommended before discharge, but they are not compulsory. Patients are discharged from the hospital within 48 h of presentation; therefore, the study protocol permits up to two nights of hospital stay. The study drug is taken for a total of at least three months. A 24-h emergency telephone number is provided by the study site to all patients enrolled.

Objectives

The primary objective of HoT-PE is to determine whether early discharge and out-of-hospital treatment of patients with acute low-risk PE with the oral factor Xa inhibitor rivaroxaban is feasible, effective, and safe. The secondary objectives of the trial are i) to determine whether early discharge and out-of-hospital treatment of acute low-risk PE with rivaroxaban result in high quality of life and patient satisfaction; and ii) to obtain valid health economic variables for evaluation of health care resource utilisation compared to standard in-hospital care.

Patient population and eligibility

Consecutive patients with objectively confirmed acute PE are screened for eligibility by the treating physicians. The complete list of the eligibility criteria is provided in Table 1.

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**IN-HOSPITAL MANAGEMENT**

- Acute PE suspected
  - PE objectively confirmed <24 h after presentation
  - Eligibility criteria fulfilled, obtained informed consent

**HOME TREATMENT**

- Transthoracic echo and compression ultrasound at baseline (optional)
- First dose of rivaroxaban
- Hospital discharge <48 h

**STUDY PERIOD**

- *follow-up visits at 8 days, 3 weeks and 3 months* (additional check of vital status at 12 months)

**PRIMARY OUTCOME**

- Symptomatic recurrent VTE or PE-related death

**SECONDARY OUTCOMES**

- All-cause mortality
- Bleeding events
- Duration of hospital stay, re-hospitalisations due to PE
- Generic and disease-specific quality of life, treatment satisfaction
- Utilisation of health care resources

**Rivaroxaban 15 mg bid for 3 weeks**

**Rivaroxaban 20 mg od for at least 3 months**

(15 mg od in selected patients)

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Figure 1: Study design. VTE, venous thromboembolism; PE, pulmonary embolism; od, once daily; bid, twice daily.
Table 1: Patient eligibility criteria.

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Age ≥18 years</td>
<td>1) Haemodynamic instability at presentation*</td>
</tr>
<tr>
<td>2) Objectively confirmed diagnosis of acute PE by multidetector CT, V/Q lung scan, or selective pulmonary angiography, according to established diagnostic criteria, with or without symptomatic DVT</td>
<td>2) Use of a fibrinolytic agent, surgical thrombectomy, interventional (transcatheter) thrombus aspiration or lysis, or use of a cava filter to treat the index episode of PE</td>
</tr>
<tr>
<td>3) Absence of RV enlargement or dysfunction, and of free floating thrombi in the right atrium or right ventricle on echocardiography or CT</td>
<td>3) Active bleeding or known significant bleeding risk</td>
</tr>
<tr>
<td>On echocardiography, RV dysfunction is absent when both of the following criteria listed below are met: (i) right/left ventricular end-diastolic diameter ratio ≤0.9 (apical or subcostal 4-chamber view); (ii) no paradoxical motion of the interventricular septum;</td>
<td>4) Need for supplemental oxygen administration to maintain oxygen saturation &gt;90%</td>
</tr>
<tr>
<td>On CT, RV enlargement is absent when the following criterion is met:</td>
<td>5) Chronic treatment with a vitamin K antagonist, rivaroxaban or any other oral or parenteral anticoagulant drug</td>
</tr>
<tr>
<td>right/left short-axis diameter ratio &lt;0.9 (transverse plane)</td>
<td>6) Pain requiring parenteral administration of analgesic agents</td>
</tr>
<tr>
<td>4) Ability of subject to understand the character and consequences of a clinical trial</td>
<td>7) Other medical conditions/comorbidities requiring hospitalisation</td>
</tr>
<tr>
<td>5) For women of childbearing potential, negative pregnancy test before enrolment and medically accepted contraception throughout the trial</td>
<td>8) Acute PE diagnosed in a patient already hospitalized for another condition</td>
</tr>
<tr>
<td>6) Signed and dated informed consent of the subject available before the start of any trial procedures</td>
<td>9) Non-compliance or inability to adhere to treatment or to the follow-up visits; or lack of a family environment or support system for home treatment</td>
</tr>
<tr>
<td></td>
<td>10) Severe renal insufficiency (eGFR &lt;15 ml/min/1.73 m² by the MDRD formula), or end-stage renal disease</td>
</tr>
<tr>
<td></td>
<td>11) Severe hepatic failure</td>
</tr>
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<td></td>
<td>12) Pregnancy or lactation</td>
</tr>
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<td></td>
<td>13) History of hypersensitivity to the study drug</td>
</tr>
<tr>
<td></td>
<td>14) Treatment of the acute (index) episode with unfractionated heparin, low-molecular-weight heparin, fondaparinux, or a new oral anticoagulant for more than 48 hours, or with more than a single dose of a vitamin K antagonist prior to inclusion in the study</td>
</tr>
<tr>
<td></td>
<td>15) Concomitant administration of strong inhibitors of P-gp and CYP3A4 such as azole antifungal or antiviral agents or HIV protease inhibitors</td>
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<tr>
<td></td>
<td>16) Need for long-term treatment vitamin K antagonists, or for antplatelet agents except acetylsalicylic acid at a dosage ≤100 mg/day</td>
</tr>
<tr>
<td></td>
<td>17) Participation in other clinical trials within the last six months</td>
</tr>
<tr>
<td></td>
<td>18) Medical or psychological condition that would not permit completion of the trial or signing of informed consent</td>
</tr>
<tr>
<td></td>
<td>19) Life expectancy less than 3 months</td>
</tr>
</tbody>
</table>

