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Stefano Barco, Irene Schmidtmann, Walter Ageno, Toni Anušić, Rupert M. Bauersachs, Cecilia Becattini, Enrico Bernardi, Jan Beyer-Westendorf, Luca Bonacchini, Johannes Brachmann, Michael Christ, Michael Czihal, Daniel Duerschmied, Klaus Empen, Christine Espinola-Klein, Joachim H. Ficker, Cândida Fonseca, Sabine Genth-Zotz, David Jiménez, Veli-Pekka Harjola, Matthias Held, Lorenzo Iogna Prat, Tobias J. Lange, Mareike Lankeit, Athanasios Manolis, Andreas Meyer, Thomas Münzel, Pirjo Mustonen, Ursula Rauch-Kroehnert, Pedro Ruiz-Artacho, Sebastian Schellong, Martin Schwaiblmair, Raoul Stahrenberg, Luca Valerio, Peter E. Westerweel, Philipp S. Wild, Stavros V. Konstantinides

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Survival and Quality of Life after Early Discharge in Low-Risk Pulmonary Embolism

Stefano Barco[1,2]; Irene Schmidtmann[3]; Walter Ageno[4]; Toni Anušić[3]; Rupert M. Bauersachs[5]; Cecilia Becattini[6]; Enrico Bernardi[7]; Jan Beyer-Westendorf[8,9]; Luca Bonacchini[10]; Johannes Brachmann[11]; Michael Christ[12]; Michael Czihal[13]; Daniel Duerschmied[14]; Klaus Empen[15]; Christine Espinola-Klein[16]; Joachim H. Ficker[17]; Cândida Fonseca[18]; Sabine Genth-Zotz[19]; David Jiménez[20]; Veli-Pekka Harjola[21]; Matthias Held[22]; Lorenzo Iogna Prat[23]; Tobias J. Lange[24]; Mareike Lankeit[1,25,26]; Athanasios Manolis[27]; Andreas Meyer[28]; Thomas Münzel[16,29]; Pirjo Mustonen[30]; Ursula Rauch-Kroehnert[31]; Pedro Ruiz-Artacho[32,33]; Sebastian Schellong[34]; Martin Schwaiblmair[35]; Raoul Stahrenberg[36]; Luca Valerio[1]; Peter E. Westerweel[37]; Philipp S. Wild[1,29,38]; and Stavros V. Konstantinides[1,39], on behalf of the HoT-PE Investigators

1) Center for Thrombosis and Hemostasis (CTH), University Medical Center of the Johannes Gutenberg University, Mainz, Germany;
2) Clinic of Angiology, University Hospital Zurich, Zurich, Switzerland;
3) Institute of Medical Biostatistics, Epidemiology and Informatics (IMBEI), University Medical Center Mainz, Germany;
4) Research Center on Thromboembolic Diseases and Antithrombotic Therapies, Department of Medicine and Surgery, University of Insubria, Varese, Italy;
5) Department of Vascular Medicine, Klinikum Darmstadt, Darmstadt, Germany;
6) Internal and Cardiovascular Medicine - Stroke Unit, University of Perugia, Perugia, Italy;
7) Department of Emergency Medicine, ULSS 2 Marca Trevigiana – Ospedale di Treviso (Treviso), Italy;
8) Thrombosis Research Unit, Division of Hematology, Department of Medicine I, University Hospital "Carl Gustav Carus", Dresden, Germany;
9) Kings Thrombosis Service, Department of Hematology, Kings College London, London, United Kingdom;
10) S.C. Medicina d'Urgenza e Pronto Soccorso, ASST Grande Ospedale Metropolitano Niguarda, Milano;
11) II Medical Department, Coburg Hospital, Coburg, Germany;
12) Emergency Care (Notfallzentrum), Luzerner Kantonsspital, Switzerland;

13) Division of Vascular Medicine, Hospital of the Ludwig-Maximilians-University, Munich, Germany;
14) Cardiology and Angiology I, Heart Center, Faculty of Medicine, University of Freiburg, Freiburg, Germany;
15) Department of Internal Medicine, Städtisches Klinikum Dessau, Germany;
16) Department of Cardiology, Cardiology I, University Medical Center Mainz of the Johannes Gutenberg-University, Mainz, Germany;
17) Department of Respiratory Medicine, Nuremberg General Hospital / Paracelsus Medical University, Nuremberg, Germany
18) Department of Internal Medicine, Hospital S. Francisco Xavier/CHLO, NOVA Medical School, Faculdade de Ciências Médicas, Universidade Nova de Lisboa, Lisbon, Portugal;
19) Department of Internal Medicine I, Katholisches Klinikum Mainz, Mainz, Germany;
20) Respiratory Department, Ramón y Cajal Hospital, Universidad de Alcala, IRYCIS, CIBER de Enfermedades Respiratorias, CIBERES, Madrid, Spain;
21) Emergency Medicine, University of Helsinki and Department of Emergency Medicine and Services, Helsinki University Hospital, Helsinki, Finland;
22) Medical Mission Hospital, Department of Internal Medicine, Respiratory Medicine and Ventilatory Support, Academic Teaching Hospital of the Julius-Maximilian University of Wuerzburg, Wuerzburg, Germany;
23) Pronto Soccorso-Medicina d'Urgenza Ospedale Santa Maria del Carmine, Rovereto, Italy;
24) Department of Internal Medicine II, Division of Pneumology, University Medical Center Regensburg, Regensburg, Germany;
25) Department of Internal Medicine and Cardiology, Campus Virchow Klinikum, Charité - University Medicine Berlin, Germany;
26) Clinic of Cardiology and Pneumology, Heart Center, University Medical Center Goettingen, Germany;
27) Department of Cardiology, General Hospital ´Asklepeion Voulas´, Athens, Greece;
28) Kliniken Maria Hilf, Klinik für Pneumologie, Krankenhaus St. Franziskus, Mönchengladbach;
29) German Center for Cardiovascular Research (DZHK), Partner Site Rhine Main, Mainz, Germany;
30) Keski-Suomi Central hospital and University of Jyväskylä, Finland;
31) Department of Cardiology, University Heart Center Berlin and Charité Universitätsmedizin Berlin, Germany; German Center for Cardiovascular Research (DZHK), Berlin, Germany;
32) Emergency Department, Clinico San Carlos Hospital, IdISSC, Madrid, Spain;
33) Internal Medicine Department, Clinica Universidad de Navarra, Madrid, Spain; CIBER de Enfermedades Respiratorias, CIBERES, Madrid, Spain; Interdisciplinar Teragnosis and Radiosomics (INTRA) Research Group, Universidad de Navarra, Spain;
34) Medical Department 2, Municipal Hospital Dresden, Dresden, Germany;

35) Department of Cardiology, Respiratory Medicine and Intensive Care, Klinikum Augsburg, Ludwig-Maximilians-University Munich, Germany;
36) Helios Albert-Schweitzer-Klinik, Northeim, Germany;
37) Department of Internal Medicine, Albert Schweitzer Hospital, Dordrecht, The Netherlands;
38) Preventive Cardiology and Preventive Medicine, Center for Cardiology, University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany;
39) Department of Cardiology, Democritus University of Thrace, Alexandroupolis, Greece;

Corresponding Author

Stavros V. Konstantinides, MD

Center for Thrombosis and Hemostasis, University Medical Center Mainz

Langenbeckstrasse 1, Building 403, 55131 Mainz, Germany

Phone: +49 6131 17 8382; Fax: +49 6131 17 3456.

