



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

<sup>1</sup> AP-HP, hôpital européen Georges-Pompidou, Service de Pneumologie et de Soins Intensifs, APHP.Centre - Université de Paris, Paris, France

<sup>2</sup> INSERM UMR S 1140 Innovative Therapies in Hemostasis, Paris, France

<sup>3</sup> Université de Paris, Paris, France

<sup>4</sup> FCRI INNOVTE, St-Etienne, France

<sup>5</sup> AP-HP, hôpital européen Georges-Pompidou, Unité de Recherche Clinique, APHP.Centre, Paris, France

<sup>6</sup> INSERM, Centre d'Investigation Clinique 1418 (CIC1418) Épidémiologie Clinique, Paris, France

<sup>7</sup> Department of Medicine and Surgery, University of Insubria, Varese, Italy

<sup>8</sup> Center for Thrombosis and Hemostasis (CTH), University Medical Center Mainz, Mainz, Germany

<sup>9</sup> Clinic of Angiology, University Hospital Zurich, Zurich, Switzerland

<sup>10</sup> Institute of Medical Biometry and Statistics, Faculty of Medicine and Medical Center, University of Freiburg, Freiburg im Breisgau, Germany

<sup>11</sup> Department of Cardiology and Angiology I, University Heart Center Freiburg - Bad Krozingen, Faculty of Medicine, University of Freiburg, Freiburg, Germany

<sup>12</sup> Department of Internal Medicine, Städtisches Klinikum Dessau, Germany

<sup>13</sup> Internal Medicine Department, Hospital Garcia de Orta, Almada, Portugal

<sup>14</sup> Département Thoracique, Institut Mutualiste Montsouris, Paris, France

Address for correspondence 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).

<sup>15</sup> Department of Thrombosis and Hemostasis, Leiden University Medical Center, Dutch Thrombosis Network, Leiden, The Netherlands

<sup>16</sup> Department of Respiratory Diseases, Ramon y Cajal Hospital, Universidad de Alcalá (IRYCIS), CIBER Enfermedades Respiratorias (CIBERES), Madrid, Spain

<sup>17</sup> INSERM UMR\_S 1138 équipe 22, Centre de Recherche des Cordeliers, Paris, France

<sup>18</sup> Department of Vascular Diseases, University Medical Center, Ljubljana, Slovenia

<sup>19</sup> Department of Internal Medicine, Vascular Medicine and Haemostaseology, Vivantes Klinikum im Friedrichshain, Berlin, Germany

<sup>20</sup> Clinic of Cardiology and Pneumology, University Medical Center Goettingen, Goettingen, Germany

<sup>21</sup> Department of Cardiology, University Hospital Jean Minjoz, Besançon, France

<sup>22</sup> EA3920, University of Burgundy Franche-Comté, Besançon, France

<sup>23</sup> Department of Internal Medicine and Cardiology, Medical University of Warsaw, Warsaw, Poland

<sup>24</sup> Grigore T. Popa University of Medicine and Pharmacy Iasi, Cardiology Clinic, “St. Spiridon” County Clinical Emergency Hospital, Iasi, Romania

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† Deceased.

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Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

<sup>25</sup>Division of Angiology and Haemostasis, Geneva University Hospital, University of Geneva, Geneva, Switzerland

<sup>26</sup>Department III of Internal Medicine and Cologne Cardiovascular Research Center (CCRC), Cologne University Heart Center, Cologne, Germany

<sup>27</sup>Department of Internal Medicine 2, Municipal Hospital Dresden, Dresden, Germany

<sup>28</sup>Cardiology Clinic, Emergency Center, University Clinical Center of Serbia, School of Medicine University Belgrade, Belgrade, Serbia

<sup>29</sup>Vascular Medicine and Haemostasis, Department of Cardiovascular Medicine, University Hospitals Leuven, Leuven, Belgium

<sup>30</sup>Department of Medicine, McMaster University, Hamilton, Ontario, Canada

<sup>31</sup>AP-HP, Unité de Recherche Clinique St-Louis-Lariboisière, Université Denis Diderot, Paris, France

<sup>32</sup>Division of Cardiology, Department of Internal Medicine, Medical University of Graz, Graz, Austria

<sup>33</sup>Department of Cardiology, Democritus University of Thrace, Alexandroupolis, Greece

