

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

Stefano Barco ¹, **Irene Schmidtmann** ², **Walter Ageno**³, **Rupert M. Bauersachs**⁴, **Cecilia Becattini**⁵, **Enrico Bernardi**⁶, **Jan Beyer-Westendorf**^{7,8}, **Luca Bonacchini** ⁹, **Johannes Brachmann**¹⁰, **Michael Christ**¹¹, **Michael Czihal**¹², **Daniel Duerschmied**¹³, **Klaus Empen**¹⁴, **Christine Espinola-Klein**^{1,15}, **Joachim H. Ficker**¹⁶, **Cândida Fonseca**¹⁷, **Sabine Genth-Zotz**¹⁸, **David Jiménez** ¹⁹, **Veli-Pekka Harjola**²⁰, **Matthias Held**²¹, **Lorenzo Iogna Prat** ²², **Tobias J. Lange**²³, **Athanasios Manolis**²⁴, **Andreas Meyer**²⁵, **Pirjo Mustonen**²⁶, **Ursula Rauch-Kroehnert**²⁷, **Pedro Ruiz-Artacho**^{28,29}, **Sebastian Schellong**³⁰, **Martin Schwaiblmair**³¹, **Raoul Stahrenberg**³², **Peter E. Westerweel** ³³, **Philipp S. Wild**^{1,34,35}, **Stavros V. Konstantinides**^{1,36*}, and **Mareike Lankeit** ^{1,37,38}; on behalf of the **HoT-PE Investigators**[†]