E-mail: stavros.konstantinides@unimedizin-mainz.de

COMMITTEES

Principal Investigator and Steering Committee Members

Stavros V. Konstantinides (Principal Investigator), Rupert Bauersachs, Christoph Bode, Michael Christ, Christine Espinola-Klein, Annette Geibel, Mareike Lankeit, Michael Pfeifer, Sebastian Schellong, Philipp Wild, Harald Binder, Kurt Quitzau

Writing Committee

Stefano Barco, Irene Schmidtmann, Stavros Konstantinides

Clinical Events Committee

Michael Czihal, Tobias J. Lange, Raoul Stahrenberg

Data and Safety Monitoring Board

Thomas Meinertz, Menno V. Huisman, Paolo Prandoni, Walter Lehmacher

Academic Sponsor

University Medical Center of the Johannes Gutenberg University, Mainz, Germany

Academic Research Organization of the Sponsor

Interdisciplinary Center for Clinical Studies (IZKS) Mainz

Study Coordination and Management

Kurt Quitzau, Nadine Martin, Dorothea Becker, Stanislav Gorbulev, Kai Kronfeld

Trial Statisticians

Irene Schmidtmann, Harald Binder, Toni Anusic.

NATIONAL COORDINATORS, LOCAL INVESTIGATORS AND STUDY CENTERS

Germany (Stavros V. Konstantinides)

1. Martin Schwaiblmair (Department of Cardiology, Respiratory Medicine and Intensive Care, Klinikum Augsburg, Ludwig-Maximilians-University Munich)
2. Ursula Rauch-Kröhnert (Department of Cardiology, University Heart Center Berlin and Charité Universitätsmedizin Berlin, Germany; German Center for Cardiovascular Research (DZHK), Berlin)
3. Martin Möckel (Innere Medizin mit Schwerpunkt Gastroenterologie und Nephrologie, Notfallmedizin, Chest Pain Units, Charité Universitätsmedizin Berlin)
4. Johannes Brachmann (II Medical Department, Coburg Hospital, Coburg)
5. Rupert Martin Bauersachs (Department of Vascular Medicine, Klinikum Darmstadt, Darmstadt)
6. Sebastian Schellong (Vascular Center, Municipal Hospital of Dresden-Friedrichstadt, Dresden)
7. Jan Beyer-Westendorf (Thrombosis Research Unit, Division of Hematology, Department of Medicine I, University Hospital "Carl Gustav Carus", Dresden)
8. Daniel Duerschmied (Cardiology and Angiology I, Heart Center, Faculty of Medicine, University of Freiburg, Freiburg)
9. Sabine Blaschke (Interdisziplinäre Notaufnahme, Universitätsmedizin Göttingen)
10. Marius M. Hoeper (Klinik für Pneumologie, Medizinische Hochschule Hannover)
11. Evangelos Giannitis (Innere Medizin III, Universitätsklinikum Heidelberg)
12. Klaus Empen (Department of Internal Medicine, University Medical Center, Greifswald)
13. Rainer Schmiedel (Praxis für Interventionelle Angiologie, Kaiserslautern)
14. Ulrich Hoffman (Angiologie - Interdisziplinäres Gefäßzentrum, Klinikum der Universität München)
15. Ibrahim Akin (1. Medizinische Klinik, Universitätsmedizin Mannheim, Mannheim)
16. Andreas Meyer (Kliniken Maria Hilf, Klinik für Pneumologie, Krankenhaus St. Franziskus, Mönchengladbach)
17. Stavros V. Konstantinides (Center for Thrombosis and Hemostasis (CTH), University Medical Center of the Johannes Gutenberg University, Mainz)
18. Sabine Genth-Zotz (Department of Internal Medicine I, Katholisches Klinikum Mainz, Mainz)

19. Joachim Ficker (Department of Respiratory Medicine, Nuremberg General Hospital / Paracelsus Medical University, Nuremberg)
20. Tobias Geisler (Medizinische Klinik, Abt. III/Kardiologie, Universitätsklinikum Tübingen)
21. Matthias Held (Medical Mission Hospital, Department of Internal Medicine, Academic Teaching Hospital of the Julius-Maximilian University of Wuerzburg, Wuerzburg)

Italy (Cecilia Becattini)
1. Walter Ageno (Research Center on Thromboembolic Diseases and Antithrombotic Therapies, Department of Medicine and Surgery, University of Insubria, Varese)
2. Lorenzo Iogna Prat (Emergency Medicine, Santa Maria della Misericordia Hospital, Udine)
3. Cecilia Becattini (Internal Vascular and Emergency Medicine and Stroke Unit, University of Perugia, Perugia)
4. Enrico Bernardi (Department of Emergency Medicine, ULSS n.7, Conegliano, Treviso)
5. Giuseppe Bettoni (S.C. Medicina d'Urgenza e Pronto Soccorso, ASST Grande Ospedale Metropolitano Niguarda, Milano)
6. Roberto Cosentini (Emergency Medicine Department, ASST Papa Giovanni XIII, Bergamo)
7. Paolo Moscatelli (Emergency Medicine Department, San Martino Teaching Hospital, Genova University, Genova)
8. Cinzia Nitti (Internal and Subintensive Medicine Department, Azienda OspedalieroUniversitaria "Ospedali Riuniti", Ancona)
9. Lucia Pierpaoli (Pronto Soccorso e Medicina d´Urgenza, Ospedale di Ravenna, Ravenna)
10. Raffaele Pesavento (Department of Medicine, University Hospital of Padua, Padua),
11. Alessandra Ascani (Medicina di Urgenza, Azienda Ospedaliera ´Santa Maria´, Terni)
12. Nicola Montano (Emergency Department, Fondazione IRCCS Ca' Granda - Ospedale Maggiore Policlinico, Milan, Italy; Department of Clinical Sciences and Community Health, Università degli Studi di Milano, Milano)
13. Francesca Cortellaro (Emergency Medicine Department, ASST Grande Ospedale Metropolitano Niguarda, Milan)

The Netherlands (Peter E. Westerweel)
1. Peter E. Westerweel (Department of Hematology, Albert Schweitzer Hospital, Dordrecht)

Spain (David Jiménez)

