Survival and quality of life after early discharge in low-risk pulmonary embolism

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The results of the complete primary outcome analysis of the HoT-PE study, as well as long-term mortality and quality-of-life data, support early discharge and ambulatory oral anticoagulation with rivaroxaban for selected patients with acute low-risk PE https://bit.ly/32qX0mu

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ABSTRACT

Introduction: Early discharge of patients with acute low-risk pulmonary embolism requires validation by prospective trials with clinical and quality-of-life outcomes.

Methods: The multinational Home Treatment of Patients with Low-Risk Pulmonary Embolism with the Oral Factor Xa Inhibitor Rivaroxaban (HoT-PE) single-arm management trial investigated early discharge followed by ambulatory treatment with rivaroxaban. The study was stopped for efficacy after the positive results of the predefined interim analysis at 50% of the planned population. The present analysis includes the entire trial population (576 patients). In addition to 3-month recurrence (primary outcome) and 1-year overall mortality, we analysed self-reported disease-specific (Pulmonary Embolism Quality of Life (PEmb-QoL) questionnaire) and generic (five-level five-dimension EuroQoL (EQ-5D-5L) scale) quality of life as well as treatment satisfaction (Anti-Clot Treatment Scale (ACTS)) after pulmonary embolism.

Results: The primary efficacy outcome occurred in three (0.5%, one-sided upper 95% CI 1.3%) patients. The 1-year mortality was 2.4%. The mean±SD PEmb-QoL decreased from 28.9±20.6% at 3 weeks to 19.9±15.4% at 3 months, a mean change (improvement) of −9.1% ($p<0.0001$). Improvement was consistent across all PEmb-QoL dimensions. The EQ-5D-5L was 0.89±0.12 at 3 weeks after enrolment and improved to 0.91±0.12 at 3 months ($p<0.0001$). Female sex and cardiopulmonary disease were associated with poorer disease-specific and generic quality of life; older age was associated with faster worsening of generic quality of life. The ACTS burden score improved from 40.5±6.6 points at 3 weeks to 42.5±5.9 points at 3 months ($p<0.0001$).

Conclusions: Our results further support early discharge and ambulatory oral anticoagulation for selected patients with low-risk pulmonary embolism. Targeted strategies may be necessary to further improve quality of life in specific patient subgroups.

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Introduction

The severity spectrum of acute pulmonary embolism is broad, ranging from asymptomatic, incidentally diagnosed events to cases in which pulmonary embolism compromises the patient's haemodynamic status and represents an immediately life-threatening condition. Initial risk assessment is mandatory for optimising initial treatment and deciding on the most appropriate setting in which this treatment will be delivered. As proposed by the recent 2019 European Society of Cardiology guidelines for the diagnosis and management of acute pulmonary embolism, developed in collaboration with the European Respiratory Society, such a risk-adjusted management strategy consists of a stepwise approach combining clinical findings, imaging and biochemical markers [1]. Criteria for identifying the group of patients whose risk is "sufficiently low" to permit early discharge and ambulatory treatment have been tested in prospective management studies, and include the absence of severe comorbidities, the absence of signs of right ventricular dysfunction, and adequate social and familiar support [2–7]. Despite these efforts, registry data indicate that only 10% of patients admitted to large European centres with acute pulmonary embolism are discharged "immediately" and more than half of the patients spend ⩾5 days in hospital [8]. Early discharge and home treatment may minimise hospitalisation-related complications [9], reduce healthcare costs [10, 11] and improve the quality of life of affected patients [12].

Over the past decade, non-vitamin-K-dependent oral anticoagulants (NOACs) became the standard of care for the treatment of acute pulmonary embolism [1]. The fact that their use requires no periodic blood testing explains, at least in part, the higher patient-reported treatment satisfaction [13, 14]. Furthermore, early transition from hospital to ambulatory care may be facilitated, since at least some of the NOACs do

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not require an initial lead-in treatment with parenteral low-molecular-weight heparin and thus offer an appealing perspective both for (selected) patients and for caregivers.

In 2019, the results of the predefined interim analysis of the multinational Home Treatment of Patients with Low-Risk Pulmonary Embolism with the Oral Factor Xa Inhibitor Rivaroxaban (HoT-PE) trial were published [5]. Initiation of anticoagulation with rivaroxaban followed by early discharge and continuation of treatment at home was shown to be effective and safe in patients with acute low-risk pulmonary embolism based on a combination of clinical criteria and the absence of right ventricular dysfunction on imaging. These findings permitted premature termination of the study after completion of the 3-month follow-up of the first 525 patients. The present study provides the results of the complete analysis of the HoT-PE study, including the patients enrolled while the interim analysis was being performed and focusing on the evaluation of key long-term outcomes, such as quality of life and treatment satisfaction, along with 12-month mortality.