¹Center for Thrombosis and Hemostasis (CTH), University Medical Center of the Johannes Gutenberg University, Langenbeckstrasse 1, Building 403, 55131 Mainz, Germany; ²Institute of Medical Biostatistics, Epidemiology and Informatics (IMBEI), University Medical Center Mainz, Obere Zahlbacher Strasse 69, 55131 Mainz, Germany; ³Department of Medicine and Surgery, Research Center on Thromboembolic Diseases and Antithrombotic Therapies, University of Insubria, Viale Luigi Borri 57, 21100 Varese, Italy; ⁴Department of Vascular Medicine, Klinikum Darmstadt, Grafenstrasse 9, 64283 Darmstadt, Germany; ⁵Internal and Cardiovascular Medicine - Stroke Unit, University of Perugia, Via G. Dottori 1, 06129 Perugia, Italy; ⁶Department of Emergency Medicine, ULSS n.7, Via Brigata Bisagno 4, 31015 Conegliano (Treviso), Italy; ⁷Thrombosis Research Unit, Division of Hematology, Department of Medicine I, University Hospital "Carl Gustav Carus", Fetscherstrasse 74, 01307 Dresden, Germany; ⁸Kings Thrombosis Service, Department of Hematology, Kings College London, Denmark Hill, Brixton, SE5 9RS, London, UK; ⁹S.C. Medicina d'Urgenza e Pronto Soccorso, ASST Grande Ospedale Metropolitano Niguarda, Piazza dell'Ospedale Maggiore 3, 20162 Milano, Italy; ¹⁰II Medical Department, Coburg Hospital, Ketschendorfer Strasse 33, 96450 Coburg, Germany; ¹¹Emergency Care (Notfallzentrum), Luzerner Kantonsspital, 6000 Luzern, Switzerland; ¹²Division of Vascular Medicine, Hospital of the Ludwig-Maximilians-University, Georgenstrasse 5, 80799 Munich, Germany; ¹³Department of Cardiology and Angiology I, Heart Center, Faculty of Medicine, University of Freiburg, Hugstetter Strasse 55, 79106 Freiburg, Germany; ¹⁴Department of Internal Medicine, University Medical Center, Fleischmannstrasse 6, 17489 Greifswald, Germany; ¹⁵Center for Cardiology, Cardiology 1, University Medical Center of the Johannes Gutenberg-University, Langenbeckstrasse 1, 55131 Mainz, Germany; ¹⁶Department of Respiratory Medicine, Nuremberg General Hospital/Paracelsus Medical University, Prof.-Ernst-Nathan-Strasse 1, 90419 Nuremberg, Germany; ¹⁷Department of Internal Medicine, Hospital S. Francisco Xavier/CHLO, NOVA Medical School, Faculdade de Ciências Médicas, Universidade Nova de Lisboa, Campo Mártires da Pátria 130, 1169-056 Lisbon, Portugal; ¹⁸Department of Internal Medicine I, Katholisches Klinikum Mainz, An der Goldrube 11, 55131 Mainz, Germany; ¹⁹Respiratory Department, Ramón y Cajal Hospital, Universidad de Alcalá, IRYCIS, Ctra. Colmenar Viejo, km. 9, 100, 28034 Madrid, Spain; ²⁰Emergency Medicine, University of Helsinki, Department of Emergency Medicine and Services, Helsinki University Hospital, Tukholmantatu 8A, 00290 Helsinki, Finland; ²¹Department of Internal Medicine, Medical Mission Hospital, Academic Teaching Hospital of the Julius-Maximilian University of Würzburg, Josef-Schneider-Strasse 2, 97080 Würzburg, Germany; ²²Department of Emergency Medicine, Santa Maria della Misericordia Hospital, Piazzale Santa Maria della Misericordia 15, 33100 Udine, Italy; ²³Department of Internal Medicine II, Division of Pneumology, University Medical Center Regensburg, Franz-Josef-Strauss-Allee 11, 93053 Regensburg, Germany; ²⁴Department of Cardiology, General Hospital 'Asklepeion Voulas', Leof. Vasileos Pavlou 1, 166 73 Athens, Greece; ²⁵Kliniken Maria Hilf, Klinik für Pneumologie, Krankenhaus St. Franziskus, Viersener Str. 450, 41063 Mönchengladbach, Germany; ²⁶Department of Medicine, Keski-Suomi Central Hospital and University of Jyväskylä, Keskussairaalaantie 19, 40620 Jyväskylä, Finland; ²⁷Department of Cardiology, University Heart Center Berlin, Charité Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany; ²⁸German Center for Cardiovascular Research (DZHK), Berlin, Germany; ²⁹Emergency Department, Clinico San Carlos Hospital, IdISSC, alle del Prof Martín Lagos, s/n, 28040 Madrid, Spain; ³⁰Internal Medicine Department, University Clinic of Navarra, Calle Marquesado de Sta. Marta 1, 28027 Madrid, Spain; ³¹Vascular Center, Municipal Hospital of Dresden-Friedrichstadt, Friedrichstraße 41, 01067 Dresden, Germany; ³²Department of Cardiology, Respiratory Medicine and Intensive Care, Klinikum Augsburg, Ludwig-Maximilians-University Munich, Stenglinstrasse 2, 86156 Munich, Germany; ³³Helios Albert-Schweitzer-Klinik, Albert-Schweitzer-Weg 1, 37154 Northeim,

* Corresponding author. Tel: +49 6131 17 8382, Fax: +49 6131 17 3456, Email: stavros.konstantinides@unimedizin-mainz.de

† HoT-PE Investigators are listed in the Acknowledgements section.

All HoT-PE Investigators, including those cited in the Supplementary material online, contributed to the collection of data, interpretation of the results, critical revision of the manuscript for important intellectual content, and gave final approval.

© The Author(s) 2019. Published by Oxford University Press on behalf of the European Society of Cardiology.

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

Germany; ³³Department of Internal Medicine, Albert Schweitzer Hospital, Albert Schweitzerplaats 25, 3318 AT Dordrecht, The Netherlands; ³⁴German Center for Cardiovascular Research (DZHK), Partner Site Rhine Main, Mainz, Germany; ³⁵Center for Cardiology, Preventive Cardiology and Preventive Medicine, University Medical Center of the Johannes Gutenberg University, Langenbeckstrasse 1, 55131 Mainz, Germany; ³⁶Department of Cardiology, Democritus University of Thrace, 68100 Alexandroupolis, Greece; ³⁷Department of Internal Medicine and Cardiology, Campus Virchow Klinikum, Charité - University Medicine Berlin, Augustenburgerplatz 1, 13353 Berlin, Germany; and ³⁸Clinic of Cardiology and Pneumology, Heart Center, University Medical Center Goettingen, Robert-Koch-Strasse 40, 37075 Goettingen, Germany.

