Thrombosis and Haemostasis

Reduced-dose intravenous thrombolysis for acute intermediate high-risk pulmonary embolism: Rationale and design of the PEITHO-3 trial


Affiliations below.

DOI: 10.1055/a-1653-4699

Please cite this article as: Sanchez O, Charles-Nelson A, Ageno W et al. Reduced-dose intravenous thrombolysis for acute intermediate high-risk pulmonary embolism: Rationale and design of the PEITHO-3 trial. Thromb Haemost 2021. doi: 10.1055/a-1653-4699

Conflict of Interest: O.S. has received institutional research grants from Bayer, Leo Pharma, Bristol-Myers Squibb, Merck Sharp and Dome, Daiichi-Sankyo, Boehringer Ingelheim and Sanofi and personal consultancy/speaker fees from Bayer, Bristol-Myers Squibb, Pfizer, Boston scientifics, Merck Sharp and Dome, Boehringer Ingelheim, Sanofi and Chiesi. S.B. has received congress and travel payments from Daiichi-Sankyo and Bayer AG, honoraria from BTG Pharmaceuticals, Boston Scientific, Bayer HealthCare and LeoPharma, and institutional grants from Sanofi, outside the submitted work. W.A. reports research support from Bayer; activity in advisory boards for Bayer, Boehringer Ingelheim, Daiichi Sankyo, Portola, Janssen, Aspen, Sanofi. D.D. has received speaker’s honoraria from Bayer Vital, Daiichi-Sankyo, Pfizer/ Bristol-Myers Squibb and consulting fees from Bayer Vital and Daiichi-Sankyo. In addition, D.D. is a member of SFB1425, funded by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation #422681845). K.E. reports lecture fees by AstraZeneca, Bayer Vital, Berlin Chemie, Boehringer Ingelheim and Novartis, and consulting fees by Bayer Vital, Boehringer Ingelheim, Novartis and Novo Nordisk. M.F. reports lecture fees and travel grants from Bayer, Bristol Myers Squibb, Pfizer, and Travel grants from Daiichi-Sankyo and Leo Pharma. M.V.H. reports grants from ZonMW Dutch Healthcare Fund, and grants and personal fees to the hospital from Boehringer Ingelheim, Bristol-Myers Squibb/Pfizer, Bayer Health Care, Aspen, Daiichi-Sankyo, all outside the submitted work. D.J. has served as an advisor or consultant for Bayer Healthcare Pharmaceuticals, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Leo Pharma, Pfizer, ROVI and Sanofi; served as a speaker or a member of a speakers’ bureau for Bayer Healthcare Pharmaceuticals, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Leo Pharma, Pfizer, ROVI and Sanofi; received grants for clinical research from Daiichi Sankyo, Sanofi and ROVI. M.K. reports speaker fees from Pfizer, Boehringer Ingelheim and Bayer AG outside the submitted work. M.L. reports consultant and speaker fees from Actelion, Bayer, Thermo Fisher Scientific, Daiichi-Sankyo, MSD and Bristol-Myers Squibb/Pfizer and project funding from Thermo Fisher Scientific. N.M. reports consulting fees, speaker fees and project funding from Bayer AG and Bristol-Myers Squibb/Pfizer, speaker fees from AstraZeneca and Boehringer Ingelheim, and consulting fees from Abbott and Terumo. A.P. reports speaker fees from S.C. Pfizer Romania SRL, Servier Pharma SRL, Novartis Pharma Services Romania SRL, Bayer SRL, and SC Sanience SRL. S.R. received honoraria for lectures and/or consultancy from Abbott, Acceleron, Actelion, Arena, Bayer, BMS, Ferrer, Janssen, MSD, Novartis, Pfizer, United Therapeutics, and Vifor, and institutional research grants from Actelion, AstraZeneca, Bayer, Janssen, and Novartis. S.S. has received consulting fees and speaker fees from Aspen and Boehringer Ingelheim, speaker fees from Bayer AG and Daiichi-Sankyo, and project funding and speaker fees from Pfizer/ Bristol-Myers Squibb. P.V. received honoraria for lectures and/or consultancy from Anthon Therapeutics, Bayer, Boehringer, Daiichi-Sankyo, BMS and Pfizer and research support from Bayer, Daiichi-Sankyo, BMS and Pfizer. S.K. reports institutional research grants and personal consultancy/speaker fees from Actelion/ Janssen, Bayer AG, Daiichi-Sankyo and Boston Scientific, institutional research grants from Boehringer Ingelheim and Servier, and personal consultancy/speaker fees from Bristol-Myers Squibb/Pfizer and Novartis. All other authors report no conflict of interest.

This study was supported by Deutsche Forschungsgemeinschaft, KO 1939/3-1, Programme hospitalier de recherche clinique, PHR-CN-16-0580

This article is protected by copyright. All rights reserved.
Trial registration: NCT04430569, ww.clinicaltrials.gov, Prospective, Randomized, Multi-Center Study

Abstract:
Intermediate high-risk pulmonary embolism (PE) is characterised by right ventricular (RV) dysfunction and elevated circulating cardiac troponin levels despite apparent haemodynamic stability at presentation. In these patients, full-dose systemic thrombolysis reduced the risk of haemodynamic decompensation or death but increased the risk of life-threatening bleeding. Reduced-dose thrombolysis may be capable of improving safety while maintaining reperfusion efficacy. The Pulmonary Embolism International Trial (PEITHO)-3 study (EudraCT 2018-000816-96) is a randomised, placebo-controlled, double-blind, multicentre, multinational trial with long-term follow-up. We will compare the efficacy and safety of a reduced-dose alteplase regimen with standard heparin anticoagulation. Patients with intermediate high-risk PE will also fulfil at least one clinical criterion of severity: systolic blood pressure ≤ 110 mmHg, respiratory rate > 20 breaths/min, or history of heart failure. The primary efficacy outcome is the composite of all-cause death, haemodynamic decompensation or PE recurrence within 30 days of randomisation. Key secondary outcomes, to be included in hierarchical analysis, are fatal or GUSTO severe or life-threatening bleeding; net clinical benefit (primary efficacy outcome plus severe or life-threatening bleeding); and all-cause death, all within 30 days. All outcomes will be adjudicated by an independent committee. Further outcomes include PE-related death, haemodynamic decompensation, or stroke within 30 days; dyspnoea, functional limitation or RV dysfunction at 6 months and 2 years; and utilisation of healthcare resources within 30 days and 2 years. The study is planned to enrol 650 patients. The results are expected to have a major impact on risk-adjusted treatment of acute PE and inform guideline recommendations.

