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ABSTRACT

Background: Catheter-directed thrombectomy (CDT) is a promising alternative to full dose thrombolysis in patients with acute high-risk pulmonary embolism (PE), expected to have a more direct effect on pulmonary artery clot burden and a better safety profile. Randomized trials evaluating the safety and efficacy of CDT in high-risk patients are currently unavailable.

Methods and results: The TORPEDO-NL study is an investigator-initiated, publicly-funded, multicenter, open-label randomized controlled trial designed to evaluate the superiority of CDT over systemic thrombolysis in patients with high-risk PE. Adults with: 1) confirmed acute PE, 2) a high risk for mortality, and 3) CDT available and technically feasible, will be randomized 2:1 to CDT versus systemic thrombolysis. The primary outcome is the composite incidence of all-cause mortality, treatment failure, major bleeding, and all-cause stroke at day 30. Secondary outcomes include desirability of outcome ranking (DOOR) at day 7, length of hospital stay, patient-reported outcomes including quality of life and symptom burden, functional recovery, and 1-year cost-effectiveness. The trial anticipates recruiting 111 patients and is funded by the The Netherlands Health Care Institute, The Netherlands Organization for Health Research and Development, the Dutch Heart Foundation, and unrestricted grants from Penumbra Inc. and Inari Medical. ClinicalTrials.gov number, NCT06833827.

Conclusions: TORPEDO-NL is the first publicly-funded randomized trial to investigate the effect of CDT treatment specifically in high-risk PE patients. The trial is anticipated to play an important role in revising recommendations for high-risk PE treatment in international guidelines.

1. Background and rationale

1.1. Current treatment of high-risk pulmonary embolism

Patients with acute pulmonary embolism (PE) usually have good outcomes and can be treated at home with oral anticoagulation [1–3]. However, their prognosis may vary dramatically according to whether the patient is hemodynamically stable. High-risk PE (5–7 % of hospitalized patients with PE) is defined by hemodynamic instability and encompasses the clinical presentations of cardiac arrest, obstructive shock, or persistent hypotension [2]. These high-risk patients have 30-day mortality rates ranging from 15 % to as high as 77 % [1,2]. Immediate reperfusion therapy on top of anticoagulation is therefore required in these patients. The standard reperfusion treatment is thrombolytic therapy (class 1-B recommendation, the 2019 European Society of Cardiology (ESC)/European Respiratory Society (ERS) guidelines) [2], with the idea of accelerated fragmentation of the thrombus by systemically administered lytic medication. This however carries a considerable risk of major bleeding (10–25 %) and intracranial hemorrhage (ICH, 3 %) [2]. Unsuccessful thrombolysis, defined as persistent clinical instability and/or unchanged cardiac dysfunction after 36 h, has been reported in 8 % of high-risk PE patients [4]. Notably, the evidence for systemic thrombolysis in high-risk PE is limited to trials focusing on heterogeneous populations including high-risk but also intermediate-risk patients, while only one trial focused on high-risk patients and clinical rather than imaging outcomes [5,6]. The latter trial was terminated after randomization of 8 patients due to the high mortality rate in the heparin-only arm [6]. The high risk of bleeding and the uncertainty of the evidence for using systemic thrombolysis remain a major barrier for administering lifesaving systemic thrombolysis in daily practice: systemic thrombolysis was administered to only 23 % of hemodynamically unstable patients in a German nationwide registry [7].

[1] Equally contributed.
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This may be one of the driving reasons for the still substantial PE attributable mortality rates globally [8,9]. Indeed, multiple studies have shown that mortality in high-risk PE patients remains high to date and has not improved compared to the ICOPER study 25 years ago [10].

1.2. Introduction of catheter-directed thrombectomy

Mechanical reperfusion is based on the insertion of a catheter into the pulmonary arteries via the femoral or transjugular route to remove embolic material via aspiration [11]. Currently, several companies offer catheter-directed mechanical thrombectomy devices. The FlowTriever device (Inari Medical, Irvine, CA, USA) and the Indigo Aspiration/Lightning device (Penumbra Inc., Alameda, CA, USA) are CE mark-approved for the treatment of acute PE. The safety and efficacy of both systems have been assessed in prospective single-arm studies and registries, albeit mostly in intermediate-risk PE. In the FlowTriever Pulmonary Embolectomy Clinical Study (FLARE) study, 106 intermediate-risk patients with acute PE were treated with FlowTriever: a reduction in right ventricle/left ventricle (RV/LV) ratio at 48 h post-procedure was observed [12]. Major adverse events and death occurred in 3.8 % and 1.0 %, respectively. Major bleeding occurred in 1.0 %. The FlowTriever for Acute Massive pulmonary Embolism (FLAME) study was a prospective cohort observational study, designed to evaluate treatment outcomes in patients with high-risk PE treated with the FlowTriever catheter. The primary endpoint, evaluated through hospital discharge or at 45 days (whichever came first), was a composite of all-cause mortality, clinical deterioration, bailout, and major bleeding [13]. A total of 53 patients were enrolled. The primary outcome occurred in 17 % of patients with the following rates for each component of the endpoint: death 1.9 %, clinical deterioration 15 %, and major bleeding 11 %. Device-related complications occurred in 22.6 % of the patients and included, hemoglobin decrease (15 %), vascular access bleeding (7.5 %), and hypotension (1.9 %). As this was not a randomized controlled trial (RCT), it remains unclear whether the remarkable low mortality was due to selection bias or the beneficial effect of the intervention.

In the Evaluating the Safety and Efficacy of the Indigo aspiration system in Acute Pulmonary Embolism (EXTRACT-PE) study, 119 intermediate-risk PE patients were treated with the Indigo thromboaspiration device and a relevant RV/LV ratio reduction at 48 h post-procedure was reported [14]. Major adverse events and death occurred in 1.7 and 0.8 %, respectively. Major bleeding occurred in 1.7 % of patients. Comparable results were reported for the Prospective, Multicenter Study of the Indigo™ Aspiration System Seeking to Evaluate the Long-Term Safety and Outcomes of Treating Pulmonary Embolism (STRIKE-PE) study [15]. Another prospective analysis of mechanical thrombectomy with the Indigo system, followed by local low-dose catheter-directed thrombolysis in 54 patients with systemic hypotension and a contraindication for systemic thrombolysis, was associated with an 11 % in-hospital mortality and a low risk of major bleeding (2.1 %) [16]. Positive impact on total duration of hospitalization and length of stay at the intensive care unit (ICU) have been described in patients with intermediate-high-risk PE, as well as fast recovery of the RV and relief of symptoms. Notably, throughout the studies, the thrombectomy procedure is not standardized nor are the periprocedural anticoagulation regimes and measures for organ support.

1.3. Remaining uncertainties and the need for a large randomized controlled trial

Despite the accumulation of data from these studies that to a certain extent substantiate the potential role of catheter-directed thrombectomy in high-risk patients with acute PE, considerable shortcomings in our understanding of mechanical thrombectomy in these patients remain. In particular, the lack of a direct comparison to systemic thrombolysis, the unavailability of outcome measures with relevant clinical impact, and the likelihood for relevant variability in the performance of thrombectomy procedures. Moreover, application of thrombectomy procedures in patients with high-risk PE exposes the patients to the burden of a catheterization procedure including radiation exposure, and contrast fluid load compared to systemic thrombolysis. Also, such procedures may induce delay in treatment, since catheter-directed thrombectomy requires the (fast) deployment of an (24/7 available) intervention team, and transport of the patient to the intervention theater. Important clinical endpoints such as 'treatment failure' (a lack of improvement or deterioration [11]) and 'ischemic stroke', mostly from migrating emboli from the venous circulation to the arterial system through a patent foramen ovale or atrial septal defect, were insufficiently explored and reported in the abovementioned studies.