Received 10 April 2019; revised 27 April 2019; editorial decision 13 May 2019; accepted 13 May 2019; online publish-ahead-of-print 23 May 2019

See page 519 for the editorial comment on this article (doi: 10.1093/eurheartj/ehz484)

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 worldwide¹ 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 hospitalization⁵ and have an impact on healthcare costs⁶ 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 ≥ 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 previously¹⁷ and are provided in the study protocol available in the [Supplementary online material](#).

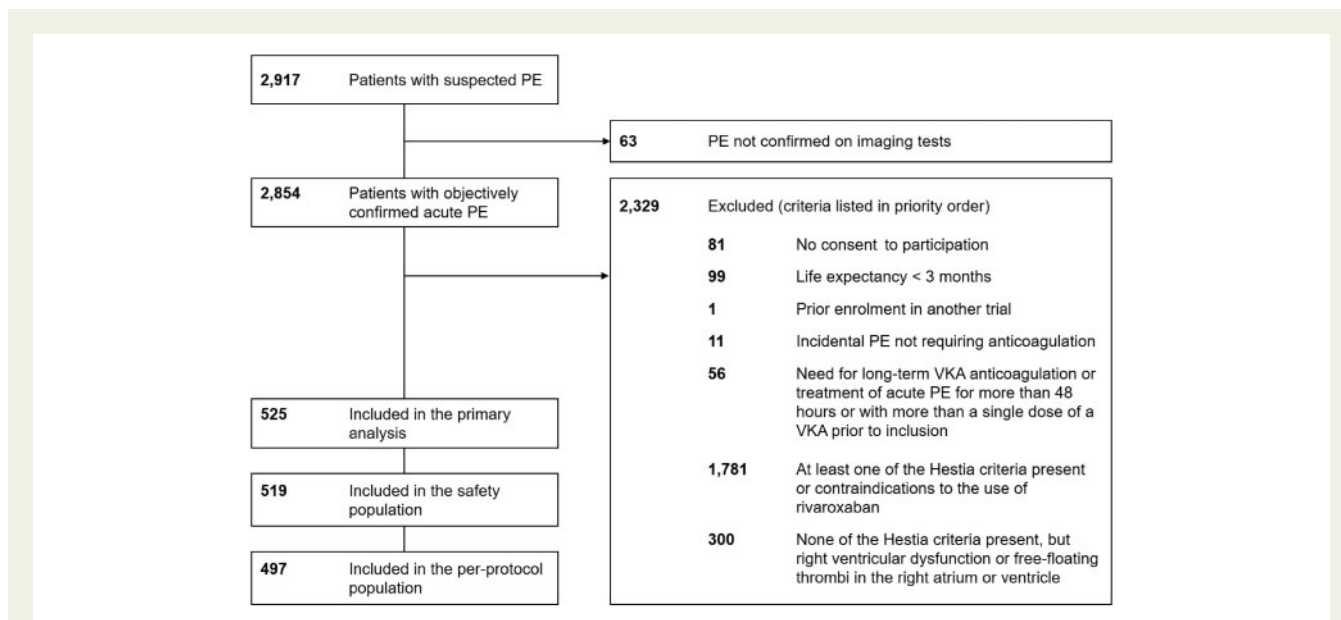


Figure 1 Flow diagram of the screening, selection, and enrolment process. PE, pulmonary embolism; VKA, vitamin K antagonist.