Corresponding Author:
Stavros Konstantinides, University Medical Centre, Johannes Gutenberg University Mainz, Centre for Thrombosis and Haemostasis, Langenbeckstrasse 1, 55131 Mainz, Germany, stavros.konstantinides@unimedizin-mainz.de

Affiliations:
Olivier Sanchez, Université Paris Descartes, Sorbonne Paris Cité, and INSERM UMR S 1140, Paris, FRANCE, Université Paris Descartes, Sorbonne Paris Cité, and INSERM UMR S 1140, Paris, FRANCE, Paris, France
Anais Charles-Nelson, Hopital European Georges Pompidou, Hopital European Georges Pompidou, Paris, France
Walter Ageno, University of Insubria, Medicine and Surgery, Varese, Italy
G. Meyer, Hopital European Georges Pompidou, Hopital European Georges Pompidou, Paris, France
Reduced-dose intravenous thrombolysis for acute intermediate high-risk pulmonary embolism

Rationale and design of the Pulmonary Embolism International THrombolysis (PEITHO)-3 trial

Olivier Sanchez,1,2,3,4 Anaïs Charles-Nelson,5,6 Walter Ageno,7 Stefano Barco,8,9 Harald Binder,10 Gilles Chatellier,3,5,6 Daniel Duerschmied,11 Klaus Empen,12 Melanie Ferreira,13 Philippe Girard,4,14 Menno V. Huisman,15 David Jiménez,16 Sandrine Katsahian,3,5,6,17 Matija Kozak,18 Mareike Lankeit,8,19,20 Nicolas Meneveau,4,21,22 Piotr Pruszczzyk,23 Antoniu Petris,24 Marc Righini,25 Stephan Rosenkranz,26 Sebastian Schellong,27 Branislav Stefanovic,28 Peter Verhamme,29 Kerstin de Wit,30 Eric Vicaut,31 Andreas Zirlik,32 Stavros V. Konstantinides,8,33 and Guy Meyer,1,3,4† for the PEITHO-3 Investigators

1. AP-HP, hôpital européen Georges-Pompidou, Service de Pneumologie et de Soins Intensifs, APHP, Centre - Université de Paris, Paris, France
2. INSERM UMR S 1140 Innovative therapies in hemostasis; Paris, France
3. Université de Paris, Paris, France
4. FCRIN INNOVTE, St-Etienne, France
5. AP-HP, hôpital européen Georges-Pompidou, Unité de Recherche Clinique, APHP, Centre, Paris, France.
6. INSERM, Centre d’Investigation Clinique 1418 (CIC1418) Épidémiologie Clinique, Paris, France
7. Department of Medicine and Surgery, University of Insubria, Varese, Italy
8. Center for Thrombosis and Hemostasis (CTH), University Medical Center Mainz, Germany
9. Clinic of Angiology, University Hospital Zurich, Zurich, Switzerland
10. Institute of Medical Biometry and Statistics, Faculty of Medicine and Medical Center, University of Freiburg, Freiburg im Breisgau, Germany
11. Department of Cardiology and Angiology I, University Heart Center Freiburg - Bad Krozingen, Faculty of Medicine, University of Freiburg, Germany
12. Department of Internal Medicine, Städtisches Klinikum Dessau, Germany
13. Hospital Garcia de Orta, Internal Medicine Department, Almada, Portugal
14. Département Thoracique, Institut Mutualiste Montsouris, Paris, France
15. Department of Thrombosis and Hemostasis, Leiden University Medical Center, Leiden; Dutch Thrombosis Network, The Netherlands
16. Department of Respiratory Diseases, Ramon y Cajal Hospital, Universidad de Alcalá (IRYCYIS), CIBER Enfermedades Respiratorias (CIBERES), Madrid, Spain
17. INSERM UMR_S 1138 équipe 22, Centre de Recherche des Cordeliers, Paris, France
18. Department of Vascular Diseases, University Medical Center, Ljubljana, Slovenia
19. Department of Internal Medicine, Vascular Medicine and Haemostaseology, Vivantes Klinikum im Friedrichshain, Berlin, Germany
20. Clinic of Cardiology and Pneumology, University Medical Center Goettingen, Goettingen, Germany
21. Department of Cardiology, University Hospital Jean Minjoz, Besançon, France
22. EA3920, University of Burgundy Franche-Comté, Besançon, France
23. Department of Internal Medicine & Cardiology, Medical University of Warsaw, Warsaw, Poland
24. Grigore T. Popa University of Medicine and Pharmacy Iasi, Cardiology Clinic, “St. Spiridon” County Clinical Emergency Hospital, Iasi, Romania
25. Division of Angiology and Haemostasis, Geneva University Hospital, University of Geneva, Geneva, Switzerland
26. Department III of Internal Medicine and Cologne Cardiovascular Research Center (CCRC), Cologne University Heart Center, Cologne, Germany
27. Department of Internal Medicine 2, Municipal Hospital Dresden, Germany
28. Cardiology Clinic, Emergency Center, University Clinical Center of Serbia, School of Medicine University Belgrade, Belgrade, Serbia
29. Vascular Medicine and Haemostasis, Department of Cardiovascular Medicine, University Hospitals Leuven, Leuven, Belgium
30. Department of Medicine, McMaster University, Hamilton, Ontario, Canada
31. AP-HP, Unité de Recherche Clinique St-Louis-Lariboisière, Université Denis Diderot, 75009 Paris, France
32. Division of Cardiology, Department of Internal Medicine, Medical University of Graz, Austria
33. Department of Cardiology, Democritus University of Thrace, Alexandroupolis, Greece.

