www.brn.cat

PERMANYER

BRN Rev. 2024;10(3):115-128

BRN Reviews

REVIEW ARTICLE

Novelties on treatment of hemodynamically stable pulmonary embolism from 2019 to present

Riccardo Ripamonti* and Giuseppe Paciocco

Pulmonology Department, Fondazione IRCCS "San Gerardo dei Tintori", Monza, Italy

ABSTRACT

Pulmonary embolism is a potentially life-threatening condition requiring prompt diagnosis and treatment. Despite the clear guidelines, this disease still represents a great challenge in both diagnosis and treatment in hemodynamically stable patients, especially with signs of right ventricular dysfunction proven by echocardiography and/or positive biomarker values (pulmonary embolism of intermediate–high risk). The heterogeneous clinical picture, often without pathognomonic signs and symptoms, represents a huge problem even for experienced doctors. Recent advances have led to the development of newer techniques and drugs aimed at improving pulmonary embolism management, reducing its associated morbidity and mortality, and the complications related to anticoagulation. The latest recommendations give preference to new oral anticoagulants compared to vitamin K antagonists, except for certain categories of patients (patients with antiphospholipid syndrome, mechanical valves, pregnancy). This review provides an overview of hemodynamically stable pulmonary embolism management and treatment.

Keywords: Anticoagulation. Pulmonary embolism. VTE.

***Correspondence to:**
Riccardo Ripamonti
E-mail: r.ripamonti@campus.unimib.it

Received: 09-10-2024
Accepted: 28-10-2024
DOI: 10.23866/BRNRev:2024-M0116
www.brnreviews.com

INTRODUCTION

Venous thromboembolism (VTE), which comprehends deep venous thrombosis (DVT) and pulmonary embolism (PE), represents the third most frequent acute cardiovascular syndrome, with an annual incidence estimated at one to two cases per 1,000 people, according to epidemiology studies[1,2]. Moreover, it is the third most common cause of death worldwide[3,4]. The percentage of PE varies from 30% to 40% of all the VTE episodes and it seems to be more frequent in the last years[5]. In Italy, the incidence of PE ranges from 0.41 to 0.55 per 1,000 person-years[3]. It is estimated that about one-third of patients presenting VTE have PE[6]. The incidence of PE is increasing within VTE patients so that the significant increase in VTE incidence registered lately is mostly due to more frequent PE[7].

The clinical picture of PE is wide, spanning from asymptomatic, dyspnea, and fatigue to sudden death[4,8]. Due to the high percentage of diagnostic pitfalls, it is crucial to treat this condition with the right therapy for the right patients in a timely fashion[9].

Once the diagnosis of PE is made, the 2019 European Society of Cardiology (ESC) guidelines recommend risk stratification based on hemodynamic stability, clinical prediction scores, cardiac biomarkers, and imaging of the right ventricle (RV) using echocardiography or computed tomography[10].

The aim of this review is to highlight the new strategies for the treatment of hemodynamically stable PE (i.e., PE with an intermediate or low early mortality risk), since the last guidelines on the diagnosis and the treatment of the PE were released in January 2020 by the ESC and the European Respiratory Society (ERS).

How to define the circle stability?

The 2020 ESC-ERS guidelines define PE as hemodynamically unstable when one of the following situations occurs[10]:

1. Cardiac arrest, as in need for cardiopulmonary resuscitation.

2. Obstructive shock is defined as the combination of (a) systolic blood pressure (BP) <90 mmHg or need for vasopressors to maintain BP ≥90 mmHg despite euvolemic status and (b) end-organ hypoperfusion.

3. Persistent hypotension is defined as systolic BP <90 mmHg or a systolic BP drop ≥40 mmHg, which requires (a) duration longer than 15 min and (b) exclusion of new-onset arrhythmia, hypovolemia, or sepsis as causative event.