1. Jaime Abelaira (Emergency Department, Clinico San Carlos Hospital, IdISSC, Madrid)
2. David Jiménez (Respiratory Department, Hospital Ramón y Cajal and Medicine Department, Universidad de Alcalá-IRYCIS, Madrid)
3. Aitor Ballaz-Quincoces (Servicio de Neumología, Hospital de Galdakao-Usansolo Barrio Labeaga, Galdakao, Bizkaia)
4. Raquel Lopez Reyes (Pneumology Department, Hospital Universitario y Politécnico la Fe de Valencia, Valencia)
5. Remedios Otero (Respiratory Department, Instituto de Biomedicina de Sevilla-IBiS, Centro de Investigación Biomédica en Red de Enfermedades Respiratorias-CIBERES, Hospital Universitario Virgen del Rocio, Sevilla)

Portugal (Candida Fonseca)

1. Tiago Judas (Department of Internal Medicine, Hospital Garcia de Orta, Almada)
2. Inês Araujo (Unidade de Insuficiência Cardíaca, Serviço de Medicina III, Hospital São Francisco Xavier, Lisbon, Portugal; NOVA Medical School, Faculdade de Ciências Médicas, Universidade Nova de Lisboa)
3. Sergio Baptista (Hospital da Luz, Lisbon)
4. Fabienne Goncalves (Unidade de Doença Vascular Pulmonar, Hospital Santo António, Centro Hospitalar do Porto, Porto, Portugal; Serviço de Medicina Interna, Hospital Santo António, Centro Hospitalar do Porto)

Finland (Veli-Pekka Harjola)

1. Pirjo Mustonen (Keski-Suomi Central Hospital, Jyväskylä)
2. Veli-Pekka Harjola (Emergency Medicine, University of Helsinki and Department of Emergency Medicine and Services, Helsinki University Hospital, Helsinki)

Greece (Athanasios Manolis)

1. Georgios Hahalis (Department of Cardiology, University General Hospital of Patras, Rio Achaia)
2. Athanasios Manginas (Department of Cardiology, Mediterraneo Hospital, Athens)
3. Konstantinos Gougoulianis (Department of Pulmonology, University of Thessaly, Larissa)
4. Athanasios Manolis (Department of Cardiology, General Hospital ´Asklepeion Voulas´, Athens)

Abstract

Background. Early discharge of patients with acute low-risk pulmonary embolism (PE) requires validation by prospective trials with clinical and quality of life outcomes.

Methods. The multinational Home Treatment of Pulmonary Embolism (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 three-month recurrence (primary outcome) and one-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 PE.

Results. The primary efficacy outcome occurred in three (0.5%; upper 95.0% CI 1.3%) patients. One-year mortality was 2.4%. The mean PEmb-QoL decreased from 28.9±20.6% at three weeks to 19.9±15.4% at three months, a mean change (improvement) of -9.1% ($p < 0.0001$). Improvement was consistent across all PEmb-QoL dimensions. EQ-5D-5L was 0.89±0.12 three weeks after enrolment and improved to 0.91±0.12 at three months ($p<0.0001$). Female sex and cardiopulmonary disease were associated with poorer disease-specific and generic quality of life; older age, with faster worsening of generic quality of life. The ACTS burden score improved from 40.5±6.6 points at three weeks to 42.5±5.9 at three months ($p<0.0001$).

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

Introduction

The severity spectrum of acute pulmonary embolism (PE) is broad, ranging from asymptomatic, incidentally diagnosed events to cases in which PE 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 (ESC) Guidelines for the diagnosis and management of acute pulmonary embolism, developed in collaboration with the European Respiratory Society (ERS), 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 an 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 or more in hospital [8]. Early discharge and home treatment may minimise hospitalization-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 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. 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 (RV) dysfunction on imaging [5]. These findings permitted premature termination of the study after completion of three-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 the quality of life and treatment satisfaction, along with 12-month mortality.

Methods

Study Design and Participants

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 [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 explained previously [15]. Briefly, adult patients were eligible for inclusion if they had objectively confirmed acute pulmonary embolism without RV enlargement or dysfunction (right/left ventricular [RV/LV] diastolic diameter ratio ≥ 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 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 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 three hours after pulmonary embolism diagnosis was allowed before enrolment in the study. Patients received the first dose of the study medication, rivaroxaban, within two hours 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 three weeks followed by the maintenance regimen of 20 mg once daily for at least three 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 below 50 ml/min. The trial protocol mandated discharge within 48 hours of admission, or a maximum of two nights in hospital [15].

Study Outcomes

The primary efficacy outcome was symptomatic recurrent venous thromboembolism, or pulmonary embolism-related death within three months of enrolment. The secondary efficacy outcomes included all-cause death within three months and one year of enrolment, rehospitalisations due to PE or to a bleeding event within three 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 non-major 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]. In brief, 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 one year before, and do not contribute to the total score. The six dimensions contributing to scores are summed, weighted, and transformed to a percentage scale (0 to 100), with higher scores indicating worse quality of life and lower scores indicating better quality of life.

EQ-5D-5L (© EuroQol Research Foundation; EQ-5D™ is a trade marke of the EuroQol Research Foundation) is a validated instrument designed to provide a simple and direct profile of the patient's generic health status (https://euroqol.org/publications/user-guides). It comprises a short descriptive system questionnaire covering five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) and a visual analogue scale 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 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/.

Finally, the ACTS (ACTS © Bayer AG, 2006. All Rights Reserved.) includes 12 items assessing perceived burden, and 3 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 comprised between 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 $p \geq 0.03$ (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 (2-stage adaptive design based on an O'Brien Fleming design) and assuming a 3-month symptomatic VTE 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 three-month recurrence rate observed in the EINSTEIN-PE rivaroxaban phase 3 trial [20]. The study was stopped after the preplanned 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 $\alpha = 0.004$ (<6 patients developing the primary efficacy outcome) in the intention-to-treat (ITT) population [5].

Statistical Analysis

The primary and secondary outcome analysis was 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 done using paired t-tests in case of normally distributed data or using the Wilcox-signed-rank test. To check for associations between baseline pre-defined explanatory variables characterized by low multicollinearity and an outcome variable (PEmb-QoL, Visual Analogue Scale), a linear regression model was fitted for the 3-week and 3-month visit 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 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 the informed consent for participation in the HoT-PE trial at 49 centres in 7 countries and were included in the ITT population. The mean age was 57 (range 18-90) years and 266 (46.2%) were women. **Table 1** displays 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 preceeded the diagnosis of acute pulmonary embolism by a median of 4 (Q1-Q3: 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 453 patients in whom compression ultrasound was performed.

A total of of 569 (98.8%) patients who received at least one dose of rivaroxaban were included in the safety population. The median length of hospitalisation was 33 (Q1-Q3: 23-47) hours, and 551 patients were hospitalised for up to two nights in compliance with the study protocol. A total of 547 (95.0%) patients were included in the per-protocol population.