* Corresponding author.

† Deceased.
Correspondence to

Stavros V. Konstantinides, MD

Center for Thrombosis and Hemostasis, University Medical Center of the Johannes Gutenberg University Mainz

Langenbeckstrasse 1, Building 403, 55131 Mainz, Germany

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

Abstract

Intermediate high-risk pulmonary embolism (PE) is characterised by right ventricular (RV) dysfunction and elevated circulating cardiac troponin levels despite apparent haemodynamic stability at presentation. In these patients, full-dose systemic thrombolysis reduced the risk of haemodynamic decompensation or death but increased the risk of life-threatening bleeding. Reduced-dose thrombolysis may be capable of improving safety while maintaining reperfusion efficacy. The Pulmonary Embolism International Trial (PEITHO)-3 study (ClinicalTrials.gov Identifier: NCT04430569) is a randomised, placebo-controlled, double-blind, multicentre, multinational trial with long-term follow-up. We will compare the efficacy and safety of a reduced-dose alteplase regimen with standard heparin anticoagulation. Patients with intermediate high-risk PE will also fulfil at least one clinical criterion of severity: systolic blood pressure ≤ 110 mmHg, respiratory rate >20 breaths/min, or history of heart failure. The primary efficacy outcome is the composite of all-cause death, haemodynamic decompensation or PE recurrence within 30 days of randomisation. Key secondary outcomes, to be included in hierarchical analysis, are fatal or GUSTO severe or life-threatening bleeding; net clinical benefit (primary efficacy outcome plus severe or life-threatening bleeding); and all-cause death, all within 30 days. All outcomes will be adjudicated by an independent committee. Further outcomes include PE-related death, haemodynamic decompensation, or stroke within 30 days; dyspnoea, functional limitation or RV dysfunction at 6 months and 2 years; and utilisation of healthcare resources within 30 days and 2 years.
The study is planned to enrol 650 patients. The results are expected to have a major impact on risk-adjusted treatment of acute PE and inform guideline recommendations.

Keywords
Pulmonary embolism; intermediate-high-risk; reduced-dose thrombolysis; prognosis; randomised trial

Background and rationale

**Advanced risk stratification of pulmonary embolism**

Assessment of the clinical severity of acute pulmonary embolism (PE) is based on the estimated risk of early (in-hospital or 30-day) mortality. High-risk PE, defined by the presence of haemodynamic instability at presentation, is a life-threatening condition in which prompt reperfusion treatment is needed to increase the chances of survival (1). However, the vast majority of patients with acute PE do not present with overt haemodynamic compromise (2, 3). Within this large, apparently stable group, prediction scores derived from clinical variables permit further risk stratification. For example, a Pulmonary Embolism Severity Index (PESI) risk class of I or II, a simplified PESI (sPESI) of 0, or the absence of Hestia criteria, all have a high negative predictive value for ruling out an early adverse outcome (low-risk PE) (4-6). On the other hand, haemodynamically stable patients who do not fulfil these criteria, belong to the intermediate-risk category. Numerous studies could show that, in intermediate-risk PE, imaging parameters and laboratory biomarkers possess additive prognostic value, complementing each other (7, 8) as well as baseline clinical parameters (9, 10). Accordingly, patients are classified into the intermediate-high-risk category if they have evidence of right ventricular (RV) dysfunction on echocardiography or computed tomography pulmonary angiography (CTPA), in combination with elevated plasma cardiac troponin levels (1).
Unfavourable risk-to-benefit profile of full-dose systemic thrombolysis

The superior haemodynamic effects and faster onset of action (compared to heparin anticoagulation alone) of systemic thrombolytic (fibrinolytic) treatment have been established, and its use is recommended in the emergency setting of acute high-risk PE (11). However, it has remained controversial for decades whether systemic thrombolysis might also improve the clinical outcome of haemodynamically stable patients (12), particularly those with intermediate-high-risk PE. Following first promising data in the early 2000’s (13), the Pulmonary Embolism International THrOmbolysis (PEITHO) trial confirmed the clinical efficacy of full-dose thrombolysis (using tenecteplase) in this risk group (14). That study showed a significant reduction (odds ratio 0.44; 95% confidence interval 0.23 to 0.87) in the clinical composite of death from any cause or haemodynamic collapse within 7 days after randomisation. However, this benefit came at a high price: in PEITHO, stroke occurred in 12 patients (2.4%) randomised to the thrombolysis arm (odds ratio 12.10 [confidence interval 1.57–93.39] versus heparin alone), being haemorrhagic in 10 cases (14). Considering the high risk of intracranial or other life-threatening bleeding events, which was subsequently confirmed by meta-analyses (15), current guidelines do not recommend systemic thrombolysis as first-line treatment in intermediate-high-risk PE (1, 16). Lastly, the PEITHO trial had not been designed to answer the question whether early systemic thrombolysis may prevent the development of late sequelae thromboembolic pulmonary hypertension (CTEPH) after intermediate-risk PE (17).