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 supra-therapeutic 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 pre-defined 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, <i>n/N</i> (%)	344/525 (65.5)	0
Enoxaparin, <i>n</i>	234	0
Dalteparin, <i>n</i>	20	0
Nadroparin, <i>n</i>	17	0
Tinzaparin, <i>n</i>	39	0
Certoparin, <i>n</i>	30	0
Other or not specified, <i>n</i>	4	0
Unfractionated heparin, <i>n/N</i> (%)	43/525 (8.2)	0
Fondaparinux, <i>n/N</i> (%)	19/525 (3.6)	0
Rivaroxaban, <i>n/N</i> (%)	96/525 (18.3)	0
Apixaban, <i>n/N</i> (%)	3/525 (0.6)	0
No initial anticoagulation, <i>n/N</i> (%)	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, <i>n</i>	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, <i>n/N</i> (%)	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 guidelines³ 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, <i>n/N</i> (%; one-sided upper 99.6% CI)	3/525 (0.6; 2.1)
Recurrent PE, <i>n</i> (%; 95% CI)	3/525 (0.6; 0.1–1.7)
Recurrent deep vein thrombosis, <i>n</i>	0
Death related to PE, <i>n</i>	0
Safety outcomes	
Major bleeding, ^a <i>n/N</i> (%; 95% CI)	6/519 (1.2; 0.4–2.5)
Clinically relevant bleeding, <i>n/N</i> (%; 95% CI)	31/519 (6.0; 4.1–8.4)
At least one serious adverse event, <i>n/N</i> (%; 95% CI)	58/519 (11.2; 8.6–14.2)
Secondary efficacy outcomes	
Serious adverse events requiring prolonged initial hospitalization, or rehospitalization, <i>n/N</i> (%)	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, <i>n/N</i> (%)	12/525 (2.3)
Pneumonia, <i>n/N</i> (%)	4/525 (0.8)
Recurrent PE, <i>n/N</i> (%)	2/525 (0.4)
Major bleeding, <i>n/N</i> (%)	4/525 (0.8)
Clinically-relevant-non-major bleeding, <i>n/N</i> (%)	1/525 (0.2)
Other, <i>n/N</i> (%)	1/525 (0.2)
Death of any cause within 3 months, <i>n/N</i> (%; 95% CI)	2/525 (0.4; 0.1–1.4)
Advanced cancer as cause of death, <i>n</i>	2

CI, confidence interval; IQR, interquartile range; PE, pulmonary embolism.

^aAs 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 be 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.

^aAs 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.

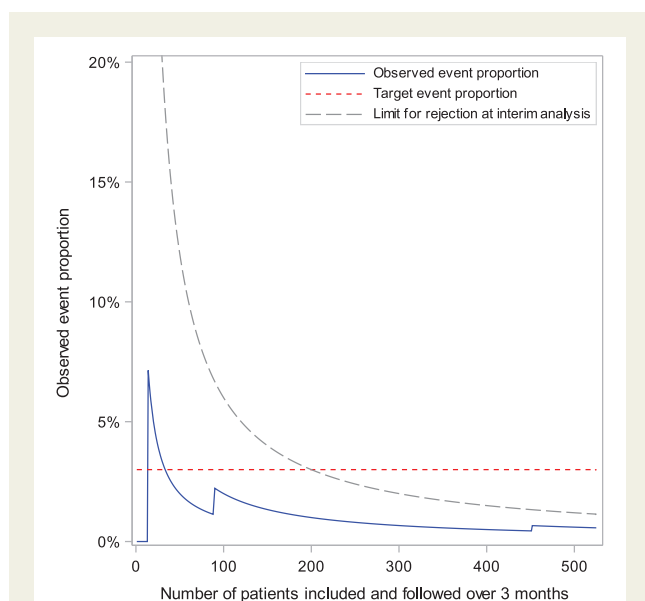


Figure 2 Early stopping boundaries along subject-by-subject accounting of the event rate.