## Abstract

Intermediate–high-risk pulmonary embolism (PE) is characterized by right ventricular (RV) dysfunction and elevated circulating cardiac troponin levels despite apparent hemodynamic stability at presentation. In these patients, full-dose systemic thrombolysis reduced the risk of hemodynamic 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 Thrombolysis (PEITHO)-3 study (ClinicalTrials.gov Identifier: NCT04430569) is a randomized, placebo-controlled, double-blind, multicenter, 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 fulfill at least one clinical criterion of severity: systolic blood pressure  $\leq 110$  mm Hg, respiratory rate  $>20$  breaths/min, or history of heart failure. The primary efficacy outcome is the composite of all-cause death, hemodynamic decompensation, or PE recurrence within 30 days of randomization. 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, hemodynamic decompensation, or stroke within 30 days; dyspnea, functional limitation, or RV dysfunction at 6 months and 2 years; and utilization of health care resources within 30 days and 2 years. The study is planned to enroll 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
- ▶ randomized 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 hemodynamic instability at presentation, is a life-threatening condition in which prompt reperfusion treatment is needed to increase the chances of survival.<sup>1</sup> However, the vast majority of patients with acute PE do not present with overt hemodynamic compromise.<sup>2,3</sup> 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).<sup>4–6</sup> On the other hand, hemodynamically stable patients who do not fulfill 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<sup>7,8</sup> as well as baseline clinical parameters.<sup>9,10</sup> 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, in combination with elevated plasma cardiac troponin levels.<sup>1</sup>

### Unfavorable Risk-to-benefit Profile of Full-Dose Systemic Thrombolysis

The superior hemodynamic effects and faster onset of action (compared with 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.<sup>11</sup> However, it has remained controversial for decades whether systemic thrombolysis might also improve the clinical outcome of hemodynamically stable patients,<sup>12</sup> particularly those with intermediate–high-risk PE. Following first promising data in the early 2000s,<sup>13</sup> the Pulmonary Embolism International Thrombolysis (PEITHO) trial confirmed the clinical efficacy of full-dose thrombolysis (using tenecteplase) in this risk group.<sup>14</sup> That study showed a significant reduction (odds ratio [OR]: 0.44; 95% confidence interval [CI]: 0.23–0.87) in the clinical composite of death from any cause or hemodynamic collapse within 7 days after randomization. However, this benefit came at a high price: in PEITHO, stroke occurred in 12 patients (2.4%) randomized to the thrombolysis arm (OR: 12.10; 95% CI: 1.57–93.39 vs. heparin alone), being hemorrhagic in 10 cases.<sup>14</sup> Considering the high risk of intracranial or other life-threatening bleeding events, which was subsequently confirmed by meta-analyses,<sup>15</sup> current guidelines do not recommend systemic thrombolysis as first-line treatment in intermediate–high-risk PE.<sup>1,16</sup> 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 (chronic thromboembolic pulmonary hypertension) after intermediate-risk PE.<sup>17</sup>

### Reduced-Dose Thrombolysis Might Improve Safety While Maintaining Efficacy

In patients with acute PE, three small randomized 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).<sup>18–20</sup> The reduced-dosage regimens varied amongst the studies: in one of them, 50 mg of alteplase was infused over 2 hours,<sup>20</sup> whereas in the two other studies, a weight-adapted dose of 0.6 mg/kg, up to a total of 50 mg, was given over 15 minutes.<sup>18,19</sup> 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.<sup>18–20</sup> 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: 0.12–0.91).<sup>21</sup>

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

Taken together, reperfusion treatment employing systemic thrombolysis exerts favorable hemodynamic 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 randomized 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 randomized, placebo-controlled, double-blind, multicenter, multinational trial with long-term follow-up. The primary objective is to assess the efficacy (defined as the ability to prevent death, hemodynamic 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 randomization. The secondary objectives are to assess (1) 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 (2) the effect on long-term mortality, functional impairment, residual RV dysfunction, and the incidence of chronic thromboembolic pulmonary hypertension.