According to current guidelines, catheter-directed treatment of acute high-risk PE should only be considered for patients with high-risk PE in whom thrombolysis is contraindicated or has failed, or as a rescue treatment for initially stable patients who transition to high-risk PE, i.e. who experience hemodynamic deterioration despite adequate-dose initial anticoagulation [2,11,17]. Only an adequately powered randomized trial comparing catheter-directed thrombectomy to the standard of care, focusing on clearly defined high-risk PE patients, measuring relevant clinical outcomes, applying standardized procedures and involving blinded endpoint adjudication will provide the evidence to potentially evolve guideline recommendations towards a more first-line role of catheter-directed thrombectomy in high-risk PE. Of note, for patients in whom systemic thrombolysis is contraindicated, catheter-directed thrombectomy or surgical embolectomy are the treatment options of first choice.

2. Study overview

2.1. Study design and objectives

TORPEDO-NL is an investigator-initiated, publicly-funded, multicenter, open-label RCT. The primary aim of the study is to assess whether catheter-directed thrombectomy with any commercially available system on top of regular anticoagulation, is associated with a relevant reduction in the composite outcome of all-cause mortality, treatment failure, major bleeding and all-cause stroke at day 30, compared to full-dose systemic thrombolysis on top of regular anticoagulation in patients with high-risk PE in the Netherlands. Additional objectives are to provide further evidence on the treatment and outcomes of acute high-risk PE, to set the standard for future clinical trials in high-risk PE with regard to the definition of treatment success and treatment failure, and to provide high-quality, controlled data comparing a catheter-based intervention to the current standard of care.

A 2:1 (catheter-directed thrombectomy: systemic thrombolysis) randomization is applied. The randomization procedure is web-based, using randomly sized blocks consisting of 3, 6 or 9 patients, stratified by center. While trial centers must have a proven sufficient level of experience in performing catheter-directed thrombectomy before they are cleared to enroll, the 2:1 ratio ensures continuing exposure to the intervention team. In addition, a larger sample size in the active novel product group gives more power to detect adverse events. Randomization will be performed after verification that a thrombectomy procedure can be started within 60 min (randomization-to-needle time); 60 minutes was chosen to ensure the safety of patients, but also to establish feasibility of the logistics that accompany the interventional procedure. The primary outcome will be assessed after a 30-day follow-up period. 30 Days was chosen, since this is conventional in time frame studies involving critically ill patients. Patients will be followed for 1 year after randomization; this timeframe was chosen to evaluate Quality of Life (QoL) and cost-effectiveness, according to the most validated and widely used questionnaires, and is routinely used in economic evaluations.

The estimated duration of enrolment is 2.5 years. Allocation to treatment arms is open-label to investigators and patients, but

adjudication of the composite primary outcome and safety outcomes will be performed by an independent, blinded Clinical Events Committee.

2.2. Patient population and eligibility

The TORPEDO-NL trial aims to enroll consecutive adult patients with acute PE presenting with respiratory failure, persistent hypotension or shock, who do not have a contraindication for systemic thrombolysis or catheter-directed thrombectomy. PE patients with respiratory failure who do not fulfil shock criteria are currently not considered high risk in the ESC guideline, but do also face a > 30 % risk of death and further respiratory failure [18–21]. For this reason, they are also considered as having an imminent indication for pulmonary artery reperfusion therapy, and for that reason eligible for this study. At the other end of the high-risk spectrum, patients with 'catastrophic PE' will not be enrolled, i.e. those with ongoing cardiac arrest and/or need for extracorporeal cardiopulmonary resuscitation (ECPR) and/or immediate indication for venoarterial extracorporeal membrane oxygenation (VA-ECMO) as judged by the treating physicians. These patients follow a different treatment algorithm and have a notable mortality of often >70 %, especially for those in ongoing cardiac arrest. Patients post cardiac arrest after temporary need for cardiopulmonary resuscitation can be enrolled. The more comprehensive inclusion and exclusion criteria are summarized in Table 1.

Patients will be screened for inclusion upon arrival of the local EXPERT-PE team (also known as Pulmonary Embolism Response Team (PERT) in the North American literature). The diagnostic criteria for acute PE in this trial are 1) a contrast filling defect in a lobar or more proximal pulmonary artery on computed tomography pulmonary angiography (CTPA), and/or 2) obstructive shock with echocardiographic confirmed dilatation of the right ventricle as well as a congested vena cava inferior, both with/without echocardiographic signs of a clot in transit or deep vein thrombosis of the leg [2,22,23]. Upon confirmation that patients fulfil the criteria of study participation, they will be randomized.

A deferred informed consent procedure will be applied. Deferred consent enables subjects to participate in medical research without their prior written consent, which is imperative due to their medical status in an emergency setting.

2.3. Patient and public involvement

Patient representatives were involved in the design of the study, where their main focus was based on patient's perspective while participating in the study. Experiencing potential benefit or disadvantage was evaluated carefully to meet standards that can be considered appropriate and well-balanced.

2.4. Intervention and treatment regimens

The study flow diagram is shown in Fig. 1. The standard of care for patients eligible for the TORPEDO-NL trial is parenteral anticoagulation and systemic thrombolysis (Actilyse® [manufactured by Boehringer Ingelheim Pharmaceuticals, Inc., Ingelheim am Rhein, Germany] 10 mg bolus followed by 90 mg in 2 h). The intervention consists of parenteral anticoagulation and immediate catheter-directed thrombectomy without systemic or locally administered systemic thrombolysis. Catheter-directed thrombectomy is performed according to the instructions for use (IFU) for the particular device and occurs via echo-guided femoral or jugular venous access by an interventional cardiologist, interventional radiologist or vascular surgeon. The catheter is advanced over a preplaced guidewire across the right heart into the pulmonary arteries to the location of proximal thrombus. After removal of the dilator, the thrombus is extracted by controlled volume aspiration through an aspiration catheter using either a syringe or the dedicated

Table 1
Key inclusion and exclusion criteria.