The HoT-PE Trial Investigators are Stavros V. Konstantinides, Rupert Martin Bauersachs, Christoph Bode, Michael Christ, Christine Espinola-Klein, Annette Geibel, Mareike Lankeit, Michael Pfeifer, Sebastian Schellong, Philipp S. Wild, Harald Binder, Kurt Quitzau, Nadine Martin, Dorothea Becker, Stefano Barco, Irene Schmidtmann, Toni Anusic, Martin Schwaiblmair, Ursula Rauch-Kröhnert, Martin Möckel, Johannes Brachmann, Jan Beyer-Westendorf, Daniel Duerschmied, Sabine Blaschke, Marius M. Hoepfer, Evangelos Giannitis, Klaus Empen, Rainer Schmiedel, Ulrich Hoffman, Ibrahim Akin, Andreas Meyer, Sabine Genth-Zotz, Joachim Ficker, Tobias Geisler, Matthias Held, Cecilia Becattini, Ludovica Cimini, Jörg Herold, Walter Ageno, Rodolfo Sbrojavacca, Enrico Bernardi, Giuseppe Bettoni, Roberto Cosentini, Paolo Moscatelli, Cinzia Nitti, Maria Pazzaglia, Raffaele Pesavento, Alessandra Ascani, Francesca Cortellaro, Nicola Montano, Peter E. Westerweel, Pedro Ruiz-Artacho, David Jiménez, Aitor Ballaz-Quincoces, Raquel Lopez Reyes, Remedios Otero, Candida Fonseca, Tiago Judas, Inês Araujo, Sergio Batista, Fabienne Goncalves, Veli-Pekka Harjola, Pirjo Mustonen, Georgios Hahalis, Athanasios Manginas, Konstantinos Gougoulianis, Athanasios Manolis, Michael Czihal, Tobias J. Lange, Raoul Stahrenberg, Thomas Meinertz, Menno V. Huisman, Paolo Prandoni, Walter Lehmacher, Stanislav Gorbulev, Kai Kronfeld.

Acknowledgements

We would like to thank Ms Sabrina Rump (Center for Thrombosis and Hemostasis, Mainz, Germany), Dr Luigi Visani and Dr Chiara Colombo (EXOM Group-the Human Digital CRO, Milano, Italy), for their help. The manuscript is dedicated to the memory of Annette Geibel, MD, one of the pioneers of risk-adapted management of acute pulmonary embolism, who contributed substantially to the design and initiation of the HoT-PE trial.

Funding

HoT-PE is an independent, investigator-initiated trial with an academic sponsor (Centre for Thrombosis and Haemostasis, University Medical Centre Mainz, Germany). The work of Stefano Barco, Philipp S. Wild, Stavros V. Konstantinides, and Mareike Lankeit was supported by the German Federal Ministry of Education and Research [BMBF 01EO1003 and 01EO1503]. In addition, the sponsor has obtained the study drug (rivaroxaban) and a grant from the market authorization holder of rivaroxaban, Bayer AG.