Any patient presenting with PE and none of the aforementioned conditions can be classified as hemodynamically stable PE. These patients are also a very heterogeneous group, ranging from patients with small PE, stable BP, normal RV size and function, normal biomarkers, and a normal simplified Pulmonary Embolism Severity Index (sPESI) (low risk) to those patients with extensive emboli with

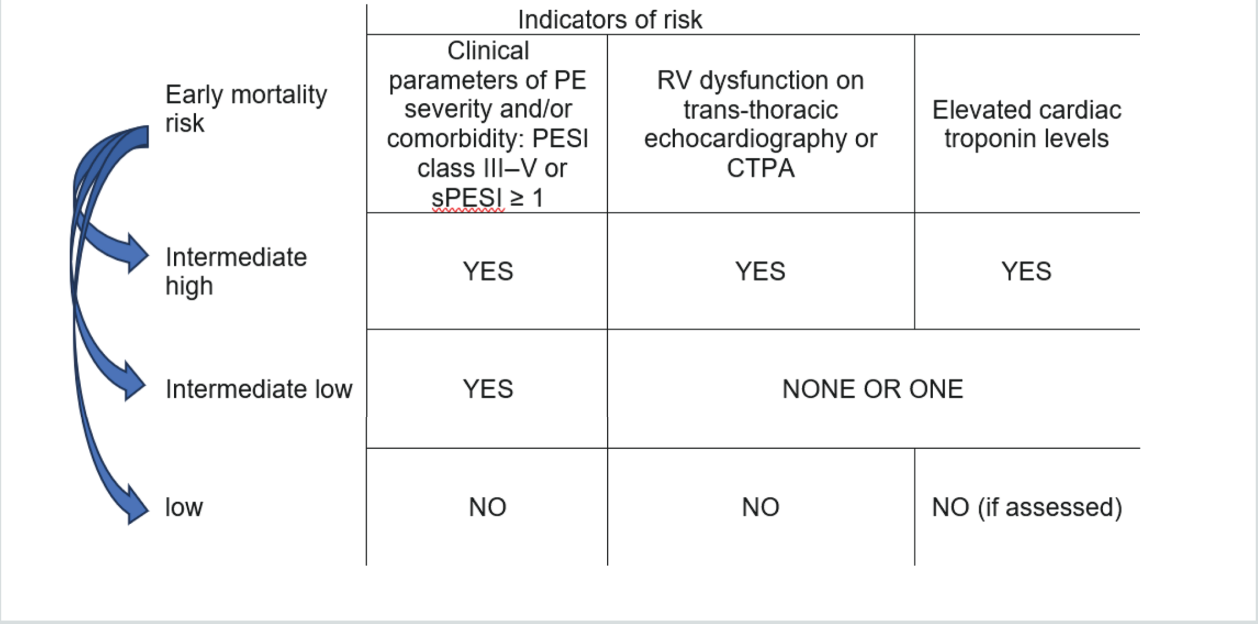

Figure 1. Classification of PE severity and mortality risk (*modified from ESC-ERS 2020 guidelines on PE*[10]).
CTPA: computed tomography pulmonary angiography; PE: pulmonary embolism; sPESI: Pulmonary Embolism Severity Index.

tachycardia, right ventricular dysfunction (RVD), abnormal biomarkers, and borderline BP[10-13]. Based upon the ESC guidelines[10], these patients have been categorized as "intermediate–low risk" (abnormal RV function or elevated serum troponin) and intermediate–high risk (abnormal RV function and elevated serum troponin).

The treatment varies according to the early (in-hospital or 30 days) mortality risk (Fig. 1). This risk stratification is based on the presence of hemodynamic instability, clinical severity, worse prognostic signs at echocardiography, and/or computed tomography pulmonary angiography (CTPA), and serum troponin levels. It should be noted that whenever there is hemodynamic instability, PE is stratified as high risk, but this picture is not mentioned in this review. This risk stratification is based on the presence of clinical, echocardiographic, CTPA signs, and serum troponin levels.

The role of systemic thrombolysis in those with hemodynamically stable disease is less clear. RVD is central to this risk stratification because of its critical role in disease severity; that is, consequent RV failure is the primary cause of death in PE[14,15].