Rivaroxaban 15 mg twice daily was given for a mean period of 21 (standard deviation [SD] 5) days after the diagnosis of acute pulmonary embolism. Patients received the maintenance dosage of rivaroxaban over an additional period of 69 (SD 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, symptomatic recurrent venous thromboembolism or pulmonary embolism-related death occurred in three (0.5%; one-sided upper 95.0% confidence interval [CI] 1.3%; one-sided p-value <0.0001) of the 576 patients of the ITT population within three months of enrolment; **Table 2**. All three recurrent events were nonfatal recurrent PE (*Supplementary Material I, Table S1*). The primary outcome occurred in two (0.4%; two-sided 95% CI 0.04-1.3%; two-sided p-value <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 non-major bleeding was recorded in 30 (5.3%; two-sided 95% CI 3.6-7.4%) patients. The median duration of first rehospitalisation was 6 (Q1-Q3: 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 *Table S2*. Twelve (2.1%) patients were hospitalised for suspected pulmonary embolism recurrence or bleeding within 3 months of enrolment, which was then confirmed in 7 (1.2%).

Fourteen patients died after a median of 6.8 (Q1-Q3 4.7-11.4) months, corresponding to a one-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 three-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

Analysis of the PEmb-QoL was conducted on a total of 425 patients who completed the questionnaire at both visits. The formulas for the calculation of the PEmb-QoL questionnaire are shown in *Supplementary Material II*. The mean PEmb-QoL score decreased from 28.9% (SD 20.6%) at 3 weeks to 19.9% (SD 18.4%) at 3 months; this corresponds to a mean reduction of -9.1% (SD 15.4%; paired t-test <0.0001), indicating a significant improvement in the patients' self-reported quality of life. As displayed 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 the follow-up. Of note, older age and the presence of cancer were not associated with worse quality of life at these timepoints, 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 *Tables S3* and *S4 (Supplementary Material I)*, 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 one year before (Dimension 3). The characteristics of the patients with and without complete PEmb-QoL assessment at both visits are reported in *Table S5*.

The EQ-5D-5L analysis was conducted in a total of 473 patients who filled the questionnaire at both visits. The EQ-5D-5L index score was 0.89 (SD 0.12) 3 weeks after

enrolment and improved to 0.91 (SD 0.12) at 3 months (paired t-test for difference; p<0.0001). The number 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 (from 1.9% to 1.8%), or extreme (from 0.3% to 0.2%) problems. As displayed in **Figure 2,** these positive changes were consistent across all five EQ-5D-5L dimensions.

The Visual Analogue Scale of the EQ-5D-5L increased from 76.2 (SD 16.1) to 80.2 (SD 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 Visual Analogue Scale, 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 Visual Analogue Scale (-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 *Table S6*.

Anti-Clot Treatment Scale (ACTS)

The 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 none of the ACTS burden items was 56.9%, and increased to 66.0% after 3 months. The ACTS burden score increased from 40.5 (SD 6.6) at week 3 to 42.5 (SD 5.9) points at month 3, indicating an improvement in terms treatment satisfaction (paired t-test; p<0.0001). Three weeks after acute PE, 26.3% of the patients reported to be 'extremely satisfied' based on the ACTS benefit items; this percentage increased to 31.7% at 3 months. The ACTS benefit score was 11.4 (SD 2.9) at week 3, and 11.4 (SD 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, symptomatic or fatal recurrence of venous thromboembolism at three-month follow-up [5], and thus allowed for early termination of the trial. The present analysis focuses on long-term survival as well as the 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 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 three 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 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 [22, 23]. This is also true for the rate of safety outcomes, notably major haemorrhage [21-23]. We recently reported that, within this low-risk population, 'fragile' patients defined by age above 75 years, a low body mass index (<18.5 kg/m^2), or a creatinine clearance of less than 50 mL/min, exhibited a higher rate of major bleeding (2.7%, compared to 0.7% among patients with none of these characteristics) [24]. 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 one-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, one-year mortality rate overall exceeded 15% among unselected patients with pulmonary embolism [25, 26] or venous thromboembolism in the broader sense [27-29], ranging between 40% among patients with cancer and 10% among those without it.

Beyond delivering data on recurrence, bleeding and overall mortality, HoT-PE is the largest study that has prospectively evaluated, using established standardised questionnaires, the patients' quality of life three weeks and three months after acute (low-risk) pulmonary embolism. Both the disease-specific and the generic tools measuring the 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 Visual Analogue Scale (**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 [30-32]. 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 [33-35], indicating that the impact of specific baseline characteristics on the quality of life over time is consistent across a broad spectrum of acute cardiovascular syndromes.

Our study has some limitations which need to be pointed out. Routine assessment of RV function has been proposed to possess added value for risk stratification of pulmonary embolism independently from clinical assessment tools [36], but the optimal imaging method, 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 PE in the vast majority (> 90%) of the study patients. It has been shown that a simple parameter of RV function on CTPA, the calculation of the RV/LV ratio, was accurate and reproducible after minimal training [37]. 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 approximately 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]. On the other hand, 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 three 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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Group information

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, Luca Valerio, 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. Hoeper, 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, 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, Athanassios Manginas, Konstantinos Gougoulianis, Athanasios Manolis, Michael Czihal, Tobias J. Lange, Raoul Stahrenberg, Thomas Meinertz, Menno V. Huisman, Paolo Prandoni, Walter Lehmacher.

Conflict of Interest

Dr. Barco reports personal fees from Biocompatibles Group UK, LeoPharma, and Bayer, non-financial support from Bayer, non-financial support from Daiichi Sankyo, institutional grant from Sanofi, outside the submitted work. Dr. Schmidtmann reports grants from Merck Serono, outside the submitted work. Dr. Ageno reports grants from Bayer, personal fees from Boehringer Ingelheim, personal fees from Daiichi Sankyo, personal fees from BMS/Pfizer, outside the submitted work. Dr. Bauersachs reports personal fees from Bayer Health Care, personal fees from BMS/Pfizer, personal fees from Daiichi-Sankyo, during the conduct of the study. Dr. Becattini reports personal fees from Bayer Health Care, personal fees from Daiichi Sankyo, personal fees from Bristol Meyer Squibb, outside the submitted work. Dr. Bernardi has nothing to disclose. Dr. Beyer-Westendorf reports other from CTH Mainz (Sponsor), during the conduct of the study; grants and personal fees from Bayer, outside the submitted work. Dr. Bonacchini has nothing to disclose. Dr. Brachmann reports grants and personal fees from Medtronic, during the conduct of the study; grants from Medtronic, grants from St. Jude, grants from Biotronik, outside the submitted work. Dr. Christ reports grants from the University of Mainz during the conduct of the study. Dr. Czihal reports personal fees from Bayer Health Care, personal fees from Roche, personal fees from Astra-Zeneca, personal fees from MSD Sharp & Dohme, personal fees from Leo Pharma, outside the submitted work. Dr. Duerschmied reports personal fees and non-financial support from Bayer, personal fees and non-financial support from Pfizer, personal fees and non-financial support from Daiichi Sankyo, personal fees and non-financial support from CytoSorbents, outside the submitted work. Dr. Empen reports non-financial support from Bayer HeathCare, personal fees from Bayer HeathCare, outside the submitted work. Dr. Espinola-Klein reports other from Bayer Health Care, outside the submitted work. Dr. Ficker reports personal fees from Daiichi Sankyo, outside the submitted work. Dr. Fonseca reports personal fees from Bayer, outside the submitted work. Dr. Genth-Zotz has nothing to disclose. Dr. Jiménez reports personal fees and other from Bayer, personal fees and other from 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. Dr. Harjola reports personal fees from Boehringer-Ingelheim outside the submitted work. Dr. Held reports other from Actelion, Bayer, Boehringer, MSD, Daiichii Sankyo, Roche, other from Actelion, Bayer, Berlin Chemie, BMS, MSD, Daichii Sankyo, Pfizer, OMT, grants from Actelion, outside the submitted work. Dr. Prat has nothing to disclose. Dr. Lange reports non-financial support from Center for Thrombosis and Hemostasis, University Medical Center Mainz, during the

