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Master of Science Thesis

“MANAGEMENT OF INTERMEDIATE-HIGH RISK PULMONARY EMBOLISM: THROMBOLYSIS, INTERVENTIONAL TREATMENT AND NOVEL THERAPIES”

by

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Abstract

Introduction: Pulmonary embolism (PE) is a potentially life-threatening condition with an increasing global incidence and a significant impact on morbidity and mortality. Risk stratification is based on clinical presentation, echocardiographic findings, and laboratory parameters, guiding the selection of the appropriate therapeutic approach. The management of low-risk and high-risk PE is well established in the current literature. However, intermediate-high risk PE represents a clinical gray area, raising ongoing questions regarding the optimal treatment strategy.

Purpose: The purpose of the present study is to critically review the current literature regarding the management and therapeutic strategies for patients with intermediate-high risk pulmonary embolism, and to explore existing discrepancies between established clinical guidelines and real-world clinical practice.

Methods: This review was based on systematic research of international literature, conducted using a predefined algorithm and relevant keywords. No publication date restrictions were applied. Only studies published in English and involving adult patients were included.

Results: DOACs are first-line treatment for intermediate-high-risk PE but require caution in renal/hepatic impairment. LMWH and fondaparinux are preferred in pregnancy, cancer, or history of HIT. Systemic thrombolysis is not routinely recommended. CDT shows lower mortality and bleeding in high-risk patients. Surgical embolectomy has shown promising outcomes but limited evidence. Comparisons between CDT, USAT, and mechanical techniques show conflicting results, highlighting the need for further research.

Conclusions: Therapeutic decisions for intermediate-high-risk PE often rely on the physician's judgment. Due to the lack of large-scale studies comparing anticoagulation and reperfusion strategies, the optimal approach remains unclear. Prospective cohort studies are needed to optimize care, reduce long-term complications, and improve survival.

Keywords: Pulmonary embolism, intermediate-high risk, anticoagulation, reperfusion, catheter-directed, thrombolysis, embolectomy

Περίληψη στα Ελληνικά

Εισαγωγή: Η πνευμονική εμβολή αποτελεί μια δυνητικά θανατηφόρα κατάσταση με αυξανόμενη επίπτωση παγκοσμίως και σημαντική συμβολή στη νοσηρότητα και θνητότητα. Η ταξινόμηση της βαρύτητας βασίζεται σε κλινικά, υπερηχοκαρδιογραφικά και εργαστηριακά ευρήματα και καθορίζει την εκάστοτε θεραπευτική προσέγγιση. Η αντιμετώπιση της πνευμονικής εμβολής σε περιπτώσεις υψηλού ή χαμηλού κινδύνου είναι σαφώς καθορισμένη από τη διεθνή βιβλιογραφία. Αντιθέτως, η πνευμονική εμβολή ενδιάμεσου προς υψηλού κινδύνου αποτελεί μία «γκρίζα ζώνη», γύρω από την οποία ανακύπτουν ερωτήματα αναφορικά με τη βέλτιστη στρατηγική αντιμετώπισης.

Σκοπός: η παρούσα μελέτη στοχεύει στην κριτική ανασκόπηση της σύγχρονης βιβλιογραφίας αναφορικά με τις στρατηγικές αντιμετώπισης και θεραπείας ασθενών με πνευμονική εμβολή ενδιάμεσου προς υψηλού κινδύνου, καθώς και στη διερεύνηση των υπάρχουσών αποκλίσεων μεταξύ των κατευθυντήριων οδηγιών και της κλινικής πρακτικής.

Μέθοδοι: Η παρούσα ανασκόπηση βασίστηκε σε συστηματική αναζήτηση της διεθνούς βιβλιογραφίας, η οποία πραγματοποιήθηκε με τη χρήση προκαθορισμένου αλγορίθμου και κατάλληλων λέξεων-κλειδιών. Δεν εφαρμόστηκε χρονικός περιορισμός κατά την αναζήτηση. Συμπεριλήφθηκαν μελέτες στην αγγλική γλώσσα που αφορούσαν αποκλειστικά ενήλικες ασθενείς.

Αποτελέσματα: Τα νεότερα αντιπηκτικά αποτελούν θεραπεία πρώτης γραμμής για την πνευμονική εμβολή ενδιάμεσου προς υψηλού κινδύνου, αλλά απαιτείται προσοχή σε περιπτώσεις νεφρικής ή ηπατικής δυσλειτουργίας. Η ΗΧΜΒ και η φονταπαρινόξη προτιμώνται σε εγκυμοσύνη, ενεργό κακοήθεια ή ιστορικό HIT. Η συστηματική θρομβόλυση δεν συνιστάται ως θεραπεία ρουτίνας. Η CDT παρουσιάζει χαμηλότερη θνησιμότητα και αιμορραγία σε υψηλού κινδύνου ασθενείς. Η χειρουργική εμβολεκτομή δείχνει ενθαρρυντικά αποτελέσματα, αν και τα διαθέσιμα δεδομένα είναι περιορισμένα. Οι συγκρίσεις μεταξύ CDT, USAT και μηχανικών τεχνικών καταλήγουν σε αντικρουόμενα αποτελέσματα, αναδεικνύοντας έτσι την ανάγκη για περαιτέρω έρευνα.

Συμπεράσματα: Οι θεραπευτικές αποφάσεις για τη διαχείριση της πνευμονικής εμβολής ενδιάμεσου προς υψηλού κινδύνου βασίζονται συχνά στην κλινική κρίση του θεράποντα ιατρού. Εξαιτίας της έλλειψης μεγάλων μελετών που συγκρίνουν στρατηγικές αντιπηκτικής θεραπείας και θεραπειών επαναιμάτωσης, η βέλτιστη προσέγγιση παραμένει ασαφής. Απαιτούνται προοπτικές μελέτες για τη βελτιστοποίηση της φροντίδας, τη μείωση των μακροχρόνιων επιπλοκών και τη βελτίωση της επιβίωσης.

Λέξεις-κλειδιά: Πνευμονική εμβολή, ενδιάμεσου-υψηλού κινδύνου, αντιπηκτική αγωγή, θεραπείες επαναιμάτωσης, καθοδηγούμενη μέσω καθετήρα, θρομβόλυση, εμβολεκτομή

Index of Acronyms

ABG	Arterial Blood Gas
AHA	American Heart Association
APC	Active Protein C
APL	Antiphospholipid Syndrome
APTT	Activated Partial Thromboplastin Time
ART	Angiojet Rheolytic Thrombectomy
AT	Antithrombin III
BNP	Brain Natriuretic Peptide
CDF	Catheter-Directed thrombus Fragmentation
CDT	Catheter-Directed Thrombolysis
CHEST	American College of Chest Physicians
CKD	Chronic Kidney Disease
CNS	Central Nervous System
CTEPH	Chronic Thromboembolic Pulmonary Hypertension
CTPA	Computed Tomography Pulmonary Angiogram
CrCl	Creatinine Clearance
DOAC	Direct Oral Anticoagulant
DVT	Deep Vein Thrombosis
ECG	Electrocardiography
ESC	European Society of Cardiology
FDA	Food and Drug Administration
FXa	Factor Xa
HIT	Heparin-Induced Thrombocytopenia

INR	International Normalized Ratio
IVC	Inferior Vena Cava
LMWH	Low Molecular Weight Heparin
LV	Left Ventricle
PASP	Pulmonary Artery Systolic Pressure
PC	Protein C
PE	Pulmonary Embolism
PS	Protein S
RPVO	Residual Pulmonary Vascular Obstruction
rTPA	Recombinant Tissue Plasminogen Activator
RV.....	Right Ventricle
SPE	Surgical Pulmonary Embolectomy
sPESI	simplified PESI
ST	Systemic Thrombolysis
SPECT	Single-Photon Emission Computed Tomography
TTE	Transthoracic Echocardiogram
UFH	Unfractionated Heparin
USAT	Ultrasound-Assisted Thrombolysis
VKA	Vitamin K antagonist
V/Q	Ventilation/Perfusion
VTE	Venous Thromboembolism

Table of Contents

Introduction	15
Definition	15
Epidemiology	15
Pathophysiology.....	15
Predisposing factors	16
Diagnosis	20
Predictive tools	20
Diagnostic algorithm	21
D-dimers	22
Computed Tomography Pulmonary Angiography – CTPA	22
Ventilation/Perfusion (V/Q) Lung Scintigraphy - SPECT.....	22
Echocardiography.....	23
Chest Xray.....	23
ECG.....	23
Arterial Blood Gas	24
Clinical Presentation	24
Risk Stratification	24
Literature review	25
Aim of review	25
Methods	25
Current Therapies in Acute PE	26
Parenteral anticoagulants.....	26
LMWH	26
Fondaparinux	27
UFH.....	27
Oral anticoagulants.....	27