Methods

Study design and participants

HoT-PE (EudraCT identifier 2013-001657-28) is a prospective multicentre single-arm investigator-initiated phase 4 interventional trial sponsored by the University Medical Center Mainz, Mainz, Germany [15]. The institutional Ethics Review Board of each participating site approved the study and patients provided written informed consent for participation. A description of the study rationale and background for the eligibility criteria has been published previously [15]. Briefly, adult patients were eligible for inclusion if they had objectively confirmed acute pulmonary embolism without right ventricular enlargement or dysfunction (right/left ventricular diastolic diameter ratio $\geqslant$1.0) and no free-floating thrombi in the right atrium or ventricle by echocardiography or computed tomographic pulmonary angiography (CTPA). Patients were also excluded if they had haemodynamic instability at presentation; 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 hospitalisation; noncompliance 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 therapy.

Treatment

Initiation of treatment with an approved parenteral or oral anticoagulant (unfractionated heparin, low-molecular-weight heparin, fondaparinux, rivaroxaban or apixaban) no later than 3 h after pulmonary embolism diagnosis was allowed before enrolment in the study. Patients received the first dose of the study medication, rivaroxaban, within 2 h of the next due dose of subcutaneous injection of low-molecular-weight heparin or fondaparinux (or oral rivaroxaban or apixaban), or at the time of discontinuation of intravenous unfractionated heparin. The rivaroxaban regimen corresponded to the label of the marketed product, consisting of 15 mg twice daily for 3 weeks followed by the maintenance regimen of 20 mg once daily for at least 3 months. Reduction of the maintenance dose to 15 mg once daily was allowed in patients estimated to have a high risk of bleeding, including those with a creatinine clearance <50 $mL \cdot min^{-1}$. The trial protocol mandated discharge within 48 h of admission or a maximum of 2 nights in hospital [15].

Study outcomes

The primary efficacy outcome was symptomatic recurrent venous thromboembolism or pulmonary embolism-related death within 3 months of enrolment. The secondary efficacy outcomes included all-cause death within 3 months and 1 year of enrolment, rehospitalisation due to pulmonary embolism or to a bleeding event within 3 months as well as the assessment of validated quality-of-life and treatment satisfaction questionnaires. The safety outcomes included major bleeding (defined by the criteria of the International Society on Thrombosis and Haemostasis) [16], clinically relevant nonmajor bleeding and serious adverse events. All efficacy and safety outcomes were adjudicated by an independent clinical events committee.

Quality of life and treatment satisfaction questionnaires

We analysed the data on the Pulmonary Embolism Quality of Life (PEmb-QoL) questionnaire for the assessment of disease-specific quality of life [17]; the five-level five-dimension EuroQoL (EQ-5D-5L) scale for generic quality of life measured 3 weeks and 3 months after enrolment [18]; and the Anti-Clot Treatment Scale (ACTS), a patient-reported measure of anticoagulant treatment satisfaction [13].

The PEmb-QoL is composed of 40 items and serves to quantify health-related quality of life across six health dimensions: 1) frequency of complaints, 2) activities of daily living limitations, 3) work-related problems, 4) social limitations, 5) intensity of complaints and 6) emotional complaints. Two questions of

the questionnaire focus on the time of the day at which the symptoms appear and the state of the patient's current condition compared with 1 year before, and do not contribute to the total score. The six dimensions contributing scores are summed, weighted and transformed to a percentage scale (0–100%), with higher scores indicating worse quality of life and lower scores indicating better quality of life.

The EQ-5D-5L (EuroQol Research Foundation) is a validated instrument designed to provide a simple and direct profile of the patient's generic health status. It comprises a short descriptive system questionnaire covering five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) and a visual analogue scale (VAS) ranging from 0 ("the worst health the patient can imagine") to 100 ("the best health the patient can imagine"). Each of the five dimensions is composed of five levels of severity. EQ-5D-5L can also be analysed after conversion and weighting of the results of these dimensions into a single summary index value. Calculation of the EQ-5D-5L index score was based on the coding available at https://euroqol.org/eq-5d-instruments/eq-5d-5l-about/valuation-standard-value-sets/crosswalk-index-value-calculator.

The ACTS (Bayer AG) includes 12 items assessing perceived burden and three items assessing perceived benefits from treatment. Each item can be rated from the lowest intensity 1 (not at all) to the highest intensity 5 (extremely) with totals in the range 12–60 (burdens) and 3–15 (benefits). After reversing of the scale, higher ACTS scores indicate greater treatment satisfaction.