### Patient Population and Eligibility

The key inclusion and exclusion criteria are summarized 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<sup>24</sup> and current<sup>1</sup> 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 Konstantinides et al<sup>24</sup>), their prognostic specificity as standalone tools may be too low to predict threatening cardiorespiratory decompensation.<sup>13,14</sup> 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.<sup>14</sup> We found that initial systolic blood pressure  $\leq 110$  mm Hg, respiratory

**Table 1** Key inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
<ol style="list-style-type: none"> <li>1. Age 18 years or older</li> <li>2. Objectively confirmed acute PE with first symptoms <math>\leq 2</math> weeks before randomization, <math>\geq 1</math> of the following criteria required: <ol style="list-style-type: none"> <li>a. <math>\geq 1</math> segmental ventilation-perfusion mismatch on lung scan</li> <li>b. CTPA/pulmonary angiography showing filling defect or abrupt obstruction of a segmental/more proximal pulmonary artery</li> </ol> </li> <li>3. Elevated risk of early death or hemodynamic collapse, indicated by <math>\geq 1</math> of the following criteria: <ol style="list-style-type: none"> <li>a. SBP <math>\leq 110</math> mm Hg over <math>\geq 15</math> minutes</li> <li>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 stabilized within 2 hours of admission and maintains SBP of <math>\geq 90</math> mm Hg and adequate organ perfusion without catecholamine infusion</li> <li>c. Respiratory rate <math>&gt; 20</math> per minute or oxygen saturation on pulse oximetry (<math>SpO_2</math>) <math>&lt; 90\%</math> or partial arterial oxygen pressure <math>&lt; 60</math> mm Hg at rest while breathing room air</li> <li>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</li> </ol> </li> <li>4. RV dysfunction, indicated by RV/LV diameter ratio <math>&gt; 1.0</math> on echocardiography (apical four-chamber or subcostal four-chamber view) or on CTPA (transverse plane)</li> <li>5. Serum troponin I or T concentration above the upper limit of local normal using a high-sensitive assay</li> <li>6. Signed informed consent</li> </ol> <p>Note: Patients who test positive for SARS-CoV-2 may be randomized, 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.</p>	<ol style="list-style-type: none"> <li>1. High-risk PE with hemodynamic instability<sup>1</sup></li> <li>2. Active bleeding</li> <li>3. History of nontraumatic intracranial bleeding</li> <li>4. Acute ischemic stroke or transient ischemic attack in the past 6 months</li> <li>5. Neurosurgery or eye surgery; abdominal, cardiac, thoracic, or vascular surgery; or orthopaedic surgery or trauma, in the past 3 weeks</li> <li>6. Known central nervous system neoplasm or metastasis</li> <li>7. Platelet count <math>&lt; 100 \times 10^9/L</math></li> <li>8. INR <math>&gt; 1.4</math></li> <li>9. Administration of thrombolytic agents in the preceding 4 days</li> <li>10. Antiplatelet agents other than ASA <math>\leq 100</math> mg once daily; clopidogrel 75 mg once daily or a single loading dose of ASA or clopidogrel</li> <li>11. Any direct oral anticoagulant within 12 hours of randomization</li> <li>12. Known significant bleeding risk according to investigator's judgment</li> <li>13. Vena cava filter insertion in the preceding 4 days</li> <li>14. Current participation in another clinical trial</li> <li>15. Previous enrolment in this study</li> <li>16. Known hypersensitivity to alteplase, gentamicin, any of the excipients of the trial drug, or low-molecular weight heparin</li> <li>17. Known severe hepatic disease, portal hypertension (with esophageal varices), or active hepatitis</li> <li>18. Peptic ulcer diagnosed in the past 3 months</li> <li>19. Pregnancy or parturition within the previous 30 days, or current breastfeeding</li> <li>20. Women of childbearing potential who do not have a negative pregnancy test and do not use an effective method of birth control</li> <li>21. Any other condition that the investigator feels would place the patient at increased risk upon start of the investigational treatment</li> <li>22. Life expectancy <math>&lt; 6</math> months or inability to participate at 6-month follow-up visit</li> </ol>