DOACs	27
Vitamin K antagonists.....	28
Duration of Therapy	29
Reperfusion Treatments	32
Systemic Thrombolysis (ST).....	32
Catheter-directed therapies	34
Catheter-directed thrombolysis (CDT).....	34
Ultrasound-assisted thrombolysis (USAT).....	35
Catheter-directed thrombus fragmentation (CDF)	36
Aspiration Embolectomy.....	37
Rheolytic embolectomy	38
Surgical embolectomy (SPE).....	38
Special populations.....	39
Recurrence	42
Residual Pulmonary Vascular Obstruction.....	43
Results.....	44
Discussion	46
Conclusion	48
References	49

Tables and Figures

Table 1. Predisposing factors for VTE	13
Table 2. Predisposing risk factors based on the long-term risk of VTE recurrence	15
Table 3. Geneva score	17
Table 4. Wells score	18
Table 5. Anticoagulation therapy regimens (dosage and duration of therapy) based on the treatment phase	26
Table 6. Thrombolysis therapeutic regimens	29
Table 7. Contradictions to systemic thrombolysis	30
Figure 1. Prisma Flow Diagram	42

Introduction

Definition

Acute pulmonary embolism (PE) is a major cause of in-hospital mortality and morbidity, as well as a frequent cause of sudden death. It is defined as the occlusion of a pulmonary artery, most frequently caused by a thrombus originating from the deep venous system of the lower extremities. Amniotic fluid, fat, and gas can also cause pulmonary embolism, but the occurrence is rare (1).

Epidemiology

The incidence of PE in the general population is estimated to be 39–115 per 100,000 population. Over the years, PE incidence has substantially increased and can be partly attributed to the greater use of objective imaging techniques and enhanced image quality, especially with computed tomography, pulmonary angiography, scintigraphy, and magnetic resonance imaging. Moreover, after the beginning of the COVID-19 pandemic, a significant rise in venous thromboembolism (VTE) incidence, including PE, has been observed, leading to a further increase in medical awareness and imaging testing. Despite the increase in PE occurrence, observational data have shown that all-cause and PE-related mortality follows a downward trend in recent decades and has been associated with more efficient therapeutic management (1–4).

Pathophysiology

PE is typically caused when a thrombus that has formed in the valves of the peripheral venous system, usually those of the lower extremities, travels to the pulmonary circulation. Small emboli obstruct peripheral or subsegmental arterial branches, whereas larger-sized thrombi occlude segmental branches or even the main pulmonary artery. Venous thrombosis is based on the principle of Virchow's triad, which includes hemostasis, endothelial vascular damage, and blood hyperviscosity. This principle, in combination with predisposing risk factors, leads to the occurrence of PE.

Obstruction of pulmonary circulation leads to impaired gas exchange, ventilation-perfusion mismatch, and consequently disturbance of acid-base balance. More specifically, decreased perfusion of the pulmonary capillaries results in insufficient oxygen uptake, carbon dioxide release, and, therefore hypoxemia, compensatory tachypnea, and respiratory alkalosis (5).

Moreover, the intravascular occlusion leads to a series of hemodynamic alterations in the pulmonary circulation and cardiac function. It causes a rise in pulmonary vascular resistance, pulmonary hypertension, and thus an increase in the right ventricle (RV) afterload. Subsequently, it provokes increased tension in the RV walls, which causes RV diastolic dysfunction and decreases coronary blood flow, leading to further myocardial injury of the already stunned RV. Gradually, RV systolic dysfunction is established, and the interventricular septum flattens due to the RV diastolic overload, resulting in a reduction of left ventricle (LV) preload, stroke volume, cardiac output, and finally hemodynamic collapse (6).

Predisposing factors

Predisposing risk factors for VTE, including PE, are categorized into strong, moderate, and weak as shown in Table 1.

Table 1. Predisposing factors for VTE

Strong risk factors (Odds ratio >10)	Moderate risk factors (Odds ratio 2-9)
Fracture of the lower limb	Arthroscopic knee surgery
Hospitalization for heart failure or atrial fibrillation/flutter (within the previous 3 months)	Hormone replacement therapy (depends on formulation)
Hip or knee replacement	Blood transfusion
Major trauma	Central venous lines
Myocardial infarction (within the previous 3 months)	Congestive heart failure or respiratory failure
Previous VTE	Chemotherapy

Spinal cord injury	Intravenous catheters and leads
Weak risk factors (Odds ratio <2)	Cancer (highest risk in metastatic disease)
Bed rest >3 days	Autoimmune diseases
Diabetes mellitus	In vitro fertilization
Arterial hypertension	Oral contraceptive therapy
Immobility due to sitting (e.g., prolonged car or air travel)	Infection (specifically pneumonia, urinary tract infection, and HIV)
Increasing age	Post-partum period
Obesity	Inflammatory bowel disease
Laparoscopic surgery	Erythropoiesis-stimulating agents
Pregnancy	Paralytic stroke
Varicose veins	Superficial vein thrombosis
	Thrombophilia

Thrombophilias form a distinct group of predisposing factors. They can be either inherited or acquired. In inherited thrombophilias, the presence of a single pathological polymorphism, or the combination of multiple, enhances the likelihood of thromboembolism. The mutation of homozygous factor V Leiden that causes active protein C (APC) resistance has been strongly associated with VTE occurrence and has been linked to up to 40% of VTE events, including PE. Deficiencies of antithrombin III (AT), protein S (PS), protein C (PC), and homozygous prothrombin G20210A (PT20210A) mutation are also associated with VTE. In the general population, the prevalence of hereditary thrombophilia varies, with factor V Leiden occurring in 4 to 5% of individuals, PC deficiency in 0.2 to 0.4%, PS deficiency in 0.2%, and AT deficiency in 0.02%. A retrospective study published in 2020 involving 227 patients explored the link between thrombophilia and PE. In this study, 47.6% had thrombophilia, with deficiencies in PS, PC, ATIII, and hyperhomocysteinemia being the most commonly detected abnormalities. Patients with thrombophilia were, on average, 10 years younger, and prior deep vein thrombosis (DVT) or PE were significant risk factors. The most common acquired thrombophilia is antiphospholipid syndrome (APL). Its presence determines the choice and duration of

anticoagulation therapy, as will be discussed below in the “oral anticoagulants” section. PE can be the presenting clinical manifestation in 9-12% of patients with APL syndrome. Current literature advises against preventive screening for inherited thrombophilias. However, thrombophilia testing (including antiphospholipid antibodies and lupus anticoagulant) may be considered for patients who experience VTE at an early age (e.g., under 50 years) without any other obvious risk factors, particularly if there is a strong family history of VTE.

Another classification of predisposing risk factors is based on the long-term risk of VTE recurrence. They are divided into major or minor transient and persistent risk factors (Table 2). The occurrence of thromboembolism is usually a result of the combination of permanent and temporary risk factors (1,7,8).

Table 2. Predisposing risk factors based on the long-term risk of VTE recurrence

Estimated risk for long-term recurrence	Risk factor category for index VTE	Examples
Low <3% per year	Major transient or reversible factors associated with > 10-fold increased risk for the index VTE event (compared to patients without the risk factor)	• Surgery with general anesthesia>30min • Confined in bed hospital ("only bathroom privileges") for ≥3 days due to an acute illness, acute exacerbation, or a chronic illness • Trauma with fractures
Intermediate 3-8% per year	Major transient or reversible factors associated with ≤10-	• Minor surgery (general

	time or greater increased risk for the first (index) VTE event	anesthesia <30min) • Admission to hospital for <3 days with an acute illness • Estrogen therapy or contraception • Pregnancy or puerperium • Confined to bed out of hospital for ≥3 days with an acute illness • Leg injury (without fracture) associated with reduced mobility for ≥3 days • Long-haul flight
	Non-malignant persistent risk factors	• Inflammatory bowel disease • Active autoimmune disease
	Nonidentifiable risk factor	
High >8% per year		• Active cancer • One or more previous episodes of VTE in the absence of a

		major transient or reversible factor • Antiphospholipid antibody syndrome
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Diagnosis

Predictive tools

The clinical (pre-test) probability of PE is estimated by using predictive models such as the revised Geneva score and the Wells score. All the parameters used in score calculations are demonstrated in Tables 3 and 4. Based on these scores, clinical probability is stratified into low, intermediate, and high. The revised Geneva rule provides an advantage over the Wells score, as it does not include a physician's clinical judgment.