Reduced-dose thrombolysis might improve safety while maintaining efficacy
In patients with acute PE, three small randomised trials compared a reduced dose of alteplase with the conventional 100 mg regimen (received by a total of 162 and 99 patients, respectively, in the pooled study population) (18-20). The reduced-dosage regimens varied amongst the studies: in one of them, 50 mg of alteplase were infused over two hours (20), whereas in the two other studies, a weight-adapted dose of 0.6mg/kg, up to a total of 50 mg, was given over 15 minutes (18, 19). There were no significant differences in efficacy between the reduced-dose and the standard-dose regimen, as judged by changes in pulmonary artery pressure, cardiac index or residual vascular obstruction at 24 hours, or the incidence of PE recurrence (18-20). In addition, and importantly, a meta-analysis suggested that a reduced dosage may be associated with reduction in the risk of major bleeding (OR 0.33; 95% CI 0.12 to 0.91) (21).

The efficacy of the reduced-dose regimen is further supported by two studies comparing alteplase, at the dose of 0.6 mg/kg (22) or 0.5 mg/kg (maximum of 50 mg) (23), with heparin alone in patients with acute PE. A greater improvement of vascular obstruction was observed with alteplase in the former study (22), whereas the latter reported a reduction in the combined endpoint of persistent pulmonary hypertension or recurrent PE over the long term (23).

Taken together, reperfusion treatment employing systemic thrombolysis exerts favourable haemodynamic effects, and thrombolytic regimens may be capable of improving the prognosis of patients with acute intermediate-high-risk PE. Nevertheless, the bleeding risk of full-dose intravenous thrombolysis is too high to justify its use as first-line therapy in this risk category. Today, reduced-dose regimens are becoming increasingly popular in clinical practice worldwide, despite the explicit warning by scientific societies and guidelines that the available evidence is not (yet) sufficient to support their efficacy and safety. This potentially
dangerous gap in knowledge must therefore be closed as soon as possible. An adequately powered randomised placebo-controlled clinical trial, focusing on clinically relevant efficacy and safety outcomes, is the only way to determine the benefits versus risks of reduced-dose thrombolysis in acute PE.

**Study Overview**

**Study design and objectives**

The Pulmonary Embolism International Trial (PEITHO)-3 study (ClinicalTrials.gov Identifier: NCT04430569) is a randomised, placebo-controlled, double-blind, multicentre, multinational trial with long-term follow-up. The primary objective is to assess the efficacy (defined as the ability to prevent death, haemodynamic decompensation or PE recurrence) of reduced-dose intravenous thrombolytic therapy with alteplase, against the background of standard care (heparin anticoagulation), in patients with acute intermediate-high-risk PE, 30 days after randomisation. The secondary objectives are to assess (i) the safety, net clinical benefit and impact of reduced-dose thrombolytic therapy on overall mortality in patients with intermediate-high-risk PE; as well as (ii) the effect on long-term mortality, functional impairment, residual right ventricular (RV) dysfunction and the incidence of chronic thromboembolic pulmonary hypertension.

**Patient population and eligibility**

The key inclusion and exclusion criteria are summarised in Table 1. In this context, it is important to explain the rationale for the advanced definition of intermediate-high-risk PE used in the present study. In fact, both past (24) and current (1) guidelines defined intermediate-high-risk PE based ‘exclusively’ on imaging (evidence of RV dysfunction) and
biochemical (circulating levels of elevated laboratory biomarkers) criteria. Although these modalities generally possess high sensitivity, validated in several cohort studies and a randomized trial (reviewed in (24)), their prognostic specificity as standalone tools may be too low to predict threatening cardiorespiratory decompensation (13, 14). They may thus not suffice to identify the patients closer to the ‘upper border’ of the intermediate-risk zone, who are expected to obtain the largest possible clinical benefit from early thrombolytic treatment. To address this limitation, we sought to identify additional baseline predictors of early life-threatening events in the population of the large PEITHO trial, in which overall early mortality was low (14). We found that initial systolic blood pressure ≤110 mm Hg, respiratory rate >20 breaths/min (or, as a surrogate, an arterial oxygen saturation <90% on room air) at presentation, or a history of chronic heart failure, predicted, alone or in combination, death from any cause, haemodynamic decompensation, or objectively confirmed recurrent PE within 30 days of randomisation. The presence of at least one of these criteria thus defined an enriched patient population (53% of the patients enrolled in that study), in which the incidence of the composite clinical outcome was 11.2% in the control group as opposed to as low as 3.7% in the thrombolysis group (25). This group was defined as the target population in the present trial, with the aim to obtain an optimised benefit-to-risk ratio from early thrombolysis.

Treatment regimens

The diagram shown in Figure 1 depicts the study flow and the allowed time intervals between consecutive trial procedures and visits. An overview of the tests to be performed and parameters to be collected upon enrolment and at the follow-up visits is provided in Table 2. Patients fulfilling all the inclusion criteria and none of the exclusion criteria (Table 1) will be
randomised into the experimental or the reference treatment arm. Patients will receive alteplase (if randomised into the experimental arm) or placebo (if randomised into the reference arm), to be given within 30 minutes of randomisation as a 15-minute intravenous infusion; the dosage will be 0.6 mg/kg, with the total dose not exceeding 50 mg. If the experimental treatment cannot be given within 30 minutes of randomisation, the patient will be analysed according to the intention-to-treat (ITT) principle.

Both treatment arms will receive anticoagulant treatment using low molecular weight heparin (LMWH) or any other type of heparin approved for the treatment of acute PE, according to local practice. If anticoagulation has been initiated using unfractionated heparin (UFH) and a switch to LMWH is envisaged after randomisation, the UFH infusion will be stopped at the time of randomisation and the first LMWH subcutaneous injection will be given within 3 hours of the end of UFH infusion. If anticoagulation has been initiated with LMWH as a twice-daily regimen, the next LMWH injection will be given 12 hours after the previous one. If fondaparinux, or LMWH as once-daily injection, has been given before randomisation, the next injection will be given 24 hours after the previous one. Due to the longer half-life of fondaparinux as compared to LMWH, a switch from that drug to LMWH (or UFH) is generally recommended over the first 48 hours. The use of direct oral anticoagulants (apixaban, betrixaban, dabigatran, edoxaban, rivaroxaban) and vitamin K antagonists will not be allowed within the first 48 hours after randomisation. All approved anticoagulant regimens will be allowed 48 hours after randomisation.