Inclusion criteria (all criteria should be met)	Exclusion criteria
1. Adult patients with confirmed acute PE, i.e. contrast filling defect in a lobar or more proximal pulmonary artery on CTPA, and/or obstructive shock with echocardiographic confirmed dilatation of the right ventricle and a congested vena cava inferior, both with/without echocardiographic signs of clot in transit or deep vein thrombosis of the leg. 2. High risk for mortality, i.e. a. post cardiac arrest (after temporary need for cardiopulmonary resuscitation), OR b. obstructive shock (systolic blood pressure < 90 mm Hg and signs of end-organ hypoperfusion (e.g. elevated lactate levels >2 mmol/L) or the need for vasopressors (noradrenalin or adrenalin) to maintain an adequate blood pressure), OR c. persistent hypotension (systolic blood pressure < 90 mm Hg or systolic blood pressure drop ≥40 mm Hg for at least 15 min) not caused by new onset arrhythmia, hypovolemia, or sepsis, OR d. abnormal RV function on transthoracic echocardiography or CTPA AND elevated cardiac troponin levels AND respiratory failure defined as hypoxemia (SaO2 < 90 %) refractory to O2 supplementation by nasal cannula or Venturi mask, requiring full face mask O2 supplementation (100 % FiO2), high-flow nasal O2, or (non-)invasive mechanical ventilation. 3. CDT available and technically feasible so as to allow for a randomization-to-needle time of 60 min or less.	1. "Catastrophic PE", i.e. ongoing cardiac arrest and/or need for ECPR and/or immediate indication for VA-ECMO as judged by the responsible physicians 2. Glasgow Coma Scale <8 following resuscitation for cardiac arrest 3. Alternative diagnosis than acute PE contributing largely to the acute hemodynamic and/or respiratory failure, e.g. sepsis, COPD GOLD 3 or 4, or known heart failure with NYHA Functional Classification of 4, as judged by the treating physician. 4. A known "do not admit to the ICU" or "do not resuscitate" directive 5. An absolute contraindication to systemic thrombolysis, i.e. ✓ History of hemorrhagic stroke ✓ Ischemic stroke in past 6 months ✓ Central nervous system neoplasm ✓ Major trauma, major surgery or major head injury in past 3 weeks (note: mild external laceration of the head after, e.g. syncope, does not count as major head injury, especially when a CT scan of the head shows no hematoma) ✓ Active bleeding, life-threatening or into a critically organ/area; OR known severe bleeding diathesis with previous bleeding fulfilling these criteria 6. Reperfusion therapy (systemic thrombolysis, surgical thrombectomy or CDT/other catheter directed therapy), or placement of a non-retrieved inferior vena cava filter for acute PE in the past 3 months 7. Thrombus in transit through a patent foramen ovale. 8. Known CTEPH, or strong suspicion of CTEPH based on pre-existing clinical findings and combinations of signs of PE chronicity on echocardiography and/or CTPA [2,41]. 9. Known hypersensitivity to systemic thrombolysis, heparin, or to any of the excipients 10. If, in the Investigator's opinion, or after consultation with the local EXPERT-PE team or EC-members, the patient is not appropriate for thrombectomy 11. Chronic use of full-dose oral or parenteral anticoagulation before presentation. 12. Pregnancy 13. Current participation in another study that would interfere with participation in this study 14. Previous enrolment in this study 15. Refusal of deferred consent by the next of kin or by the patient himself to use the data. Deferred consent will not be asked to relatives of patients who die in scene, but are included in the study.

Note: PE: pulmonary embolism, CTPA: computed tomography pulmonary angiography, RV: right ventricle, CDT: catheter-directed thrombectomy, ECPR:

extracorporeal cardiopulmonary resuscitation, VA-ECMO: venoarterial extracorporeal membrane oxygenation, COPD: chronic obstructive pulmonary disease, GOLD: Global Initiative for Chronic Obstructive Lung Disease, NYHA: New York Heart Association, ICU: intensive care unit, CT: computed tomography, CTEPH: chronic thromboembolic pulmonary hypertension, EC: executive committee.

aspiration system depending on the device of choice, with multiple aspirations performed as needed. Investigators will determine when to terminate the procedure based on their assessment of patients respiratory and hemodynamic status. Procedural objectives will be clearly stated prior to the intervention and respiratory and hemodynamic parameters, including pulmonary artery pressures, will be evaluated per protocol pre- and post-thrombectomy, to inform each operator's decision to determine completion. Re-evaluation of the patient's condition should be carried out using blood loss as a reference, establishing a maximum of 400 cc of blood loss as a cut-off value. A detailed description and standardization of the procedure can be found in Appendix A.

All study patients will additionally be treated with parenteral therapeutic anticoagulation. Patients will receive an intravenous (IV) bolus of 80 U/kg unfractionated heparin (UFH) immediately upon confirmation of the diagnosis 'high-risk PE', before or immediately after randomization, not to exceed a total of 8000 U [2]. UFH will be continued during the procedure. Within 4 h after the received reperfusion treatment (or immediately upon completion of the reperfusion therapy), the patient should have been transitioned to full dose parenteral anticoagulation, either therapeutically dosed low molecular weight heparin (LMWH) or UFH (based on local protocols). Upon stabilization (i.e. no longer need for organ support, transition to normal hospital ward) and after at least 24 h, the anticoagulation therapy may be switched to oral anticoagulation.

Participating centers have an institutionalized multidisciplinary EXPERT-PE team in place, including at least an intensive care specialist, an interventionalist and a pulmonologist, hematologist/internist-vascular medicine or emergency medicine specialist. The involved intervention team should have ample experience with endovascular interventions. At least one member of the intervention team should have sufficient experience with thrombectomy for PE and should have completed at least 3 full procedures (logged) with one of the devices.

2.5. Outcomes

An overview of the tests to be performed and parameters to be collected upon enrollment and at the follow-up visits is provided in Table 2; the primary outcome and secondary outcomes of the trial are presented in Table 3. The primary outcome is the composite outcome of all-cause mortality, treatment failure, major bleeding and all-cause stroke at day 30. Major bleeding is defined as Bleeding Academic Research Consortium (BARC) 3b and BARC3c bleeding [24]. All-cause stroke is defined as both hemorrhagic stroke and ischemic stroke (National Institutes of Health Stroke Scale $\geq$ 1). Treatment failure (Table 4)

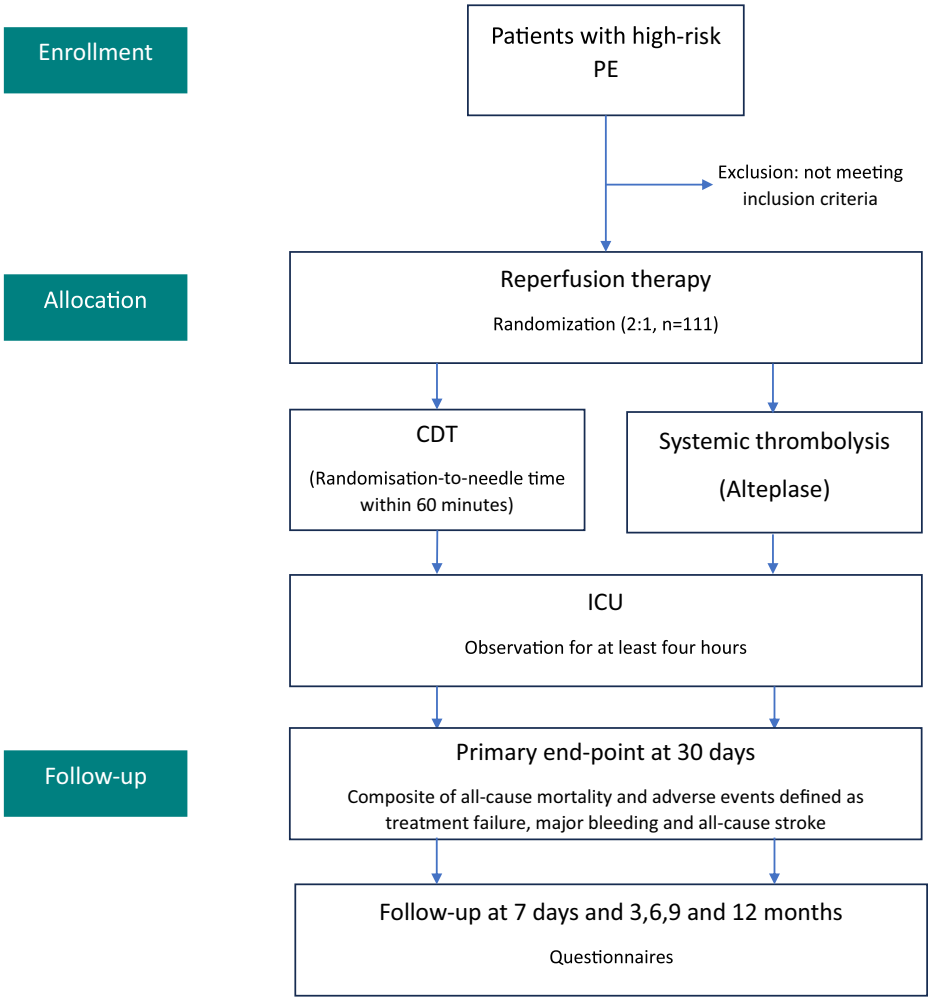

Fig. 1. Flow diagram of the TORPEDO-NL study.
Note: PE: pulmonary embolism, CDT: catheter-directed thrombectomy, ICU: intensive care unit.

