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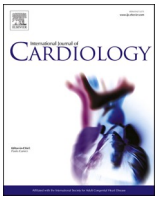

Review Article

Management of high and intermediate-high risk pulmonary embolism: A position paper of the Interventional Cardiology Working Group of the Italian Society of Cardiology

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ABSTRACT

Pulmonary embolism (PE) is a potentially life-threatening condition that remains a major global health concern. Noteworthy, patients with high- and intermediate-high-risk PE pose unique challenges because they often display clinical and hemodynamic instability, thus requiring rapid intervention to mitigate the risk of clinical deterioration and death. Importantly, recovery from PE is associated with long-term complications such as recurrences, bleeding with oral anticoagulant treatment, pulmonary hypertension, and psychological distress.

Several novel strategies to improve risk factor characterization and management of patients with PE have recently been introduced. Accordingly, this position paper of the Working Group of Interventional Cardiology of the Italian Society of Cardiology deals with the landscape of high- and intermediate-high risk PE, with a focus on bridging the gap between the evolving standards of care and the current clinical practice. Specifically, the growing importance of catheter-directed therapies as part of the therapeutic armamentarium is highlighted. These interventions have been shown to be effective strategies in unstable patients since they offer, as compared with thrombolysis, faster and more effective restoration of hemodynamic stability with a consistent reduction in the risk of bleeding. Evolving standards of care underscore the need for continuous re-assessment of patient risk

Abbreviations: CiT, clot-in-transit; CTEPH, chronic thromboembolic pulmonary hypertension; CTPA, computed tomography pulmonary angiography; ECMO, extracorporeal membrane oxygenation; NEWS2, National Early Warning Score 2; PE, pulmonary embolism; PERT, pulmonary embolism response team; PESI, pulmonary embolism severity index; RV, right ventricle; sPESI, simplified PESI; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography.

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stratification. To this end, a multidisciplinary approach is paramount in refining selection criteria to deliver the most effective treatment to patients with unstable hemodynamics. In conclusion, the current management of unstable patients with PE should prioritize tailored treatment in a patient-oriented approach in which transcatheter therapies play a central role.

1. Introduction

Pulmonary embolism (PE), a potentially life-threatening condition characterized by the obstruction of pulmonary arteries by thromboembolic material, remains a significant global health problem [1]. Importantly, PE is often unrecognized as the ultimate cause of hospitalization or death because it frequently coexists with major surgery and other serious medical conditions, such as cancer, sepsis, or trauma [2]. Among the diverse spectrum of PE presentations, high- and intermediate-high risk PE pose unique challenges because these patients often present with clinical and hemodynamic instability, necessitating rapid and precise interventions to mitigate the risk of clinical deterioration and mortality [3]. Recovery from PE is associated with long-term complications such as recurrence, bleeding due to anticoagulant therapy, pulmonary hypertension, and psychological distress [1]. Up to half of the patients with a previous PE have dyspnea and functional and exercise limitations at 1 year that adversely affect their quality of life [4].

This position paper, which expresses the perspective of the Interventional Cardiology Working Group of the Italian Society of Cardiology, explores the landscape of high- and intermediate-high risk PE, with a focus on bridging the gap between the evolving standards of care and current practice. We provide an interventional cardiologists' perspective on the management of these patients (Fig. 1), emphasizing the growing importance of catheter-directed therapies as part of the therapeutic armamentarium [5] and of rigorous diagnostic and therapeutic follow-up [6]. In addition, we highlight how a multidisciplinary approach can improve outcomes and redefine the outlook of PE management.

2. Gaps between current recommendations and clinical practice

The incidence of acute PE has significantly increased over the past years [1], apparently due to both the increased incidence of deep vein thrombosis and improved diagnostic capabilities with the introduction in the late '90s of computed tomography pulmonary angiography (CTPA). Conversely, acute mortality has nearly halved, although it has plateaued in recent years, stabilizing at around 8% [1]. Both the diagnosis and treatment of PE have therefore improved substantially, likely because of a higher level of suspicion and clinicians' awareness, of better standardized clinical prediction rules [7] and diagnostic modalities including the use of D-dimer testing, of higher accuracy of multidetector CTPA and high efficacy of low-molecular-weight heparins and direct oral anticoagulants.

Patients with acute PE can manifest a wide spectrum of clinical presentations, from incidental findings to unpredictable hemodynamic deterioration or sudden cardiac death. Risk assessment in acute PE, according to current European Society of Cardiology (ESC) guidelines [3], is based on evaluation of hemodynamic profile, of validated scores -the Pulmonary Embolism Severity Index (PESI) or simplified PESI (sPESI)-, of clinical, humoral and imaging criteria of right ventricle (RV) dysfunction and myocardial injury. In case of hemodynamic instability, immediate referral for reperfusion therapy is mandatory; in stable patients, further risk stratification is based on imaging and laboratory findings. However, hemodynamic collapse can suddenly occur in stable patients; therefore, careful evaluation is essential [8]. Nevertheless, the guidelines do not prescribe a specific tool for intensive monitoring. The National Early Warning Score 2 (NEWS2), which is recommended in the UK for monitoring acute illness [9], may be useful. The NEWS2 is based