Systematic reviews (SRs) have encouraged confusion by reaching different indications in "intermediate-risk" PE treatment regimens. Four meta-analyses have assessed the prognostic value of trans-thoracic echocardiography (TTE)-derived RVD in hemodynamically stable patients, all evaluating short-term

all-cause mortality as the primary outcome. Prosperi-Porta et al.[16] assessed the prognostic value of TTE-derived RVD in intermediate-risk patients as defined by ESC criteria (sPESI > 0 and/or positive cardiac biomarkers and/or imaging evidence of RVD), which had not been previously assessed. Interestingly, there seems to be a numerical trend of a diminishing prognostic value of RVD with increasing risk categories. In a meta-analysis of low-risk patients, Becattini et al.[17] showed that RVD identified on TTE carried an odds ratio (OR) for in-hospital/30-day mortality of 5.86 (confidence interval [CI] 2.3–14.86) compared with our data showing an OR of 2.00 (CI 1.66–2.40) in hemodynamically stable patients and 1.63 (CI 0.76–3.48) in intermediate-risk patients. While this trend is only hypothesis-generating due to the few studies with intermediate-risk patients that we identified, it is possible that as patients develop additional risk markers, they may become preselected where categorical RVD becomes more common and less specific for adverse events.

Current ESC guidelines provide a class IIa recommendation to consider RV assessment by imaging methods or laboratory markers in all patients regardless of risk category[10]. However, apart from increased hospital monitoring, the presence of RVD in hemodynamically stable patients has failed to alter initial management as shown in the Pulmonary embolism thrombosis: hemodynamic instability and thrombolysis optimization (PEITHO) trial of fibrinolytic therapy[18]. The presence of traditional TTE RVD definitions is ubiquitous in hemodynamically stable PE (37.8% of patients in this meta-analysis). Similar to the PEITHO trial, which defined RVD by the presence of RV end-diastolic diameter > 30 mm or RV/left ventricle (LV) > 0.9 or hypokinesis of the RV free wall or tricuspid regurgitation velocity >2.6 m s^{-1}, 70% of the studies in this meta-analysis used similar composite definitions of RVD[18]. Given its high prevalence, these current definitions of RVD lack the specificity to define a truly intermediate–high-risk subpopulation that might benefit from upfront reperfusion strategies.

The core therapy for VTE is anticoagulation. There are six types of anticoagulants[1,10]:

1. Non-vitamin K oral anticoagulants (NOACs)
2. Low-molecular-weight heparin (LMWH)
3. Fondaparinux
4. Unfractionated heparin (UFH)
5. Vitamin K antagonists (VKAs)
6. Direct thrombin inhibitors (DTIs).

Lasica et al.[1] pointed out that these drugs are used in the treatment of thrombosis in patients who developed heparin-induced thrombocytopenia (HIT). The most studied DTI are lepirudin and argatroban. Lepirudin can be used intravenously or subcutaneously while argatroban is administered parenterally. Dose adjustments are required in patients with renal failure for lepirudin and hepatic damage for argatroban. Their

effect needs to be monitored by dosing the activated partial thromboplastin time (aPTT).

Since these inhibitors, except dabigatran (which is described under NOACs), have not been studied in the treatment of acute PE, they are not treated in this review.

There are no recommendations regarding which anticoagulant is preferred in intermediate- or low-risk PE, but it should be noted that:[1,10,19,20]

– Anticoagulation should be started during the diagnostic workup in patients with the high or intermediate clinical probability of PE, according to risk scores such as PESI and sPESI.

– LMWH and fondaparinux are the recommended parenterally anticoagulants over UFH for most patients, except in cases of creatinine clearance <30 ml/min, severe obesity (as in body mass index above 40 kg/m^2), and clinically suspected imminent hemodynamic decompensation. Imminent hemodynamic decompensation is not a clearly defined condition, but can be considered as a condition in which intermediate–high-risk PE patients are worsening despite anticoagulation and there could be the need for reperfusion treatment.