Table 3. Geneva score

Geneva score	Revised	Simplified
Age >65 years	1	1
Previous DVT or PE	3	1
Surgery or fracture within the past month	2	1
Active cancer	2	1
Unilateral lower-limb pain	3	1
Hemoptysis	2	1
Heart rate (beats per minute)		1
• 75-94 bpm	2	1
• ≥95 bpm	5	1
Pain on lower-limb palpation and unilateral edema	4	1
Clinical probability – Three-level score		
Low	0-3	0-1
Intermediate	4-10	2-4
High	≥11	≥5

PE likelihood – Two-level score		
PE-unlikely	0-5	0-2
PE-likely	≥6	≥3

Table 4. Wells score

Wells score	Original	Modified
Clinical signs and symptoms of DVT	3	1
Heart rate >100 bpm	1,5	1
PE is the #1 diagnosis or equally likely	3	1
Previous PE or DVT	1,5	1
Hemoptysis	1	1
Cancer	1	1
Immobilization ≥3 days or surgery within the past 4 weeks	1,5	1
Clinical Probability – Three-level score		
Low	>6	
Intermediate	2-6	
High	<2	
PE likelihood – Two-level score		
PE-unlikely	≤4	≤1
PE- likely	>4	>1

Regardless of the scoring system applied, the percentage of patients with confirmed PE is approximately 10% in the low-probability group, 30% in the intermediate-probability group, and 65% in the high-probability group (8).

Diagnostic algorithm

The diagnostic algorithm for PE is based on patients' hemodynamic status. Hemodynamically unstable patients with suspected PE undergo echocardiography to assess the RV function or an emergent Computed Tomography Pulmonary Angiography (CTPA), to promptly initiate treatment. In hemodynamically stable patients, clinical probability is assessed using the

revised Geneva or Wells score, in combination with laboratory testing using D-dimer levels. Negative D-dimer results are only evaluated in cases where clinical suspicion is weak, to rule out the diagnosis. A positive D-dimer result strengthens the suspicion of the diagnosis, prompting further imaging testing with CTPA. In the case of moderate or high clinical suspicion, D-dimer is not assessed, and CTPA should be performed (9).

D-dimers

D- dimers are produced as a result of fibrinolysis. Apart from acute thrombosis, D-dimer levels are elevated in active cancer, during pregnancy, in inflammatory disease or inflammation, and hospitalized patients. The specificity of d-dimers is strongly associated with age, and it is estimated to decrease by around 10% in patients over 80 years. Thus, age-adjusted d-dimers cut-offs are used when tested in the elderly ($\text{age} \times 10 \mu\text{g/L}$, for patients aged >50 years) (8,9).

Computed Tomography Pulmonary Angiography (CTPA)

CTPA is the gold-standard imaging testing when PE is suspected, with sensitivity and specificity ranging from 96 to 100% and 89 to 98%, respectively. Beyond imaging the pulmonary vasculature and identifying the thrombus, CTPA allows for the assessment of RV/LV ratio, pulmonary artery and coronary sinus diameter, left atrium size, inferior vena cava reflux, displacement of the interventricular septum, pulmonary artery distensibility, and coronary artery calcifications. Normal CTPA in patients with low or intermediate clinical probability can exclude PE diagnosis without further testing. However, the excessive use of CTPA to rule out PE represents a significant financial burden on the healthcare system (10).

Ventilation/Perfusion (V/Q) Lung Scintigraphy – Single-Photon Emission Computed Tomography (V/Q SPECT)

In cases where CTPA is contraindicated, such as pregnancy or a history of hypersensitivity to contrast agents, planar V/Q scintigraphy is considered the alternative imaging method in the diagnosis of PE. It evaluates the functional impact of the thrombus, alongside the ventilatory response of the affected lung tissue, in contrast to CTPA, which detects the location of the thrombus within

the pulmonary artery network. Tomographic imaging using single-photon emission computed tomography (V/Q SPECT) has been introduced to lung scintigraphy practice, aiming to ameliorate diagnostic accuracy. The European Association of Nuclear Medicine guidelines strongly advocate for the use of SPECT imaging in the diagnosis of PE (11,12).

Echocardiography

Transthoracic echocardiography (TTE) is a cornerstone in the management algorithm and risk stratification of both diagnosed and suspected PE. In patients with hemodynamic instability, the absence of RV dysfunction rules out the diagnosis, whereas the presence of impaired RV function supports the diagnosis and allows for immediate initiation of treatment. Pathological TTE findings in PE include RV enlargement, an RV/LV ratio >1.0 , the McConnell sign, flattening of the interventricular septum (D-shape), distention of the inferior vena cava (IVC) with reduced collapsibility, thrombus inside the right heart chambers, and signs of pulmonary hypertension. Furthermore, wall motion abnormalities and dissecting aortic flaps may be detected when acute coronary syndrome and acute aortic dissection are included in the differential diagnosis (13).

Chest Xray

The role of a chest Xray in diagnosing PE is primarily to exclude other potential causes of chest pain, shortness of breath, and hypoxemia. It is often abnormal, with cardiomegaly being the most common finding in acute PE, observed in 27% of cases. Other potential findings include pulmonary artery dilation, atelectasis, and pulmonary infiltrates. However, none of these radiological signs are sensitive or specific for diagnosing acute PE (14).

Electrocardiography (ECG)

ECG findings in PE are non-specific, and the most common is sinus tachycardia. Other findings include S1Q3T3 morphology, right bundle branch block morphology, inverted T waves in leads V1-V4, and QR in lead V1. These ECG findings may indicate impaired RV function (15).

Arterial Blood Gas (ABG)

ABG analysis provides limited diagnostic value in suspected PE. Hypoxemia, detected in up to 40% of patients, hypocapnia, and respiratory alkalosis are the most common findings. However, gas exchange translated into arterial oxygen saturation and acid-base balance may be preserved (16).

Clinical Presentation

PE may be symptomatic or asymptomatic if discovered as an incidental imaging finding. In most cases, PE is symptomatic, and clinical presentation varies from mild to severe and potentially life-threatening. Patients may experience symptoms such as pleuritic chest pain, dyspnea, syncope or pre-syncope, cough, or hemoptysis. PE may also present as sudden cardiac death in almost one-quarter of patients. The onset and number of symptoms are related to the extent and severity of PE and depend on the number and location of the thrombi in the pulmonary arterial tree, as well as the patient's comorbidities. Pleuritic chest pain is usually due to pleural irritation caused by peripheral thromboembolism. However, it may present as angina, underlying myocardial ischemia due to RV dysfunction. Dyspnea is caused by hypoxemia due to impaired gas exchange, following perfusion impairment in the pulmonary circulation. It is usually severe in central or segmental PE, while it may be mild or even transient in distal embolism. Syncope and pre-syncope indicate hemodynamic instability and underlying RV dysfunction. Cough and hemoptysis are usually secondary to increased vascular resistance and alveolar damage, due to embolism in peripheral arterial branches. The clinical signs of PE include tachycardia, tachypnea, and hypoxemia (1,8,17).

Risk Stratification

Risk stratification is defined as the assessment of factors that can indicate a higher risk of early death in patients with suspected or diagnosed PE. The classification of PE severity is of utmost importance, as it determines the optimal therapeutic approach. According to current American Heart Association (AHA) guidelines, PE is stratified to massive, submassive, and low risk depending on the hemodynamic status and right ventricular (RV) function (18).

According to current European Society of Cardiology (ESC) guidelines, PE is stratified to low-risk, intermediate-low risk, intermediate-high risk, and high-risk. In modern practice, the mortality rate for high-risk PE is reported to range from 15% to 30%, while for intermediate-risk PE, it falls between 3% and 15% (19). Indicators of mortality risk are the presence of hemodynamic instability, RV dysfunction, clinical parameters as assessed by the simplified pulmonary severity index (sPESI score), and elevated cardiac enzyme levels (troponin or BNP). The presence of three of the above criteria classifies patients in the intermediate-high-risk category. These patients depending on the close clinical evaluation, intense monitoring, and their comorbidities, can be treated either with anticoagulant therapy or with reperfusion therapies such as systematic thrombolysis, catheter-directed thrombolysis, or surgical embolectomy (20).

Literature review

Aim of review

The aim of this literature review is to present and analyze all currently available therapeutic options for intermediate-high risk pulmonary embolism, as they have evolved to date. It examines their implementation in accordance with established clinical guidelines and the findings of high-impact scientific studies. Furthermore, the review aims to highlight emerging therapeutic approaches and alternative perspectives in the management of this clinical entity, while also identifying gaps and limitations in the current literature.