As recommended by current guidelines (1), all patients will receive therapeutic anticoagulation for at least 3 months. After the first 3 months, discontinuation or extension of the anticoagulant treatment will be at the discretion of the treating physician.
Outcomes

The efficacy and safety outcomes of the PEITHO-3 trial are summarised in Table 3. The primary efficacy outcome is the clinical composite of death from any cause, haemodynamic decompensation, or objectively confirmed recurrent PE within 30 days of randomisation. When defining the primary efficacy outcome, we took into account that early mortality is relatively low in patients with intermediate-risk PE receiving contemporary, state-of-the-art supportive care such as that provided in the setting of a randomised controlled trial (14). Thus, the sample size required for a trial aiming to show a ‘pure mortality benefit’ from thrombolysis would be prohibitively large. On the other hand, other relevant adverse outcomes, notably early haemodynamic collapse or decompensation, are more frequent in patients with intermediate-high-risk PE treated with anticoagulation, and they represent a valid component of overall clinical efficacy (14). In addition, by including all-cause (and not only PE-related) mortality in the composite primary outcome, we aim to ensure that, if superiority of reduced-dose thrombolysis over heparin alone is shown in the present study, it will have accounted for any thrombolysis-related fatal bleeding events. In the same context, the GUSTO definition of bleeding was chosen because it directly reflects the possible impact of bleeding complications on death or haemodynamic compromise/decompensation. Consequently, possible opposing effects of reduced-dose thrombolysis on efficacy and safety (such as prevention of PE-related death or decompensation at the cost of excessive fatal bleeding or haemorrhage-induced haemodynamic compromise), will both be taken into account in the primary clinical outcome. PEITHO-3 thus aims to provide a clear message to physicians regarding the overall clinical benefit of thrombolysis in patients with intermediate-high-risk PE rigorously defined by clinical, imaging, and biochemical criteria (25).

All primary and secondary outcomes will be adjudicated by an independent Clinical Events Committee.
Sample size calculation and statistical analysis plan

To calculate the sample size for the present study, we performed a *post hoc* analysis of the population of the PEITHO trial, the largest (full-dose) thrombolysis trial with clinical outcomes conducted to this date (25). This analysis helped to estimate the incidence of the primary efficacy outcome (death from any cause or haemodynamic collapse or objectively confirmed recurrent PE within 30 days of randomisation) as defined in the present study, PEITHO-3. More specifically, in the subgroup of patients included in PEITHO, who would have fulfilled the ‘enriched’ inclusion criteria of the present study, the rates were 11.2% and 3.7% in the control and (standard-dose) thrombolysis group respectively (relative risk reduction 67%). For estimating efficacy in PEITHO-3, we conservatively assumed a 55% relative risk reduction, corresponding to a 5.0% expected incidence in the reduced-dose thrombolysis group. Taking into account a planned interim analysis (see below) with the Lan and De Mets methods, we calculated that a number of n = 305 patients per treatment arm will allow a 80% power to show the expected relative risk reduction. The nominal alpha at final analysis will be set at 0.049 for the primary analysis according to the Lan-DeMets (26) monitoring boundary with an O’Brien-Fleming stopping rule, provided that no sample size modification will be needed; otherwise, the final significance level will be adjusted accordingly (27). Accounting for possible early dropouts, it is planned to enroll and randomize a total of 650 patients; the final size of the trial population will depend on the results of the interim analysis as explained below.

The primary analysis on the primary outcome will be carried out in the ITT population applying a logistic regression analysis to account for stratification factors (28, 29); the group variables age (> 75 years versus ≤ 75 years) and country will be included in the model.
Results will be presented as odds ratio and associated 95% confidence interval. In addition, two exploratory subgroup analyses will be performed for the primary outcome in the ITT population, according to the following variables: (i) > 75 years vs ≤ 75 years; and (ii) presence of ≥ 2 clinical criteria of PE severity at presentation (among the following inclusion criteria: systolic blood pressure ≤ 110 mmHg; respiratory rate > 20/min or, as a surrogate, arterial oxygen saturation < 90% on room air; history of chronic heart failure) versus one criterion. An interaction term between subgroup variable and the treatment variable will be included in the logistic model, to assess whether the interaction is significantly associated to the primary outcome. Results will be presented as a Forest plot.

In addition to improving early clinical outcomes, utilisation of healthcare resources will be recorded for each patient at two time points (30 days and 180 days) post randomisation. For outpatient visits and periods of hospitalisation, country-specific standardised unit costs will be applied, representing costs from a societal perspective. In addition, PE-related resource utilisation will be recorded.

_Safety monitoring, interim analysis and stopping rules_

An independent data and safety monitoring board (DSMB) will be assessing the safety of the study. The DSMB will periodically review the serious adverse events (SAEs) with a special attention to the major bleeding events and will communicate its recommendations to the sponsor about stopping or continuing the trial. As specified in a dedicated charter, the frequency of DSMB meetings will be scheduled every 20 SAEs. Additional meetings may be arranged, especially if the SAE numbers are higher than anticipated. An independent statistician will conduct a formal efficacy interim analysis and sample size re-estimation based on the adjudicated primary efficacy outcome of 50% of the expected total number of
patients. The superiority of the experimental treatment versus control arm will be assessed by chi-square test. To provide an overall two-sided significance level close to 0.05 for the study, the interim analysis will have a Lan-DeMets monitoring boundary with an O'Brien-Fleming stopping rule (26). The study will stop for efficacy if the p value provided by the chi-square test is $< 0.003$. The study will stop for futility if the conditional probability (based on the observed treatment effect) of rejecting the null hypothesis is $< 0.5$.