Table 2
Trial visit plan and data collection schedule [43].

Procedure/Assessment	Screening (baseline)	Enrollment	Index procedure	Every 6 hours until stabilization	0-72 hours post-treatment	48 hours post-randomization	Follow-up					
							7 days	30 days	3 months	6 months	9 months	12 months
CTPA/TTE	x											
Conformation of eligibility*		x										
Randomization		x										
Informed consent**					x							
SCAI SHOCK stage ***	x			x								
Initiation of assigned therapy¶			x									
Oxygen suppletion∞						x						
DOOR							x					
Primary outcome¥								x				
Secondary outcomes¥							x	x	x	x	x	x
EQ-5D-5L							x		x	x	x	x
ICHOM-VTE – Core set – Individual Questions (Satisfaction with treatment / Changes in life view)[42]									x	x		x
PEmb-QoL[43]									x	x		x
PROMIS GH ten items									x	x		x
PROMIS Numeric Rating Scale v1.0 - Pain Intensity 1a_DUT_FLE									x	x		x
PROMIS SF v1.0 - Dyspnea Severity short form 10a									x	x		x
Cost questionnaires[33]									x	x	x	x
PVFS scale.[28 29]									x	x		x
Adverse event assessment		x	x	x	x	x	x	x	x	x	x	x

Note: CTPA: computed tomography pulmonary angiography, TTE: transthoracic echocardiogram, SCAI SHOCK: Society for Cardiovascular Angiography and Interventions Shock, DOOR: desirability of outcome ranking, ICU: intensive care unit, ICHOM: International Consortium for Health Outcomes Measurement, VTE: venous thromboembolism, PEmb-QoL: Pulmonary Embolism Quality of Life, PROMIS: Patient-Reported Outcomes Measurement Information System, GH: Global Health, PVFS: Post-Venous thromboembolism Functional Status.
*Conformation of eligibility in accordance with the interventional cardiologist/radiologist/vascular surgeon regarding CDT.
**Deferred consent will be obtained from the patient 0–72 h post procedure. If the patient is not able to provide consent, a patient representative will be asked for consent after 72 h.
***The SCAI SHOCK stage will be established following Table 5.
¶Systemic thrombolysis will be administered directly after diagnosis, catheter-directed thrombectomy must be started (randomization-to-needle time) within 60 min.
∞The amount and mode of oxygen (LO_2/min) delivered.
¥The primary and secondary outcome(s) can be found in Table 3.

in the first 6 h after randomization is defined as life-threatening hemodynamic or respiratory deterioration. This deterioration is the clinical scenario if, following randomization, the patient develops overt cardiorespiratory instability over at least 15 min necessitating CPR, escalation of respiratory support, or ECMO. After these first 6 h, treatment failure will also be defined by increasing dosages of cardiorespiratory support (e.g. oxygen, catecholamines), and lack of improvement. Lack of improvement is defined by the presence of at least one of the following criteria:

I. An equal or rising Society for Cardiovascular Angiography and Interventions (SCAI) shock stage [25,26] (Table 5)

Table 3
Overview of primary and secondary outcomes.

Primary outcome	Composite incidence of all-cause mortality, treatment failure, major bleeding and all-cause stroke at day 30
Secondary outcomes	- Survival at day 7 and day 30 - Treatment failure at day 7 and day 30 - All-cause mortality at day 7, day 30 and day 90 - All-cause stroke at day 7 and day 30 - The composite incidence of all-cause mortality, treatment failure, major bleeding and all-cause stroke at day 7 - DOOR at day 7 [28,29] - BARC3b and BARC3c bleeding at day 7 and day 30 [24] - ISTH major and non-major clinically relevant bleeding at day 7 and day 30 - Oxygen supplementation (LO_2/min) at 48 h - Length of stay (days) at the ICU and in-hospital at day 30 - Quality of life, functional status and symptom burden at day 7 and after 3, 6, 9 and 12 months according to the ICHOM-VTE set [42] - Cost-effectiveness analysis after a time horizon of one year and budget impact analysis

Note: DOOR: Desirability of Outcome Ranking, BARC: Bleeding Academic Research Consortium, ISTH: International Society on Thrombosis and Hemostasis, ICU: intensive care unit, ICHOM: International Consortium for Health Outcomes Measurement, VTE: venous thromboembolism.

II. An equal or rising Fraction of Inspired Oxygen (FiO_2) level to maintain adequate oxygen saturation (i.e. ≥92 %)
III. An equal or decreasing PaO2/FiO_2 (P/F) ratio.

The SCAI SHOCK classification classifies shock severity and provides a risk stratification of mortality in patients with cardiogenic shock [25,26]. Validation studies have underscored the correlation of the SCAI SHOCK stage with mortality across all clinical subgroups, including cardiogenic shock with and without acute coronary syndrome, ICU patients, and those presenting with out-of-hospital cardiac arrest (OHCA). Progression across the SCAI SHOCK stage continuum is a dynamic process, incorporating new information as it comes available. The SCAI SHOCK stage classification has been endorsed by the American College of Cardiology (ACC), American College of Emergency Physicians (ACEP), American Heart Association (AHA), European Society of Cardiology (ESC), Association for Acute Cardiovascular Care (ACVC), International Society for Heart and Lung Transplantation (ISHLT), Society of Critical Care Medicine (SCCM), and Society of Thoracic Surgeons (STS) [27].

Table 4
Detailed overview of the definition **treatment failure.**

The first 6 h following randomization:	After the first 6 h following randomization:
Life-threatening hemodynamic or respiratory deterioration: • Cardiorespiratory instability over at least 15 min necessitating CPR • Escalation of respiratory support • ECMO	**Life-threatening hemodynamic or respiratory deterioration:** • Cardiorespiratory instability over at least 15 min necessitating CPR • Escalation of respiratory support • ECMO
	Increasing dosages of cardiorespiratory support (e.g., oxygen, catecholamines)
	Lack of improvement: • An equal or rising SCAI SHOCK stage[a] • Equal or rising Fraction of Inspired Oxygen (FiO2) level to maintain adequate oxygen saturation (i.e. ≥ 92%)[b] • An equal or decreasing P/F ratio[c]

Note: CPR: cardiopulmonary resuscitation, ECMO: Extracorporeal Membrane Oxygenation, SCAI SHOCK: Society for Cardiovascular Angiography and Interventions Shock, P/F ratio: PaO2/FiO2 ratio.