Sample size calculation

The null hypothesis (H_0) that $p \geqslant 0.03$ (p being the probability of recurrent venous thromboembolism or pulmonary embolism-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 venous thromboembolism recurrence rate of 1.7%, similar to that reported in a meta-analysis of studies dating back to the vitamin K antagonist era [19] and to the 3-month recurrence rate observed in the EINSTEIN-PE rivaroxaban phase 3 trial [20]. The study was stopped after the pre-planned interim analysis performed after enrolment and 3-month evaluation of the first 525 patients, as H_0 could be rejected at the local level of $\alpha=0.004$ (less than six patients developing the primary efficacy outcome) in the intention-to-treat (ITT) population [5].

Statistical analysis

The primary and secondary outcome analyses were done in the ITT population, consisting of 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.

Differences of the quality-of-life scores between 3-week and 3-month visits were determined using paired t-tests in the case of normally distributed data or using the Wilcoxon signed-rank test. To check for associations between baseline predefined explanatory variables characterised by low multicollinearity and an outcome variable (PEmb-QoL and EQ-5D-5L VAS), a linear regression model was fitted for the 3-week and 3-month visits as well as for the difference between 3 weeks and 3 months. For each linear regression model, the assumption of normal distributed residuals was confirmed. In case the number of missing values for both the explanatory and outcome variable(s) was low (<5%), an imputation technique was not deemed to be crucial.

Results

From May 2014 through June 2018, a total of 576 patients signed informed consent for participation in the HoT-PE trial at 49 centres in seven countries and were included in the ITT population. The mean (range) age was 57 (18–90) years and 266 (46.2%) were female. Table 1 shows the baseline characteristics of the study population. Dyspnoea (61.3%), pleuritic pain (40.6%), cough (10.7%) and retrosternal pain (20.7%) represented the most frequent symptoms of pulmonary embolism, followed by fever (7.5%), haemoptysis (4.9%) and syncope (3.0%). Unilateral leg pain and unilateral oedema were present in 24.8% and 15.6% of patients, respectively. The onset of symptoms preceded the diagnosis of acute pulmonary embolism by a median (interquartile range (IQR)) of 4 (2–8) days. CTPA was the most frequently used imaging test for diagnosis (n=528 (91.7%)). Deep vein thrombosis was present in 241 (53.2%) of the 453 patients in whom compression ultrasound was performed.

A total of 569 (98.8%) patients who received at least one dose of rivaroxaban were included in the safety population. The median (IQR) length of hospitalisation was 33 (23–47) h and 551 patients were hospitalised for up to 2 nights in compliance with the study protocol. A total of 547 (95.0%) patients were included in the per-protocol population.

TABLE 1 Baseline characteristics of the study population

Patient demographics	
Age years	56.5±16.6 (18–90)
Female	266/576 (46.2)
Caucasian	567/576 (98.4)
Education level	
Elementary school	20/519 (3.9)
Basic primary school	58/519 (11.2)
Secondary general school	123/519 (23.7)
Intermediate secondary school	132/519 (25.4)
A-level	95/519 (18.3)
University degree	90/519 (17.3)
Doctorate	1/519 (0.2)
Functional parameters and biochemical markers	
Body mass index kg·m^{-2}	27.1 (24.3–30.5)
Systolic/diastolic blood pressure mmHg	136±19/80±12
Heart rate beats·min^{-1}	78±13
Oxygen saturation %	97 (96–98)
Respiratory rate breaths·min^{-1}	16 (15–18)
Creatinine clearance <50 mL·min^{-1}	32/575 (5.6)
Risk factors for pulmonary embolism and comorbidities	
Oestrogen use	92/571 (16.1)
Immobilisation (for at least 3 days)	58/570 (10.2)
Previous deep vein thrombosis	87/566 (15.4)
Previous pulmonary embolism	44/572 (7.7)
Recent major surgery (past 30 days)	38/574 (6.6)
Recent major trauma (past 30 days)	25/575 (4.3)
Long travel (>4 h, past 30 days)	70/567 (12.3)
Active cancer	38/567 (6.7)
Chronic obstructive pulmonary disease	28/569 (4.9)
Chronic heart failure	7/575 (1.2)
Coronary artery disease	41/570 (7.2)
Arterial hypertension	241/574 (42.0)
Diabetes mellitus	38/576 (6.6)
Simplified Pulmonary Embolism Severity Index ⩾1	127/556 (22.8)
Baseline imaging tests for venous thromboembolism	
Computed tomography pulmonary angiogram	528/575 (91.8)
Lung ventilation/perfusion scan	48/574 (8.4)
Pulmonary angiogram	27/560 (4.8)
Compression ultrasound	453/573 (79.1)
Deep vein thrombosis confirmed	241/453 (53.2)

Data are presented as mean±SD (range), n/N (%), median (interquartile range) or mean±SD. For categorical variables, the proportion and percentage of valid (nonmissing) cases are reported. Continuous variables with missing information: body mass index (18 patients), blood pressure (19 patients), oxygen saturation (20 patients) and respiratory rate (70 patients).