Conflict of interest: S.B. reports personal fees from BTG/EKOS and Bayer HealthCare, non-financial support from Bayer HealthCare and Daiichi Sankyo, outside the submitted work. I.S. reports grants from Merck Serono, outside the submitted work. W.A. reports grants from Bayer, personal fees from Boehringer Ingelheim, Daiichi Sankyo, and BMS/Pfizer, outside the submitted work. R.M.B. reports personal fees from Bayer Health Care, BMS/Pfizer, and Daiichi-Sankyo, during the conduct of the study. C.B. reports personal fees from Bayer Health Care, Daiichi Sankyo, and Bristol Meyer Squibb, outside the submitted work. J.B.-W. reports other from CTH Mainz (Sponsor), during the conduct of the study; grants and personal fees from Bayer, outside the submitted work. J.B. reports grants and personal fees from Medtronic, during the conduct of the study; grants from Medtronic, St. Jude, and Biotronik, outside the submitted work. M.C. reports grants from the University of Mainz during the conduct of the study. M.C. reports personal fees from Bayer Health Care, personal fees from Roche, Astra-Zeneca, MSD Sharp & Dohme, and Leo Pharma, outside the submitted work. D.D. reports personal fees and non-financial support from Bayer, Pfizer, Daiichi Sankyo, and CytoSorbents, outside the submitted work. K.E. reports non-financial support from Bayer HealthCare; personal fees from Bayer HealthCare, outside the submitted work. C.E.-K. reports other from Bayer Health Care, outside the submitted work. J.H.F. reports personal fees from Daiichi Sankyo, outside the submitted work. C.F. reports personal fees from Bayer, outside the submitted work. D.J. reports personal fees and other from Bayer and Bristol-Myers Squibb; grants and personal fees from Daiichi Sankyo, personal fees from Sanofi, personal fees and other from Pfizer, personal fees from Leo-Pharma, outside the submitted work. V.P.H. reports personal fees from Bayer, Boehringer-Ingelheim, MSD, and Pfizer, outside the submitted work. M.H. reports other from Actelion, Bayer, Boehringer, MSD, Daiichi Sankyo, and Roche; other from Actelion, Bayer, Berlin Chemie, BMS, MSD, Daiichi Sankyo, Pfizer, and OMT; grants from Actelion, outside the submitted work. T.J.L. reports non-financial support from Center for Thrombosis and Hemostasis, University Medical Center Mainz, during the conduct of the study; personal fees from Bayer and Pfizer, outside the submitted work. P.M. reports personal fees from Boehringer-Ingelheim, Bayer, Sanofi-Anetis, LeoPhrama, BMS-Pfizer, and MSD, outside the submitted work. U.R.-K. reports personal fees from Bayer Vital GmbH, outside the submitted work. P.R.-A. reports personal fees from Bayer, Daiichi Sankyo, Sanofi, Pfizer, and Leo-Pharma and Rovi, outside the submitted work. S.S. reports personal fees from Bayer, Boehringer Ingelheim, grants and personal fees from BMS, personal fees from Daiichi Sankyo, and Aspen, outside the submitted work. P.S.W. reports grants and personal fees from Boehringer Ingelheim, grants from Philips Medical Systems, grants and personal fees from Sanofi-Aventis, Bayer Vital, grants from Daiichi Sankyo Europe, personal fees from Bayer Health Care, personal fees from Astra Zeneca, personal fees and non-financial support from DiaSorin, non-financial support from I.E.M., outside the submitted work. S.V.K. reports grants and non-financial support from Bayer AG, during the conduct of the study; grants and personal fees from Boehringer Ingelheim, personal fees from Bayer AG, grants and personal fees from Actelion, grants and personal fees from Daiichi-Sankyo, grants and personal fees from Biocompatibles

Group UK, personal fees from Pfizer—Bristol-Myers Squibb, grants and personal fees from MSD, outside the submitted work. M.L. reports personal fees and non-financial support from Actelion, personal fees and non-financial support from Bayer, personal fees and non-financial support from Daiichi-Sankyo, personal fees from MSD, personal fees from Pfizer—Bristol-Myers Squibb, grants from BRAHMS—Thermo Fisher scientific, outside the submitted work. E.B., L.B., S.G.-Z., L.I.P., A.M., A.M., M.S., R.S., and P.E.W. have nothing to disclose.