Methods

A computer search for published studies (systematic reviews, systematic meta-analysis, literature reviews) was conducted in the PubMed and Cochrane databases up to 25 February 2025. The search algorithm used was as follows: (pulmonary embolism) AND ((intermediate) OR (high)) AND ((anticoagul*) OR (thrombolysis) OR (fibrinolysis) OR (embolectomy) OR (catheter-directed)). Also, we used the keyword "pulmonary embolism" along with the following keywords: epidemiology, prevalence, incidence, mortality, morbidity, pathophysiology, clinical presentation, diagnosis, risk stratification, therapy,

treatment, anticoagulation, low molecular heparin, unfractionated heparin, fondaparinux, direct oral anticoagulant, vitamin K antagonist, reperfusion, thrombolysis, fibrinolysis, catheter-directed, embolectomy, residual pulmonary obstruction. Restrictions in searching were the English language and the studies on adults. Although no restrictions were placed based on the publication date the most up-to-date articles were preferred. The search was performed on the title, abstracts, and keywords of the studies. Citations were exported to the Zotero library. The list of citations was then exported to a Word document that included the citation number, title, list of authors, the full abstract, and the journal citation.

Current Therapies in Acute PE

Prompt initiation of treatment in PE is paramount as the mortality risk is significantly higher within the first few hours to days of symptoms onset (21). Current guidelines suggest anticoagulation as the first-line treatment in intermediate-high-risk patients (8). Therapeutic strategies include parenteral anticoagulation with low molecular weight heparin (LMWH), fondaparinux, unfractionated heparin (UFH), direct oral anticoagulants (DOAC), and vitamin K antagonists (VKA).

Parenteral anticoagulants

Low Molecular Weight Heparin (LMWH)

LMWHs inhibit the coagulation cascade by activating antithrombin III (AT). AT binds to factor Xa, effectively inhibiting the conversion of prothrombin to thrombin and thus fibrinogen to fibrin. AT binds to and inhibits factor Xa (FXa) (22). In PE treatment with LMWH includes enoxaparin, tinzaparin, deltaparin, or nadroparin. Enoxaparin is administered subcutaneously at a weight-adjusted dose (1mg/kg), either twice or once daily if creatinine clearance (CrCl) is less than 30ml/min. Tinzaparin is administered subcutaneously once a day at weight-adjusted doses (175 IU/kg and up to 26,000 IU daily). Deltaparin is administered subcutaneously once or twice a day at weight-adjusted doses (100 IU/kg b.i.d. or 200 IU/kg q.d. up to 18,000 IU daily). Nadroparin is approved for PE treatment only in some European countries (8). Treatment with heparin

should be accompanied by platelet count monitoring and must be dose-adjusted based on renal function. According to ESC and AHA guidelines, LMWH is the treatment of choice during pregnancy and the standard of care in patients with cancer-related PE (8,18).

Fondaparinux

Fondaparinux facilitates the neutralization of FXa by increasing its affinity to AT and therefore inhibits the coagulation cascade. It is administered subcutaneously once daily based on body weight (5 mg q.d. if <50kg, 7,5 mg q.d. if 50-100 kg, 10 mg if >100 kg) (8). In patients with severe renal impairment (CrCl 20-30 mL/min), administration is not recommended and is contraindicated if CrCl is less than 20 mL/min. Fondaparinux is the treatment of choice in patients with a history of heparin-induced thrombocytopenia, as LMWH and UFH are contraindicated (8).

Unfractionated Heparin (UFH)

UFH, like LMWH, binds with AT, causing FXa inhibition and blocking the conversion of prothrombin to thrombin and fibrinogen to fibrin. It is administered by continuous venous infusion at a weight-adjusted dose (23). Administration requires continuous monitoring of activated partial thromboplastin time (APTT) levels and frequent dose adjustments. UFH is recommended for patients with severe obesity. For patients with end-stage chronic kidney disease (CKD), UFH is also recommended, but dose adjustment based on anti-factor Xa (anti-Xa) rather than APTT is required (8,24). Current ESC guidelines recommend parenteral anticoagulation with LMWH or fondaparinux over UFH (8). However, a recent meta-analysis has shown no difference in the efficacy and safety of LMWH and UFH in acute PE, based on short-term and long-term mortality and major bleeding (25).

Oral anticoagulants

Direct Oral Anticoagulants (DOACs)

DOACs interfere in the coagulation cascade either by direct and reversible inhibition of FXa (rivaroxaban, apixaban, edoxaban, betrixaban) or by direct and reversible inhibition of Factor IIa (dabigatran). DOACs are administered at fixed

doses and do not require weight-dose adjustments or laboratory monitoring. Based on the trials RE-COVER, EINSTEIN-PE, AMPLIFY, and Hokusai-VTE, current guidelines suggest the following regimens in acute PE: parenteral anticoagulation for ≥ 5 days followed by dabigatran 150mg b.i.d., rivaroxaban 15mg b.i.d. for 21 days followed by a reduction to 20mg q.d., apixaban 10mg b.i.d. for 7 days followed by a reduction to 5mg b.i.d., parenteral anticoagulation for ≥ 5 days followed by edoxaban 60mg q.d. (26–29). Patients with mild to moderate CKD (CrCl 30-60mL/min) require dose adjustment when treated with edoxaban (reduction to 30mg q.d.). Patients with severe and end-stage CKD were excluded from the trials studying PE treatment with apixaban, dabigatran, edoxaban (CrCl <30 ml/min), and rivaroxaban (CrCl <25 ml/min) (8). Thus, DOACS are not recommended in patients with severe renal dysfunction. Recent studies demonstrate promising results regarding the efficacy and safety of apixaban and potentially noninferiority compared to dalteparin in the treatment of acute PE (30,31). Contrary to ESC and AHA guidelines, CHEST and NICE guidelines strongly recommend treatment with oral FXa inhibitors (rivaroxaban, edoxaban, apixaban) over LMWH for PE in the setting of non-gastrointestinal cancer (32–34). Currently, there are no studies investigating the association between the selection of one DOAC over another based on PE risk stratification.

Vitamin K antagonists - VKAs

VKAs reduce the anticoagulation activity by inhibiting the formation of factors II, VII, IX, and X. VKAs include warfarin, acenocoumarol, phenprocoumon, and fluindione. Warfarin and acenocoumarol are the most studied, and therefore most prescribed VKAs. All VKAs share a similar mechanism of action but differ in their pharmacokinetic and pharmacodynamic properties. Most importantly, they exhibit different half-life durations with phenprocoumon having notably the longest at around 150 hours, followed by warfarin at around 40 hours, fluindione at 35 hours, and lastly, acenocoumarol with 8-11 hours of half-life, similarly to DOACs. A shorter half-life translates into a rapid onset of action and rapid reversal of its anticoagulant activity upon administration of vitamin K (35,36). VKAs are administered daily at an adjusted dose based on INR levels, therefore, requiring frequent monitoring of INR levels, aiming for an INR range

of 2-3. Initiation of treatment requires overlapping with parenteral anticoagulation until a therapeutic INR target is achieved. VKAs efficacy is counterbalanced by concomitant medication and the nutritional intake of vitamin K. The trials RE-COVER, EINSTEIN-PE, AMPLIFY, and Hokusai-VTE studied the efficacy and safety of DOACs versus warfarin in VTE, including PE. Findings demonstrated non-inferiority of dabigatran, apixaban, and edoxaban, and superiority of rivaroxaban regarding efficacy, as well as superiority regarding safety with a lower risk of major bleeding compared to warfarin treatment (26–29). Current guidelines recommend the use of DOACs over VKAs in eligible patients. They remain the gold standard treatment for PE in patients with APL syndrome. Although optimal anticoagulation treatment for patients with severe or end-stage CKD is not yet clear, all guidelines agree on the use of VKAs as an alternative option if DOACs are contraindicated (8,18,32,34).

Duration of Therapy

Treatment of PE is divided into three phases based on the duration of anticoagulation therapy: acute, maintenance or sub-acute, and extended phase. The acute phase starts from the first day of treatment and lasts from 7 to 21 days, depending on the administered anticoagulant. The maintenance or sub-acute phase starts right after the acute phase and lasts 3 to 6 months. The extended phase refers to the period after 6 months of anticoagulation therapy and has an indefinite duration. The duration of treatment phases based on the chosen therapeutic regimen is shown in Table 3.