Rivaroxaban 15 mg twice daily was given for a mean±SD period of 21±5 days after the diagnosis of acute pulmonary embolism. Patients received the maintenance dosage of rivaroxaban over an additional period of 69±10 days. Continuation of anticoagulant treatment beyond the study period was at the discretion of the patient's physician [15].

Primary efficacy outcome

The primary efficacy outcome, *i.e.* symptomatic recurrent venous thromboembolism or pulmonary embolism-related death, occurred in three (0.5%, one-sided upper 95% CI 1.3%; one-sided p<0.0001) of the 576 patients of the ITT population within 3 months of enrolment (table 2). All three recurrent events were nonfatal recurrent pulmonary embolism (supplementary table S1). The primary outcome occurred in two (0.4%, two-sided 95% CI 0.04–1.3%; two-sided p<0.0001) of the 547 patients included in the per-protocol population.

Safety and secondary efficacy outcomes

Of the 569 patients included in the safety population, six (1.1%, two-sided 95% CI 0.4–2.3%) had a major bleeding episode during rivaroxaban treatment within 3 months of enrolment. Clinically relevant

TABLE 2 Study outcomes

Primary efficacy outcome	
Primary outcome (intention-to-treat population): recurrent venous thromboembolism or fatal pulmonary embolism	3/576 (0.5, 1.3)
Recurrent pulmonary embolism	3
Recurrent deep vein thrombosis	0
Death related to pulmonary embolism	0
Primary outcome (per-protocol population): recurrent venous thromboembolism or fatal pulmonary embolism	2/547 (0.4, 0.04–1.3)
Secondary efficacy outcomes	
Death of any cause within 3 months	2/576 (0.4, 0.04–1.25)
Death of any cause within 12 months	14/576 (2.4, 1.3–4.0)
Advanced cancer as cause of death	9
Intracranial haemorrhage	1
Sepsis	1
Other	3
Safety outcomes	
Major bleeding[#]	6/569 (1.1, 0.4–2.3)
Clinically relevant bleeding	30/569 (5.3, 3.6–7.4)
At least one serious adverse event	68/569 (12.0, 9.5–14.9)
Serious adverse events requiring prolonged initial hospitalisation or rehospitalisation	64/576 (11.1, 8.8–13.9)

Data are presented as n/N (%, one-sided upper 95% CI), n or n/N (%, two-sided 95% CI). [#]: as defined by the criteria of the International Society of Thrombosis and Haemostasis [16].

nonmajor bleeding was recorded in 30 (5.3%, two-sided 95% CI 3.6–7.4%) patients. The median (IQR) duration of first rehospitalisation was 6 (3–9) days. Serious adverse events within 3 months of enrolment occurred in 68 (12.0%) patients, of which 64 required rehospitalisation. An overview of these events is provided in supplementary table S2. 12 (2.1%) patients were hospitalised for suspected pulmonary embolism recurrence or bleeding within 3 months of enrolment, which was then confirmed in seven (1.2%) patients.

14 patients died after a median (IQR) of 6.8 (4.7–11.4) months, corresponding to a 1-year mortality rate of 2.4% (95% CI 1.3–4.0%). Cancer was the most frequent cause of death and was recorded in nine patients. The 3-month mortality rate was 0.4% (95% CI 0.04–1.25%) and both deaths were due to progressive metastatic cancer.

Analysis of quality-of-life questionnaires

The PEmb-QoL analysis was conducted on a total of 425 patients who completed the questionnaire at both visits. The formulas for the calculation of the PEmb-QoL score are given in the supplementary material. The mean±SD PEmb-QoL score decreased from 28.9±20.6% at 3 weeks to 19.9±15.4% at 3 months; this corresponds to a mean±SD reduction of −9.1±15.4% (paired t-test; p<0.0001), indicating a significant improvement in the patients' self-reported quality of life. As shown in figure 1, the improvement was consistent across all PEmb-QoL dimensions. In our multivariable linear regression model (table 3), female sex, higher body mass index and the presence of cardiopulmonary disease were associated with a poorer quality of life (indicated by a higher PEmb-QoL score) at both week 3 and month 3 of follow-up. Of note, older age and the presence of cancer were not associated with worse quality of life at these time-points, but they were associated with "faster worsening" of disease-specific quality of life over time. Specifically, we documented a +0.2% relative increase in the slope (per unit increase) between week 3 and month 3 per year of age (p=0.001), and a +6.4% relative increase in patients with (*versus* without) cancer (p=0.001).