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

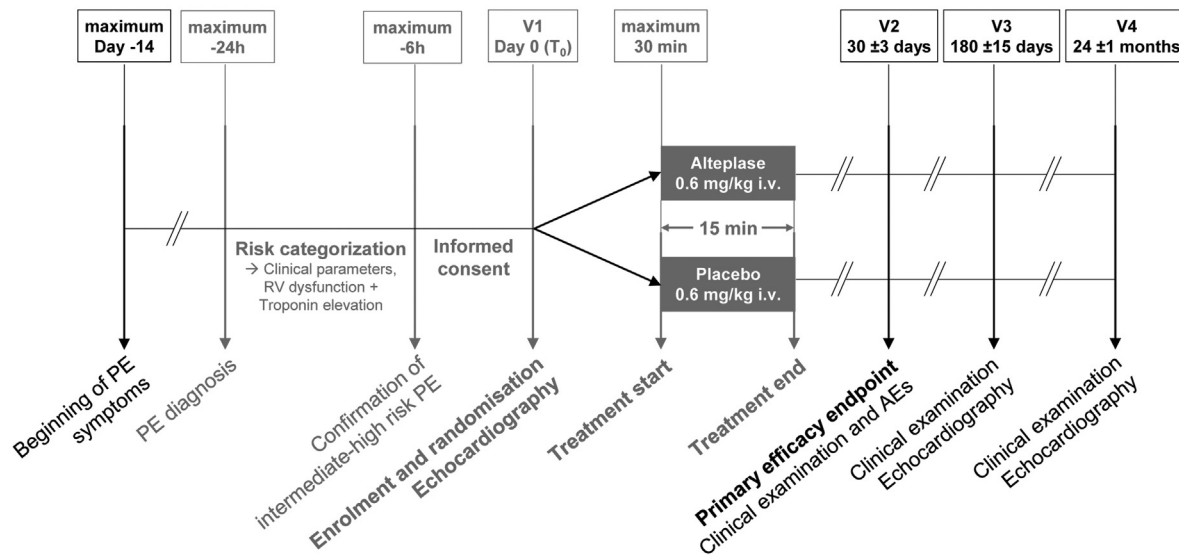
rate  $> 20$  breaths/min (or, as a surrogate, an arterial oxygen saturation  $< 90\%$  on room air) at presentation, or a history of chronic heart failure, predicted, alone or in combination, death from any cause, hemodynamic decompensation, or objectively confirmed recurrent PE within 30 days of randomization. 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.<sup>25</sup> This group was defined as the target population in the present trial, with the aim to obtain an optimized benefit-to-risk ratio from early thrombolysis.

### Treatment Regimens

The diagram shown in ►Fig. 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 fol-

low-up visits is provided in ►Table 2. Patients fulfilling all the inclusion criteria and none of the exclusion criteria (►Table 1) will be randomized into the experimental or the reference treatment arm. Patients will receive alteplase (if randomized into the experimental arm) or placebo (if randomized into the reference arm), to be given within 30 minutes of randomization 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 randomization, the patient will be analyzed 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 randomization, the UFH infusion will be stopped at the time of randomization and the first LMWH subcutaneous injection will be given within 3 hours



**Fig. 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 2** Trial visit plan and data collection schedule

	Day (D)0 Inclusion visit	D30 ± 3 days after randomization	Month (M)6 ± 15 days after randomization	M24 ± 30 days after randomization/end of study
	<i>In hospital</i>	<i>Outpatient follow-up</i>		
Verification of inclusion and exclusion criteria	X			
Signed informed consent	X			
Randomization	X			
Medical interview - Demographics - Medical history - Concomitant antiplatelet and anticoagulant treatment	X			
Clinical examination <sup>a</sup>	X	X	X	X
Troponin I and/or t-test	X			
Further laboratory tests <sup>b</sup>	X			
RV/LV diastolic diameter ratio	X			
sPESI	X			
Study drug administration	X			
Echocardiography	X		X	X
Pregnancy test (for women of childbearing age)	X			
Documentation of (serious) adverse events <sup>c</sup>	X	X		
Utilization of health care resources		X	X	

Abbreviations: LV, left ventricular; RV, right ventricular; sPESI, simplified Pulmonary Embolism Severity Index.

<sup>a</sup>Including body weight, blood pressure, heart rate, arterial oxygen saturation, respiratory rate, clinical signs of right heart failure.

<sup>b</sup>Creatinine, international normalized ratio, hemoglobin (1 day after randomization), platelet count (before and after randomization).

<sup>c</sup>Patients will be continuously monitored for early detection of hemodynamic instability or major bleeding.



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 randomization, the next injection will be given 24 hours after the previous one. Due to the longer half-life of fondaparinux as compared with 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 randomization. All approved anticoagulant regimens will be allowed 48 hours after randomization.