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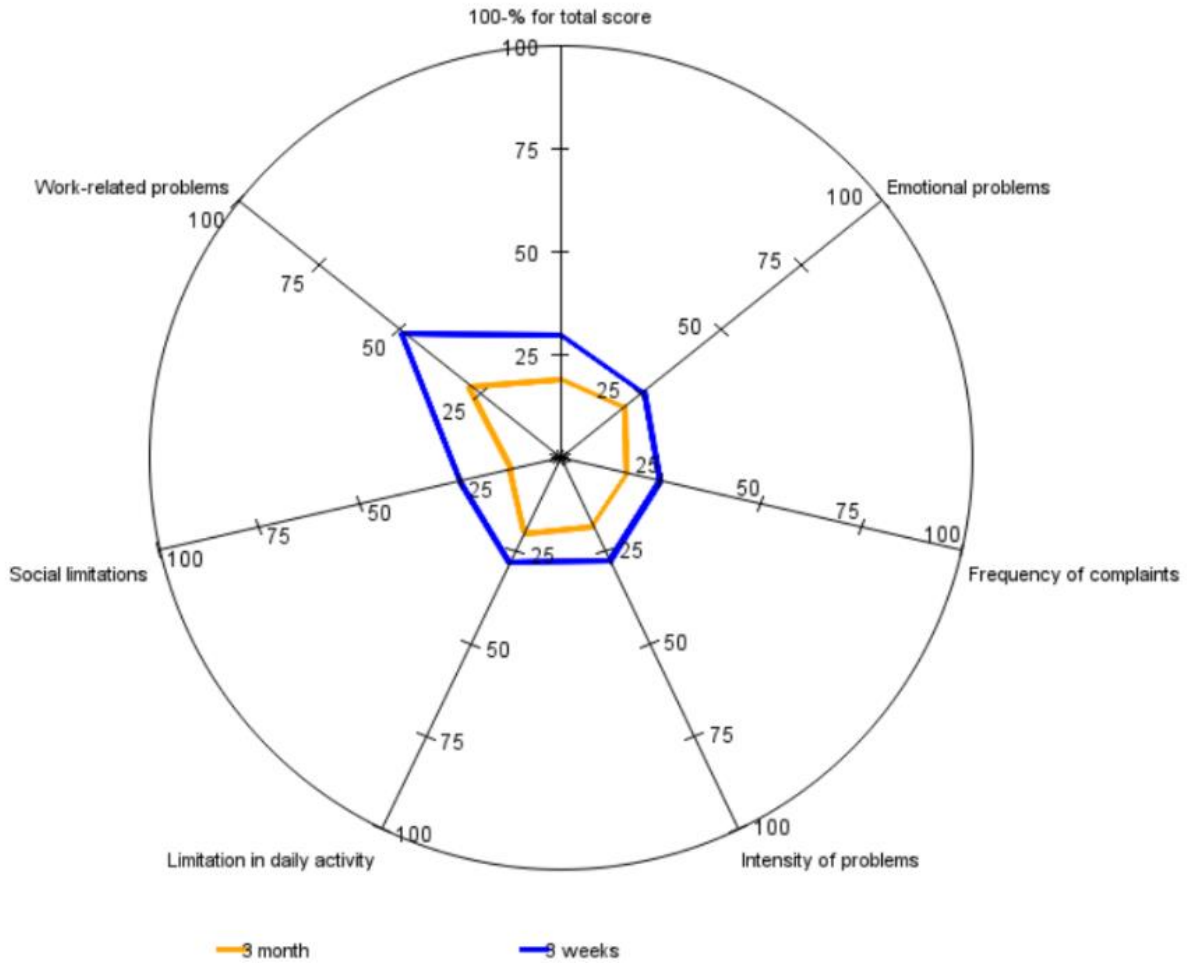
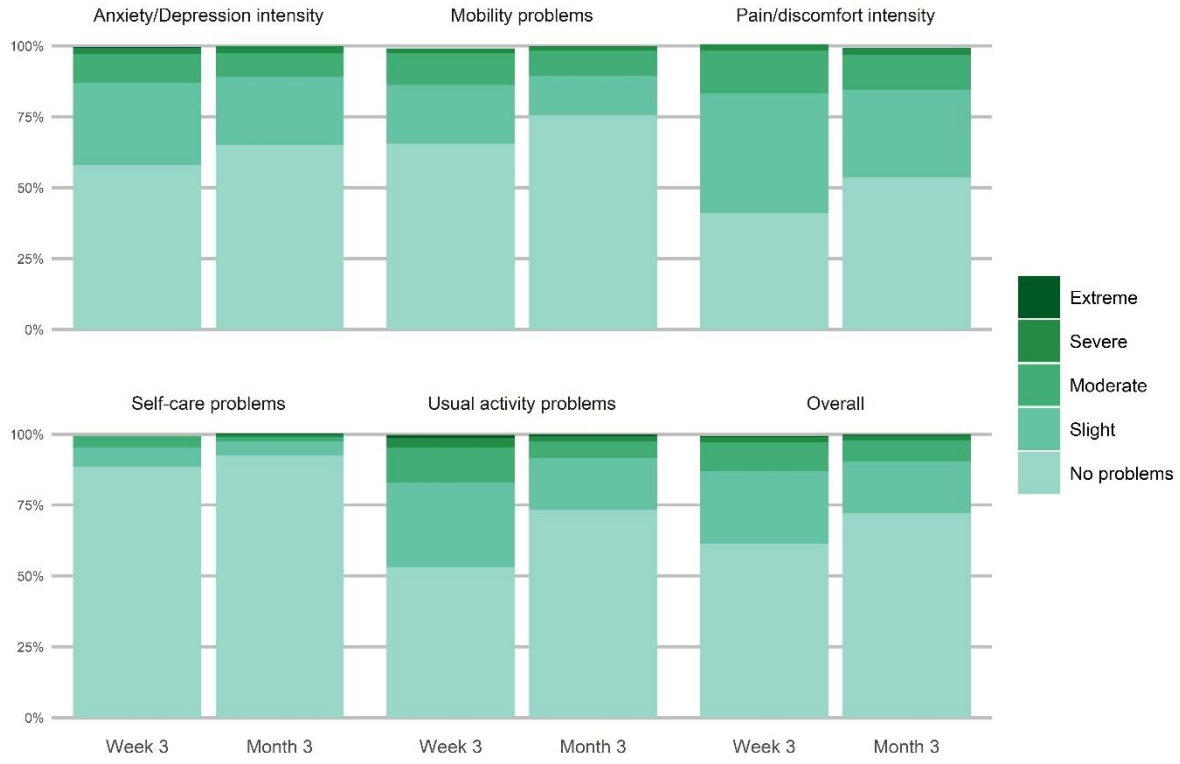
FIGURE 1 Improvement of quality of life after acute pulmonary embolism according to the Pulmonary Embolism Quality of Life score