– NOACs are the recommended parenterally anticoagulants over VKAs, if patients are eligible. VKAs are recommended over NOACs in severe renal impairment (creatinine clearance <15 ml/min) and in patients affected by anti-phospholipid antibody syndrome.

PE is a highly heterogeneous clinical entity, sometimes misdiagnosed, sometimes complicating preexistent acute conditions, so that the treatment can be delayed or that the right choice about treatment can be tricky.

There are three phases of treatment[6].

1. Initial management: first 5–21 days after diagnosis.

2. Primary treatment: from 3 to 6 months.

3. Secondary prevention: after 3–6 months.

The third phase is not deepened in this review because it is not required for every patient; it is necessary to evaluate different aspects and target the decision on the single patient, balancing risk factors for VTE, bleeding risk, and VTE triggers[21]. Ortel et al.[6,10,22] and the 2020 guidelines on VTE point out that secondary prevention is indicated in:

– Unprovoked VTE defined as a DVT or PE in people with no predisposing risk factors.

– Chronic risk factors for VTE (Table 1).

Non-vitamin K oral anticoagulants

Four drugs belong to this class: three inhibitors of the activated X factor – rivaroxaban, apixaban, and edoxaban – and one inhibitor of the activated thrombin, dabigatran[1,23].

Nowadays, new oral anticoagulants are the first-choice drugs for the treatment of most

Table 1. Chronic risk factors for VTE

Strong risk factors	Previous VTE
Moderate risk factors	Autoimmune disease
	Blood transfusion
	Central venous lines or intravenous catheters and leads
	Chemotherapy
	Congestive heart failure or respiratory failure
	Erythropoiesis-stimulating agents, hormone replacement therapy, oral contraceptive therapy
	In vitro fertilization
	Postpartum period
	Inflammatory bowel disease and cancer (highest risk in metastatic disease)
	Thrombophilia
Weak risk factors	Bed rest >3 days or immobility due to sitting
	Diabetes mellitus, arterial hypertension, obesity
	Increasing age
	Laparoscopic surgery
	Pregnancy
	Varicose veins

VTE: venous thromboembolism.

PE patients[10,24], because they have predictable pharmacokinetics, short half-lives, and few pharmacological interactions, so that there is a less need for monitoring[25]. Moreover, they showed a similar efficacy towards traditional anticoagulation, as in LMWH, VKAs, and fondaparinux, and a lower risk of bleeding complications[26,27]. However, it should be pointed out that NOACs' pharmacodynamics is not evaluated with usual coagulation tests[28].

The duration of the initial management varies according to the choice of the molecule (Fig. 2).

Of note, only rivaroxaban and apixaban are validated in both phases; edoxaban and dabigatran are validated only in the primary treatment, while for the initial phase they require LMWH or fondaparinux[25]. Moreover, recently apixaban and rivaroxaban were found to be appropriate in the treatment of severely obese patients or whose weight is >120 kg[20]. On the other hand, edoxaban should be administered at 30 mg daily for patients weighing less than 60 kg[20].

Regarding renal impairment[20]:

- Apixaban cannot be used if creatinine clearance is less than 25 ml/min.
- Dabigatran cannot be used if creatinine clearance is less than 30 ml/min.
- Edoxaban cannot be used if creatinine clearance is less than 15 ml/min, but between 15 and 50 ml/min, it can be