As recommended by current guidelines,<sup>1</sup> 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 summarized in ► **Table 3**. The primary efficacy outcome is the clinical composite of death from any cause, hemodynamic decompensation, or objectively confirmed recurrent PE within 30 days of randomization. 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 randomized controlled trial.<sup>14</sup> 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 hemodynamic 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.<sup>14</sup> 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 hemodynamic 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 hemorrhage-induced hemodynamic 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.<sup>25</sup>

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

**Table 3** Primary and secondary outcomes

Primary outcome	Clinical composite of death from any cause or hemodynamic decompensation or objectively confirmed recurrent PE within 30 days of randomization
Secondary outcomes	To be included in a hierarchical analysis:
	<ol style="list-style-type: none"> <li>1. Fatal or GUSTO severe or life-threatening bleeding, defined as either intracranial bleeding or bleeding leading to significant hemodynamic compromise requiring treatment,<sup>38</sup> within 30 days</li> <li>2. Net clinical benefit, defined as the composite of the primary efficacy outcome and GUSTO severe or life-threatening bleeding, within 30 days</li> <li>3. All-cause mortality within 30 days</li> </ol>
	Not to be included in the hierarchical analysis:
	<ol style="list-style-type: none"> <li>4. PE-related death within 30 days of randomization</li> <li>5. Hemodynamic decompensation within 30 days</li> <li>6. Recurrent PE within 30 days</li> <li>7. Need for rescue thrombolysis, catheter-directed treatment, or surgical embolectomy within 30 days</li> <li>8. Ischemic or hemorrhagic stroke within 30 days</li> <li>9. Serious adverse events within 30 days</li> <li>10. Utilization of health care resources within 30 days and 6 months</li> <li>11. All-cause mortality at 2 years</li> <li>12. Persisting dyspnea assessed by the Medical Research Council (MRC) scale at 6 months and at 2 years</li> <li>13. Functional outcome, using the post-VTE functional scale,<sup>39</sup> at 6 months and at 2 years</li> <li>14. Persistent RV dysfunction, defined as an intermediate or high probability of pulmonary hypertension on echocardiography according to ESC criteria,<sup>40</sup> at 6 months and 2 years</li> <li>15. Confirmed chronic thromboembolic pulmonary hypertension according to ESC criteria<sup>40</sup> at 2 years</li> </ol>

Abbreviations: 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.

clinical outcomes conducted to this date.<sup>25</sup> This analysis helped to estimate the incidence of the primary efficacy outcome (death from any cause or hemodynamic collapse or objectively confirmed recurrent PE within 30 days of randomization) 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 groups, 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 DeMets methods, we calculated that several ( $n = 305$ ) 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<sup>26</sup> 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.<sup>27</sup> Accounting for possible early drop-outs, 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 performed in the ITT population applying a logistic regression analysis to account for stratification factors<sup>28,29</sup>; the group variables age ( $>75$  vs.  $\leq 75$  years) and country will be included in the model. Results will be presented as OR and associated 95% CI. In addition, two exploratory subgroup analyses will be performed for the primary outcome in the ITT population, according to the following variables: (1)  $>75$  versus  $\leq 75$  years, and (2) presence of  $\geq 2$  clinical criteria of PE severity at presentation (among the following inclusion criteria: systolic blood pressure  $\leq 110$  mm Hg; 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, utilization of health care resources will be recorded for each patient at two time points (30 days and 180 days) postrandomization. For outpatient visits and periods of hospitalization, country-specific standardized unit costs will be applied, representing costs from a societal perspective. In addition, PE-related resource utilization 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 the control arm will be assessed by the 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.<sup>26</sup> 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.<sup>30,31</sup> 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 hemodynamic effects.<sup>14</sup> In view of these results, the focus of the debate has shifted toward 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 hemodynamic parameters.<sup>32–35</sup> 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 randomized 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,<sup>15,36</sup> that the use of alteplase in the present trial will be associated with a lower risk of intracranial hemorrhage and other major bleeding compared with tenecteplase used in PEITHO.<sup>14</sup> 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,<sup>37</sup> provided that it can demonstrate clinical efficacy and

safety in future state-of-the-art randomized 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 organization).

### Trial Statisticians

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

### Data Safety Monitoring Board

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.