The figure illustrates the evolution in disease-specific quality of life for each of the PEmb-QoL dimensions and for the whole PEmb-QoL score between Week 3 (blue line) and Month 3 (orange line). The six dimensions contributing to scores are summed, weighted, and transformed to a percentage scale (0 to 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.

PEmb-QoL: Pulmonary Embolism Quality of Life questionnaire.

FIGURE 2 Graphic representation of the course of EQ-5D-5L assessed 3 weeks and 3 months after enrolment



Stacked bar plots showing the percentage of patients reporting “no problems”, “slight problems”, “moderate problems” or “severe problems” in each of the five dimensions of the EQ-5D-5L health-related quality of life questionnaire and in the overall questionnaire at 3 weeks and 3 months.

TABLE 1 Baseline characteristics of the study population

Variable	**Value**
Patient Demographics	
Age (years), mean (SD; range)	56.5 (16.6; 18-90)
Women, n/N (%)	266/576 (46.2)
Caucasian	567/576 (98.4)
Education Level	
Elementary school, n/N (%)	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/m²), median (Q1-Q3)	27.1 (24.3-30.5)
Systolic / diastolic blood pressure (mm Hg), mean (SD)	136 (19) / 80 (12)
Heart rate (beats per minute), mean (SD)	78 (13)
Oxygen saturation (%), median (Q1-Q3)	97 (96-98)
Respiratory rate (breaths per minute), median (Q1-Q3)	16 (15-18)
Creatinine clearance < 50 mL/min	32 (5.6)
Risk Factors for Pulmonary Embolism and Comorbidities, n/N (%)	
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 hours, 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 (sPESI) ≥ 1	127/556 (22.8)
Baseline Imaging Tests for Venous Thromboembolism, n/N (%)	
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 (41.8)

For categorical variables, the proportion and percentage of valid (non-missing) cases are reported. Continuous variables with missing information: body mass index (18 patients), blood pressure (19 patients), oxygen saturation (20 patients), respiratory rate (70 patients).

Q1-Q3: first and third quartile; SD: standard deviation.

TABLE 2 Study outcomes

Primary Efficacy Outcome	
Primary outcome (intention-to-treat population): recurrent venous thromboembolism or fatal PE, n/N (%; one-sided upper 95.0% CI)	3/576 (0.5; 1.3)
Recurrent PE, n	3
Recurrent deep vein thrombosis, n	0
Death related to PE, n	0
Primary outcome (per-protocol population): recurrent venous thromboembolism or fatal PE, n/N (%; two-sided 95% CI)	2/547 (0.4; 0.04-1.3)
Secondary Efficacy Outcomes	
Death of any cause within 3 months, n/N (%)	2/576 (0.4)
Death of any cause within 12 months, n/N (%; two-sided 95% CI)	14/576 (2.4; 1.3-4.0)
Advanced cancer as cause of death, n	9
Intracranial haemorrhage, n	1
Sepsis, n	1
Other, n	3
Safety Outcomes	
Major bleeding[a], n/N (%; 95% CI)	6/569 (1.1; 0.4-2.3)
Clinically relevant bleeding, n/N (%; 95% CI)	30/569 (5.3; 3.6-7.4)
At least one serious adverse event, n/N (%; 95% CI)	68/569 (12.0; 9.5-14.9)
Serious adverse events requiring prolonged initial hospitalization, or rehospitalization, n/N (%; 95% CI)	64/576 (11.1; 8.8-13.9)

[a]As defined by the criteria of the International Society of Thrombosis and Haemostasis [16].

CI: confidence interval; PE: pulmonary embolism.

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

	PEmb-QoL (Week 3)			*PEmb-QoL (Month 3)*			*Visual Analogue Scale (Week 3)*			*Visual Analogue Scale (Month 3)*		
Parameter	**Estimate* (%)**	**Standard error**	**p-value**	**Estimate* (%)**	**Standard error**	**p-value**	**Estimate** (%)**	**Standard error**	**p-value**	**Estimate** (%)**	**Standard error**	**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
Women vs men	11.2	2.3	<0.0001	8.2	2.1	<.0001	-3.9	1.7	0.02	-4.6	1.7	0.007
BMI (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 VTE	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

The beta estimates for the difference of Pulmonary Embolism Quality of Life (PEmb-QoL) score between Week 3 and Month 3 were +0.2 (standard error 0.05; p=0.001) relative increase for age and +6.4 (standard error 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 (vs. without) cancer. The beta estimates for the difference of Visual Analogue Scale between Week 3 and Month 3 were -0.1 (standard error 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 (vs. reference group, corresponding to the absence of the factor, or per unit increase) 3 weeks and 3 months after enrolment. **Positive estimates of the Visual Analogue Scale indicate an association with a better quality of life (vs. reference group, corresponding to the absence of the factor, or per unit increase) 3 weeks and 3 months after enrolment.

Supplementary Material I

TABLE S1 **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 Rehospitalisation (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.

[a] As defined by the criteria of the International Society of Thrombosis and Haemostasis.[16]

LMWH: low-molecular-weight heparin; PE: pulmonary embolism; sPESI: simplified Pulmonary Embolism Severity Index.