Table 5. Anticoagulation therapy regimens (dosage and duration of therapy) based on the treatment phase

	Acute	Maintenance	Extended
LMWH	1mg/kg b.i.d. or q.d. if CrCl <30ml/min	1mg/kg b.i.d. or q.d. if CrCl <30ml/min	1mg/kg b.i.d. or q.d. If CrCl <30ml/min
Duration	7 days	3-6 months	indefinite
Fondaparinux	5 mg q.d. if <50kg	5 mg q.d. if <50kg	5 mg q.d. if <50kg

	7,5 mg q.d. if 50-100 kg 10 mg if >100 kg	7,5 mg q.d. if 50-100 kg 10 mg if >100 kg	7,5 mg q.d. if 50-100 kg 10 mg if >100 kg
Duration	7 days	3-6 months	indefinite
UFH	80 U/kg then continuous infusion at 18 U/kg/hour Or 5000 units bolus then continuous infusion at 1300 units/hour and APTT- adjusted dose	N/A	N/A
Duration	7 days	N/A	N/A
Apixaban	10mg b.i.d.	5mg b.i.d. or 2,5mg b.i.d. if CrCl<30ml/min	2,5mg b.i.d.
Duration	7 days	3-6 months	indefinite
Rivaroxaban	15mg b.i.d.	20mg q.d. or 15mg q.d. if CrCl 30-49 ml/min	10mg q.d.
Duration	21 days	3-6 months	indefinite
Dabigatran	LMWH 1mg/kg b.i.d. or q.d. if CrCl <40ml/min	150mg q.d. or 150mg q.d if CrCl 30-49 ml/min	150mg q.d. or 150mg q.d if CrCl 30-50 ml/min

Duration	7 days	3-6 months	indefinite
Edoxaban	Bridging with LMWH or UFH	60mg q.d. or 30mg q.d. if CrCl<30 ml/min	60mg q.d. or 30mg q.d. if CrCl<30 ml/min
Duration	5-10 days	3-6 months	indefinite
Warfarin	Bridging with LMWH or UFH until INR>2	Adjusted dose with INR target (2-3)	Adjusted dose with INR target (2-3)
Duration	7 days	3-6 months	indefinite

The choice of the duration of anticoagulant therapy intends to prevent the recurrence of pulmonary embolism and is based on the assessment of risk factors causing the index episode. ESC guidelines propose a categorization of risk factors for VTE based on the risk of recurrence per year as shown in Table 2. Major transient or reversible risk factors are associated with a low risk of recurrence (<3% per year). Nonidentifiable, non-malignant, and non-major transient or reversible risk factors are linked to an intermediate risk of recurrence (3-8% per year). Lastly, active cancer, APL syndrome, or previous VTE episodes in the absence of major transient or reversible risk factors are associated with a high risk of recurrence (>8% per year). ESC guidelines recommend discontinuation of anticoagulant treatment after 3 months. For patients with an intermediate risk of recurrence, indefinite duration of anticoagulation should be considered. For patients with a high risk of recurrence, indefinite duration of anticoagulation is recommended (8). CHEST guidelines recommend treatment for 3 months for PE provoked by surgery and nonsurgical transient risk factors. For unprovoked PE, treatment for at least 3 months is recommended. Extension of anticoagulation therapy over 3 months is suggested if accompanied by low or moderate bleeding risk, whereas treatment for 3 months is recommended if the bleeding risk is high.

Furthermore, for patients presenting with the second episode of VTE and who have a low bleeding risk, extended therapy over 3 months is recommended, but for those with high bleeding risk, anticoagulation for 3 months is suggested. In cancer-related PE with or without high bleeding risk, anticoagulant therapy over 3 months is suggested (33).

Reperfusion Treatments

Management of intermediate-high-risk patients requires close clinical monitoring, especially for the first 24 to 48 hours. In case of clinical deterioration or in the absence of significant clinical improvement, the possibility of systemic thrombolysis or more invasive methods of reperfusion should be re-evaluated by the treating physician.

Systemic Thrombolysis (ST)

Approved thrombolytic regimens include recombinant tissue-type plasminogen activator (rtPA), streptokinase, and urokinase. Tenecteplase, reteplase, and desmoteplase have been studied, but approval for acute PE therapy has not yet been granted. All fibrinolytic agents act by converting plasminogen to plasmin, therefore converting fibrinogen to fibrin, leading to the dissolution of thrombus. Therapeutic regimens are shown in Table 4.

Table 6. Thrombolysis therapeutic regimens

IV administration	Loading dose	Continuous infusion	Alternative accelerated infusion
rtPA	100mg over 2 hours	0,6mg/kg over 15 minutes (maximum dose 50mg)	N/A
Streptokinase	250 000 IU over 30 minutes	100 000 IU/h over 12–24 hours	3 million IU over 2 hours
Urokinase	4400 IU/kg over 10 minutes	4400 IU/kg/h	1.5 million IU over 2 hours

		over 12–24 hours	
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Rapid rtPA regimen creates an advantage over the prolonged infusion of streptokinase and urokinase. Although official guidelines do not recommend one fibrinolytic agent over another, recent meta-analyses have shown the superiority of alteplase (rtPA) regarding the reduction of PE recurrence and mortality, as well as pulmonary artery systolic pressure (PASP) (37). Contradictions to ST are associated with higher bleeding risk and can be absolute or relative (Table 5).

Table 7. Contradictions to systemic thrombolysis

Absolute	Relative
History of hemorrhagic stroke or stroke of unknown origin	Transient ischemic attack in the previous 6 months
Ischemic stroke in the previous 6 months	Oral anticoagulation
Central nervous system neoplasm	Pregnancy or first post-partum week
Major trauma, surgery, or head injury in the previous 3 weeks	Non-compressible puncture sites
Bleeding diathesis	Traumatic resuscitation
Active bleeding	Refractory hypertension (systolic blood pressure >180 mmHg)
	Advanced liver disease
	Infective endocarditis
	Active peptic ulcer

Hemodynamic decompensation in PE is presented as persistent hypotension, cardiogenic shock, or cardiac arrest. It demonstrates the collapse of the RV and the myocardial injury following the hemodynamic imbalance in cardiopulmonary circulation, as well as the establishment of acute pressure overload secondary

to pulmonary artery obstruction. ST is the rescue treatment for high-risk PE, whereas it is not recommended for intermediate-high-risk patients (8). Patients with compensated RV dysfunction, i.e., those in the intermediate to high-risk spectrum usually present with persistent but normotensive tachycardia. Large multicenter studies suggest that normotensive patients with RV dysfunction experience a significant increase in all-cause and in-hospital mortality, as well as an increased likelihood of PE recurrence (38–40).

Only a few studies have investigated the efficacy and safety of ST in intermediate-high-risk PE. PEITHO is a multicenter, double-blind, placebo-controlled randomized trial published in 2014 that investigated the use of fibrinolysis with tenecteplase in normotensive PE patients with confirmed RV dysfunction and myocardial injury. The study showed that thrombolysis was associated with a reduction in all-cause mortality and hemodynamic decompensation due to improved RV function, over standard anticoagulation therapy, but was also related to a higher risk of intracranial hemorrhage and overall bleeding risk, especially in older adults (41). A large meta-analysis, also published in 2014, reached similar results, except that bleeding risk did not differ significantly between those who received thrombolysis and those who did not, in patients under 65 years of age (42). A recently updated Cochrane study, originally published in 2006, which included patients with massive and submassive embolism, showed a low-certainty association of thrombolysis with a reduction in mortality, PE recurrence, and an increase in major and minor bleedings (43).

Catheter-Directed Therapies

Catheter-Directed Thrombolysis (CDT)

Catheter-directed thrombolysis is a minimally invasive procedure that delivers low-dose thrombolytic agents directly into the pulmonary arteries to dissolve thrombi causing PE. This targeted approach aims to rapidly reduce thrombus burden and alleviate RV strain, potentially improving short-term and long-term outcomes compared to ST while minimizing the risk of hemorrhage. It involves inserting a small plastic side-hole catheter through the venous system, typically via the femoral or the internal jugular vein, and advancing it to the site of the

PE under fluoroscopic guidance. Once positioned, thrombolytic agents such as alteplase, urokinase, or streptokinase, are infused directly into the thrombus, facilitating its resolution. This method allows for up to a 25% lower total dose of thrombolytics compared to ST, reducing the risk of systemic bleeding complications (44–46).

Based on AHA and ESC guidelines, CDT is an acceptable alternative as rescue treatment in patients with high-risk PE, when systemic thrombolysis is contraindicated or has failed. Failure, indicated by ongoing clinical instability or absence of improvement in RV function on echocardiography after 36 hours of treatment, has been observed in 8% of high-risk patients. For intermediate-high-risk PE, guidelines suggest that CDT may be beneficial when the risk of deterioration is high, however, the decision for the intervention should be individualized as the bleeding risk remains high (8,18).