**Implications of PEITHO-3**

It has been almost 18 years since the first PEITHO trial was launched. The PEITHO investigators set out to resolve a long-lasting controversy concerning the efficacy versus safety of reperfusion treatment for patients with acute PE presenting with findings of acute RV pressure overload and dysfunction despite apparently normal systemic blood pressures (30, 31). PEITHO helped to advance the definition of intermediate-risk PE, and it showed that patients belonging to the intermediate-high-risk class may clinically benefit from systemic thrombolysis as first-line treatment. However, that trial also showed that the bleeding risks of full-dose intravenous thrombolysis predominate over its clinical and haemodynamic effects (14). In view of these results, the focus of the debate has shifted towards identifying safer reperfusion modalities. Percutaneous catheter-directed treatment of acute PE, aiming a mechanical thrombus removal with or without local thrombolysis, has shown promising effects on surrogate imaging or haemodynamic parameters (32-35). However, for the majority of countries and hospitals around the world, intravenous thrombolysis is expected to remain a more affordable and more feasible option in terms of required expertise, infrastructure and resources. The present randomised controlled trial will address a large unmet need by testing the hypothesis that reduced-dose systemic thrombolysis may improve the prognosis of
patients with acute intermediate-high-risk PE at an acceptably low risk of major bleeding complications. In this context it is further anticipated, as also suggested by the results of meta-analyses (15, 36), that the use of alteplase in the present trial will be associated with a lower risk of intracranial haemorrhage and other major bleeding compared to tenecteplase used in PEITHO (14). If the hypothesis of PEITHO-3 is confirmed, international clinical practice guidelines will most likely revisit their recommendations by including reperfusion and particularly reduced-dose systemic thrombolysis as first-line treatment in this risk class. If the hypothesis is rejected, catheter-directed treatment may become the only option for improving the prognosis of patients with intermediate-high-risk PE (37), provided that it can demonstrate clinical efficacy and safety in future state-of-the-art randomised controlled trials. In any case, the results of the present trial are expected to have a major impact on future risk-adjusted treatment strategies for patients with acute PE.

**Study committees and investigators**

**Scientific steering committee**

Olivier Sanchez, Paris, France; Stavros Konstantinides, Mainz, Germany; Walter Ageno, Varese, Italy; Melanie Ferreira, Almada, Portugal; Menno V. Huisman, Leiden, The Netherlands; David Jiménez, Madrid, Spain; Sandrine Katsahian, Paris, France; Matija Kozak, Ljubljana, Slovenia; Mareike Lankeit, Berlin, Germany; Nicolas Meneveau, Besançon, France; Piotr Pruszczyk, Warsaw, Poland; Antoniu Petris, Iasi, Romania; Marc Righini, Geneva, Switzerland; Branislav Stefanovic, Serbia; Peter Verhamme, Leuven, Belgium; Kerstin de Wit, Hamilton, Ontario, Canada; Andreas Zirlik, Graz, Austria.

**Executive committee:**
Olivier Sanchez, Paris, France; Stavros Konstantinides, Mainz, Germany; Yvann Frigout, Paris, France; Aurélie Guimfack, Paris, France; Dorothea Becker, Mainz, Germany; Nadine Martin, Mainz, Germany; Louise Goedhart (Aixial, Boulogne-Billancourt, France; contract research organisation).

**Trial statisticians:**
Anaïs Charles-Nelson, Sandrine Katsahian, Eric Vicaut, Paris, France; Harald Binder, Freiburg, Germany.

**Data safety monitoring board (DSMB):**
Jean-Philippe Collet, Paris, France; Drahomir Aujesky, Bern, Switzerland; Silvy Laporte, Saint Etienne, France.

**Clinical events adjudication committee:**
Joseph Emmerich, Paris, France; Cécile Tromeur, Brest, France; Stefano Barco, Zurich, Switzerland.

**Acknowledgements**

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

The authors dedicate this manuscript to the memory of Professor Guy Meyer who died in December 2020. Guy Meyer was one of the main inspirers of the PEITHO trials and founders of the PEITHO investigator network; he worked hard on finalizing the PEITHO-3 protocol until the last days of his life. Beyond being a skilled clinician and academic researcher, he was a unique motivator and fostered the career of numerous talented physician-scientists.
Financial support

PEITHO-3 is an independent, investigator-initiated trial. The study is being supported by public funding, specifically by grants from the French Ministry of Health (PHRCN-16-0580), the German Research Foundation (Deutsche Forschungsgemeinschaft; KO 1939/3-1), the Canadian Institutes of Health Research and the Spanish Ministry of Science and Innovation. It is also supported by Life Sciences Research Partners (D. Collen Research Foundation), Belgium. In addition, the sponsor, Assistance Publique – Hôpitaux de Paris, has obtained the study drug and a grant from the market authorisation holder of alteplase, Boehringer Ingelheim. The authors are solely responsible for the design and conduct of the trial, for all study analyses, and for the drafting and editing of reports and publications and their final contents.