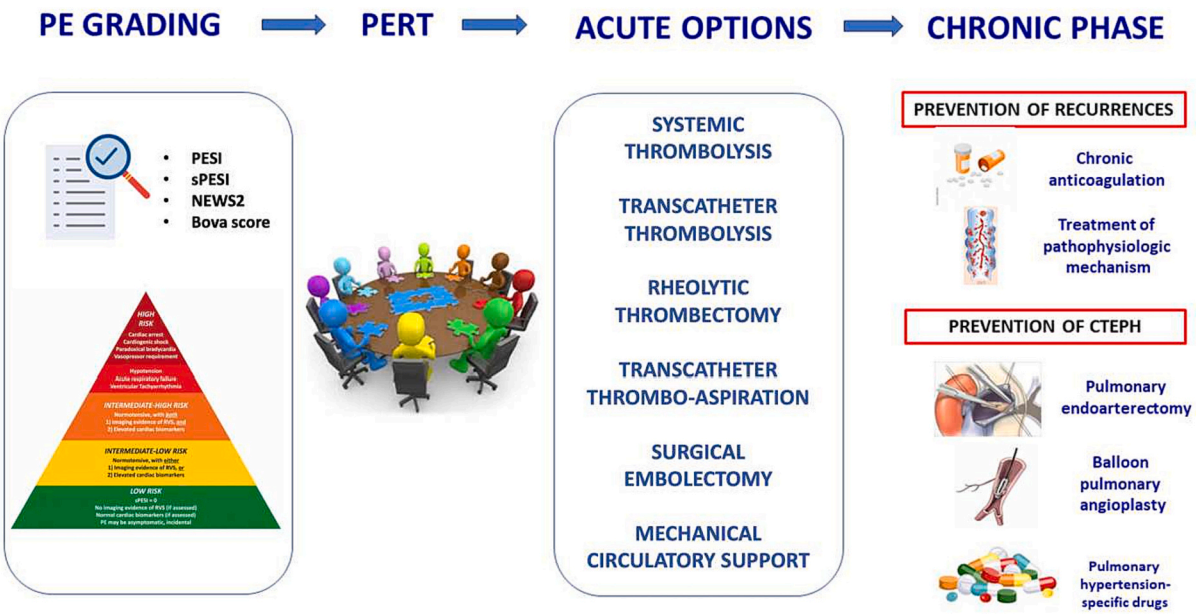

Fig. 1. Management of patients with intermediate- and high-risk pulmonary embolism.
The figure summarizes the management of patients with intermediate- and high-risk pulmonary embolism across the natural history of the condition. Risk stratification and PERT discussion are key to choose the most suitable intervention in both the acute and the chronic phase. CTEPH, chronic thromboembolic pulmonary hypertension; NEWS2, National Early Warning Score 2; PE, pulmonary embolism; PERT, pulmonary embolism response team; PESI, pulmonary embolism severity index; RVS, right ventricular strain; sPESI, simplified PESI.

on the rapid assessment of 6 parameters, yielding a severity score that can guide decision-making (e.g., the higher the score, the more urgent the need for intervention).

In the setting of acute PE, a free-floating thrombus in the right chambers – the so-called "clot-in-transit" (CiT) – may be incidentally documented by either CTPA or echocardiography and result in an abrupt change in clinical management. A "CiT patient", even if initially stable, has a greater propensity for hemodynamic instability than is usually that observed in patients without documented right ventricular thrombus [10]. Therefore, the identification of a CiT should raise awareness. Careful evaluation of these patients is essential to recognize early signs of instability and to act promptly. However, current ESC guidelines do not mention CiT, leaving such a significant grey area. Treatment options include heparin anticoagulation, thrombolysis, catheter-directed intervention, or open surgical embolectomy [11]. Occasionally, a right heart mass in the setting of PE may require a differential diagnosis between thrombus [10], cancer, or endocarditis, and the use of multimodality imaging is invaluable. CTPA is not the optimal imaging technique of the right heart and for the diagnosis of CiT for several reasons and should be performed only after the patient has stabilized [12]. Transthoracic echocardiography (TTE) remains the initial imaging modality of choice, while transesophageal echocardiography (TEE) should be considered if TTE is nondiagnostic and the clinical concern is high. In addition, TEE allows detailed anatomical imaging of the right heart and atrial septal abnormalities and is key whenever concern exists that a CiT is crossing a patent foramen ovale. The sequence of imaging modalities should prioritize speed and directness and the judgment of a multidisciplinary team convened in real time to improve clinical decision-making - the Pulmonary Embolism Response Team (PERT) [13] - becomes crucial.

Timely and appropriate management of PE remains central: the definition of treatment effectiveness, a term with prolonged uncertainty and absence of clear delineation in current guidelines, has recently been categorized by the consensus of the ESC Working Group on Pulmonary Circulation and Right Ventricular Function and the European Association of Percutaneous Cardiovascular Interventions (Table 1) [14]. Escalation therapy must be prompted by the PERT, choosing between traditional options such as conventional-dose systemic thrombolysis and surgical pulmonary embolectomy, or considering newer treatment options such as reduced-dose systemic thrombolysis or catheter-direct interventions, with systemic support by extracorporeal membrane oxygenation (ECMO), if necessary.