* Indicated by at least one of the following criteria: (i) systemic blood pressure less than 100 mmHg, or heart rate above 100 bpm, or a drop in systemic blood pressure by more than 40 mmHg for at least 15 min; (ii) need for catecholamines to maintain organ perfusion and systolic blood pressure above 100 mm Hg; (iii) need for cardiopulmonary resuscitation. Abbreviations: CT, computed tomographic pulmonary angiography; DVT, deep vein thrombosis; eGFR, estimated glomerular filtration rate; HIV, human immunodeficiency virus; MDRD, Modified Diet in Renal Disease formula for calculation of the glomerular filtration rate; PE, pulmonary embolism; RV, right ventricular; V/Q, ventilation-perfusion (lung scan).

A key inclusion criterion is the absence of right ventricular enlargement or dysfunction, and of free floating thrombi in the right atrium or right ventricle on echocardiography or computed tomographic pulmonary angiography. The aim of this criterion is to address the concerns generated after the premature termination of an earlier randomised trial on home treatment of PE (6). In that study, short-term (10-day) mortality in the early-discharge group was overall higher than expected (2.8%, compared to 0% in the standard hospitalisation group); the most alarming observation was that a young patient, who had been randomised to early discharge and home treatment and did not undergo echocardiography, died suddenly before leaving the hospital and was diagnosed with a large right heart thrombus at autopsy (6).

Most of the HoT-PE exclusion criteria (1 through 12; Table 1) correspond to those used in the Hestia management study (11) (Table 2); they serve to exclude haemodynamic instability, serious comorbidity or any other condition which might per se mandate hospitalisation, and a familial or social environment unable to support early discharge. The remaining exclusion criteria pertain to the study drug rivaroxaban, or are common to all intervention trials (Table 1).

**Intervention**

Patients enrolled in the study receive the first dose of rivaroxaban 2 h or less before the time that the next subcutaneous injection of LMWH (or the next oral dose of rivaroxaban or apixaban) would have been due, or at the time of discontinuation of intravenous unfractionated heparin. The approved dose of rivaroxaban for the treatment of acute PE is 15 mg twice daily over the first three weeks followed by 20 mg once daily. A reduction of the maintenance dose from 20 to 15 mg once daily should be considered if the
Table 2: Study design and main results of previous major home treatment trials, and comparison to the ongoing HoT-PE study.