TABLE S2 **Serious adverse events (n=68) in the safety population within 3 months of enrolment**

Adverse event	**Time of Onset (Days After Enrolment)**	**Hospitalization Necessary**
Progression of oedema (left leg)	49	Yes
Kidney stones	74	Yes
Retrosternal pain	5	Yes
Removal of external bone fixator and suspected recurrent pulmonary embolism	2	Yes
Gastritis	81	Yes
Suspected recurrent pulmonary embolism	7	Yes
Schizoaffective disorder (maniac phase)	64	Yes
Anaemia	55	Yes
Ankle fracture	49	Yes
Infarct pneumonia	2	Yes
Proximal tibial facture	71	Yes
Gastrointestinal bleeding	13	Yes
Chest pain	20	Yes
Exertional dyspnoea	37	Yes
Paradoxical septal motion	91	No
Upper gastrointestinal bleeding	5	Yes
Acute cytomegalovirus (momonucleosis-like) infection	2	Yes
Pleuritis	1	Yes
Reflux oesophagitis	2	Yes
Syncope	12	Yes
Hypermenorrhoea	12	Yes
Urosepsis and pyelonephritis	13	Yes
Allergic reaction (rivaroxaban)	2	Yes
Acute renal failure	53	Yes
Hypermenorrhoea	20	Yes
Pneumonia	2	Yes
Panic attack	57	Yes
Renal colic	1	Yes
Cancer	47	No
Infarction pneumonia	4	Yes
Dyspnoea	4	Yes

Gastrointestinal bleeding	57	Yes
Angina pectoris	57	Yes
Pancreatic cancer	1	Yes
Bronchial cancer	13	Yes
Suspected pancreatic cancer	2	Yes
Fever	3	Yes
Pneumonia	2	Yes
Chronic obstructive pulmonary disease	33	Yes
Bleeding	57	Yes
Bronchial asthma	35	Yes
Pneumonia	4	Yes
Elevation of troponin	1	Yes
Thoracic pain	32	Yes
Anxious disorder	4	Yes
Suspected deep vein thrombosis	63	No
Prostate cancer	55	No
Chronic inflammatory demyelinating polyneurophathy	4	Yes
Advanced mesothelioma	34	Yes
Bladder-bowel fistula	33	Yes
Lobar pneumonia	70	Yes
Elevation of troponin	1	Yes
Diarrhea	85	Yes
Chest pain	36	Yes
Sepsis	22	Yes
Suspected recurrent pulmonary embolism	75	No
Exacerbation of chronic obsctructive pulmonary disease	7	Yes
Pneumonia	12	Yes
Suspected esophagus cancer	13	Yes
Pneumonia	26	Yes
Pneumonia	34	Yes
Chest pain	5	Yes
Hypotension	29	Yes
Non-ST elevation myocardial infarction	3	Yes
Suspected deep vein thrombosis	2	Yes
Stroke	53	Yes
Chest pain	2	Yes

Advanced endometrial cancer	26	Yes

TABLE S3 **Answers to Dimension 2 of PEmb-QoL "At what time of day are your lung symptoms most intense?"**

	Week 3	**Month 3**
When waking up	8.2%	6.1%
At mid-day	8.7%	6.4%
In the evening	16.0%	12.2%
During the night	5.7%	4.0%
At any time of the day	20.0%	14.8%
Never	38.1%	53.9%
Not available	3.3%	2.6%

TABLE S4 **Answers to Dimension 3 of PEmb-QoL "Compared to one year ago, how would you rate the condition of your lungs in general now?"**

		Week 3	**Month 3**
Much better		4.0%	14.1%
Slightly better		6.4%	8.5%
About the same		19.1%	30.8%
Slightly worse		27.3%	22.6%
Much worse		13.2%	6.8%
No problems		28.2%	15.8%
Not available		1.9%	1.4%

TABLE S5. Baseline characteristics of the patients who completed the Pulmonary Embolism Quality of Life questionnaire at both visits (week 3 and month 3) versus those who did not (at either or both visits)

Variable	**PEmb-QoL assessed at 3 weeks and 3 months (N=425)**	**PEmb-QoL not assessed at either visit (N=151)**
Patient Demographics		
Age (years), mean (SD; range)	57.0 (16.0; 19-90)	55.2 (18.2; 18-87)
Women, n/N (%)	192/425 (45.2)	74/151 (49.0)
Education Level, n/N (%)		
Elementary school	14/384 (3.6)	6/135 (4.4)
Basic primary school	42/384 (10.9)	16/135 (11.9)
Secondary general school	97/384 (25.3)	26/135 (19.3)
Intermediate secondary school	95/384 (24.7)	37/135 (27.4)
A-level	68/384 (17.7)	27/135 (20.0)
University degree	67/384 (17.4)	23/135 (17.0)
Doctorate	1/384 (0.3)	0
Functional Parameters and Biochemical Markers		
Body mass index (kg/m²), median (Q1-Q3)	27.1 (24.3-30.5)	27.0 (24.4-30.6)
Systolic / diastolic blood pressure (mm Hg), mean (SD)	137 (19) / 80 (12)	136 (19) / 80 (12)
Heart rate (beats per minute), mean (SD)	78 (13)	77 (13)
Oxygen saturation (%), median (Q1-Q3)	97 (96-98)	97 (95-98)
Respiratory rate (breaths per minute), median (Q1-Q3)	16 (15-18)	16 (14-18)

Risk Factors for Pulmonary Embolism and Comorbidities, n/N (%)		
Oestrogen use	70/422 (16.6)	22/149 (14.8)
Immobilisation (for at least 3 days)	46/420 (11.0)	12/150 (8.0)
Previous deep vein thrombosis	63/416 (15.1)	24/150 (16.0%)
Previous pulmonary embolism	35/421 (8.3)	9/151 (6.0)
Recent major surgery (past 30 days)	27/424 (6.4)	11/150 (7.3)
Recent major trauma (past 30 days)	17/425 (4.0)	8/150 (5.3)
Long travel (> 4 hours, past 30 days)	54/418 (12.9)	16/149 (10.7)
Active cancer	29/420 (6.9)	9/147 (6.1)
Chronic obstructive pulmonary disease	21/420 (5.0)	7/149 (4.7)
Chronic heart failure	4/425 (0.9)	3/150 (2.0)
Coronary artery disease	31/422 (7.3)	10/148 (6.8)
Arterial hypertension	172/425 (40.5)	69/149 (46.3)
Diabetes mellitus	26/425 (6.1)	12/151 (7.9)
Simplified Pulmonary Embolism Severity Index (sPESI) ≥ 1	94/412 (22.8)	33/144 (22.9)

PEmb-QoL: Pulmonary Embolism Quality of Life questionnaire.