Several studies have attempted to compare the efficacy and safety of CDT over other reperfusion therapies. In a large-scale meta-analysis published in 2022, CDT was associated with a significant decrease in 30-day, 90-day, and in-hospital mortality compared to standard anticoagulation. It showed no difference in minor or major bleeding, need for transfusion, and duration of hospitalization. In a subgroup analysis isolating only patients with intermediate-high PE, there were no significant differences between CDT and systemic therapies (47). A meta-analysis published in 2023, which included 20,006 patients, examined the differences in mortality and bleeding between CDT, ST, and anticoagulation only in submassive PE i.e. intermediate-high PE. Lower rates of mortality, intracranial hemorrhage, major bleeding, and blood transfusion were reported in patients undergoing CDT compared to those receiving fibrinolysis. Additionally, the analysis showed a reduction in mortality and no increase in intracerebral or major bleeding compared to anticoagulation (48).

Ultrasound-assisted thrombolysis (USAT)

Ultrasound-assisted thrombolysis, the most advanced therapy of PE, is a catheter-directed thrombolytic technique that was introduced in the field of pulmonary embolism during the past 15 years. Its purpose is to optimize the

thrombolytic effect achieved through disruption of fibrin connections, using a high frequency (2.2 MHz) ultrasound transducer, thereby increasing the surface area of the thrombus exposed to the fibrinolytic agent and facilitating its penetration. The OPTALYSE trial compared different regimens and established the efficacy of a low dose and short duration treatment regarding the improvement in RV function and angiographic thrombus burden in combination with low bleeding rates compared to baseline (49). In 2015 the ULTIMA study demonstrated the superiority in safety and efficacy of USAT over heparin treatment in patients with intermediate-high PE, as it displayed a more rapid improvement of RV function after treatment without increasing the bleeding risk (50). Succeeding, the SEATTLE II study assessed the safety and efficacy of USAT in patients with massive and submassive PE and showed a rapid decrease in RV dilatation and angiographic thrombus burden in 48 hours and a 30% reduction in PASP after the procedure. Bleedings occurred in 10% of patients, but no intracranial hemorrhage was recorded (51).

Data comparing standard CDT and USAT is scarce. A few retrospective studies have attempted to compare the two techniques, but due to the small sample size, they are considered underpowered (52–55). The SUNSET sPE trial published in 2021 was the first randomized controlled trial that investigated intermediate-high PE patients undergoing standard CDT versus USAT, evaluating the efficacy of the reduction of thrombus burden after therapy. The study included 89 patients and demonstrated similar effects on thrombotic load in both groups using comparable lytic doses and duration of therapy (56). A recent meta-analysis published in 2024 examined the outcomes of conventional CDT versus USAT in 39,430 patients with intermediate- or high-risk PE. The study demonstrated no difference regarding in-hospital mortality or bleeding (57).

Catheter-directed thrombus fragmentation (CDF)

Thrombus fragmentation is an interventional technique during which a rotating pigtail or peripheral balloon angioplasty catheter is inserted via the jugular or femoral vein, travels through the pulmonary artery network to the site of embolism, and mechanically dissolves the thrombus into fragments. Although

clot fragmentation instantly reduces proximal thrombus burden, it can evolve into clinical deterioration and worsening of the hemodynamic status due to new pulmonary embolization caused by the displacement of the fragments to the distal pulmonary vasculature. CDF is mostly combined with other recanalization techniques such as aspiration or CDT to achieve better outcomes (58).

Data regarding CDF practice is confined to underpowered studies with very small sample sizes or studies with combined catheter-directed therapies (59–61). The lack of large-scale registries and randomized controlled trials fails to establish adequate evidence regarding the safety and efficacy of CDF in intermediate-high PE. Surprisingly, a survey published in 2021 by the European Association of Percutaneous Cardiovascular Interventions (EAPCI) and ESC Working Group on Pulmonary Circulation & Right Ventricular Function, regarding current practices of CDT in acute PE, revealed that catheterization labs in Europe use the CDF pigtail catheters up to twice as often as other modalities such as AngioJet, Indigo and EKOS (62).

Aspiration Embolectomy

Thrombus aspiration is another catheter-directed technique where negative pressure is applied directly to the thrombus, through a large lumen catheter, aiming at the instant thrombus removal, while minimizing the risk of distal embolization, contrary to CDF. Several catheters have been designed specifically for this purpose (63). The FlowTrieve system, one of the most commonly used, features a large-bore catheter that allows for efficient clot extraction while maintaining blood flow to the lungs. The Aspirex catheter is smaller and designed for more distal emboli, providing a more targeted approach for clot aspiration. The Indigo system offers high-efficiency thrombus retrieval with specialized catheters that are particularly effective in peripheral pulmonary arteries. The Angiovac system, on the other hand, is used for larger, central thrombi and provides continuous suction to remove thrombus, assisted by an extracorporeal veno-veno bypass circuit (64). There is, however, a lack of head-to-head comparisons of the different aspiration techniques. Studies specifically addressing intermediate-high-risk patients undergoing aspiration thrombectomy without the concomitant use of thrombolytic agents have shown

promising results, with significant and rapid improvement in RV function and reduced rates of bleeding and mortality (65–67).

Rheolytic embolectomy (ART)

Rheolytic thrombectomy with AngioJet (ART) is a catheter-directed technique that combines thrombus fragmentation, aspiration, and targeted thrombolysis. The device uses high-pressure saline jets that create a vacuum effect, allowing for the disruption and aspiration of thrombus fragments through the lumen catheter. In addition, it can deliver low-dose thrombolytic agents directly to the clot, promoting further thrombolysis. While early studies showed promising results in high-risk PE, significant complications have been reported, including bradycardia, hypotension, hypoxia, and hemodynamic collapse. These adverse events are believed to be associated with the release of vasoactive agents, such as adenosine and bradykinin, as well as hemolysis during the procedure (63,68). As a result, the US Food and Drug Administration (FDA) issued a black box warning on the device for use in pulmonary circulation, advising against its use as a first-line therapy for acute PE (64). Despite the safety concerns, a single-center retrospective study published in 2021 suggested that, when performed by experienced operators, ART can result in significant clinical improvement, including enhanced oxygenation and hemodynamic stability in intermediate to high- and high-risk patients (69). The Bashir Endovascular Catheter is a newly designed catheter used in rheolytic thrombectomy associated with promising results in recent studies on intermediate-risk patients (70). Large-scale, multicentered studies are needed to determine the efficacy and safety of rheolytic thrombectomy and the optimal catheter design.

Surgical embolectomy (SPE)

Surgical embolectomy is the most invasive reperfusion therapy as it requires median sternotomy and the application of cardiopulmonary bypass. It is typically conducted without the use of aortic cross-clamping or cardioplegic arrest to avoid further myocardial injury (71). According to the latest ESC and AHA guidelines, SPE is only recommended for high-risk patients in whom thrombolysis is contraindicated or has failed (8,18).

However, the practice of SPE in intermediate-high-risk PE is now being reevaluated as recent research has yielded promising results. A systematic review and meta-analysis published in 2022 investigated the outcomes of SPE in patients with intermediate- or high-risk PE. It resulted in 4% and 9% in-hospital and 30-day mortality, respectively, with an increase of 2% in both outcomes at subgroup analysis for the intermediate-high-risk group. Furthermore, hemodynamic parameters, RV function, and angiographic thrombus burden significantly improved in all patients after the intervention (72). A large-scale retrospective study published in 2022 examined the outcomes of SPE in acute PE compared to SR and CDT. SPE was associated with a higher risk of in-hospital mortality, stroke, and blood transfusion. The in-patient mortality rate was 19,8%, significantly improved compared to previous data (73).

Recent comparative studies regarding the practice of SPE versus thrombolysis, CDT, or USAT in PE have generated favorable results. A retrospective study published in 2018 included patients with high- or intermediate-high-risk PE who received either thrombolysis or SPE. Results showed no difference in short- or long-term mortality and associated thrombolysis with higher rates of stroke and recurrent PE (74). A recent study compared the short- and long-term outcomes of CDT versus the surgical approach in high- and intermediate-high-risk patients. Rates of in-hospital and long-term mortality, bleeding, and recurrence of PE were similar between the two groups (75). A clinical trial conducted in 2024 compared USAT and SPE in intermediate-high and high-risk PE. USAT and SPE were shown to equally reduce the RV/LV ratio, but in post hoc analysis SPE led to greater improvement of RV function and reduction of thrombus load (76). Another study published in 2024, compared the use of USAT and mechanical thrombectomy in patients with intermediate-high and high risk. USAT was associated with lower rates of bleeding, but there was no difference between therapies in terms of mortality and readmission to the hospital (77).

Special populations

The therapeutic management of PE in patients with CKD, obesity, active malignancy, or the elderly presents a distinct clinical challenge. Despite having

multiple predisposing factors for VTE, these populations remain underrepresented in large clinical trials. Given the limited available evidence, current guidelines include cautious recommendations regarding the optimal therapeutic approach for these specific population groups.