3. Systemic thrombolysis and transcatheter thrombolysis

According to current guidelines [3], systemic thrombolysis plus unfractionated heparin infusion is the first choice for the acute-phase treatment of high-risk PE (Class I, Level of Evidence B; Class IIa, Level of Evidence C for pregnant women). For intermediate- or low-risk PE, routine use of primary systemic thrombolysis is not recommended (Class III, Level of Evidence B). However, rescue thrombolysis is indicated (Class I, Level of Evidence B) if hemodynamic deterioration occurs during anticoagulation treatment.

The preferred thrombolytic regimen is intravenous administration of recombinant tissue-type plasminogen activator (100 mg over 2 h). An accelerated regimen (0.6 mg/kg over 15 min, maximum 50 mg) is not officially approved but is sometimes used in cases of extreme hemodynamic instability, such as cardiac arrest. First-generation thrombolytic agents (streptokinase and urokinase) are less commonly used in contemporary practice because they require longer infusion times (12–24 h).

Compared to unfractionated heparin alone, systemic thrombolysis leads to more effective and faster (within 2 h) clot dissolution and reduction in RV overload as assessed by various parameters (e.g., pulmonary obstruction, mean pulmonary artery pressure, pulmonary vascular resistance, RV dilation) [15–19]. However, this hemodynamic benefit seems to translate into a net clinical benefit only in high-risk PE. In fact, in a meta-analysis including, but not limited to, high-risk acute PE, the reduction in all-cause mortality with systemic thrombolysis was statistically significant only when studies including high-risk PE were considered. Conversely, systemic thrombolysis was associated with higher rates of severe bleeding (9.9%) and intracranial hemorrhage (1.7%) [20].

After initiation of systemic thrombolysis, close and continuous monitoring is mandatory to allow early detection of treatment failure. Unsuccessful thrombolysis, as judged by persistent clinical instability and unchanged right ventricular dysfunction on echocardiography at 36 h, has been reported in 8% of high-risk PE patients [21] and requires timely escalation to different therapeutic options (e.g. repeat thrombolysis, transcatheter or surgical embolectomy). Interestingly, large national registries including unstable PE patients over the past decades [22–25] have shown that, in real-world practice, systemic thrombolysis is offered to only a minority of potentially eligible patients (<30%) for various reasons, including objective contraindications (Table 2), a perceived increased risk, or physician preference.

Intriguingly, catheter-directed thrombolysis, which involves the slow infusion of a thrombolytic agent directly into the pulmonary arteries through a multi-sided hole catheter locally embedded in the embolus, has the rationale of reducing the total dose of thrombolytic agent (about 25% of the systemic dose) and thus reducing the risk of bleeding while maintaining therapeutic effectiveness [26]. There are different protocol regimens (1–8 mg of drug / lung / 2–8 h) and different infusion modalities. Dedicated catheters with multiple distal side holes have been designed for this purpose, such as Uni-Fuse® (Angiodynamics), Cragg-McNamara® (Medtronic) and Fountain® (Merit Medical). Moreover, an ultrasound-assisted thrombolysis system (Ekos®, Boston Scientific) is available in which the infusion catheter is equipped with an ultrasonic core transducer that generates an acoustic field that greatly accelerates lytic dispersion by driving the drug deeper into the clot and unwinding the fibrin to expose plasminogen receptor sites.

Results of previous observational studies are in keeping with most

Table 1
Definitions for successful or failed treatment (modified from Pruszczyk et al) [14].

Treatment success	Improvement of initially compromised hemodynamic status
Treatment failure indicated by a lack of improvement	• High risk: no hemodynamic improvement within 2–4 h after completion of full-dose systemic thrombolysis or immediately after completion of local thrombolysis infusion • Intermediate-high risk: no vital signs improvement after 24–48 h of anticoagulation at therapeutic doses
Treatment failure indicated by hemodynamic deterioration	Development of cardiorespiratory instability and hemodynamic deterioration after the initiation of treatment (systemic thrombolysis and/or anticoagulant)

Table 2
Absolute and relative contraindications to thrombolytic treatment.

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

recent findings. A meta-analysis comparing catheter-directed thrombolysis (with or without ultrasound) versus systemic anticoagulation alone for sub-massive PE (defined by RV dysfunction without hemodynamic instability) showed that catheter-directed thrombolysis was associated with significantly lower in-hospital, 30-day, and 90-day mortality and a trend toward lower 1-year mortality with similar bleeding rates compared with systemic anticoagulation [27].

A recently published network metanalysis [26] including data from 44 studies and 20,006 patients concluded that catheter-directed thrombolysis has a lower risk of death and major bleeding complications than systemic thrombolysis, as well as a lower risk of death and a similar risk of intracerebral hemorrhage, as compared with anticoagulation. The authors suggest that, although these findings are largely based on observational data, catheter-directed thrombolysis may be considered as a first-line therapy in patients with intermediate- or high-risk PE.