In supplementary tables S3 and S4, we separately show the results of the two PEmb-QoL dimensions not included in the calculation of the score, which serve to qualitatively assess the time of the day when the patient's symptoms were perceived as being more intense (Dimension 2) and whether symptoms are more severe compared with 1 year before (Dimension 3). The characteristics of the patients with and without complete PEmb-QoL assessment at both visits are reported in supplementary table S5.

The EQ-5D-5L analysis was conducted in a total of 473 patients who completed the questionnaire at both visits. The mean±SD EQ-5D-5L index score was 0.89±0.12 at week 3 and improved to 0.91±0.12 at month 3 (paired t-test for difference; p<0.0001). The percentage of patients reporting "no problems" in any of the five dimensions increased from 61.2% at week 3 to 72.0% at month 3, paralleled by a consistent reduction of the proportion of patients with slight (from 25.7% to 18.4%), moderate (from 10.3% to 7.4%), severe

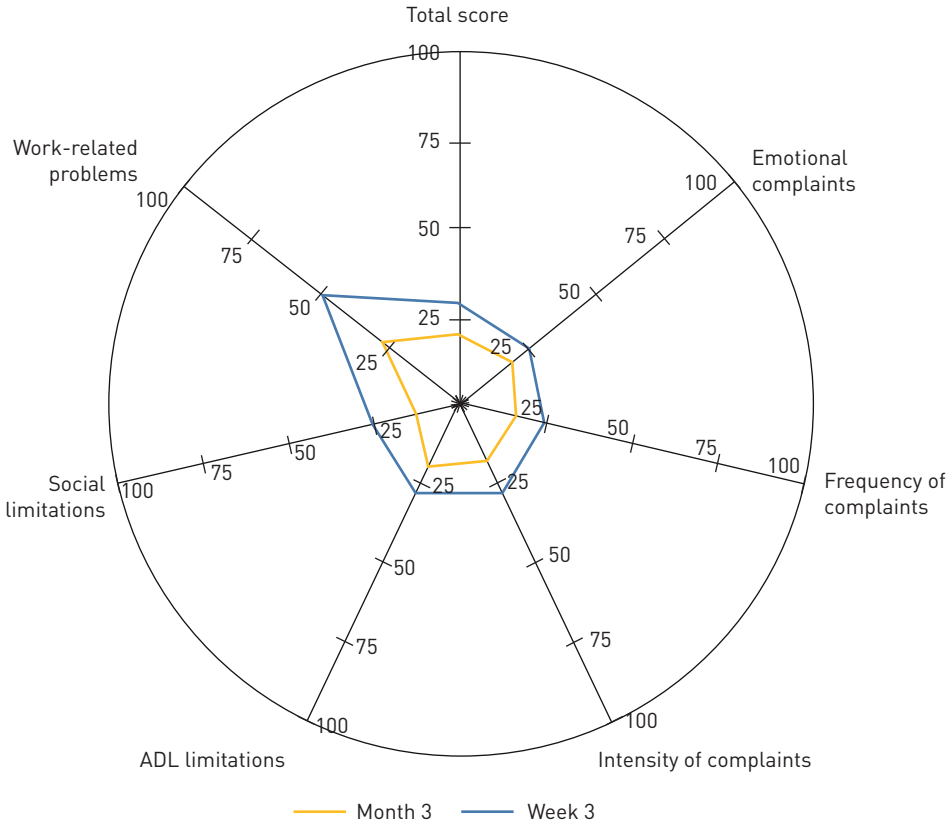

FIGURE 1 Improvement of quality of life after acute pulmonary embolism according to the Pulmonary Embolism Quality of Life (PEmb-QoL) questionnaire score. ADL: activities of daily living. The radar plot illustrates the evolution in disease-specific quality of life for each of the PEmb-QoL dimensions and for the total PEmb-QoL score between week 3 and month 3. The six dimensions contributing scores are summed, weighted and transformed to a percentage scale (0–100%), with higher scores (larger area of the polygon) indicating worse quality of life and lower scores (smaller area of the polygon) indicating better quality of life.