In patients with mild to moderate CKD, the anticoagulant treatment is either LMWH or DOACs, with dose adjustments based on the CrCl. Among DOACs, apixaban is preferred due to the least renal clearance. UFH in an anti-Xa- rather than APTT-adjusted dose is the first-line treatment in patients with severe or end-stage CKD. Vitamin K antagonists may be selected if DOACs are contraindicated and remain a valid option for patients undergoing hemodialysis (see section “DOACs”) (8,26–29). In the current literature, there are no studies focused solely on ST in patients with CKD in the context of acute PE. Although CKD is not considered a contraindication for ST, it is suggested that CKD may influence treatment outcomes due to the increased risk of hemorrhage. The only study to our knowledge that examined the safety of thrombolytic therapy in patients with CKD demonstrated no difference in bleeding or mortality compared to patients with preserved renal function (78,79). A subgroup analysis of a prospective cohort study published in 2021 indicated that patients with CKD who underwent CDT had a lower risk of in-hospital mortality and 1-year mortality compared to those treated with ST (80). However, due to the small sample size, the study was considered underpowered. There is no reliable data on USAT, CDF, aspiration, and surgical embolectomy in patients with intermediate-high-risk PE and CKD.

In patients with active cancer, who simultaneously carry high thrombotic and bleeding risk, the optimal anticoagulant choice is LMWH with a preference for dalteparin, as recommended by the American Society of Clinical Oncology (ASCO) and the European Society of Medical Oncology (ESMO) guidelines. Dalteparin demonstrates a favorable safety profile compared to DOACs, particularly in patients with gastrointestinal malignancies. DOACs remain an alternative to LMWH (81,82). A recently published meta-analysis on anticoagulant treatment in cancer-related PE, associated DOACs with a reduced rate of VTE and DVT recurrence, but not PE recurrence, compared to LMWH. In addition, treatment with rivaroxaban was linked to an increased risk

of major bleeding (83). A meta-analysis published in 2023 investigated the net clinical benefit of DOACs versus LMWH or VKA in cancer-related VTE. The study found that DOACs had a comparable or greater net clinical benefit than that of standard anticoagulation, primarily due to a significant reduction in VTE events without an increase in bleeding risk (84). The guidelines regarding the use of DOACs in cancer-related PE are conflicting. Unlike the ESC and AHA, the CHEST and NICE guidelines support the use of DOACs in patients with non-gastrointestinal malignancies (8,18,32,34). ST is contraindicated in patients with central nervous system (CNS) malignancies, but not in other types of cancer. However, due to the high hemorrhagic risk in these patients, clinicians are often cautious regarding its use (8). Patients with active malignancy were not sufficiently represented in large trials on catheter-directed therapies in acute PE, leading to uncertain conclusions regarding the optimal reperfusion treatment for this specific group. In patients with intermediate-high-risk PE, where there is sufficient time to develop a personalized treatment plan, the use of catheter-based thrombolysis or embolectomy may prove to be safe due to the administration of smaller doses of thrombolytic agents.

Although obesity constitutes a predisposing factor for VTE occurrence and a possible cause of VTE recurrence, data regarding the optimal therapeutic approach are scarce. Heparin therapy, whether with LMWH, UFH, or fondaparinux, is administered in weight-adjusted dosing regimens, thereby ensuring the safety and efficacy of anticoagulant treatment. According to ESC guidelines, UFH is indicated for patients with acute PE and severe obesity. (8,85). While not a contraindication to the use of DOACs, obesity does impact the pharmacokinetics of these agents, particularly in patients with a body mass index (BMI) over 40 kg/m² or body weight over 120 to 150 kg, due to increased volume of distribution. Although patients weighing over 100kg and less than 50kg were included in RE-COVER, EINSTEIN-PE, AMPLIFY, and Hokusai-VTE, they represented approximately 15-28% of the total sample size. Their underrepresentation in these studies raises questions regarding the optimal DOAC dosing regimen based on the patient's body weight, to achieve the safety and efficacy of anticoagulation treatment (26–29). A retrospective study published in 2021 investigating long-term outcomes after intermediate- or high-

risk PE in morbid obesity resulted in no difference in VTE recurrence, chronic thromboembolic pulmonary hypertension (CTEPH), thrombus burden detected in lung scintigraphy, or RV function compared to non-obese patients (86). Conventional-dose thrombolysis appears to have comparable efficacy and bleeding risk in obese and non-obese individuals (87). A subgroup analysis based on the SEATTLE II trial studied the use of CDT in obese patients. Results showed favorable outcomes in terms of RV recovery and risk of bleeding (51,88). However, the efficacy and safety of catheter-directed therapies, compared to ST, have yet to be fully explored. Larger randomized clinical trials are required to compare different reperfusion treatments to establish the most effective approach for intermediate-high PE in morbidly obese patients.

Elderly patients are underrepresented in studies regarding the therapeutic management of PE. They constitute a special and frail population, as they often present multiple comorbidities, an increased risk of bleeding, and reduced tolerance to nephrotoxic agents. Current guidelines recommend anticoagulation therapy with DOACs over vitamin K antagonists. However, they emphasize the assessment for potential interactions of the selected anticoagulant with concomitant medications, as well as the need for close monitoring of renal and hepatic function, with appropriate dose adjustments when necessary (8). A meta-analysis published in 2023 compared the efficacy and safety of different reperfusion therapies in the elderly, yielding encouraging findings. Findings associated CDT and catheter-directed embolectomy with decreased overall major bleeding compared to ST and SE, respectively (89). Larger studies, including elderly patients, are needed to better reflect the needs of frail and comorbid patients and to provide more individualized treatment strategies tailored to this subgroup.

Recurrence

As mentioned above, VTE recurrence is directly related to the presence or absence of predisposing factors, as well as the duration of anticoagulant therapy (see Table 2). VTE initially presenting as PE, commonly recurs in the form of PE, rather than DVT. In a recent study published in 2020, it was estimated that within two years after the first VTE episode, recurrence occurred

in 3.3% of patients with a transient risk factor, 0.7% of patients with a surgical risk factor, 4.2% of patients with a non-surgical risk factor, and up to 7.4% of patients with an unprovoked episode (90). In addition, a recent meta-analysis found that the recurrence rate of VTE in patients after a first unprovoked episode who received extended anticoagulation therapy was 10%, 25%, and 36% at 1, 5, and 10 years after treatment. Despite the relatively low recurrence rates of unprovoked PE, the risk of a subsequent and potentially fatal event remains a significant clinical concern. The absence of robust data on the likelihood of fatal PE recurrence, combined with the potential presence of undetectable thrombophilia in patients with a previously unprovoked VTE episode, provides a strong rationale for considering extended-duration anticoagulant therapy. Data from meta-analyses have introduced the concept of further individualizing the risk of recurrence based on patient-specific factors such as male sex, D-dimer levels, and prothrombotic syndrome (91). Moreover, emerging evidence suggests a potential association between the severity of the initial PE episode and the likelihood of recurrence (92,93). The potential association between increased severity of the initial PE episode, defined as elevated cardiac biomarkers or RV dysfunction, and a heightened risk of recurrence represents a significant area for future research. New data may not only refine the optimal duration of anticoagulant therapy but also reshape the initial management strategy during the acute phase in patients with intermediate-high-risk PE.

Residual Pulmonary Vascular Obstruction (RPVO)