In summary, there is a significant undertreatment of intermediate-high risk cases of PE due to the hemorrhagic risk associated with systemic reperfusion treatment and its delivery of the thrombolytic agent. Local thrombolysis (with or without ultrasound) appears to be safe and effective and may extend the treatment of patients. Randomized controlled trials are needed to confirm these results and to evaluate and compare different catheter-directed treatments. With this respect, The Higher-Risk Pulmonary Embolism Thrombolysis (HI-PEITHO, ClinicalTrials.gov Identifier: NCT04790370) study is an ongoing multinational, randomized, controlled trial designed to evaluate whether ultrasound-assisted catheter-directed thrombolysis plus anticoagulation is associated with a significant reduction in PE-related death, cardiorespiratory decompensation or collapse, or non-fatal symptomatic, or objectively confirmed, recurrent PE at 7 days compared to anticoagulation alone in intermediate-high risk PE with imminent hemodynamic collapse.

4. Rheolytic thrombectomy

A percutaneous catheter-based approach with rheolytic thrombectomy was initially shown to be safe and effective in high-risk patients with PE [13]. However, the positive findings in preliminary experiences were subsequently overshadowed by some cases of serious procedural complications and deaths. Consequently, current guidelines do not support the use of rheolytic thrombectomy in high-risk patients with PE. The American College of Chest Physicians recommends an endovascular intervention only in patients with contraindications to fibrinolysis, primarily those with a high risk of bleeding [28], Similarly, European guidelines recommends endovascular intervention as an alternative to surgical embolectomy in patients with failed thrombolysis (Class IIa, Level of Evidence C) [3]. Recently, the Food and Drug Administration has issued a block-box warning on the device label [13], indicating that the AngioJet® device (Boston Scientific) should not be used as a first-line therapy for acute PE due to safety concerns.

A review of the literature shows that potential complications associated with the use of percutaneous thrombectomy include bradyarrhythmia, hypotension, kidney injury, major and minor bleeding [29]. Bradyarrhythmia and hypotension may be caused by the release of neurohormonal substances such as adenosine and bradykinin associated with the concomitant activation of stretch receptors in the pulmonary arteries. Hemolysis and hemoglobinuria may contribute to the development of acute renal failure. Hyperkalemia may also induce electrical instability leading to severe ventricular arrhythmias. Anemia may result from access-site related complications and/or from comorbidities that increase the risk of bleeding (such as malignancy) [29]. Recently, Pelliccia et al. [30] described 33 consecutive patients with acute PE and contraindications to thrombolytic therapy who received rheolytic thrombectomy with Angiojet®. Catheter thrombectomy resulted in angiographic improvement (Fig. 2) in 32 patients (96%), with a rapid amelioration in functional class (from 3.3 ± 0.9 to 2.1 ± 0.7, $p < 0.001$), and an increase in oxygen saturation (from 71 ± 15 to $92 \pm 17\%$, $p < 0.001$). No patient died. Adverse events included transient heart block ($n = 1$), hypotension ($n = 3$) and bradycardia ($n = 5$). Anemia occurred in 4 patients, whereas renal failure was not detected. Clinical improvement was maintained during follow-up. At 1-year, systolic pulmonary pressure was significantly lower than at baseline (65 ± 31 vs 31 ± 19 mmHg, $p < 0.001$). These findings are consistent with the data from the Nationwide Readmissions Database by Sedhom et al., which showed an inverse association between hospital catheter-directed interventions volume and in-hospital mortality [31]. Thus, mechanical treatment of acute PE may be associated with favorable outcomes only when performed by well-trained, experienced operators. This is in line with the recommendation that tertiary referral centers should have a PERT to rapidly assess and develop tailored treatment plans [13].