[a] SCAI SHOCK stage classification is an indication of shock severity.

[b] FiO_2 stands for Fraction of Inspired Oxygen, which is the percentage (or fraction) of oxygen in the air mixture that is inhaled.

[c] The P/F ratio, or PaO_2/FiO_2 ratio, is a measure used in respiratory medicine to evaluate lung function, particularly the efficiency of oxygen exchange in the lungs.

Treatment failure will be determined every 6 h from randomization until the patient meets the primary outcome or is considered stable and transferable to the ward. Employing the SCAI SHOCK stage classification in TORPEDO-NL will uniquely provide a standardized objective assessment and monitoring of each patient's vital status after randomization, in an interventional randomized controlled trial in acute high-risk PE. This will facilitate objective confirmation of treatment failure by lack of improvement and, if needed, prompt institution of rescue therapy before further hemodynamic or respiratory compromise occurs. At the same time, the SCAI SHOCK stage classification is a valuable tool for preventing arbitrary or premature crossover from the control to the intervention arm, or to other rescue reperfusion treatment outside the trial protocol. It helps to provide clear rules and transparent criteria on how and when the investigator should declare 'failure' of the assigned treatment. If patients meet the primary outcome, the clinical management is left to the treating physician and is not part of the primary outcome of TORPEDO-NL.

One of the key secondary outcomes is the desirability of outcome ranking (DOOR) at day 7. The DOOR concept provides assessment of benefit and harm using endpoints of efficacy, safety, and functional outcomes. Patients are classified into an ordinal global outcome based on the overall outcome desirability. Once patients have been classified, the probability of a more desirable result with one treatment relative to the other is assessed. The superiority of the investigated treatment is calculated by tabulating the pairwise comparison results after further ranking by the number of days that a patient needs organ support. The following DOOR outcomes (from most to least desirable) are evaluated: 1. Survival with no new severe functional limitations, no treatment failure and no adverse event; 2. Survival with new severe functional limitations, but no adverse events and no treatment failure; 3. Survival with Bleeding Academic Research Consortium (BARC) 3b bleeding; 4. Survival with BARC3c bleeding or all-cause stroke; 5. Survival with treatment failure; 6. Death. Organ support is defined as respiratory organ support with high-flow nasal cannula or (non-)invasive mechanical ventilation, or cardiovascular organ support with a vasopressor or inotropic agent. Functional limitations are defined according to the post-venous thromboembolism functional status (PVFS) scale; grade 4 = severe limitations [28,29]. All secondary endpoints will be evaluated after randomization.

2.6. Sample size calculation and statistical analysis

For the primary endpoint, we calculated the desired sample size largely based on the data from the FLAME prospective registry [13]. This study used a somewhat different composite primary endpoint of all-cause mortality, bailout to alternative thrombus removal strategy, clinical deterioration and major bleeding. These endpoints were however not well enough defined and the clinically important endpoint of stroke was not a component of the primary outcome. Nevertheless, we can state that "bailout" and "clinical deterioration" may match our proposed component of treatment failure. The primary endpoint in FLAME occurred in 17 % and in 64 % (absolute risk (AR) difference 47 %) in the FlowTriever and context arm, respectively. Including ischemic stroke, the event rates were 19 % and 67 % (AR difference 48 %), respectively [13]. This study suffered from selection bias and confounding by indication, and therefore the suggested treatment effect is likely overestimated. Patients were enrolled in the FlowTriever arm in 2021 and 2022, where event rates in the Context arm were obtained from historical data (2010–2020) derived from a meta-analysis.

Table 5
SCAI SHOCK stage overview [25,26].

Stage	A	B	C	D	E
Condition	Hemodynamically stable	Hemodynamically unstable	Hypoperfusion = Shock	Failure to stabilize with initial therapy	Extremis / refractory shock
Hypotension*:					
- **SBP**	>90 mm Hg	60-90 mm Hg	60-90 mm Hg	60-90 mm Hg	<60 mm Hg
- **MAP**	>65 mm Hg	50-65 mm Hg	50-65 mm Hg	50-65 mm Hg	<50 mm Hg
		OR	AND	AND	OR
Hypoperfusion					
- **Arterial lactate**	<2 mmol/L	2-5 mmol/L OR	2-5 mmol/L OR	>5-10 mmol/L OR	>10 mmol/L OR
- **ALAT**	<200 U/L	200-500 U/L	200-500 U/L	>500 U/L	
- **pH**	≥ 7.2	≥ 7.2	≥ 7.2	≥ 7.2	< 7.2
		AND	AND	OR	OR
Treatment intensity	No Drugs** No Devices#	No Drugs No Devices	No Drugs No Devices	2 Drugs	≥3 Drugs OR Device
			OR	OR	OR
			1 Drug without hypotension or hypoperfusion	1 Drug with persistent hypotension or hypoperfusion	Out-of- or in-hospital cardiac arrest

Note: SCAI SHOCK: Society for Cardiovascular Angiography and Interventions Shock, SBP: systolic blood pressure; MAP: mean arterial pressure; ALAT: alanine aminotransferase, pH: potential of hydrogen.
* Hypotension: SBP ≤90 mm Hg or MAP ≤65 mm Hg.
** Drugs: intravenous vaso-active drugs.
# Devices: RV support or VA-ECMO.

To assess statistical power, the probability of the primary outcome was assumed to be 0.19 in the thrombectomy arm (based on the most recent data available) and 0.46 in the systemic thrombolysis arm (corresponding with a treatment odds ratio (OR) of 3.71 and a risk difference of 27.5 %; number needed to treat 3.6). The minimum clinically important difference was set at 27.5 % based on discussion within the project group, scientific societies and patient representatives, and on clinical relevance for the different facets of the composite endpoints. The assumed absolute risk reduction (ARR) of 27.5 % consists of 5 % decrease in mortality, 21.5 % reduction in treatment failure or major bleeding and 1 % reduction in ischemic stroke (the latter both based on expert opinion) [30]. Given a power of 80 %, a two-sided α-level of 5 %, and a 2:1 (catheter-directed thrombectomy: systemic thrombolysis) patient allocation, 35 patients are needed in the systemic thrombolysis arm and 70 patients in the catheter-directed thrombectomy arm. Assuming a 5 % drop-out, 37 patients (systemic thrombolysis) and 74 patients (catheter-directed thrombectomy) will be recruited, with a total of 111 patients. The calculation was done using G*Power (version 3.1.9.6) and is based on the proportion difference tested with an anticipated OR.

Data will be analyzed on an intention-to-treat (ITT) basis in several steps. The ITT population consists of all subjects who have been randomized, i.e. when the subject number and allocated regimen are recorded. Patients will be analyzed in accordance with the randomized treatment assignment irrespective of the factual implementation of the assigned treatment regimen. Baseline characteristics in each trial arm will be described. Continuous variables will be described as mean with standard deviation (SD) or median with interquartile range (IQR) for continuous variables depending on the normality of their distribution. The Shapiro–Wilk test will be used to assess normality. Categorical variables are presented as numbers and percentages.