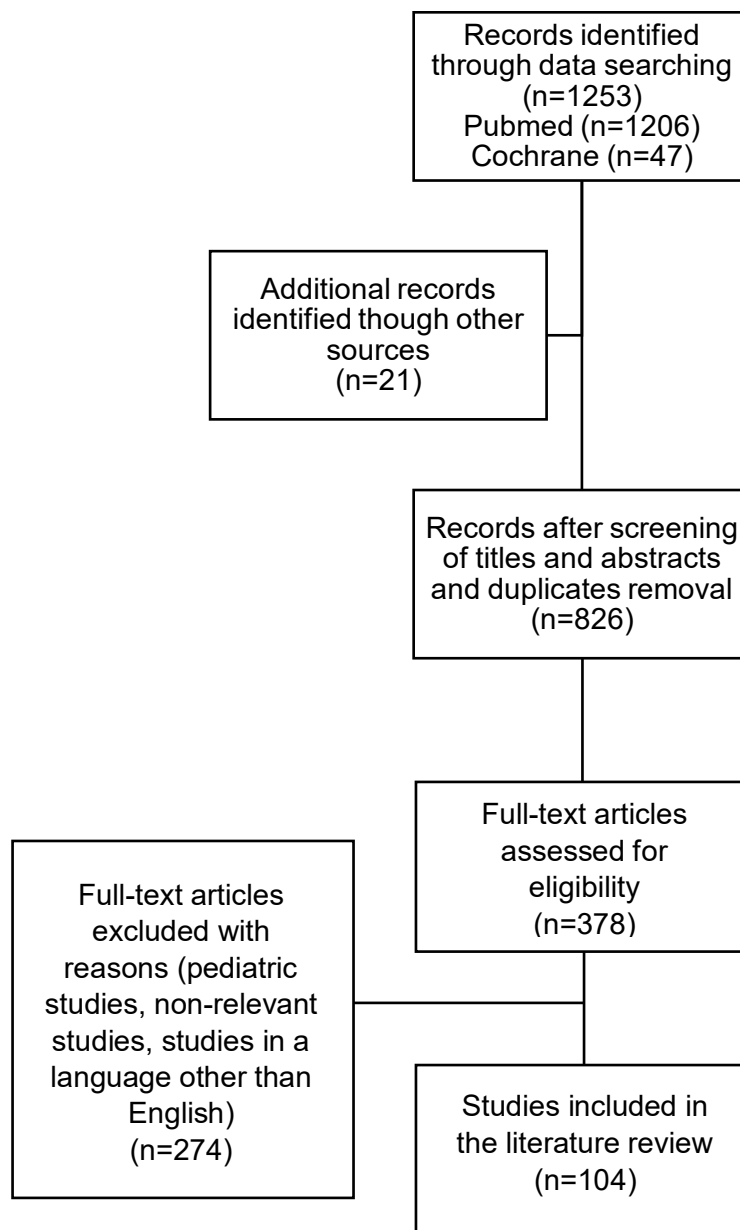
RV strain caused by increased pulmonary resistance and pulmonary hypertension following PE is strongly associated with the extent of thrombotic burden. Patients with significant thrombus load are those with established or imminent hemodynamic decompensation and based on the risk stratification they are classified as high-risk and intermediate-high risk respectively. High-risk patients receive emergent thrombolysis, unless contraindicated, followed by immediate thrombus burden relief. Patients with intermediate-high-risk PE are most often treated with anticoagulation therapy. Therefore, the significant thrombotic load remains in the pulmonary vasculature for a longer period, called

the residual pulmonary vascular obstruction (RPVO). This condition creates a conducive environment for the development of long-term implications such as CTEPH and post-PE syndrome (94). Studies suggest that the presence of RPVO >5% assessed by V/Q lung scan after 3 months of anticoagulant therapy is linked to an increased risk of recurrent VTE in the first year after the index episode. Interestingly, some studies have indicated that in patients with DVT, the presence of residual venous obstruction (RVO) may also be linked to an increased risk of recurrent VTE. So far, there is no definitive pathophysiological explanation for the association between RPVO and recurrent thrombosis, nor is it clear whether this relationship is causal. Based on the existing evidence, it is implied that screening of RPVO after 3-6 months on anticoagulation, could define the optimal duration of treatment and lead to early detection of CTEPH (95–98). In addition, the effect of catheter-directed treatments and other reperfusion therapies on RPVO in patients with intermediate-high-risk PE is currently being explored. A recent retrospective study resulted in a possible association between RPVO reduction after 3 months and catheter-directed therapies (99).

Results

The database search process identified a total of 1253 studies (1206 in PubMed and 47 in Cochrane). Following additional research, another 21 studies were included, reaching a total of 1274 studies. From the initial screening of titles and abstracts and the removal of duplicates, 826 studies remained. After evaluating their full texts and the studies were narrowed down to 378. Finally, after excluding pediatric studies, studies in languages other than English, and non-relevant studies, a total of 105 studies were included in the present literature review. The Prisma flow diagram is presented below.

Figure 1. Prisma flow diagram



Based on the evidence discussed in the present study, DOACs are the first-line treatment in intermediate-high PE but should be administered carefully in case of renal and hepatic impairment. There is still controversy in current guidelines regarding their use in non-gastrointestinal cancers. DOAC recommendation based on existing stratification models has not yet been investigated. LMWH is recommended in pregnancy and active cancer, while fondaparinux is recommended for patients with a history of HIT. Both LMWH and Fondaparinux are preferred over UFH, although recent data show no difference in terms of efficacy and safety. Vitamin K antagonists are recommended only when DOACs are contraindicated, or in the presence of absolute indications, such as in APL syndrome, mechanical heart valves, and in patients undergoing dialysis.

Regarding reperfusion therapies, ST is not recommended for intermediate-high risk patients and is considered precarious, unless hemodynamic instability is established. Evidence from older studies suggesting a superiority of ST over standard anticoagulation in terms of mortality is weakened by more recent findings. CDT is currently recommended only when the risk of deterioration is high. The latest evidence has associated CDT with reduced rates of mortality and bleeding, compared to ST and standard anticoagulation in intermediate-high-risk PE. So far, studies comparing USAT versus CDT demonstrated no differences regarding in-hospital mortality, bleeding, and thrombus burden. There is no sufficient evidence for CDF practice in intermediate-high-risk patients. Studies on aspiration thrombectomy have shown favorable results in terms of RV improvement but its implementation in clinical practice is still limited. The use of rheolytic thrombectomy has recently raised safety concerns. SPE in intermediate-high-risk PE has been lately evaluated and compared to ST, concluding with promising results regarding mortality, bleeding risk, RV function, and thrombus load. When compared to USAT, mechanical embolectomy was associated with higher rates of bleeding. Lastly, so far SPE compared to CDT has not demonstrated any differences in efficacy and safety.

Discussion

The optimal approach for managing intermediate-high-risk PE remains unclear. These patients form a special category and present a unique challenge

regarding the therapeutic approach. Not fulfilling the absolute criteria of high-risk PE and thus, for emergent reperfusion, but at the same time presenting signs of imminent hemodynamic decompensation, they can be managed with different therapeutic approaches. Some undergo standard anticoagulation treatment, following the “watch and wait” approach, while others are subjected to reperfusion therapy.

In recent decades, particularly following the publication of PEITHO and ULTIMA trials, catheter-directed therapies have emerged at the forefront of management in intermediate-high risk PE and have become a significant area of research in PE treatment. Current studies demonstrate promising results when comparing this approach to ST and anticoagulation therapies. Transcatheter techniques often involve or are combined with the infusion of thrombolytic agents directly into the thrombus. Their primary advantage is the rapid reduction of thrombotic risk through targeted treatment, leading to immediate improvement in RV function. Fast RV recovery may be the key to the prevention of short-term and long-term outcomes for patients with intermediate-high-risk PE.

There is still limited comparative data to support the superiority or inferiority of catheter-directed treatment and other reperfusion therapies over standard anticoagulation or ST. Further research is warranted to establish the safety and efficacy of these interventions in the future, as well as their long-term benefits. Additionally, research should be conducted separately on specific groups who are poorly represented in clinical trials, including the elderly, obese, patients with CKD, active cancer or contraindication to anticoagulation, and those at higher risk of bleeding. The Higher-Risk Pulmonary Embolism Thrombolysis (HI-PEITHO) trial is an ongoing multinational multicenter randomized controlled trial that examines the safety and efficacy of USAT in patients who present a higher risk of hemodynamic decompensation in PE, i.e. intermediate-high risk category (101). The PEERLESS is an ongoing randomized controlled trial of large-bore thrombectomy versus anticoagulation focusing on patients with intermediate-high-risk PE (102). The RE-TRACT trial is a multicentered randomized controlled trial that will investigate the use of catheter-directed therapy in intermediate-risk PE versus the use of anticoagulation alone (103).

The PEITHO-3 trial is a randomized, placebo-controlled, double-blind, multicenter, multinational trial designed to compare the efficacy and safety of reduced-dose intravenous thrombolysis using alteplase in addition to standard heparin versus heparin alone in patients with intermediate-high-risk PE (104).

Conclusion

The management of intermediate-high-risk PE has been, and remains, a significant clinical challenge for the medical community. In this thesis, we aimed to explore the current strategies in the management of intermediate-high-risk PE, examining the diagnostic tools, therapeutic options, and the role of advanced treatments. We highlighted the weaknesses of current guidelines and the gaps in the literature. Decisions regarding the therapeutic approach of patients with intermediate-high risk PE are often based on the clinical judgment and experience of the attending physician. The lack of sufficient data highlights the need for additional research with large-scale cohort studies and randomized control trials. Moreover, comparison of the safety and efficacy of different anticoagulation strategies and reperfusion techniques, focusing on this specific clinical entity, is needed. Studies specifically designed for special populations such as patients with CKD, obesity, active malignancy, or the elderly are essential to better navigate across a broader range of patients. The evaluation of clinical evidence and emerging approaches for intermediate-high risk PE will contribute to the optimization of patient care, the reduction of long-term PE implications, including recurrence of VTE, CTEPH, and the improvement of survival rates.

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