References

- Wendelboe AM, Raskob GE. Global Burden of Thrombosis: epidemiologic aspects. *Circ Res* 2016;**118**:1340–1347.
- Konstantinides S, Torbicki A. Management of venous thrombo-embolism: an update. *Eur Heart J* 2014;**35**:2855–2863.
- Konstantinides SV, Torbicki A, Agnelli G, Danchin N, Fitzmaurice D, Galie N, Gibbs JS, Huisman MV, Humbert M, Kucher N, Lang I, Lankeit M, Lekakis J, Maack C, Mayer E, Meneveau N, Perrier A, Pruszczyk P, Rasmussen LH, Schindler TH, Svitil P, Vonk Noordegraaf A, Zamorano JL, Zompatori M; Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC). 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. *Eur Heart J* 2014;**35**:3033–3069, 3069a–3069k.
- Becattini C, Agnelli G, Lankeit M, Masotti L, Pruszczyk P, Casazza F, Vanni S, Nitti C, Kamphuisen P, Vedovati MC, De Natale MG, Konstantinides S. Acute pulmonary embolism: mortality prediction by the 2014 European Society of Cardiology risk stratification model. *Eur Respir J* 2016;**48**:780–786.
- Conley J, O'Brien CW, Leff BA, Bolen S, Zulman D. Alternative strategies to inpatient hospitalization for acute medical conditions: a systematic review. *JAMA Intern Med* 2016;**176**:1693–1702.
- Barco S, Woerschling AL, Spyropoulos AC, Piovella F, Mahan CE. European Union-28: an annualised cost-of-illness model for venous thromboembolism. *Thromb Haemost* 2016;**115**:800–808.
- Bledsoe JR, Woller SC, Stevens SM, Aston V, Patten R, Allen T, Horne BD, Dong L, Lloyd J, Snow G, Madsen T, Elliott CG. Management of low-risk pulmonary embolism patients without hospitalization: the low-risk pulmonary embolism prospective management study. *Chest* 2018;**154**:249–256.
- Aujesky D, Roy PM, Verschuren F, Righini M, Osterwalder J, Egloff M, Renaud B, Verhamme P, Stone RA, Legall C, Sanchez O, Pugh NA, N'Gako A, Cornuz J, Hugli O, Beer HJ, Perrier A, Fine MJ, Yealy DM. Outpatient versus inpatient treatment for patients with acute pulmonary embolism: an international, open-label, randomised, non-inferiority trial. *Lancet* 2011;**378**:41–48.
- Otero R, Uresandi F, Jimenez D, Cabezudo MA, Oribe M, Nauffal D, Conget F, Rodriguez C, Cayuela A. Home treatment in pulmonary embolism. *Thromb Res* 2010;**126**:e1–e5.
- Agterof MJ, Schutgens RE, Snijder RJ, Epping G, Peltenburg HG, Posthuma EF, Hardeman JA, van der GR, Koster T, Prins MH, Biesma DH. Out of hospital treatment of acute pulmonary embolism in patients with a low NT-proBNP level. *J Thromb Haemost* 2010;**8**:1235–1241.
- Zondag W, Mos IC, Creemers-Schild D, Hoogerbrugge AD, Dekkers OM, Dolsma J, Eijsvogel M, Faber LM, Hofstee HM, Hovens MM, Jonkers GJ, van Kralingen KW, Kruij MJ, Vlasveld T, DE Vreede MJ, Huisman MV. Outpatient treatment in patients with acute pulmonary embolism: the Hestia Study. *J Thromb Haemost* 2011;**9**:1500–1507.
- den Exter PL, Zondag W, Klok FA, Brouwer RE, Dolsma J, Eijsvogel M, Faber LM, van GM, Grootenboers MJ, Heller-Baan R, Hovens MM, Jonkers GJ, van Kralingen KW, Melissant CF, Peltenburg H, Post JP, Van De Ree MA, Vlasveld T, DE Vreede MJ, Huisman MV. Efficacy and safety of outpatient treatment based on the Hestia clinical decision rule with or without NT-proBNP testing in patients with acute pulmonary embolism: a randomized clinical trial. *Am J Respir Crit Care Med* 2016;**194**:998–1006.
- Mastroiacovo D, Dentali F, di Micco P, Maestre A, Jimenez D, Soler S, Sahuquillo JC, Verhamme P, Fidalgo A, Lopez-Saez JB, Skride A, Monreal M; RIETE Investigators. Rate and duration of hospitalisation for acute pulmonary embolism in the real-world clinical practice of different countries: analysis from the RIETE registry. *Eur Respir J* 2019;**53**:1801677.