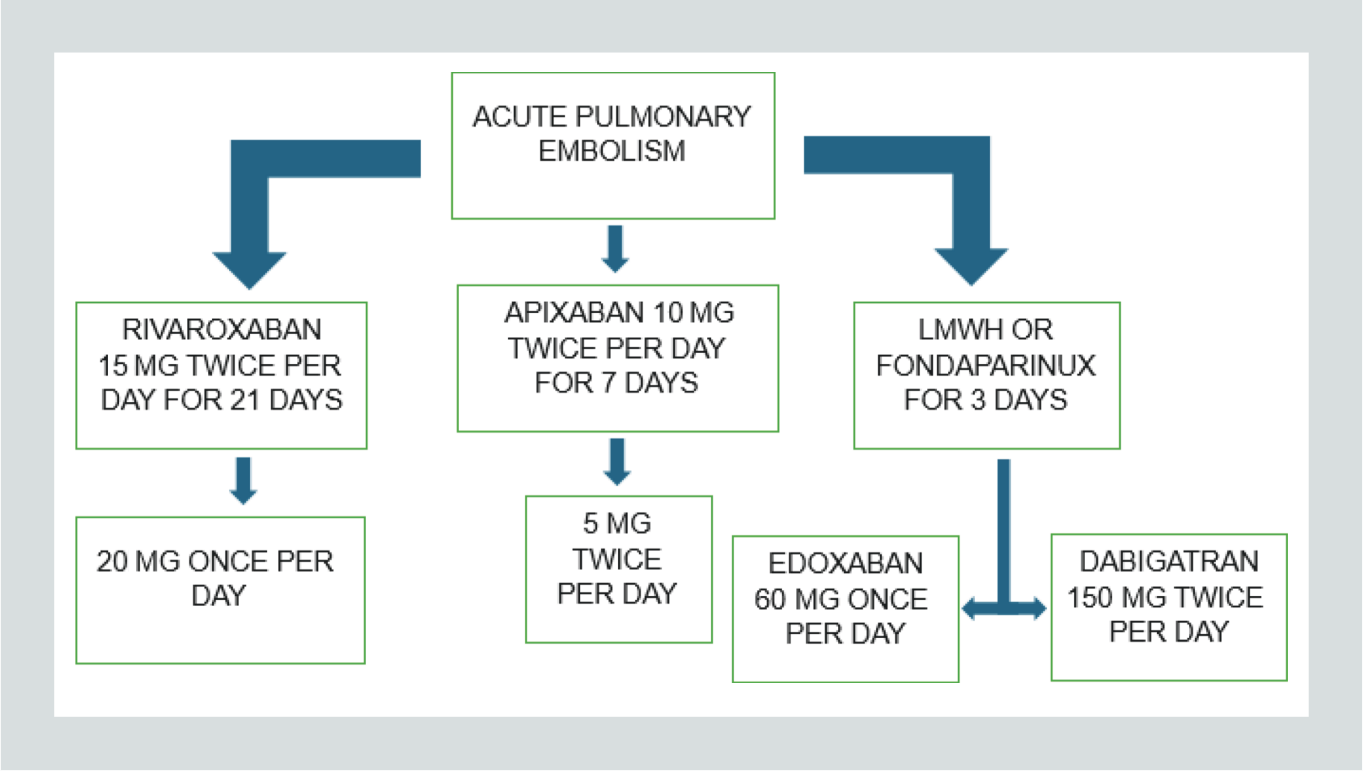

Figure 2. Initial and primary phase treatment using NOACs[25,29-31].
NOACs: non-vitamin K oral anticoagulants.

administered using a reduced dose of 30 mg daily.

– Rivaroxaban cannot be used if creatinine clearance is less than 15 ml/min.

NOACs cannot be used in pregnancy and during breastfeeding[25].

Low-molecular-weight heparin

LMWH achieves its anticoagulant effect by inhibiting the activated X factor and binding to the anti-thrombin III[32].

Hemodynamically stable PE is usually treated with LMWH rather than UFH, due to its major safety profile (less bleedings and HIT), better predictable anticoagulant response, and faster attainment of therapeutic levels – in 3–4 h[29,33-35].

Recent data show that initial management with LMWH can be reduced to 3 days[30], so that it is possible to switch to NOACs after 72 h of treatment with LMWH if patients remain stable[29].

Usually, the LMWH dose correlates with patients' weight: 1 mg/kg twice daily, although it is possible to administer 1.5 mg/kg once daily. LMWH is administered subcutaneously and does not require aPTT monitoring[1,36].