(from 1.9% to 1.8%) or extreme (from 0.3% to 0.2%) problems. As shown in figure 2, these positive changes were consistent across all five EQ-5D-5L dimensions.

The mean±SD VAS of the EQ-5D-5L increased from 76.2±16.1 to 80.2±16.4 points (paired t-test for difference; p<0.0001). In our multivariable linear regression model (table 3), female sex and the presence of cardiopulmonary disease were associated with a lower VAS, indicating a poorer quality of life, at both week 3 and month 3. Older age was associated with faster worsening of generic quality of life according to the VAS (−0.1% relative decrease per year of age between week 3 and month 3; p=0.02). The characteristics of the patients with and without complete EQ-5D-5L assessment are reported in supplementary table S6.

Anti-Clot Treatment Scale

The ACTS analysis was conducted on a total of 421 patients who completed the questionnaire at both visits. After 3 weeks, the percentage of patients not reporting any of the ACTS burden items was 56.9% and increased to 66.0% after 3 months. The mean±SD ACTS burden score increased from 40.5±6.6 at week 3 to 42.5±5.9 at month 3, indicating an improvement in terms of treatment satisfaction (paired t-test; p<0.0001). At 3 weeks after acute pulmonary embolism, 26.3% of the patients reported being "extremely satisfied" based on the ACTS benefit items; this percentage increased to 31.7% at 3 months. The mean±SD ACTS benefit score was 11.4±2.9 at week 3 and 11.4±3.1 at month 3 (paired t-test; p=0.4189).

Discussion

This report presents a comprehensive analysis of clinical outcomes and self-reported quality of life in the entire population of the HoT-PE study, a prospective multinational investigator-initiated and academically sponsored phase 4 trial. The results of the predefined interim analysis yielded low rates of the primary outcome, *i.e.* symptomatic recurrent venous thromboembolism or pulmonary embolism-related death, at

TABLE 3 Association between baseline clinical characteristics and quality-of-life scores 3 weeks and 3 months after enrolment

	PEmb-QoL						EQ-5D-5L VAS					
	Week 3			Month 3			Week 3			Month 3		
	Estimate[#] %	SE	p-value	Estimate[#] %	SE	p-value	Estimate[¶] %	SE	p-value	Estimate[¶] %	SE	p-value
Age (per unit increase)	−0.1	0.07	0.09	0.1	0.06	0.38	−0.1	0.05	0.13	−0.2	0.05	0.0006
Females *versus* males	11.2	2.3	<0.0001	8.2	2.1	<0.0001	−3.9	1.7	0.02	−4.6	1.7	0.007
Body mass index (per unit increase)	0.5	0.2	0.02	0.5	0.2	0.008	0.04	0.1	0.77	0.1	0.1	0.52
Oestrogen use	−4.1	3.3	0.21	−2.2	3.0	0.45	2.5	2.5	0.30	1.6	2.4	0.51
Immobilisation, major surgery or trauma	3.0	2.6	0.24	1.0	2.3	0.67	−3.3	1.9	0.08	−0.5	1.9	0.80
Prior venous thromboembolism	0.1	2.6	0.97	−0.2	2.3	0.95	0.9	1.9	0.66	1.1	1.9	0.58
Cardiopulmonary disease	7.9	3.1	0.02	5.9	2.8	0.03	−8.4	2.4	0.0005	−9.1	2.4	0.0002
Active cancer	−1.1	4.1	0.79	5.4	3.6	0.14	−4.6	3.1	0.15	−7.2	3.1	0.02
Intercept	16.4	7.0	0.02	−1.4	6.2	0.82	82.7	5.1	<0.0001	90.9	5.1	<0.0001

PEmb-QoL: Pulmonary Embolism Quality of Life; EQ-5D-5L: five-level five-dimension EuroQoL; VAS: visual analogue scale. The β-estimates for the difference of PEmb-QoL score between week 3 and month 3 were +0.2 (SE 0.05; p=0.001) relative increase for age and +6.4 (SE 3.1; p=0.04) relative increase for cancer, indicating a faster worsening of quality of life with progressively older age and in patients with (*versus* without) cancer. The β-estimates for the difference of VAS between week 3 and month 3 were −0.1 (SE 0.04; p=0.02), indicating a faster worsening of quality of life with progressively older age. [#]: positive estimates of the PEmb-QoL questionnaire score indicate an association with a worse quality of life (*versus* reference group, corresponding to the absence of the factor, or per unit increase) 3 weeks and 3 months after enrolment; [¶]: positive estimates of the VAS indicate an association with a better quality of life (*versus* reference group, corresponding to the absence of the factor, or per unit increase) 3 weeks and 3 months after enrolment.