<table>
<thead>
<tr>
<th>Study sites</th>
<th>Design</th>
<th>Main study-specific eligibility criteria*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study sites</td>
<td>Design</td>
<td>≤48 h of admission</td>
</tr>
<tr>
<td>n=19 (ED)</td>
<td>Open-label, randomised, non-inferiority</td>
<td>Prospective cohort (single-arm)</td>
</tr>
<tr>
<td>n=12 (ED and OC)</td>
<td>≤75 000/mm³</td>
<td>≥100 mmHg</td>
</tr>
<tr>
<td>No arterial hypoxaemia, respiratory disorder</td>
<td>No history of HIT</td>
<td>Excluded in Hestia criteria</td>
</tr>
<tr>
<td>No recent surgery</td>
<td>No history of HIT (Inclu- ded in Hestia criteria)</td>
<td>LMWH od + VKAs started early</td>
</tr>
<tr>
<td>Time of discharge</td>
<td>&lt;24 h vs inpatient management</td>
<td>≤80 mmHg</td>
</tr>
<tr>
<td>Time of discharge</td>
<td>&lt;24 h</td>
<td>No need for O₂ supply to maintain O₂ saturation &gt;90%</td>
</tr>
<tr>
<td>Others</td>
<td>No arterial hypoxaemia, respiratory disorder</td>
<td>No arterial hypoxaemia, respiratory disorder</td>
</tr>
<tr>
<td>Others</td>
<td>No history of HIT (Inclu- ded in Hestia criteria)</td>
<td>No history of HIT</td>
</tr>
<tr>
<td>Others</td>
<td>No recent surgery (&lt;15 days)</td>
<td>No recent surgery</td>
</tr>
<tr>
<td>Others</td>
<td>Rivaroxaban 15 mg bid for 3 weeks followed by 20 mg od over 3 months</td>
<td>Rivaroxaban 15 mg bid for 3 weeks followed by 20 mg od over 3 months</td>
</tr>
<tr>
<td>Outcomes at 90 days§</td>
<td>Outcomes at 90 days§</td>
<td>Outcomes at 90 days§</td>
</tr>
<tr>
<td>Symptomatic recurrent VTE</td>
<td>H: 0.6 % (UCL, 2.7)</td>
<td>H: 2.0 % (95 CI, 0.8–4.3)</td>
</tr>
<tr>
<td>Symptomatic recurrent VTE</td>
<td>H: 1.8 % (UCL, 4.5)</td>
<td>H: none</td>
</tr>
<tr>
<td>Mortality</td>
<td>H: 0.6 % (UCL, 2.9)</td>
<td>H: 1.0 % (95 CI, 0.2–2.9)</td>
</tr>
</tbody>
</table>

* Eligibility criteria common to all studies include: Haemodynamically stable adults with acute, objectively diagnosed PE; no active bleeding or high risk of bleeding; no requirement for parenteral analgesics; index PE not occurring during anticoagulation, pregnancy, or hospitalisation for another illness; absence of other reasons for hospitalisation; no familial or social barriers to home treatment; anticipated good compliance of the patient; life expectancy longer than 3 months. † The Hestia criteria include the following questions, all of which must be answered with ‘no’: Is the patient haemodynamically unstable? Is thrombolysis or embolobectomy necessary? Active bleeding or high risk of bleeding? 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? Does the patient have severe liver impairment? Is the patient pregnant? Does the patient have a documented history of heparin-induced thrombocytopenia? Includes the following variables: recent major bleeding (4 points); metastatic cancer (4 points); non-metastatic cancer (2 points); serum creatinine >2mg/dl (3 points); immobility due to a recent medical condition (2 points); absence of surgery in the past 2 months (1 point); and age >60 years (1 point). § Outcomes were assessed at 10 days in the study by Agterof et al. (5). Abbreviations: bid, twice daily; BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CrCl, creatinine clearance; CT, computed tomography (pulmonary angiography); ED, emergency department; H, early discharge and home treatment; I, in-hospital treatment; HIT, heparin-induced thrombocytopenia; HoT-PE, Home Treatment of Pulmonary Embolism trial (EudraCT Nr. 2013–001657–28); LMWH, low-molecular-weight heparin; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association class; OC, outpatient clinic; od, once daily; PESI, Pulmonary Embolism Severity Index; PO2, partial oxygen pressure; RV, right ventricular; TTE, transthoracic echocardiography; UCL, upper confidence limit; VKA, vitamin K antagonist(s); VTE, venous thromboembolism.
patient's assessed risk for bleeding outweighs the risk for recurrent VTE. Rivaroxaban should be taken for at least three months. After that period, the decision whether to continue anticoagulation treatment, and the choice of the anticoagulant drug, are at the discretion of the patient's physician.

Outcomes

The primary efficacy outcome is symptomatic recurrent VTE or PE-related death within three months of enrolment.