Authors’ disclosures

O.S. has received institutional research grants from Bayer, Leo Pharma, Bristol-Myers Squibb, Merck Sharp and Dome, Daiichi-Sankyo, Boehringer Ingelheim and Sanofi and personal consultancy/speaker fees from Bayer, Bristol-Myers Squibb, Pfizer, Boston scientifics, Merck Sharp and Dome, Boehringer Ingelheim, Sanofi and Chiesi. S.B. has received congress and travel payments from Daiichi-Sankyo and Bayer AG, honoraria from BTG Pharmaceuticals, Boston Scientific, Bayer HealthCare and LeoPharma, and institutional grants from Sanofi, outside the submitted work. W.A. reports research support from Bayer; activity in advisory boards for Bayer, Boehringer Ingelheim, Daiichi Sankyo, Portola, Janssen, Aspen, Sanofi. D.D. has received speaker’s honoraria from Bayer Vital, Daiichi-Sankyo, Pfizer/ Bristol-Myers Squibb and consulting fees from Bayer Vital and Daiichi-Sankyo. In addition, D.D. is a member of SFB1425, funded by the Deutsche
Forschungsgemeinschaft (DFG, German Research Foundation #422681845). K.E. reports lecture fees by AstraZeneca, Bayer Vital, Berlin Chemie, Boehringer Ingelheim and Novartis, and consulting fees by Bayer Vital, Boehringer Ingelheim, Novartis and Novo Nordisk. M.F. reports lecture fees and travel grants from Bayer, Bristol Myers Squibb, Pfizer, and Travel grants from Daiichi-Sankyo and Leo Pharma. M.V.H. reports grants from ZonMW Dutch Healthcare Fund, and grants and personal fees to the hospital from Boehringer Ingelheim, Bristol-Myers Squibb/Pfizer, Bayer Health Care, Aspen, Daiichi-Sankyo, all outside the submitted work. D.J. has served as an advisor or consultant for Bayer HealthCare Pharmaceuticals, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Leo Pharma, Pfizer, ROVI and Sanofi; served as a speaker or a member of a speakers’ bureau for Bayer HealthCare Pharmaceuticals, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Leo Pharma, ROVI and Sanofi; received grants for clinical research from Daiichi Sankyo, Sanofi and ROVI. M.K. reports speaker fees from Pfizer, Boehringer Ingelheim and Bayer AG outside the submitted work. M.L. reports consultant and speaker fees from Actelion, Bayer, Thermo Fisher Scientific, Daiichi-Sankyo, MSD and Bristol-Myers Squibb-Pfizer and project funding from Thermo Fisher Scientific. N.M. reports consulting fees, speaker fees and project funding from Bayer AG and Bristol-Myers Squibb/Pfizer, speaker fees from AstraZeneca and Boehringer Ingelheim, and consulting fees from Abbott and Terumo. A.P. reports speaker fees from S.C. Pfizer Romania SRL, Servier Pharma SRL, Novartis Pharma Services Romania SRL, Bayer SRL, and SC Sanience SRL. S.R. received honoraria for lectures and/or consultancy from Abbott, Acceleron, Actelion, Arena, Bayer, BMS, Ferrer, Janssen, MSD, Novartis, Pfizer, United Therapeutics, and Vifor, and institutional research grants from Actelion, AstraZeneca, Bayer, Janssen, and Novartis. S.S. has received consulting fees and speaker fees from Aspen and Boehringer Ingelheim, speaker fees from Bayer AG and Daiichi-Sankyo, and project funding and speaker fees from Pfizer/ Bristol-Myers Squibb.
P.V. received honoraria for lectures and/or consultancy from Anthos Therapeutics, Bayer, Boehringer, Daiichi-Sankyo, BMS and Pfizer and research support from Bayer, Daiichi-Sankyo, BMS and Pfizer. S.K. reports institutional research grants and personal consultancy/speaker fees from Actelion/Janssen, Bayer AG, Daiichi-Sankyo and Boston Scientific, institutional research grants from Boehringer Ingelheim and Servier, and personal consultancy/speaker fees from Bristol-Myers Squibb/Pfizer and Novartis. All other authors report no conflict of interest.

References


**Figure 1. Overview of design of the Pulmonary Embolism International THrombolysis (PEITHO)-3 trial.**

AEs = adverse events; PE = pulmonary embolism, RV = right ventricular; i.v. = intravenously; V = visit.

**Table 1. Key inclusion and exclusion criteria**

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Age 18 years or older</td>
<td>1) High-risk PE with haemodynamic instability (1)</td>
</tr>
<tr>
<td>2) Objectively confirmed acute PE with first symptoms ≤ 2 weeks before randomization, ≥ 1 of the following criteria required:</td>
<td>2) Active bleeding</td>
</tr>
<tr>
<td>a) ≥ 1 segmental ventilation-perfusion mismatch on lung scan</td>
<td>3) History of non-traumatic intracranial bleeding</td>
</tr>
<tr>
<td>b) CTPA/pulmonary angiography showing filling defect or abrupt obstruction of a segmental/more proximal pulmonary artery</td>
<td>4) Acute ischaemic stroke or transient ischaemic attack in the past 6 months</td>
</tr>
<tr>
<td>3) Elevated risk of early death or</td>
<td>5) Neurosurgery or eye surgery; abdominal, cardiac, thoracic or vascular surgery; or orthopaedic surgery or trauma, in the past 3 weeks</td>
</tr>
<tr>
<td></td>
<td>6) Known central nervous system neoplasm or metastasis</td>
</tr>
</tbody>
</table>
haemodynamic collapse, indicated by ≥ 1 of the following criteria:

a) SBP ≤ 110 mm Hg over ≥ 15 minutes

b) temporary need for fluid resuscitation and/or treatment with low dose catecholamines because of arterial hypotension at presentation, provided that the patient could be stabilised within 2 hours of admission and maintains SBP of ≥ 90 mmHg and adequate organ perfusion without catecholamine infusion

c) respiratory rate > 20 per minute or oxygen saturation on pulse oximetry (SpO₂) < 90% or partial arterial oxygen pressure < 60 mm Hg at rest while breathing room air

d) history of chronic heart failure, defined as previous diagnosis of heart failure with reduced, moderately reduced or preserved ejection fraction, or treatment for heart failure at any time during the past 12 months;

4) RV dysfunction, indicated by RV/LV diameter ratio > 1.0 on echocardiography (apical four-chamber or subcostal four-chamber view) or on CTPA (transverse plane);

5) Serum troponin I or T concentration above the upper limit of local normal using a high-sensitive assay