TABLE S6 Baseline characteristics of the patients who completed the EQ-5D-5L questionnaire at both visits (week 3 and month 3) versus those who did not (at either or both visits)

Variable	**EQ-5D-5L assessed at both 3 weeks and 3 months (N=473)**	**EQ-5D-5L not assessed at either visit (N=103)**
Patient Demographics		
Age (years), mean (SD; range)	56.9 (16.1; 18-90)	55.1 (18.7; 20-86)
Women, n/N (%)	217/473 (45.9)	49/103 (47.6)
Education Level, n/N (%)		
Elementary school	15/429 (3.5)	5/90 (5.6)
Basic primary school	46/429 (10.7)	12/90 (13.3)
Secondary general school	102/429 (23.8)	21/90 (23.3)
Intermediate secondary school	113/429 (26.3)	19/90 (21.1)
A-level	78/429 (18.2)	17/90 (18.9)
University degree	74/429 (17.2)	16/90 (17.8)
Doctorate	1/429 (0.2)	0
Functional Parameters and Biochemical Markers		
Body mass index (kg/m²), median (Q1-Q3)	27.2 (24.4-30.5)	26.5 (24.0-29.5)
Systolic / diastolic blood pressure (mm Hg), mean (SD)	136 (19) / 80 (12)	136 (19) / 81 (12)
Heart rate (beats per minute), mean (SD)	78 (13)	78 (12)
Oxygen saturation (%), median (Q1-Q3)	97 (96-98)	97 (95-98)
Respiratory rate (breaths per minute), median (Q1-Q3)	16 (15-18)	16 (15-18)

Risk Factors for Pulmonary Embolism and Comorbidities, n/N (%)		
Oestrogen use	76/470 (16.2)	16/101 (15.8)
Immobilisation (for at least 3 days)	49/467 (10.5)	9/103 (8.7)
Previous deep vein thrombosis	69/464 (14.9)	18/102 (17.6)
Previous pulmonary embolism	36/469 (7.7)	8/103 (7.8)
Recent major surgery (past 30 days)	31/471 (6.6)	7/103 (6.8)
Recent major trauma (past 30 days)	21/472 (4.4)	4/103 (3.9)
Long travel (> 4 hours, past 30 days)	59/464 (12.7)	11/103 (10.7)
Active cancer	29/467 (6.2)	9/100 (9.0)
Chronic obstructive pulmonary disease	22/469 (4.7)	6/100 (6.0)
Chronic heart failure	4/473 (0.8)	3/102 (2.9)
Coronary artery disease	30/469 (6.4)	11/101 (10.9)
Arterial hypertension	194/471 (41.2)	47/103 (45.6)
Diabetes mellitus	33/473 (7.0)	5/103 (4.9)
Simplified Pulmonary Embolism Severity Index (sPESI) ≥ 1	97/457 (21.2)	30/99 (30.3)

Supplementary Material II

Formulas for the Calculation of the Pulmonary Embolism Quality of Life (PEmb-QoL) questionnaire

Frequency of complaints (Dimension 1)

The transformation from n_points} to the ratio 100–% was done using the following formula:

$$100 - \% = 100 - \frac{n_{points} - min_{n_{points}} + n_{miss} \cdot min_{point}}{\frac{max_{n_{points}} - min_{n_{points}}}{100} - \frac{max_{point} - min_{point}}{100} \cdot n_{miss}}$$
$$= 100 - \frac{n_{points} - 8 + n_{miss} \cdot min_{point}}{0.32 - 0.04 \cdot n_{miss}}$$

Limitation daily life (Dimension 4)

The transformation from n_{points} to the ratio 100–% was done using the following formula (if the first question was = 0 or missing):

$$100 - \% = 100 - \frac{n\ _{oints} - min_{n_{points}} + n_{miss} \cdot min\ _{oint}}{\frac{max_{n_{points}} - min_{n_{points}}}{100} - \frac{max\ _{oint} - min\ _{oint}}{100} \cdot n_{miss}}$$
$$= 100 - \frac{n\ _{oints} - 12 + n_{miss} \cdot min\ _{oint}}{0.24 - 0.02 \cdot n_{miss}}$$

The transformation from n_points to the ratio 100–% was done using the following formula (if the first question was > 0):

$$100 - \% = 100 - \frac{n\ _{oints} - min_{n_{points}} + n_{miss} \cdot min\ _{oint}}{\frac{max_{n_{points}} - min_{n_{points}}}{100} - \frac{max\ _{oint} - min\ _{oint}}{100} \cdot n_{miss}}$$
$$= 100 - \frac{n\ _{oints} - 13 + n_{miss}}{0.26 - 0.02 \cdot n_{miss}}$$

Work-related problems (Dimension 5)

$$100 - \% = 100 - \frac{n_{points} - min_{n_{points}} + n_{miss} \cdot min_{point}}{\frac{max_{n_{points}} - min_{n_{points}}}{100} - \frac{max_{point} - min_{point}}{100} \cdot n_{miss}}$$
$$= 100 - \frac{n_{points} - 4 + n_{miss} \cdot min_{point}}{0.04 - 1 \cdot n_{miss}}$$

Social limitations (Dimension 6)

1=0% → 5=100%

Intensity of complaints (Dimensions 7-8)

The transformation from n_points to the ratio % was done using the following formula:

$$\% = \frac{n_{points} - min_{n_{points}} + n_{miss} \cdot min_{point}}{\frac{max_{n_{points}} - min_{n_{points}}}{100} - \frac{max_{point} - min_{point}}{100} \cdot n_{miss}}$$
$$= \frac{n_{points} - 2 + n_{miss} \cdot min_{point}}{0.100 - 0.05 \cdot n_{miss}}$$

Emotional complaints (Dimension 9)

The transformation from n_points to the ratio 100−% was done using the following formula:

$$100 - \% = 100 - \frac{n_{points} - min_{n_{points}} + n_{miss} \cdot min_{point}}{\frac{max_{n_{points}} - min_{n_{points}}}{100} - \frac{max_{point} - min_{point}}{100} \cdot n_{miss}}$$
$$= 100 - \frac{n_{points} - 10 + n_{miss} \cdot min_{point}}{0.5 - 0.05 \cdot n_{miss}}$$

with the following notation:

- n_{points}: sum of points over all items per patient
- n_{miss}: number of missing items
- $max_{n_{points}}$: maximal possible sum over all items

- $min_{n_{points}}$: minimal possible sum over all items
- max_{point}: maximal possible value per item
- min_{point}: minimal possible value per item

Total

For the present analysis, the specific dimensions are are weighted based on their number of items. The number of items per dimension is distibuted as follows:

- frequency of complaints (foc): 8
- limitations of activity in daily life (adl): 12 or 13 (depending on the value of 'I do not work')
- work-related problems (wrp): 4
- social limitation (sl): 1
- intensity of problems (iop): 2
- emotional complaints (ep): 10

resulting in a total of 37 or 38 items over all six dimensions. For calculation a total of 37.5 items is used as the number of 12 or 13 items in the adl-dimension is almost 50:50. The total score is then calculated as follows:

$$\%^*_{total} = \frac{\%^*_{foc} \cdot 8}{37.5} + \frac{\%^*_{adl} \cdot 12.5}{37.5} + \frac{\%^*_{wrp} \cdot 4}{37.5} + \frac{\%_{sl} \cdot 1}{37.5} + \frac{\%_{iop} \cdot 2}{37.5} + \frac{\%^*_{ep} \cdot 10}{37.5}$$

*1-% ratio

Multiple imputation (MCMC, assuming all dimensions have a joint multivariate normal distribution) was performed if a dimension was completely missing. The number of missing dimensions was 3.6%.