The secondary efficacy outcomes include the following:
- all-cause mortality within seven days, three weeks, three months, and one year of enrolment;
- overall duration of hospital stay (related to the index event, or to repeated hospitalisations due to PE, or to a bleeding event) within three months;
- the number of rehospitalisations due to PE (index or recurrent event) or to a bleeding event within three months;
- generic and disease-specific quality of life, based on the Euro-QoL 5 Dimension (EQ-5D) and Pulmonary Embolism Quality of Life (PEmb-QoL) questionnaires (11, 12), at seven days, three weeks, and three months;
- treatment satisfaction, using the Anti-Clot Treatment Scale (13), at three weeks and three months;
- utilisation of health care resources at three weeks and three months.

The safety outcomes include major bleeding (defined by the criteria of the International Society on Thrombosis and Haemostasis [14]), clinically relevant non-major bleeding, and serious adverse events within seven days, three weeks, and three months. A detailed definition of the efficacy and safety outcomes, and of the event adjudication and adverse event reporting procedures, is provided in the Suppl. Material (available online at www.thrombosis-online.com).

Sample size calculation and statistical analysis

The primary analysis of the study will follow the intention-to-treat principle. The null hypothesis (H0) that \( p \geq 0.03 \) (where \( p \) = probability of recurrent VTE or PE-related death within 3 months) will be tested against the alternative hypothesis (H1) that \( p < 0.03 \), using a binomial test (two-stage adaptive design based on an O'Brien Fleming design). Assuming a three-month symptomatic VTE recurrence rate of 1.7% on the basis of existing data (8, 15), a study population of 1,050 patients will provide 80% power to reject the null hypothesis that VTE recurrence rate is \( p > 3% \) at an overall significance level \( \alpha \leq 0.05 \). Of note, the null hypothesis can only be rejected at the final analysis if a total of less than 22 primary outcomes are recorded and confirmed in the study population. Therefore, the study will be terminated prematurely in case 22 or more events are observed.

It is expected that all patients will complete the study with very few dropouts (less than 5% of the enrolled population), as the study period is fairly short (3 months). In order to estimate the presence of selection bias, the baseline characteristics of patients enrolled in the study and the characteristics of eligible patients who decline to participate are collected and compared. Following informed consent, the latter patients are also asked to complete the quality of life questionnaires at baseline, aiming to provide relevant information about the status of patients enrolled in comparison to those who decline to participate.

An interim analysis will be performed after evaluation of 525 patients, and the study will be terminated prematurely if \( H_0 \) can be rejected at the level of \( \alpha=0.004 \): this will be possible if less than six symptomatic recurrent VTE events are observed.

In case of large differences between per protocol and intention-to-treat populations, a sensitivity analysis using different techniques of dealing with missing data will be carried out. Sensitivity analyses will include worst case analysis, per protocol analysis, and comparison to individual data from the EINSTEIN-PE study (8) of patients stratified according to risk categories defined by the Pulmonary Embolism Severity Index (PESI) (16).

The analyses for assessing quality of life, patient satisfaction, and health care resource utilisation are provided in the Suppl. Material (available online at www.thrombosis-online.com).

Innovative features and unique aspects

Rationale for the selection criteria

Studies in Western Europe, North America, Australia, and Southern Latin America have yielded an annual VTE incidence rate of 75–269 cases per 100,000 population (1). As these numbers rise sharply after the age of 70 (1), an increasing number of individuals in ageing societies worldwide will be diagnosed with the disease in the years to come, with a substantial impact on morbidity and mortality as well as on VTE-related health care costs. In fact, in cost models built on adult incidence-based events and potential complications, the annual total VTE costs ranged between $13.5 and 69.3 billion in the United States and between €13.2 billion and €39 billion in the European Union, with preventable costs of up to $39 billion and €7.3 billion, respectively (9;10). Considering these facts, optimisation of PE management in the future will need to include the identification of candidates for early discharge and ambulatory treatment.

As PE is a potentially life-threatening acute cardiovascular syndrome, early discharge and home treatment is both medically and legally a very delicate issue which stands or falls with the robustness and reliability of the selection criteria. The principal, but not exclusive, requirement is that the acute PE episode should not per se be clinically severe, and that the patient should have no significant comorbidity. Indeed, a substantial proportion (between 25% and 46%, depending on the cohort studied) of all patients with acute PE may be classified as being at low risk of early mortality based on a PESI risk class of I or II, or a sPESI of 0 (17–19). However, and despite its uncontested prognostic value, the PESI does...
not account for the patient’s family and social environment. Moreover, it provides no information on the functional status of the right ventricle, and right ventricular dysfunction may be present on echocardiography or computed tomography despite a negative sPESI. Finally, and importantly, by relying exclusively on a clinical score, one may miss (and thus send home) patients with impending massive PE due to free-floating thrombi in the right heart cavities (6). Seen from the opposite angle, patients with either active cancer or history of cancer would immediately be excluded from ambulatory treatment based on the sPESI, even if all other clinical findings were favourable; this might lead to unnecessary hospitalisation of several of these patients with all the associated discomfort, risks, and costs.