For some authors, LMWH is still the standard of care in cancer-related thrombosis and in the prophylaxis of VTE in

cancer patients[37-39]. However, the last CHEST guidelines recommend an oral Xa inhibitor (rivaroxaban, apixaban, and edoxaban) over LMWH in the absence of high risk of gastrointestinal or genitourinary bleeding[40,41]. As a matter of fact, several large studies have investigated the role of NOACs: rivaroxaban had lower rates of VTE than LMWH in the prophylaxis, while edoxaban and apixaban had similar prophylactic efficacy compared to LWMH[42]. According to the American Society of Hematology guidelines, in cancer-related PE, apixaban, rivaroxaban, or LMWH is recommended in the first phase, while apixaban, edoxaban, and rivaroxaban are recommended over LMWH in the second phase[43].

Interestingly, NOACs are not recommended immediately after bariatric surgery, because of iatrogenous malabsorption; instead, parenteral anticoagulation is the best choice[19].

Regarding the dosage in obese patients, data can be extrapolated from a study on VTE prophylaxis in orthopedic patients, since there are no clinical trials on the efficacy of anticoagulant in obese patients presenting with VTE. Tran et al.[44] pointed out that LMWH distribution is weight-dependent, and that fixed-dose treatment could be less effective than weight-based dosing. According to this review, it is suggested to use 4,000 IU twice a day rather than daily for VTE prophylaxis in severely obese patients.

LMWH and UFH do not cross the placenta, so these are the blood thinners used in pregnancy. LMWH is the preferred choice of treatment over UFH, because the former has less adverse effects and greater reliabity[45]. LMWH is also preferred over NOACs when PE occurs during VKA treatment, unless the reason for the recurrent episode of VTE is poor international normalized ratio (INR) control, in which case NOACs can be considered[6].

Fondaparinux

Fondaparinux is an activated factor X inhibitor, administered subcutaneously once daily, according to the patients' weight[1,32]:

– 5 mg if weight is under 50 kg.

– 7.5 mg if weight is between 50 and 100 kg.

– 10 mg if weight is over 100 kg.

Fondaparinux cannot be used if creatinine clearance is below 30 ml/min and should be used carefully if creatinine clearance is below 50 ml/min[46]. The drug has almost complete bioavailability after the administration and it is used off-label in the treatment of HIT; it is also used when LMWH cannot be administered, for example, in case of LMWH allergy[1,47].

Fondaparinux can be safely used in bariatric patients and after bariatric surgery, due to its administration route and high bioavailability[19].

Unfractionated heparin

UFH was the cornerstone treatment for many years, because it was the only available option for decades[25]. Then, it was

replaced by LWMH, fondaparinux, and, more recently, NOACs. UFH is an indirect anticoagulant since it binds to AT-III; thus, the resulting complex inhibits the activated factors X, IX, XI, and XII[1].

UFH is still used in a limited number of settings such as patients with severe renal impairment (creatinine clearance below 30 ml/min), pregnancy, severe obesity, and imminent hemodynamic instability, and patients whose only options in the primary treatment are VKAs[1,6,25,48].

The initial dose varies according to patients' weight, and it is administered 80 IU/kg as an intravenous (i.v.) bolus and continuous infusion, maintaining an aPTT ratio of 1.5–2.5 times higher than the initial aPTT of the patient[1].

Alternatively, UFH can be administered with an initial bolus of 5,000 U i.v. followed by 10,000 U or more subcutaneously every 12 h. The aPTT should be maintained 1.5–2.5 times the control value measured at 6 h after injection. Anti-Xa essay can be used in the monitoring of UFH activity with a target range of 0.3–0.7 U/ml[45].

Vitamin K antagonists

VKAs lost their primacy as the first-choice anticoagulants in favor of NOACs for most patients. However, their role remains untouched in patients affected by anti-phospholipids syndrome, severe renal insufficiency, and patients with mechanical valves[1,25].

Moreover, they are often used in a specific case of PE complication (about 3% of PE survivors[1], i.e., chronic thromboembolic pulmonary hypertension [CTEPH])[49].