the 3-month follow-up [5] and thus allowed for early termination of the trial. The present analysis focuses on long-term survival as well as quality of life and its change over time following early discharge of patients with acute low-risk pulmonary embolism. Our results, obtained in 576 patients, confirm the low rate of the primary efficacy outcome and show low all-cause mortality at the 12-month follow-up (2.4%). Moreover, and importantly, the HoT-PE study quantitatively assessed the course of the patients' disease-specific and generic quality of life, as measured by established standardised scores, over the first 3 months of oral anticoagulant treatment for pulmonary embolism. By identifying predictors of a poor or worsening score among the patients' key baseline characteristics, our data may help to design future research on targeted strategies aiming to improve the quality of life of specific patient subgroups after acute pulmonary embolism.

The rate of the efficacy outcome in the entire population of our trial is in agreement with the low rates reported in phase 3 anticoagulation trials which enrolled patients with venous thromboembolism [21] and in pragmatic management studies of patients with low-risk pulmonary embolism [4, 7]. This is also true for the rate of safety outcomes, notably major haemorrhage [4, 7, 21]. We recently reported that, within this low-risk population, "fragile" patients defined by age >75 years, low body mass index (<18.5 $kg \cdot m^{-2}$) or creatinine clearance <50 $mL \cdot min^{-1}$, exhibited a higher rate of major bleeding (2.7% compared with 0.7% among patients with none of these characteristics) [22]. While these characteristics do not, by themselves, represent contraindications to early discharge and home treatment of acute low-risk pulmonary embolism, closer surveillance may be warranted for prevention or early detection of bleeding complications.

The notion that our study successfully defined and enrolled a patient population with "truly" low-risk pulmonary embolism is supported by the very low 12-month (2.4%) overall mortality rates; in fact, out of 14 total deaths recorded over the entire 1-year follow-up period, nine were due to active cancer as the underlying disease of the patient's index episode of pulmonary embolism. These numbers are in sharp contrast to the rates previously reported in the literature; in those earlier reports, the 1-year mortality rate overall exceeded 15% among unselected patients with pulmonary embolism [23, 24] or venous thromboembolism in the broader sense [25–27], ranging between 40% among patients with cancer and 10% among those without it.