An alternative approach to patient eligibility has been to develop explicit home treatment-oriented clinical criteria, either alone (Hestia criteria) (4) or in combination with biomarker testing (N-terminal pro-brain natriuretic peptide [NT-proBNP] plasma levels <500 pg/ml) (5). Two small- to medium-sized (150–300 patients) prospective cohort trials were successful in demonstrating the safety of this strategy, at least in the Netherlands, a country with a dense and highly efficient network of outpatient anticoagulation clinics (4, 5). Their results need external validation and confirmation in larger cohorts and further countries to be widely applicable.

Based on the promising data obtained from studies dating back to the ‘VKA era’ and considering the strengths and weaknesses of the selection criteria proposed thus far, the large ongoing HoT-PE study has adopted an approach which, in our opinion, combines simplicity and clinical practicability with the high degree of safety and reassurance which is required to justify early discharge from the hospital or even immediate discharge from the emergency department. Thus, a key inclusion criterion is the absence of right ventricular enlargement or dysfunction, and of free floating thrombi in the right cavities on echocardiography or computed tomographic pulmonary angiography, while the exclusion checklist is largely based on the Hestia criteria (4) which ensure that there is no haemodynamic instability, serious comorbidity or any other condition which might per se mandate hospitalisation, or a familial or social environment unable to support home treatment of the patient in the acute phase of PE.

Rationale for the trial design

The major ‘home treatment’ trials performed in patients with acute PE thus far (3–6) used the standard anticoagulation regimen of initial subcutaneous LMWH administration followed by international normalised ratio (INR)-adjusted VKA treatment; two of these trials had an in-hospital comparator arm (3, 6). Taken together, the available data suggest that a shift towards ambulatory treatment might be an option for a substantial proportion of patients with acute PE.

Since the publication of these trials we have witnessed major advances in anticoagulation treatment. For example, in the EINSTEIN-DVT (20) and EINSTEIN-PE (8) trials, single oral drug treatment with rivaroxaban was tested versus enoxaparin-warfarin using a randomised, open-label, non-inferiority design. In particular, EINSTEIN-PE enrolled 4,832 patients who had acute symptomatic PE, with or without deep venous thrombosis. Rivaroxaban was non-inferior to standard therapy for the primary efficacy outcome of recurrent fatal or symptomatic non-fatal VTE (hazard ratio [HR] 1.12, 95% confidence interval [CI] 0.75–1.68) (8). Major bleeding was less frequent in the rivaroxaban group compared to the standard-therapy group (1.1% vs 2.2%, HR 0.49, 95%CI 0.31–0.79) (8). A recent sub-analysis of the pooled EINSTEIN-DVT and -PE data further suggested that major bleeding events in the rivaroxaban arm were less severe than in the enoxaparin-VKA arm as judged by their clinical course (21). The efficacy and safety of the ‘single oral drug’ approach was also demonstrated in the apixaban trial (7).

Single oral drug regimens for PE may lessen the patients’ perceived burden of anticoagulation therapy, and possibly the costs related to prolonged hospitalisation and bleeding complications. As part of EINSTEIN-PE, 2,397 patients in seven countries completed a validated measure of treatment satisfaction, the ACTS; rivaroxaban treatment was reported to result in improved treatment satisfaction compared with enoxaparin-VKA (22). Furthermore, in an analysis based on both EINSTEIN trials, rivaroxaban was associated with greater discounted quality-adjusted life expectancy as well as per-patient cost savings for each treatment duration modelled (3, 6 and 12 months); the benefits were greatest with shorter durations (23).