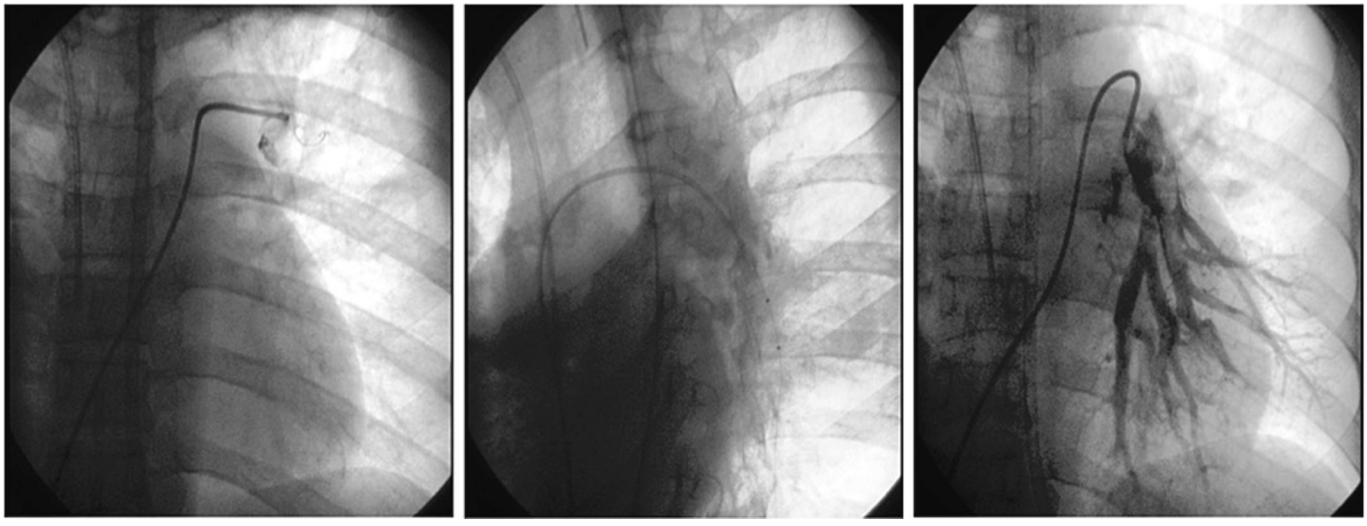

Fig. 2. Catheter thrombectomy in massive pulmonary embolism.
Selective angiography of the left main pulmonary artery demonstrated a massive embolism with contrast-filling defect in the left pulmonary parenchyma (left-hand panel). Multiple aspirations with the AngioJet® rheolytic thrombectomy device were then performed (middle panel). Catheter thrombectomy resulted in immediate angiographic improvement (right-hand panel). Reproduced with permission from Pelliccia et al. [30].

5. Transcatheter thrombo-aspiration

Advances in transcatheter technologies have made mechanical thrombo-aspiration a viable treatment option for patients with PE, particularly for those at high risk and with contraindications to systemic thrombolysis, who represent up to 10–20% of hospitalized patients.

Thrombo-aspiration catheters basically work by creating a negative pressure inside the pulmonary artery through an aspiration source, which allows for the aspiration of the embolus (Fig. 3), without concomitant use of thrombolysis. Specifically, two devices have demonstrated their efficacy and safety for the endovascular treatment of PE. The Indigo® Aspiration Catheter (Penumbra) was validated in the multicentre EXTRACT-PE (A Prospective, Multicenter Trial to Evaluate the Safety and Efficacy of the Indigo Aspiration System in Acute Pulmonary Embolism) study in 119 patients with hemodynamically stable PE and associated right ventricular dysfunction. This device, which utilizes an 8 French access, showed a significant improvement in right ventricular function, expressed as a 27.3% reduction ($p < 0.001$) in right-to-left ventricular diameter ratio, in a 4-chamber view, from baseline to 48 h post-procedure on core lab adjudicated CTPA; median procedure time was 37 min. Two patients experienced major bleeding (1.7%), which was fatal in one case [32]. The other currently used device is the FlowTriever® Retrieval/Aspiration System (Inari Medical) which was evaluated in the prospective multicenter FLARE (FlowTriever Pulmonary Embolectomy Clinical Study) trial that enrolled 106 patients with intermediate-risk PE [33]. The primary endpoint of the FLARE study was the change in right-to-left ventricular diameter ratio from baseline to 48 h or discharge, whichever occurred first. Results showed a significant reduction of 38% (25.1%; $p < 0.001$) in the primary efficacy endpoint. Furthermore, mean pulmonary artery pressure decreased on average from 29.8 mmHg pre-procedure to 27.8 mmHg post-procedure ($p = 0.001$). Four patients experienced major adverse events within 48 h of the procedure, including 1 major bleeding with pulmonary vascular injury. Consistent results in terms of safety profile, hemodynamic improvement, and outcomes were observed in a larger real-world population of intermediate- and high-risk PE enrolled in the multicentre FLASH (FlowTriever All-Comer Registry for Patient Safety and Hemodynamics) registry [34]. This device requires larger sheaths (from 16 to 24 French) with a potentially higher risk of vascular complications.

It should be noted that both devices, although tested in underpowered studies, have not yet shown a benefit in terms of hard endpoints that could be only indirectly inferred from the consistent improvement