For the primary composite endpoint, we will provide the cumulative incidence (number and percentage) for each trial arm and estimate the unadjusted OR (including the 95 % confidence interval using a binary logistic regression) to compare trial arms. For continuous secondary endpoints (e.g., DOOR in the first 7 days after randomization), we will estimate the mean or median difference between trial arms using an Independent Samples *t*-Test (mean difference) or a Mann Whitney-*U* test (median difference), depending on the normality of the distribution. Regarding categorical secondary outcomes, differences between the trial arms will be analyzed using a Chi-square test or Fisher's exact test, when appropriate. Repeated measures secondary outcomes are analyzed using mixed-effects (longitudinal) regression models. Outcomes will be (numerically) stratified according to the type of thrombectomy. A per-protocol analysis is performed as a sensitivity analysis. A cost effectiveness analysis (CEA) will be performed with a time horizon of one year for the primary outcome and QALYs. QALYs will be estimated using the EQ-5D-5L administered at day 7 and after 3, 6, 9 and 12 months, the Dutch tariff, and the "Area under the Curve" approach [31,32]. Costs will be measured from the societal perspective using Institute for Medical Technology Assessment (Imta) based cost questionnaire administered at 3, 6, 9 and 12 months [33]. Societal costs will include those related to the intervention, other healthcare use (i.e. primary care, secondary care, and medication), informal care, as well as productivity losses from paid and unpaid work. Costs will be valued following the Dutch Manual of Costing [34]. Economic evaluation analyses will be performed in accordance with the Dutch Guideline for Economic Evaluations in Health Care using the methods described by Jornada Ben et al. [35,36] Various sensitivity analyses will be performed to assess the robustness of the results (e.g. healthcare perspective). A budget impact analysis (BIA) will be conducted according to ZonMw's 'BIA, leidraad en rekentool' and ISPOR's principles of good practice [37]. Data analysis will be performed with the latest available R studio version at the data analysis stage, and where necessary graphs and visual presentations of data will be made with Graphpad. A p-value <0.05 will be considered statistically significant.

Missing data, where applicable, will be imputed with the use of multiple imputation under the missing-at-random assumption with

chained equations. Outcome variables will not be imputed. Subgroup analyses, which will primarily be hypothesis generating, will be performed (if feasible, i.e. if numbers per subgroup are sufficiently large) for man versus women, age below 75 or 75 and older, cancer, subtype of high-risk PE and different devices used.

2.7. Ethics, monitoring and dissemination

The institutional Review Board of the Leiden University Medical Center approved of the study (P24.088). The final protocol and DSMB charter are available as online Appendixes B and C. The trial is registered under Clinicaltrial.gov number NCT06833827. We will follow the FAIR Guiding Principles for scientific data management and stewardship [38]. Upon completion of the trial and publication of its primary and secondary outcomes, data will be shared upon request after the study proposal has been approved by the steering committee of TORPEDO-NL.

3. Implications and expected impact of TORPEDO-NL

Great technical progress has been achieved in catheter-directed thrombectomy of PE. To date, evidence supporting the use of these techniques is limited to registries, (retrospective) single-arm cohort studies or small RCTs focused on surrogate endpoints. As wide implementation of catheter-directed treatment of PE has major consequences for the organization of care as well as leads to considerable healthcare costs, strong evidence supporting its use is imperative. To solve this unmet need, we designed the TORPEDO-NL study, aiming to test the hypothesis that catheter-directed thrombectomy is the treatment of choice in patients with high-risk PE, both for those with or without a contraindication for full dose systemic thrombolysis. With its rigorous design and protocol, TORPEDO-NL is expected to provide answers to a large number of current questions concerning the efficacy and safety profile of catheter-directed thrombectomy in high-risk PE. More specifically:

1. TORPEDO-NL is the only ongoing publicly funded trial directly comparing catheter-directed thrombectomy to the standard of care in patients with acute high-risk PE, with unrestricted support from the catheter manufacturers. This ensures the independency and objectivity of the steering committee, data safe monitoring board (DSMB) and clinical event committee.
2. The primary outcome of the study is clinically relevant and objective, and is thus most suitable for determining the impact of the intervention on the patients' prognosis. Moreover, we have included the SCAI SHOCK stage classification to standardize treatment failure in patients who are already hemodynamically compromised. This standardized classification will be used for monitoring the patient's vital status and permit timely escalation of therapy, still ensuring the validity of the trial results. If the trial hypothesis proofs to be correct, the SCAI SHOCK stage classification can easily be adapted in daily practice to monitor the impact of treatment and make management decisions.
3. TORPEDO-NL has refined patient selection criteria to select patient at the highest risk of PE-related mortality, which go beyond those mentioned in risk stratification tables of current guidelines. The additional clinical inclusion criteria of the trial represent patients with respiratory insufficiency who do not (yet) fulfil the shock criteria. Together, the 'enriched' patient population is likely to benefit from the intervention.
4. For this study, we harmonized catheter-directed thrombectomy procedures including anticoagulant treatment during and after the procedure, ensuring the validity and applicability of the findings of this study. Also, clearly described procedures used in a major RCT may help in specifying future guideline recommendations.
5. We allow for any commercially available approved catheter-directed thrombectomy device. Applicable guidelines do not make a difference between different thrombectomy devices and the CE approval for available devices is comparable [17,39]. In this way, our results are widely applicable and truly test the concept of catheter-directed thrombectomy for high-risk PE, rather than a specific device that may no longer be available in the (near) future.
6. We have incorporated EXPERT-PE teams to be part of the study design. Along with the rise of new interventional therapies came the introduction of EXPERT-PE teams, composed of multidisciplinary experts involved in treating acute PE, recognizing that PE patients may be managed by several different specialties and departments, even within the same hospital. The EXPERT-PE concept provides a multidisciplinary and rapid platform for deciding on an individualized treatment strategy in an era of rapidly developing advanced treatment options, combining expert opinion from all involved specialties, setting the quality standards for modern PE care, and forming the base for future research in PE care [40]. Recognizing the importance of EXPERT-PE teams to safeguard the quality of care, e.g. by implementing Plan-Do-Check-Act (PDCA) cycles and monitoring the outcomes of care, only hospitals with an institutionalized EXPERT-PE team may participate in TORPEDO-NL; members of the local teams are primarily responsible for patient enrolment and adherence to the study procedures.
7. A carefully selected group of patients from multiple organizations are integral to all stages of trial design and management. Patient representatives were equal partners along with healthcare professionals to inform the selection criteria and outcomes and have contributed largely to the patient information forms of the trial. By sharing their perspectives, patients provided a nuanced insight into gaps and barriers in current knowledge, and their input assured alignment of necessary clinical outcomes with the lived experience.
8. Finally, the comprehensive long-term follow-up of TORPEDO-NL extends the scope of the trial far beyond patient survival over the first few days and weeks. The trial has been designed to meticulously evaluate the impact of the intervention on patient-relevant outcomes including functional recovery and quality of life. Moreover, these outcomes will be accompanied by extensive economic analysis to establish the overall impact of catheter-directed thrombectomy for acute high-risk PE on use of healthcare resources and society as a whole.

4. Conclusion

TORPEDO-NL will address the most important remaining gaps in evidence regarding the treatment of high-risk PE to date. Taken together, after several years of observational studies, if the intervention arm of TORPEDO-NL is confirmed to be superior to the control arm, catheter-directed thrombectomy will become the treatment of choice in this patient population, allowing for strong guideline recommendations and setting the standard for both future trials in high-risk PE as well as patient management in daily clinical practice.