In light of the available data derived from the large phase 3 randomised trials, the HoT-PE study was designed as prospective international multicentre single-arm phase 4 management trial. After careful consideration, the steering committee rejected the randomised design for the present study for the following reasons: first, the study drug, rivaroxaban, is already approved for the treatment of acute PE, and thus randomisation of 50% of the study patients ‘back’ to the enoxaparin-VKA regimen might be rejected by many physicians and patient candidates, leading to recruitment problems and, importantly, selection bias. Second, we expected recruited problems in case of randomisation of eligible patients with low-risk PE to in-hospital versus home treatment, since early discharge is already being practiced (despite the lack of conclusive evidence) to a various extent in many countries. It was thus felt that testing this strategy on the basis of standardised selection criteria approved by ethics committees, and in the ‘protective environment’ of a prospective single-armed interventional trial, would be the most efficient approach and also in the patients’ and physicians’ best interest.

Conclusion: Relevance and expected impact of the HoT-PE trial

For many years, the difficulty in translating the definition of ‘low-risk PE’ to standardised, widely acceptable selection criteria for early (or immediate) discharge and home treatment has precluded clear-cut, evidence-based recommendations by experts and scientific societies. HoT-PE, a prospective single-armed phase 4
management trial, has been designed to address this unmet need. The study uses rivaroxaban, one of the new oral anticoagulants which have been tested and approved for the treatment of acute PE; these drugs may provide superior safety compared to earlier regimes while at the same time facilitating ambulatory treatment. By analysing a population of up to 1,050 patients, HoT-PE will be the largest interventional study on home treatment of acute PE conducted thus far. Apart from VTE recurrence, data on the quality of life and patient satisfaction as well as health care resource utilisation are being collected. As of February 2016, a total of 149 patients have been enrolled at 17 active sites in Germany; further sites in Portugal, Italy, Spain, and Greece will join the HoT-PE study in 2016. The enrolment of the last patient is expected by 2018, depending on the results of the prespecified interim analysis after the inclusion of 525 patients. If the hypothesis of HoT-PE is confirmed, early discharge and oral out-of-hospital treatment may become an attractive, potentially cost-saving option for a substantial proportion of patients with acute PE.

Acknowledgements

The work of Stefano Barco, Mareike Lankeit, and Stavros Konstantinides was supported by the German Federal Ministry of Education and Research (BMBF 01EO1003 and 01EO1503). The authors are responsible for the contents of this publication.

Conflicts of interest

Stefano Barco received an educational travel grant from Daichi Sankyo. Mareike Lankeit received lecture/consultant fees from Bayer HealthCare, Pfizer/Bristol-Myers Squibb, Daichi Sankyo and Actelion. Harald Binder has nothing to disclose. Sebastian Schellong received lecture fees and consulting honoraria from Bayer, Boehringer Ingelheim, Bristol-Myers-Squibb, Daichi Sankyo and Pfizer. Michael Christ received financial support for clinical studies from Roche Diagnostics, Novartis, Alere GmbH, Philips GmbH Netherlands, and speaking honoraria from Univadis, Boehringer Ingelheim, Novartis Pharma, Roche Diagnostics, Bayer HealthCare. Jan Beyer-Westendorf reports honoraria and research support from Bayer HealthCare, Boehringer Ingelheim, Pfizer and Daichi Sankyo. Daniel Dierschmid received lecture fees and consulting honoraria from Bayer and Daichi Sankyo. Rupert Bauersachs received lecture and advisory board honoraria from Bayer Healthcare, Boehringer Ingelheim, Prizer-Bristol-Myers-Squibb, Daichi Sankyo, and LEO Pharma. Klaus Empen reports lecture honoraria from Bayer HealthCare, Boehringer Ingelheim, Novartis and Daichi Sankyo. Matthias Held received honoraria for lectures or advisory board activities from Bayer HealthCare, Pfizer, Boehringer Ingelheim, Actelion, Novartis, Berlin Chemie, GSK, United Therapeutics. Martin Schwabmair received lecture and advisory board honoraria from AstraZeneca, Bayer Healthcare, Berlin-Chemie/Menarini, Boehringer Ingelheim, GlaxoSmithKline, Novartis, Pfizer and Pulmonx. Cândida Beccattini received peer’s fee from Bayer HealthCare, Bristol-Myers-Squibb and Boehringer Ingelheim. Kurt Quitzau has nothing to disclose. Stavros Konstantinides received lecture and advisory board honoraria from Bayer Healthcare, MSD, Boehringer Ingelheim, Prizer-Bristol-Myers-Squibb, Daichi Sankyo, and institutional grants from Bayer HealthCare, Boehringer Ingelheim, Actelion.

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