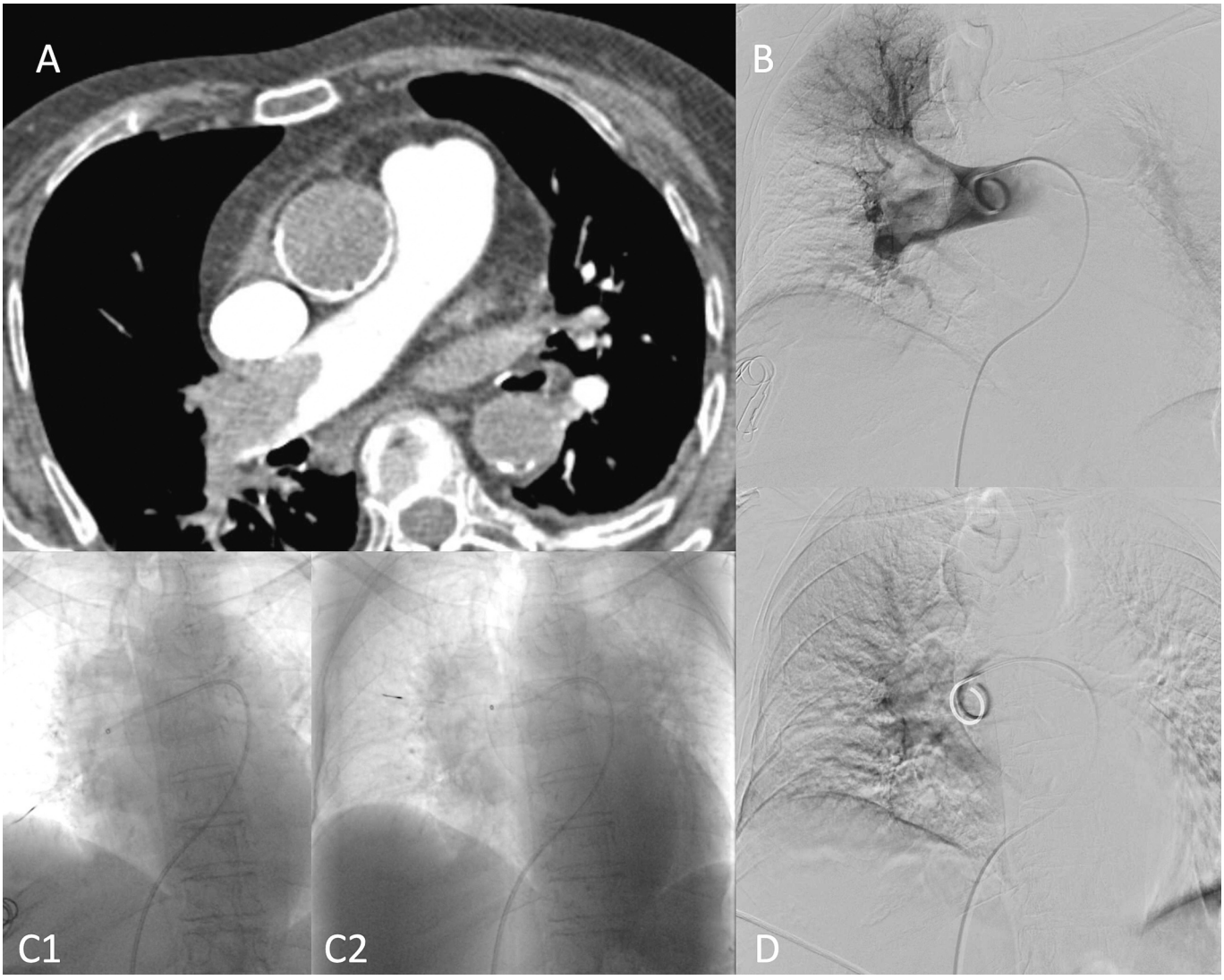

Fig. 3. Catheter thrombo-aspiration in massive pulmonary embolism.
CTPA demonstrated a massive pulmonary embolism of the right main pulmonary artery (A), later confirmed by selective angiography showing lack of perfusion of the middle and lower lobes (B). After thrombo-aspiration with the Indigo® system (C1 and C2), selective angiography demonstrates near complete removal of the embolus and restored perfusion (D).

in RV function. Despite the lack of conclusive data, a recent meta-analysis showed that the 30-day mortality of patients with intermediate-to-high risk PE treated with medical therapy alone was approximately 10%, while the mortality of patients treated with interventions (both with catheter-directed thrombolysis and Indigo® or FlowTriever® thrombo-aspiration) was only 3% [27]. Such a reduction in mortality is likely to be explained by the intervention, which is expected to reduce the risk of patient hemodynamic collapse with no additional safety concerns beyond those related to vascular access-related bleeding. Of note, the catheter-directed thrombolysis devices are minimally invasive and are expected to produce a benefit after 4 to 6 h after the placement due to their relatively slow mechanism of action acting locally on blood clots in the pulmonary vasculature. Conversely, thrombo-aspiration devices show immediate efficacy and are being considered in more unstable situations at the cost of large-bore access to the venous system. However, these considerations should be viewed as hypothesis-generating only and the reduction in in-hospital mortality with any of these approaches should be pursued and tested in dedicated randomized trials. The ongoing PEERLESS (Randomized controlled trial of mechanical thrombectomy vs catheter-directed thrombolysis for acute hemodynamically stable pulmonary embolism, ClinicalTrials.gov Identifier: NCT05111613) study is currently randomizing mechanical thrombo-aspiration with the FlowTriever® device to any commercially available system for catheter-directed thrombolysis.

6. Post-acute and chronic phase and diagnostic and therapeutic follow-up

After an episode of acute PE, the main focuses of treatment and follow-up [6] are on (1) preventing recurrences and (2) preventing and identifying cases that can evolve in chronic thromboembolic pulmonary hypertension (CTPEH) or chronic thromboembolic pulmonary disease.