CRediT authorship contribution statement

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: CAU reports financial support was provided by Netherlands Health Care Institute & the Netherlands Organization for Health Research and Development. CAU reports financial support was provided by Dutch Heart Foundation. CAU reports financial support was provided by Inari Medical Inc. CAU reports financial support was provided by Penumbra Inc. IAM received speaker fees from Penumbra Inc. and Medtronic, outside this work and paid to the institution. JMMC received research funds from Shockwave Medical and EIT Health and consultant/speaker fees from Shockwave Medical, Abiomed, Boston Scientific, Penumbra Inc. and Angiodynamics, outside this work and paid to the institution. CVEK received consultant payment from Baxter, outside this work and paid to the institution. CLM reports having received research funds from the Dutch Heart Foundation, Foundation SGS and speaker fees from AOP, outside this work and paid to the institution. NVM received research grants from Abbott Vascular, Medtronic, Boston Scientific, Daiichi Sankyo, Teleflex and advisory fees from Anteris, JenaValve, Siemens, Polares, Pie Medical, Materialise, PulseCath BV, Abiomed, Abbott Vascular, Medtronic, Boston Scientific, Daiichi Sankyo, Teleflex, outside this work and paid to the institution. MNL received research funding from Leo Pharma, outside this work and paid to her institution. SL received funding by qure.ai, outside this work and paid to the institution. HJS is paid consultant for AngioDynamiscs, outside this work and paid to the institution. SVK received institutional grants and personal lecture/consultant fees from Bayer AG, Daiichi-Sankyo, Inari Medical, Penumbra Inc. and Boston Scientific. AOK received research funding from Xenios AG and consultancy payments from Philips, all outside this work and paid to his institution. FAK received research funding from Bayer, BMS, BSCI, AstraZeneca, MSD, Leo Pharma, Actelion, VarmX, The Netherlands Organisation for Health Research and Development, The Dutch Heart Foundation, and the Horizon Europe Program, all outside this work and paid to his institution. ARB is in the advisory board BMS, AstraZeneca, all outside this work and paid to his institution. All other authors have nothing to disclose. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A–C. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.thromres.2025.109420.

References

[1] M.V. Huisman, S. Barco, S.C. Cannegieter, et al., Pulmonary embolism, Nat. Rev. Dis. Primers 4 (2018) 18028, https://doi.org/10.1038/nrdp.2018.28.
[2] S.V. Konstantinides, G. Meyer, C. Becattini, et al., 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS), Eur. Heart J. 41 (4) (2020) 543–603, https://doi.org/10.1093/eurheartj/ehz405 [published Online First: 2019/09/11].
[3] P.M. Roy, A. Penaloza, O. Hugli, et al., Triaging acute pulmonary embolism for home treatment by Hestia or simplified PESI criteria: the HOME-PE randomized trial, Eur. Heart J. 42 (33) (2021) 3146–3157, https://doi.org/10.1093/eurheartj/ehab373 [published Online First: 2021/08/08].
[4] N. Meneveau, M.F. Séronde, M.C. Blonde, et al., Management of unsuccessful thrombolysis in acute massive pulmonary embolism, Chest 129 (4) (2006) 1043–1050, https://doi.org/10.1378/chest.129.4.1043.

[5] C. Marti, G. John, S. Konstantinides, et al., Systemic thrombolytic therapy for acute pulmonary embolism: a systematic review and meta-analysis, Eur. Heart J. 36 (10) (2015) 605–614, https://doi.org/10.1093/eurheartj/ehu218 [published Online First: 20140610].

[6] C. Jerjes-Sanchez, A. Ramírez-Rivera, García M. de Lourdes, et al., Streptokinase and heparin versus heparin alone in massive pulmonary embolism: a randomized controlled trial, J. Thromb. Thrombolysis 2 (3) (1995) 227–229, https://doi.org/10.1007/bf01062714.

[7] K. Keller, L. Hobohm, M. Ebner, et al., Trends in thrombolytic treatment and outcomes of acute pulmonary embolism in Germany, Eur. Heart J. 41 (4) (2020) 522–529, https://doi.org/10.1093/eurheartj/ehz236.

[8] S. Barco, S.H. Mahmoudpour, L. Valerio, et al., Trends in mortality related to pulmonary embolism in the European region, 2000-15: analysis of vital registration data from the WHO mortality database, Lancet Respir. Med. 8 (3) (2020) 277–287, https://doi.org/10.1016/S2213-2600(19)30354-6.

[9] S. Barco, L. Valerio, W. Ageno, et al., Age-sex specific pulmonary embolism-related mortality in the USA and Canada, 2000-18: an analysis of the WHO Mortality Database and of the CDC Multiple Cause of Death database, Lancet Respir. Med. 9 (1) (2021) 33–42, https://doi.org/10.1016/S2213-2600(20)30417-3 [published Online First: 20201012].

[10] N. Kucher, E. Rossi, M. De Rosa, et al., Massive pulmonary embolism, Circulation 113 (4) (2006) 577–582, https://doi.org/10.1161/circulationaha.105.592592.

[11] P. Pruszczyk, F.A. Klok, N. Kucher, et al., Percutaneous treatment options for acute pulmonary embolism: a clinical consensus statement by the ESC working group on pulmonary circulation and right ventricular function and the European Association of Percutaneous Cardiovascular Interventions, EuroIntervention 18 (8) (2022), https://doi.org/10.4244/EIJ-D-22-00246 e623-e38.

[12] T. Tu, C. Toma, V.F. Tapson, et al., A prospective, single-arm, multicenter trial of catheter-directed mechanical thrombectomy for intermediate-risk acute pulmonary embolism: the FLARE study, JACC Cardiovasc. Interv. 12 (9) (2019) 859–869, https://doi.org/10.1016/j.jcin.2018.12.022.

[13] M.J. Silver, C.M. Gibson, J. Giri, et al., Outcomes in high-risk pulmonary embolism patients undergoing FlowTriever mechanical thrombectomy or other contemporary therapies: results from the FLAME study, Circ. Cardiovasc. Interv. 16 (10) (2023) e013406, https://doi.org/10.1161/circinterventions.123.013406.

[14] A.K. Sista, J.M. Horowitz, V.F. Tapson, et al., Indigo aspiration system for treatment of pulmonary embolism: results of the EXTRACT-PE trial, JACC Cardiovasc. Interv. 14 (3) (2021) 319–329, https://doi.org/10.1016/j.jcin.2020.09.053 [published Online First: 20210113].

[15] J.M. Moriarty, S.Y. Dohad, B.J. Schiro, et al., Clinical, functional, and quality-of-life outcomes after computer assisted vacuum thrombectomy for pulmonary embolism: interim analysis of the STRIKE-PE study, J. Vasc. Interv. Radiol. 35 (8) (2024) 1154–1165, e6, https://doi.org/10.1016/j.jvir.2024.04.028 [published Online First: 20240509].

[16] M.A. De Gregorio, J.A. Guirola, W.T. Kuo, et al., Catheter-directed aspiration thrombectomy and low-dose thrombolysis for patients with acute unstable pulmonary embolism: prospective outcomes from a PE registry, Int. J. Cardiol. 287 (2019) 106–110, https://doi.org/10.1016/j.ijcard.2019.02.061.

[17] M. Zuin, B. Bikdeli, J. Ballard-Hernandez, et al., International clinical practice guideline recommendations for acute pulmonary embolism: harmony, dissonance, and silence, J. Am. Coll. Cardiol. 84 (16) (2024) 1561–1577, https://doi.org/10.1016/j.jacc.2024.07.044.