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### 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 Scientific, 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 Leo Pharma, 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, and Sanofi. D.D. has received speaker's honoraria from Bayer Vital, Daiichi-Sankyo, and 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 from AstraZeneca, Bayer Vital, Berlin Chemie, Boehringer Ingelheim, and Novartis, and consulting fees from Bayer Vital, Boehringer Ingelheim, Novartis, and Novo Nordisk. M.F. reports lecture fees and travel grants from Bayer, Bristol-Myers Squibb, and 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, and 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



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#### References

- Konstantinides SV, Meyer G, Becattini C, et al; ESC Scientific Document Group. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). *Eur Heart J* 2020;41(04):543–603
- Becattini C, Agnelli G, Lankeit M, et al. Acute pulmonary embolism: mortality prediction by the 2014 European Society of Cardiology risk stratification model. *Eur Respir J* 2016;48(03):780–786
- Goldhaber SZ, Visani L, De Rosa M. Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). *Lancet* 1999;353(9162):1386–1389
- Aujesky D, Obrosky DS, Stone RA, et al. Derivation and validation of a prognostic model for pulmonary embolism. *Am J Respir Crit Care Med* 2005;172(08):1041–1046
- Zondag W, Mos IC, Creemers-Schild D, et al; Hestia Study Investigators. Outpatient treatment in patients with acute pulmonary embolism: the Hestia Study. *J Thromb Haemost* 2011;9(08):1500–1507
- Jiménez D, Aujesky D, Moores L, et al; RIETE Investigators. Simplification of the pulmonary embolism severity index for prognostication in patients with acute symptomatic pulmonary embolism. *Arch Intern Med* 2010;170(15):1383–1389
- Lankeit M, Jiménez D, Kostrubiec M, et al. Validation of N-terminal pro-brain natriuretic peptide cut-off values for risk stratification of pulmonary embolism. *Eur Respir J* 2014;43(06):1669–1677
- Jiménez D, Kopecka D, Tapson V, et al; On Behalf Of The Protect Investigators. Derivation and validation of multimarker prognostication for normotensive patients with acute symptomatic pulmonary embolism. *Am J Respir Crit Care Med* 2014;189(06):718–726
- Sanchez O, Trinquart L, Caille V, et al. Prognostic factors for pulmonary embolism: the prep study, a prospective multicenter cohort study. *Am J Respir Crit Care Med* 2010;181(02):168–173
- Côté B, Jiménez D, Planquette B, et al. Prognostic value of right ventricular dilatation in patients with low-risk pulmonary embolism. *Eur Respir J* 2017;50(06):1701611
- Konstantinides SV, Barco S, Lankeit M, Meyer G. Management of pulmonary embolism: an update. *J Am Coll Cardiol* 2016;67(08):976–990
- Konstantinides S. Clinical practice. Acute pulmonary embolism. *N Engl J Med* 2008;359(26):2804–2813
- Konstantinides S, Geibel A, Heusel G, Heinrich F, Kasper WM. Management Strategies and Prognosis of Pulmonary Embolism-3 Trial Investigators. Heparin plus alteplase compared with heparin alone in patients with submassive pulmonary embolism. *N Engl J Med* 2002;347(15):1143–1150
- Meyer G, Vicaut E, Danays T, et al; PEITHO Investigators. Fibrinolysis for patients with intermediate-risk pulmonary embolism. *N Engl J Med* 2014;370(15):1402–1411
- Marti C, John G, Konstantinides S, et al. Systemic thrombolytic therapy for acute pulmonary embolism: a systematic review and meta-analysis. *Eur Heart J* 2015;36(10):605–614
- Ortel TL, Neumann I, Ageno W, et al. American Society of Hematology 2020 guidelines for management of venous thromboembolism: treatment of deep vein thrombosis and pulmonary embolism. *Blood Adv* 2020;4(19):4693–4738
- Konstantinides SV, Vicaut E, Danays T, et al. Impact of thrombolytic therapy on the long-term outcome of intermediate-risk pulmonary embolism. *J Am Coll Cardiol* 2017;69(12):1536–1544
- Goldhaber SZ, Agnelli G, Levine MN. The Bolus Alteplase Pulmonary Embolism Group. Reduced dose bolus alteplase vs conventional alteplase infusion for pulmonary embolism thrombolysis. An international multicenter randomized trial. *Chest* 1994;106(03):718–724
- Sors H, Pacouret G, Azarian R, Meyer G, Charbonnier B, Simonneau G. Hemodynamic effects of bolus vs 2-h infusion of alteplase in acute massive pulmonary embolism. A randomized controlled multicenter trial. *Chest* 1994;106(03):712–717
- Wang C, Zhai Z, Yang Y, et al; China Venous Thromboembolism (VTE) Study Group. Efficacy and safety of low dose recombinant tissue-type plasminogen activator for the treatment of acute pulmonary thromboembolism: a randomized, multicenter, controlled trial. *Chest* 2010;137(02):254–262
- Zhang Z, Zhai ZG, Liang LR, Liu FF, Yang YH, Wang C. Lower dosage of recombinant tissue-type plasminogen activator (rt-PA) in the treatment of acute pulmonary embolism: a systematic review and meta-analysis. *Thromb Res* 2014;133(03):357–363
- Levine M, Hirsh J, Weitz J, et al. A randomized trial of a single bolus dosage regimen of recombinant tissue plasminogen activator in patients with acute pulmonary embolism. *Chest* 1990;98(06):1473–1479
- Sharifi M, Bay C, Skrocki L, Rahimi F, Mehdipour M. MOPETT Investigators. Moderate pulmonary embolism treated with thrombolysis (from the “MOPETT” Trial). *Am J Cardiol* 2013;111(02):273–277
- Konstantinides SV, Torbicki A, Agnelli G, et al; Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC) 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. *Eur Heart J* 2014;35(43):3033–3069
- Barco S, Vicaut E, Klok FA, Lankeit M, Meyer G, Konstantinides SV. PEITHO Investigators. Improved identification of thrombolysis candidates amongst intermediate-risk pulmonary embolism patients: implications for future trials. *Eur Respir J* 2018;51(01):1701775
- DeMets DL, Lan KK. Interim analysis: the alpha spending function approach. *Stat Med* 1994;13(13-14):1341–1352
- Gao P, Ware JH, Mehta C. Sample size re-estimation for adaptive sequential design in clinical trials. *J Biopharm Stat* 2008;18(06):1184–1196
- Kahan BC, Morris TP. Improper analysis of trials randomised using stratified blocks or minimisation. *Stat Med* 2012;31(04):328–340