- Margolis JM, Deitelzweig S, Kline J, Tran O, Smith DM, Bookhart B, Crivera C, Schein J. Shorter hospital stays and lower costs for rivaroxaban compared with warfarin for venous thrombosis admissions. *J Am Heart Assoc* 2016;**5**:e003788.
- Barco S, Mahmoudpour SH, Planquette B, Sanchez O, Konstantinides SV, Meyer G. Prognostic value of right ventricular dysfunction or elevated cardiac biomarkers in patients with low-risk pulmonary embolism: a systematic review and meta-analysis. *Eur Heart J* 2019;**40**:902–910.
- Kearon C, Akl EA, Ornells J, Blaivas A, Jimenez D, Bounameaux H, Huisman M, King CS, Morris TA, Sood N, Stevens SM, Vintch JR, Wells P, Woller SC, Moores L. Antithrombotic Therapy for VTE Disease: CHEST guideline and expert panel report. *Chest* 2016;**149**:315–352.
- Barco S, Lankeit M, Binder H, Schellong S, Christ M, Beyer-Westendorf J, Duerschmied D, Bauersachs R, Empen K, Held M, Schwaiblmair M, Fonseca C, Jimenez D, Becattini C, Quitzau K, Konstantinides S. Home treatment of patients with low-risk pulmonary embolism with the oral factor Xa inhibitor rivaroxaban. Rationale and design of the HoT-PE Trial. *Thromb Haemost* 2016;**116**:191–197.
- Schulman S, Kearon C. Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost* 2005;**3**:692–694.
- Zondag W, Kooiman J, Klok FA, Dekkers OM, Huisman MV. Outpatient versus inpatient treatment in patients with pulmonary embolism: a meta-analysis. *Eur Respir J* 2013;**42**:134–144.
- Buller HR, Prins MH, Lensin AW, Decousus H, Jacobson BF, Minar E, Chlumsky J, Verhamme P, Wells P, Agnelli G, Cohen A, Berkowitz SD, Bounameaux H, Davidson BL, Misselwitz F, Gallus AS, Raskob GE, Schellong S, Segers A. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *N Engl J Med* 2012;**366**:1287–1297.
- Torbicki A. Assessing the severity of acute pulmonary embolism: back to the future? *Eur Heart J* 2019;**40**:911–913.
- Agno W, Mantovani LG, Haas S, Kreutz R, Monje D, Schneider J, van EM, Gebel M, Zell E, Turpie AG. Safety and effectiveness of oral rivaroxaban versus standard anticoagulation for the treatment of symptomatic deep-vein thrombosis (XALIA): an international, prospective, non-interventional study. *Lancet Haematol* 2016;**3**:e12–e21.
- Beyer-Westendorf J, Forster K, Pannach S, Ebertz F, Gelbricht V, Thieme C, Michalski F, Kohler C, Werth S, Sahin K, Tittel L, Hansel U, Weiss N. Rates, management, and outcome of rivaroxaban bleeding in daily care: results from the Dresden NOAC registry. *Blood* 2014;**124**:955–962.
- Buller HR, Decousus H, Grosso MA, Mercuri M, Middeldorp S, Prins MH, Raskob GE, Schellong SM, Schwoco L, Segers A, Shi M, Verhamme P, Wells P. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. *N Engl J Med* 2013;**369**:1406–1415.
- Dentali F, Di Micco G, Giorgi Pierfranceschi M, Gussoni G, Barillari G, Amitrano M, Fontanella A, Lodigiani C, Guida A, Visona A, Monreal M, Di Micco P. Rate and duration of hospitalization for deep vein thrombosis and pulmonary embolism in real-world clinical practice. *Ann Med* 2015;**47**:546–554.
- Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, Masiukiewicz U, Pak R, Thompson J, Raskob GE, Weitz JL. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med* 2013;**369**:799–808.
- Mazzolai L, Aboyans V, Agno W, Agnelli G, Alatri A, Bauersachs R, Brekelmans MPA, Buller HR, Elias A, Farge D, Konstantinides S, Palareti G, Prandoni P, Righini M, Torbicki A, Vlachopoulos C, Brodmann M. Diagnosis and management of acute deep vein thrombosis: a joint consensus document from the European Society of Cardiology working groups of aorta and peripheral vascular diseases and pulmonary circulation and right ventricular function. *Eur Heart J* 2018;**39**:4208–4218.