[18] M. Koslow, G. Epstein Shochet, F. Fenadka, et al., Systemic thrombolysis therapy is associated with improved outcomes among patients with acute pulmonary embolism and respiratory failure, Am J Med Sci 360 (2) (2020) 129–136, https://doi.org/10.1016/j.amjms.2020.04.028.

[19] B. Ergan, R. Ergün, T. Çalışkan, et al., Mortality related risk factors in high-risk pulmonary embolism in the ICU, Can. Respir. J. 2016 (2016) 2432808, https://doi.org/10.1155/2016/2432808 [published Online First: 20161129].

[20] R. Pancani, L. Villari, F. Aquilini, et al., Prognostic role of respiratory failure in acute pulmonary embolism: a prospective multicenter study, Thromb. Res. 217 (2022) 33–35, https://doi.org/10.1016/j.thromres.2022.07.002 [published Online First: 20220709].

[21] C. Kabrhel, I. Okechukwu, P. Hariharan, et al., Factors associated with clinical deterioration shortly after PE, Thorax 69 (9) (2014) 835–842, https://doi.org/10.1136/thoraxjnl-2013-204762.

[22] M.V. Huisman, F.A. Klok, How I diagnose acute pulmonary embolism, Blood 121 (22) (2013) 4443–4448, https://doi.org/10.1182/blood-2013-03-453050.

[23] J. Helms, M. Carrier, F.A. Klok, High-risk pulmonary embolism in the intensive care unit, Intensive Care Med. 49 (5) (2023) 579–582, https://doi.org/10.1007/s00134-023-07011-0 [published Online First: 20230316].

[24] R. Mehran, S.V. Rao, D.L. Bhatt, et al., Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium, Circulation 123 (23) (2011) 2736–2747, https://doi.org/10.1161/circulationaha.110.009449.

[25] N.K. Kapur, M. Kanwar, S.S. Sinha, et al., Criteria for defining stages of cardiogenic shock severity, J. Am. Coll. Cardiol. 80 (3) (2022) 185–198, https://doi.org/10.1016/j.jacc.2022.04.049.

[26] S. Arora, S. Vallabhajosyula, V. Aggarwal, et al., Novel risk stratification and hemodynamic profiling in acute pulmonary embolism: a proposed classification inspired by Society for Cardiovascular Angiography and Intervention Shock Staging, Interv. Cardiol. Clin. 12 (3s) (2023) e1–e20, https://doi.org/10.1016/j.iccl.2024.04.002.

[27] S.S. Naidu, D.A. Baran, J.C. Jentzer, et al., SCAI SHOCK stage classification expert consensus update: a review and incorporation of validation studies: this statement was endorsed by the American College of Cardiology (ACC), American College of Emergency Physicians (ACEP), American Heart Association (AHA), European Society of Cardiology (ESC) Association for Acute Cardiovascular Care (ACVC), International Society for Heart and Lung Transplantation (ISHLT), Society of Critical Care Medicine (SCCM), and Society of Thoracic Surgeons (STS) in December 2021, J. Am. Coll. Cardiol. 79 (9) (2022) 933–946, https://doi.org/10.1016/j.jacc.2022.01.018.

[28] G. Boon, S. Barco, L. Bertoletti, et al., Measuring functional limitations after venous thromboembolism: optimization of the post-VTE functional status (PVFS) scale, Thromb. Res. 190 (2020) 45–51, https://doi.org/10.1016/j.thromres.2020.03.020.

[29] C.M.M. de Jong, G. Boon, Y.N.J. Le, et al., The post-venous thromboembolism functional status scale: from call to action to application in research, extension to COVID-19 patients, and its use in clinical practice, Semin. Thromb. Hemost. (2023), https://doi.org/10.1055/s-0043-1764467 [published Online First: 20230320].

[30] D. Abrams, S.B. Montesi, S.K.L. Moore, et al., Powering bias and clinically important treatment effects in randomized trials of critical illness, Crit. Care Med. 48 (12) (2020) 1710–1719, https://doi.org/10.1097/ccm.0000000000004568.

[31] M. Mv, K. Mv, S. Maae, et al., Dutch tariff for the five-level version of EQ-5D, Value Health 19 (4) (2016) 343–352, https://doi.org/10.1016/j.jval.2016.01.003 [published Online First: 20160330].

[32] M.F. Drummond, M.J. Sculpher, K. Claxton, et al., Methods for the Economic Evaluation of Health Care Programmes 32, Oxford univ press, 2015.

[33] iMTA, Questionnaires for the measurement of costs in economic evaluations: iMTA, Available from: https://www.imta.nl/questionnaires/.

[34] S. Peeters, T. Kanters, Z. Nederland, Kostenhandleiding voor economische evaluaties in de gezondheidszorg: Methodologie en referentieprijzen, 2024.

[35] Guideline for economic evaluations in healthcare (2024 version): Zorginstituut Nederland, Available from: https://english.zorginstituutnederland.nl/publications/reports/2024/01/16/guideline-for-economic-evaluations-in-healthcare, 2024.

[36] Á.J. Ben, J.M. van Dongen, M. El Alili, et al., Conducting trial-based economic evaluations using R: a tutorial, Pharmacoeconomics 41 (11) (2023) 1403–1413, https://doi.org/10.1007/s40273-023-01301-7.

[37] S.D. Sullivan, J.A. Mauskopf, F. Augustovski, et al., Budget impact analysis-principles of good practice: report of the ISPOR 2012 budget impact analysis good practice II task force, Value Health 17 (1) (2014) 5–14, https://doi.org/10.1016/j.jval.2013.08.2291.

[38] M.D. Wilkinson, M. Dumontier, I.J. Aalbersberg, et al., The FAIR guiding principles for scientific data management and stewardship, Sci. Data 3 (1) (2016) 160018, https://doi.org/10.1038/sdata.2016.18.

[39] J. Giri, A.K. Sista, I. Weinberg, et al., Interventional therapies for acute pulmonary embolism: current status and principles for the development of novel evidence: a scientific statement from the American Heart Association, Circulation 140 (20) (2019) e774–e801, https://doi.org/10.1161/cir.0000000000000707.

[40] L. Hobohm, I.T. Farmakis, K. Keller, et al., Pulmonary embolism response team (PERT) implementation and its clinical value across countries: a scoping review and meta-analysis, Clin. Res. Cardiol. 112 (10) (2023) 1351–1361, https://doi.org/10.1007/s00392-022-02077-0 [published Online First: 20220817].

[41] Y.M. Ende-Verhaar, L.J. Meijboom, L.J.M. Kroft, et al., Usefulness of standard computed tomography pulmonary angiography performed for acute pulmonary embolism for identification of chronic thromboembolic pulmonary hypertension: results of the InShape III study, J. Heart Lung Transplant. 38 (7) (2019) 731–738, https://doi.org/10.1016/j.healun.2019.03.003.

[42] A.M. Gwozdz, C.M.M. de Jong, L.S. Fialho, et al., Development of an international standard set of outcome measures for patients with venous thromboembolism: an International Consortium for Health Outcomes Measurement consensus recommendation, Lancet Haematol. 9 (9) (2022) e698–e706, https://doi.org/10.1016/S2352-3026(22)00215-0.

[43] F.A. Klok, D.M. Cohn, S. Middeldorp, et al., Quality of life after pulmonary embolism: validation of the PEmb-QoL questionnaire, J. Thromb. Haemost. 8 (3) (2010) 523–532, https://doi.org/10.1111/j.1538-7836.2009.03726.x.