- 29 Kahan BC, Morris TP. Reporting and analysis of trials using stratified randomisation in leading medical journals: review and reanalysis. *BMJ* 2012;345:e5840
- 30 Konstantinides S. Thrombolysis in submassive pulmonary embolism? Yes. *J Thromb Haemost* 2003;1(06):1127-1129
- 31 Dalen JE. Thrombolysis in submassive pulmonary embolism? No. *J Thromb Haemost* 2003;1(06):1130-1132
- 32 Tapson VF, Sterling K, Jones N, et al. A randomized trial of the optimum duration of acoustic pulse thrombolysis procedure in acute intermediate-risk pulmonary embolism: the OPTALYSE PE trial. *JACC Cardiovasc Interv* 2018;11(14):1401-1410
- 33 Piazza G, Hohlfelder B, Jaff MR, et al; SEATTLE II Investigators. A prospective, single-arm, multicenter trial of ultrasound-facilitated, catheter-directed, low-dose fibrinolysis for acute massive and submassive pulmonary embolism: the SEATTLE II study. *JACC Cardiovasc Interv* 2015;8(10):1382-1392
- 34 Kucher N, Boekstegers P, Müller OJ, et al. Randomized, controlled trial of ultrasound-assisted catheter-directed thrombolysis for acute intermediate-risk pulmonary embolism. *Circulation* 2014;129(04):479-486
- 35 Tu T, Toma C, Tapson VF, et al; FLARE Investigators. A prospective, single-arm, multicenter trial of catheter-directed mechanical thrombectomy for intermediate-risk acute pulmonary embolism: the FLARE study. *JACC Cardiovasc Interv* 2019;12(09):859-869
- 36 Riera-Mestre A, Becattini C, Giustozzi M, Agnelli G. Thrombolysis in hemodynamically stable patients with acute pulmonary embolism: a meta-analysis. *Thromb Res* 2014;134(06):1265-1271
- 37 Hobohm L, Keller K, Münzel T, Gori T, Konstantinides SV. EkoSonic® endovascular system and other catheter-directed treatment reperfusion strategies for acute pulmonary embolism: overview of efficacy and safety outcomes. *Expert Rev Med Devices* 2020;17(08):739-749
- 38 GUSTO investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. *N Engl J Med* 1993;329(10):673-682
- 39 Klok FA, Barco S, Siegerink B. Measuring functional limitations after venous thromboembolism: a call to action. *Thromb Res* 2019;178:59-62
- 40 Galiè N, Humbert M, Vachiery JL, et al; ESC Scientific Document Group. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Heart J* 2016;37(01):67-119