In terms of medical treatment, these goals are pursued through oral anticoagulation. The non-vitamin K antagonist direct oral anticoagulants, i.e. dabigatran, apixaban, edoxaban, and rivaroxaban, should be preferred to vitamin K antagonists, after a number of trials demonstrated their non-inferiority for the prevention of recurrence of deep venous thrombosis and/or PE, in association with a significant reduction of major bleedings [35]. Vitamin K antagonists, with an INR target of 2.5 (range 2.0–3.0), remain the only possible option in patients with severe renal impairment and antiphospholipid antibody syndrome, as well as during pregnancy and lactation [3]. The duration of oral anticoagulation is more controversial, as prolonged treatment is associated with a lower risk of recurrence but also with a higher risk of bleeding. All patients should receive at least 3 months of oral anticoagulant treatment. Selection of candidates for prolonged oral anticoagulation should be based on the stratification of the risk of recurrence, which has been estimated to be approximately 2.5% per year after PE associated with transient risk factors and 4.5% per year after PE occurring in the absence of transient risk factor or in patients with cancer or thrombophilia [36]. Estimating the actual risk of recurrence in an individual patient is a complex and multifactorial issue, and describing the inherent factors is beyond the scope of this paper. In general, patients should be classified as having low, intermediate, or high risk of recurrence, with annual estimates of $<3\%$, 3–8% and $>8\%$, respectively. This risk should then be weighed against the individual bleeding risk to recommend the most appropriate duration of oral anticoagulation. In general, extension of anticoagulation beyond 3 months and up to 6 months should be considered for patients with a first episode of PE and no identifiable risk factor. Indefinite oral anticoagulation is recommended for patients with recurrent PE or deep venous thrombosis, antiphospholipid antibody syndrome, or other persistent risk factors [3]. Beyond 6 months, a reduced dose of apixaban (2.5 mg b.i.d.) or rivaroxaban (10 mg o.d.) should be considered. Special considerations in terms of drug choice and duration of treatment apply for patients with cancer.

In most patients with PE the patency of the pulmonary arterial bed is fully restored with adequate anticoagulation. However, a sizable proportion of patients may have residual, often organized, thrombi and a large proportion of patients report poor physical performance and reduced tolerance to physical activity after PE. The objective of an efficient follow-up should be to identify patients with persistent thrombi, those with measurable reduction in cardiopulmonary function and patients who develop CTEPH. After an acute PE event, incomplete thrombus resolution occurs in 23–35% of patients, while approximately 50% report functional limitations and/or decreased quality of life, and only 0.5–4% develop CTEPH [37], although underdiagnosis is considered likely. Appropriate screening for cancer should be performed in patients with unprovoked PE. Routine imaging with computed tomography is not recommended but all patients should be followed clinically at the end of the anticoagulation period (3–6 months) and echocardiography is the first-line diagnostic tool to assess right ventricular performance and to estimate pulmonary artery systolic pressure [6]. However, patients with persistent dyspnea or poor exercise capacity despite normal echocardiogram should undergo further evaluation to rule out CTEPH or chronic thromboembolic pulmonary disease. Cardiopulmonary exercise testing can help to objectify the likely cause of symptoms, whether cardiovascular or pulmonary, or suggest other causes such as deconditioning or depression [6]. Ventilation-perfusion scanning or CTPA may confirm the persistence of pulmonary vascular obstruction. If so, patients should preferably be referred to specialized centers for a thorough evaluation for CTEPH [38]. The latter is a serious condition, defined as the presence of pre-capillary pulmonary hypertension (mean pulmonary artery pressure, PAP, $\geq$ 20 mmHg, mean pulmonary artery wedge pressure, PAWP, $\leq$15 mmHg; pulmonary vascular resistance, PVR, $\geq$3 WU) in patients with multiple occlusive thrombo-emboli in elastic pulmonary arteries (main, lobar, segmental, subsegmental) after at least 3 months of effective anticoagulation. Pulmonary hypertension is mainly due to pulmonary arteries obstruction by organized fibrotic clots but may be exacerbated by associated microvasculopathy, that progressively develops in non-obstructed segments. This highlights the need for early detection and treatment of CTEPH, which could limit the development of irreversible and dramatic changes in the pulmonary microcirculation. CTEPH is a curable form of pulmonary hypertension, and advanced treatment includes pulmonary endarterectomy, balloon pulmonary angioplasty and pulmonary hypertension-specific drugs [38,39]. Physicians should be able to recognize risk factors and predisposing conditions for CTEPH to plan closer follow-up for these patients. Risk factors for CTEPH include previous episodes of PE or deep venous thrombosis, large pulmonary arterial thrombi, echocardiographic signs of pulmonary hypertension and/or right ventricular dysfunction, infected chronic intravenous lines or pacemakers, history of splenectomy, chronic thrombophilia, hypothyroidism treated with thyroid hormones, cancer, myeloproliferative disorders, inflammatory bowel disease, chronic osteomyelitis [3]. Chronic thromboembolic pulmonary disease is a relatively new entity, defined by reduced exercise tolerance in the presence of chronic pulmonary vascular obstruction with normal mean pulmonary artery pressure at rest [40]. The management of this latter condition is more controversial and should be discussed by dedicated pulmonary hypertension teams within centers with a large experience with CTEPH patients [41].

7. Integrated in-hospital pathways of the PERT and perspectives for a PE network

In patients with PE, the choice of optimal therapy and the need for advanced therapies in addition to anticoagulation (such as local thrombolysis, surgical embolectomy, transcatheter thrombo-aspiration, mechanical circulatory support, inferior vena cava filter), should be tailored according to risk assessment and multimodality imaging evaluation [3,14]. It is well known that timely and efficient management of PE is crucial to improve outcomes. However, according to real-world

registries, only a minority of patients receive advanced treatments, and the reasons for this undertreatment include the inability to respond rapidly ("systems" issues), failure to recognize potential benefits, lack of randomized evidence, and fear of complications [23,25].