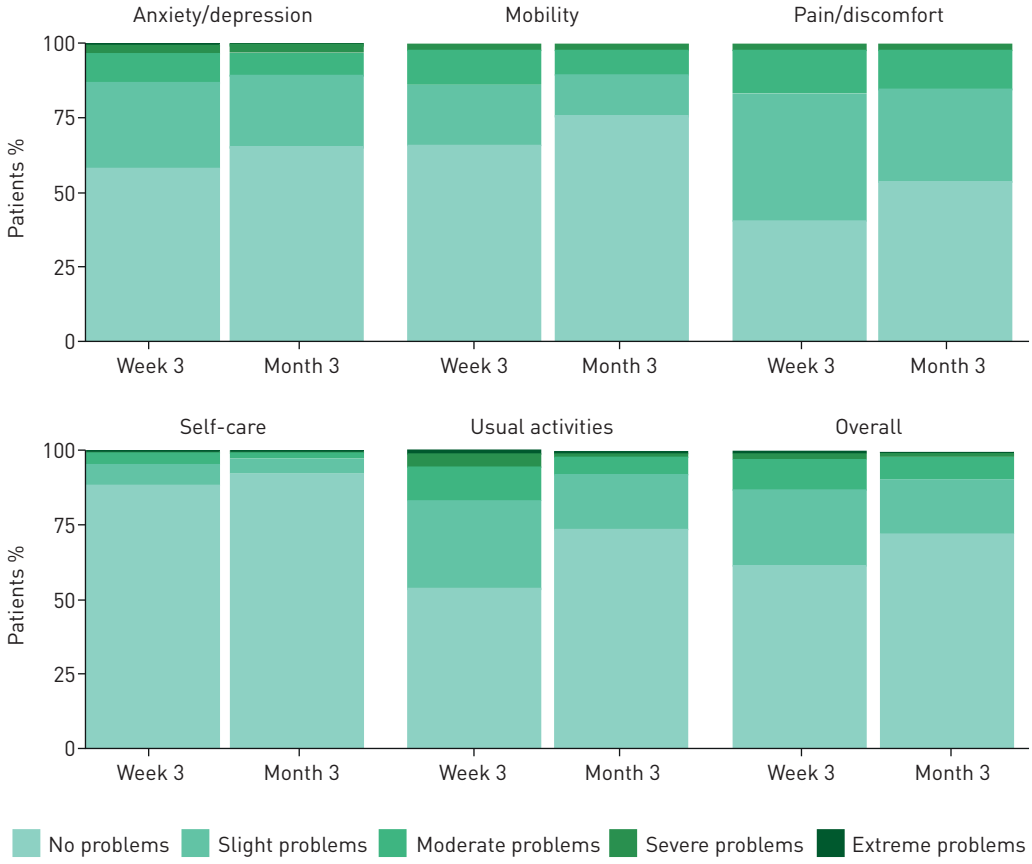

FIGURE 2 Graphic representation of the course of the five-level five-dimension EuroQoL (EQ-5D-5L) assessed 3 weeks and 3 months after enrolment. The stacked bar plots show the percentage of patients reporting "no problems", "slight problems", "moderate problems", "severe problems" or "extreme problems" in each of the five dimensions of the EQ-5D-5L health-related quality-of-life questionnaire and in the overall questionnaire at week 3 and month 3.

Beyond delivering data on recurrence, bleeding and overall mortality, HoT-PE is the largest study that has prospectively evaluated, using established standardised questionnaires, patients' quality of life 3 weeks and 3 months after acute (low-risk) pulmonary embolism. Both the disease-specific and the generic tools measuring quality of life indicated a significant improvement over time, although no definitive conclusion can be drawn that a causal association exists between early discharge followed by home oral rivaroxaban anticoagulation on quality-of-life parameters in the absence of a control group. Seen from a different perspective, however, our results also show that pulmonary embolism continues to represent, over a considerable period of several weeks or months, a source of major discomfort, and it may interfere with several aspects of the patient's work, daily activities and social life, even if the index episode fulfilled strict criteria of "low risk". The degree of improvement over time was similar across different scales and dimensions of quality of life. Female sex, higher body mass index and a history of cardiac or pulmonary disease were associated with a poorer quality of life at a given time-point in follow-up according to the validated disease-specific PEmb-QoL score; female sex and cardiac or pulmonary disease also correlated with a lower generic quality of life according with the VAS (table 3). Older age correlated with a faster worsening of both indexes over time. This analysis in a large low-risk population is generally in line with the results of prior studies reporting on follow-up after pulmonary embolism [28–30]. In fact, studies of patients suffering stroke or myocardial infarction have also pointed to a similar direction, particularly concerning age, sex and body mass index [31–33], indicating that the impact of specific baseline characteristics on quality of life over time is consistent across a broad spectrum of acute cardiovascular syndromes.

Our study has some limitations. Routine assessment of right ventricular function has been proposed to possess added value for risk stratification of pulmonary embolism independently from clinical assessment tools [34], but the optimal imaging method, *i.e.* CTPA *versus* transthoracic echocardiography, remains unclear. Moreover, it is sometimes argued that the latter imaging modality may not be available on a

continuous basis in all hospitals. In HoT-PE, CTPA was performed for diagnosis of initial acute pulmonary embolism in the vast majority (>90%) of the study patients. It has been shown that a simple parameter of right ventricular function on CTPA, *i.e.* the calculation of the right/left ventricular diameter ratio, was accurate and reproducible after minimal training [35]. These facts argue against feasibility problems in following the strategy tested in HoT-PE. A further limitation of our study is that complete data for self-reported quality of life or treatment satisfaction were available, for both follow-up visits, in only ∼75% of the study patients. For absolute transparency, we have included, in the supplementary material, two tables showing the baseline characteristics of the patients with *versus* those without complete questionnaire data. Other potential limitations of our trial, including the "cautiousness" of the eligibility criteria, have previously been addressed in detail [5]. The strengths of the prospective HoT-PE study lie in the rigorous monitoring, the independent adjudication of the efficacy and safety outcomes, the large size of the study for this particular patient population, and most of all in the fact that it can be considered a representative European management trial, having included 49 centres in seven countries with different population characteristics and healthcare systems.

In conclusion, the results of the complete analysis of the HoT-PE trial support the early discharge and ambulatory oral anticoagulation treatment of carefully selected patients with acute low-risk pulmonary embolism. Anticoagulation with rivaroxaban initiated in the hospital and continued over at least 3 months was effective and safe. All-cause mortality was extremely low over the entire 12-month follow-up period. The patients' quality of life improved early during follow-up as assessed on the basis of standardised, disease-specific and generic quality-of-life questionnaires. Future early-discharge strategies may need to target individuals with specific baseline characteristics such as female sex, an increased body mass index and a history of cardiac or pulmonary disease.

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