6) Signed informed consent

7) Platelet count < 100 x 10⁹/L
8) INR > 1.4
9) Administration of thrombolytic agents in the preceding 4 days
10) Antiplatelet agents other than ASA ≤ 100 mg once daily; clopidogrel 75 mg once daily or a single loading dose of ASA or clopidogrel.
11) Any direct oral anticoagulant within 12 hours of randomisation
12) Known significant bleeding risk according to investigator’s judgement
13) Vena cava filter insertion in the preceding 4 days
14) Current participation in another clinical trial
15) Previous enrolment in this study
16) Known hypersensitivity to alteplase, gentamicin, any of the excipients of the trial drug, or low-molecular weight heparin
17) Known severe hepatic disease, portal hypertension (with oesophageal varices) or active hepatitis
18) Peptic ulcer diagnosed in the past 3 months
19) Pregnancy or parturition within the previous 30 days, or current breastfeeding
20) Women of childbearing potential who do not have a negative pregnancy test and do not use an effective method of birth control
21) Any other condition that the investigator feels would place the patient at increased risk upon start of the investigational treatment
22) Life expectancy < 6 months or inability to participate at 6-month follow-up visit

Note: Patients who test positive for SARS-CoV-2 may be randomised, if the investigator judges that the acute PE (and not the infection with SARS-CoV-2) is responsible
for the patient’s clinical, imaging and hemodynamic parameters meeting the trial’s inclusion criteria.

ASA = acetylsalicylic acid; CTPA = computed tomography pulmonary angiography; INR = international normalised ratio; LV = left ventricular; RV = right ventricular; PE = pulmonary embolism; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SBP = systolic blood pressure.

Table 2. Trial visit plan and data collection schedule

<table>
<thead>
<tr>
<th>Day (D)0 Inclusion visit</th>
<th>D30 ± 3 days after randomisation</th>
<th>Month (M)6 ± 15 days after randomisation</th>
<th>M24 ± 30 days after randomisation / end of study</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>In hospital</strong></td>
<td><strong>Outpatient follow-up</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verification of inclusion and exclusion criteria</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Signed informed consent</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Randomisation</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical interview - demographics - medical history - concomitant antiplatelet and anticoagulant treatment</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical examination¹</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Troponin I and/or T test</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Further laboratory tests²</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study objective</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------------------------------------------</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>RV/LV diastolic diameter ratio</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>sPESI</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study drug administration</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Echocardiography</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Pregnancy test (for women of childbearing age)</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Documentation of (Serious) Adverse events(^3)</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Utilisation of health care resources</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

1 Including body weight, blood pressure, heart rate, arterial oxygen saturation, respiratory rate, clinical signs of right heart failure.

2 Creatinine, international normalised ratio, haemoglobin (one day after randomisation), platelet count (before and after randomisation).

3 Patients will be continuously monitored for early detection of haemodynamic instability or major bleeding.

LV = left ventricular; RV = right ventricular; sPESI = simplified Pulmonary Embolism Severity Index.

Table 3. Primary and secondary outcomes

<table>
<thead>
<tr>
<th>Primary outcome</th>
<th>Clinical composite of death from any cause or haemodynamic decompensation or objectively confirmed recurrent PE within 30 days of randomisation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary</td>
<td>To be included in a hierarchical analysis:</td>
</tr>
</tbody>
</table>
| Outcomes                                                                 | 1) Fatal or GUSTO severe or life-threatening bleeding, defined as either intracranial bleeding or bleeding leading to significant haemodynamic compromise requiring treatment (38), within 30 days  
|                                                                           | 2) Net clinical benefit, defined as the composite of the primary efficacy outcome and GUSTO severe or life-threatening bleeding, within 30 days  
|                                                                           | 3) All-cause mortality within 30 days  
|                                                                           | Not to be included in the hierarchical analysis:  
|                                                                           | 4) PE-related death within 30 days of randomisation  
|                                                                           | 5) Haemodynamic decompensation within 30 days  
|                                                                           | 6) Recurrent PE within 30 days  
|                                                                           | 7) Need for rescue thrombolysis, catheter-directed treatment or surgical embolectomy within 30 days  
|                                                                           | 8) Ischaemic or haemorrhagic stroke within 30 days  
|                                                                           | 9) Serious adverse events within 30 days  
|                                                                           | 10) Utilisation of health care resources within 30 days and 6 months  
|                                                                           | 11) All-cause mortality at 2 years  
|                                                                           | 12) Persisting dyspnoea assessed by the Medical Research Council (MRC) scale at 6 months and at 2 years  
|                                                                           | 13) Functional outcome, using the post-VTE functional scale (39), at 6 months and at 2 years  
|                                                                           | 14) Persistent RV dysfunction, defined as an intermediate or high probability of pulmonary hypertension on echocardiography according to ESC criteria (40), at 6 months and 2 years  
|                                                                           | 15) Confirmed chronic thromboembolic pulmonary hypertension according to ESC criteria (40) at 2 years  
| ESC = European Society of Cardiology; GUSTO = Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries; PE = pulmonary embolism; RV = right ventricular; VTE = venous thromboembolism. |
Risk categorization → Clinical parameters, RV dysfunction + Troponin elevation

Informed consent

Placebo 0.6 mg/kg i.v. → 15 min

Alteplase 0.6 mg/kg i.v.

Beginning of PE symptoms

PE diagnosis

Confirmation of intermediate-high risk PE

Enrolment and randomisation

Echocardiography

Treatment start

Treatment end

Primary efficacy endpoint

Clinical examination and AES

Clinical examination

Echocardiography

V1 Day 0 (T₀)

maximum -30 min

maximum -24h

maximum -6h

maximum 30 min

V2 30 ±3 days

V3 180 ±15 days

V4 24 ±1 months

Day -14

Day 0 (T₀)

Figure 1