Supplementary Material to Barco et al. “Home treatment of patients with low-risk pulmonary embolism with the oral factor Xa inhibitor rivaroxaban. Rationale and design of the Hot-PE Trial”
(Thromb Haemost 2016; 116.1)

Definition of recurrent venous thromboembolism

Recurrent pulmonary embolism (PE) should be diagnosed using the same diagnostic procedure(s) as the initial event and is defined,

a) as a new intraluminal filling defect on multidetector computed tomographic or invasive selective pulmonary angiography; or
b) a new perfusion defect involving at least 75% of a segment with normal ventilation on lung scan; or
c) a non-diagnostic lung scan accompanied by evidence of (new) deep vein thrombosis on compression ultrasonography; or
d) for patients who die prior to completion of the diagnostic work-up, fresh pulmonary emboli at autopsy (1;2).

Recurrent deep vein thrombosis is defined as a new, non-compressible venous segment, or a substantial increase (>4 mm) in the diameter of a preexisting thrombus during full compression (3).

Safety outcomes

Major bleeding is defined as clinically overt bleeding, which is associated with a decrease in haemoglobin levels of 2.0 g per deciliter or more, or leads to the transfusion of two or more units of red cells, or is intracranial or retroperitoneal, or occurs in another critical site, or contributes to death (4).
Clinically relevant non-major bleeding is defined as overt bleeding that does not meet the criteria for major bleeding but is associated with medical intervention, unscheduled contact with a physician, interruption or discontinuation of a study drug.

**Event adjudication and adverse event reporting**

All reported potential outcomes, including deaths within one year after enrolment in the study, hospitalisations and major or clinically relevant non-major bleeding within 3 months after enrolment, will be adjudicated by an independent critical events committee (CEC) consisting of three experienced physicians. The result of the adjudication will be a classification as primary outcome, one of the secondary outcomes, or no outcome. The internal rules of the adjudication process are described in a CEC charter.

Data are provided to an independent data safety monitoring board (DSMB) by a qualified central drug safety processing group which assesses the category classification and seriousness of reported adverse events, and their possible relation to the study drug. Adverse events are also transmitted to the study investigators, institutional Ethics Committees, and/or Review Boards as per local regulations. At regular intervals, the DSMB will independently review safety and outcome data and report to the chairperson of the steering committee. Premature termination of the study can be recommended by the DSMB after a sequential safety and outcomes monitoring approach. More specifically, safety information will be analysed by the DSMB when data are available for the first 60 patients enrolled; subsequent analyses will be performed after the enrolment of 212, 525, and 767 patients. Premature termination of the study may be recommended if there is excessive mortality, rates of rehospitalisation or rates of major bleeding assessed at specific timepoints, or if futility is demonstrated. The internal rules are described in a DSMB charter.
Quality of life after acute pulmonary embolism, patient satisfaction, health care resource utilisation: specifics and statistical analysis

Quality of life after acute PE is assessed upon enrolment and at seven days using the validated generic EuroQoL 5 Dimension (EQ-5D) (5), and at three weeks and three months based on the validated generic EuroQoL 5 Dimension (EQ-5D) and the Pulmonary Embolism Quality of Life (PEmb-QoL) questionnaires (6). Quality of life questionnaires are completed in written form without the help of a physician; partners or caregivers are permitted to assist the patient if needed. Quality of life questionnaires and stamped addressed envelopes are mailed to the patients in advance of the structured telephoned calls at eight days and three weeks. A systematic literature review will be considered for obtaining estimates of the quality of life of patients with symptomatic low-risk PE who are treated in-hospital. If applicable, EQ-5D-5L summary index estimates of the current study will be compared to respective estimates based on published literature using one-sample t-test. Study populations will be compared with regard to demographic factors, disease severity, comorbidities, and follow-up period. Further, a validation of the lingual versions of the PEmb-QoL which are not yet validated will be performed using previously described methods (6).

Treatment satisfaction is assessed using the Anti-Clot Treatment Scale (ACTS) (7;8). In addition, utilisation of medical resources will be assessed for patients recruited at the German study sites. Key parameters of medical resource utilisation are captured by asking the patients to complete a questionnaire on, (i) visits to health care providers, either general practitioners or medical specialists, and (ii) rehospitalisation, all the above being recorded at three weeks and at three months; in addition, (iii) additional medications as well as (iv) working status and/or disability are recorded at three months. Patient satisfaction with treatment is measured using the ACTS (7;8). Again, standard deviation, median, minimum, maximum and quartiles will be reported. Comparison to outcomes from the EINSTEIN-PE
trial will be made using Analysis of Variance or the Kruskall-Wallis test as appropriate. Association of ACTS with explanatory variables, i.e. demographic variables, medical history, and protocol adherence will be described by linear regression.

For patients enrolled by German sites, health care resource utilisation items will be described for the total sample in terms of absolute and relative frequencies or mean, standard deviation, median, minimum, maximum, and quartiles, respectively. Key components of resource utilisation (e.g., hospitalisation, physician visits etc.) will be evaluated in terms of their unit costs. German unit costs will be obtained using published data from the Working Group Methods in Health Economic Evaluation (9). These will be adjusted to the reference year 2013, taking inflation into account. If specific unit costs are not available in this publication, other appropriate sources of price weightings will be used. Cost of medications will be obtained applying daily defined dose prices published in the German Prescription Drug Report 2013 (Arzneiverordnungsreport 2013) (10). If available, sensitivity analysis will be performed considering hospitalisation costs based on Diagnosis Related Groups in the hospital records of at least one of the participating study centres. Cost items will be summed up to total costs per patient. For the direct comparison with the EINSTEIN-PE data, only patients with suspected outcomes (deep vein thrombosis, PE, or bleeding) will be considered in order to ensure comparability. Visits to health care providers will be compared using Chi-squared tests. Rehospitalisation days will be compared using the Kruskall-Wallis test. Mean costs will be compared a nonparametric bootstrap approach as appropriate. Indirect comparisons will be drawn using mean cost per suspected outcome from EINSTEIN-PE (7) as standardisation weights for the HoT-PE sample.

A systematic literature review will be performed for obtaining estimates of health care resource utilisation and costs of patients with symptomatic low-risk PE who are treated in-hospital. Study populations will be compared with regard to demographic factors, disease
severity, comorbidities, and follow-up period. Transition probabilities between different health states will be compared to corresponding probabilities reported in a published Markov model estimating the cost-effectiveness of treatment of PE with low-molecular-weight heparin (11) with appropriate Chi-squared tests.

**Sources of funding and disclosures**

HoT-PE is an independent, investigator-initiated trial. The study has an academic sponsor (University Medical Center Mainz, Germany) and is supported by public funding (federal German ministry of education and research; BMBF 01E01003). In addition, the sponsor has obtained the study drug (rivaroxaban) and a grant from the market authorisation holder (MAH) of rivaroxaban, Bayer HealthCare. Neither the MAH nor any other part of the industry is involved at any stage of study planning or conduct, data management or data analysis, or may exert any influence on decisions to discontinue the trial due to futility or safety concerns. The authors are solely responsible for the design and conduct of this study, for all study analyses, and for the drafting and editing of reports and publications and their final contents.
Suppl. References