The current European guidelines recommend the formation of a PERT in individual hospitals, depending on the local resources and access to specialists (Class IIa, Level of Evidence C) [3]. PERT should be composed of various specialists, including emergency medicine physicians, intensivists, cardiologists, interventional cardiologists, anesthesiologists, radiologists, pulmonologists, cardiac surgeons, hematologists, and others, depending on local circumstances and resources. Moreover, it is key to elaborate a clear PERT operating protocol for each center, standardizing and clearly defining the PERT components as well as activation pathways and operating modes. This multidisciplinary integrated in-hospital pathways protocol is designed to streamline the diagnosis and standardize the management of PE, thereby enhancing communication and collaboration among various medical specialties [42,43]. It is crucial that a PERT coordinator be always available (24/7 mode) to quickly arrange ad hoc real-time face-to-face or web conferences to discuss the case and make management decisions (ideally within 60 min). Typical clinical scenarios warranting PERT consultation include hemodynamically unstable patients with either absolute contraindications to or after ineffective systemic thrombolysis, as well as patients with acute intermediate-high-risk PE with clinical and hemodynamic deterioration or no improvement on anticoagulation [44]. A comprehensive integrated in-hospital PERT pathway involves a rapid patient assessment and risk stratification, multidisciplinary consultation, and the selection of the optimal individualized treatment based on the patient's risk profile and available resources. In addition, PERT can play a role during follow-up, by optimizing the mode and duration of long-term anticoagulant treatment, evaluating the potential need for an inferior vena cava filter, and monitoring the patient to detect and manage CTEPH.

Globally, the role of PERT in making individualized therapeutic decisions in acute PE has increased significantly over the past decade. The first PERT was established in 2012 in Boston at Massachusetts General Hospital [45]. Since then, this model has grown in popularity, and other hospitals worldwide have established their own PERTs. With the introduction of such model, a considerable increase in the use of catheter-based and any advanced therapy in general has been observed in patients with acute PE. Moreover, the availability of multidisciplinary PERT has been associated with improved outcomes, including 30-day mortality [46–49]. In 2015, a PERT Consortium including members from Europe, United States, Asia, South America, and Australia, has been established (https://pertconsortium.org) [50]. The mission of the Consortium is to facilitate the exchange of ideas and information related to the care of patients with PE and to advance the science of PE care through research, developing advanced treatment protocols, and educating clinicians and community members.

In addition, while integrated in-hospital PERT pathways have shown significant benefits, extending this approach to a broader PE network has the potential to further improve patient care in other aspects, such as: (a) telemedicine integration and remote consultations to improve access to PERT expertise, especially in underserved areas, and reduce delays in care; (b) regional collaboration (hub and spoke model) to improve resource allocation and facilitate patient transfers for specialized care when necessary; (c) data sharing and research to centralize data collection and enable large-scale research and quality improvement initiatives; (d) patient education to ensure that individuals at risk of PE are aware of the symptoms and seek prompt medical attention; (e) standardized protocols to promote uniform and evidence-based care for PE patients.

8. Conclusions

The management of high- and intermediate-high-risk PE has evolved significantly over the past decades. Evolving standards of care underscore the need for continuous re-assessment of patient risk. The PERT multidisciplinary approach is paramount in refining selection criteria to provide the most effective treatment for patients with hemodynamic instability. Such collaboration facilitates rapid decision-making and ensures the tailoring of therapeutic options. Catheter-directed interventions have emerged as a promising strategy in unstable patients offering faster and more effective restoration of hemodynamic stability with a reduction of bleeding risk compared with thrombolysis. Future research should focus on evaluating the long-term effects of catheter-directed interventions on patients' quality of life. In conclusion, the current management of unstable patients with PE should prioritize tailored treatment in a patient-oriented approach in which transcatheter therapies play a central role.

CRediT authorship contribution statement

Giuseppe Andò: Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration, Methodology, Conceptualization. **Francesco Pelliccia:** Writing – review & editing, Writing – original draft, Conceptualization. **Francesco Saia:** Writing – original draft. **Giuseppe Tarantini:** Writing – original draft. **Chiara Fraccaro:** Writing – original draft. **Fabrizio D'Ascenzo:** Writing – original draft. **Marco Zimarino:** Writing – original draft. **Mario Di Marino:** Writing – original draft. **Giampaolo Niccoli:** Writing – review & editing, Supervision. **Italo Porto:** Writing – review & editing, Validation, Supervision. **Paolo Calabrò:** Writing – review & editing, Validation, Supervision. **Felice Gragnano:** Writing – review & editing, Validation. **Salvatore De Rosa:** Writing – review & editing, Validation, Supervision. **Raffaele Piccolo:** Writing – review & editing, Validation. **Elisabetta Moscarella:** Writing – review & editing, Validation, Supervision. **Enrico Fabris:** Validation. **Rocco Antonio Montone:** Writing – review & editing, Validation. **Carmen Spaccarotella:** Writing – review & editing, Validation, Supervision. **Ciro Indolfi:** Validation, Supervision. **Gianfranco Sinagra:** Validation, Supervision. **Pasquale Perrone Filardi:** Validation, Supervision.

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