In this setting, lifelong anticoagulation is recommended, but there are no randomized clinical trials regarding which anticoagulant should be used[50]. Despite this, experts recommend VKAs over NOACs, due to lower recurrent VTE rates using the first class rather than the latter[50]. It is noteworthy that 10% of people affected by CTEPH also suffer from anti-phospholipids syndrome, so in this case, VKAs are the only recommended anticoagulants[50].

There are three main drugs in this class: warfarin, acenocoumarol, and phenprocoumon. The most common is warfarin and most studies consider this drug, while similar effects are assumed for the others[51]. The main difference among the drugs is the half-life: 8–24 h for acenocoumarol, 36–42 h for warfarin, and 72–270 h for phenprocoumon[51,52]. The anticoagulant effect is reached by the inhibition of the vitamin K epoxide reductase, thus decreasing the activity of factors II, VII, IX, and X and proteins S, C, and Z[23]. These drugs are metabolized by the CYP2C9 and CYP3A4 and eliminated through liver and kidney[52].

The effect of VKAs is monitored with the dosage of INR, which needs to be between 2 and 3[1]. The bioavailability greatly varies according to two kinds of factors: genetic and nongenetic factors[52]. The former kind represents single nucleotide polymorphisms in the liver enzymes adhibited

Table 2. List of agents interfering with warfarin mechanism[51-53]

Drugs class	Examples
Antiplatelet agents	Clopidogrel, ticlopidine, aspirin, dipyridamole
Antimicrobials	Azole antifungals, cephalosporins, sulfonamides, penicillins, quinolones, tetracyclines, rifampicin
Analgesics	Nonsteroidal anti-inflammatory drugs, opioids, acetaminophen, anticonvulsants (gabapentin, pregabalin)
Central nervous system agents	Serotonin reuptake inhibitors, tetracyclic antidepressants, serotonin-norepinephrin reuptake inhibitors, barbiturates, valproate
Cardiovascular system agents	Amiodarone, amlodipine, isosorbide mononitrate, loop diuretics
Gastrointestinal agents	Proton pump inhibitors, loperamide, cholestyramine

to drug metabolism, while the latter comprehends food intake, polypharmacotherapy, and patients' compliance[52].

Many drugs interfere with warfarin activities (Table 2). Increased risk of hemorrhage in patients under VKAs is observed if concomitant therapy with anti-platelet drugs, nonsteroidal anti-inflammatory drugs, serotonin reuptake inhibitors, antibiotics such as macrolides and trimethoprim-sulfamethoxazole, azoles, amiodarone, statins, and lipid-lowering agents is taken[1,52]. On the other hand, the effect of VKAs is reduced whenever an inductor of liver cytochromes is taken, that is, rifampicin, azathioprine, carbamazepine, barbiturates, glucocorticoids, St. John's Wort, and green tea[51,52].

As a matter of fact, whenever a new drug is added, an acute condition arises, or a chronic disease deteriorates, INR must be monitored more frequently than usual, since an INR out of range is very dangerous: if INR is lower than 2, there is a risk of thromboembolic event, and if INR is greater than 4, the risk of bleeding is heightened (exponentially if INR is above 6)[1,52,54].

When VKAs are the drugs of choice, it is necessary to start with VKAs plus a parental anticoagulation, usually LMWH, combined for about 5 days, until after two consecutive INRs are >2, after which it is possible to continue with VKAs alone, monitoring INR[55,56].

Inferior vena cava filters

According to the 2020 ESC-ERS guidelines, inferior vena cava (IVC) filters should be placed for any of the following indications:

- Contraindication for anticoagulation (active hemorrhage, excessive bleeding risk), especially in the first month after an acute PE[40,57,58].
- Anticoagulation-related complication.
- Recurrent PE despite therapeutic anticoagulation and in high-risk VTE patients, as primary prophylaxis[59].

However, a meta-analysis of three randomized controlled studies by Jiang et al.[59], which included 863 patients with DVT, concluded that the addition of an IVC filter to

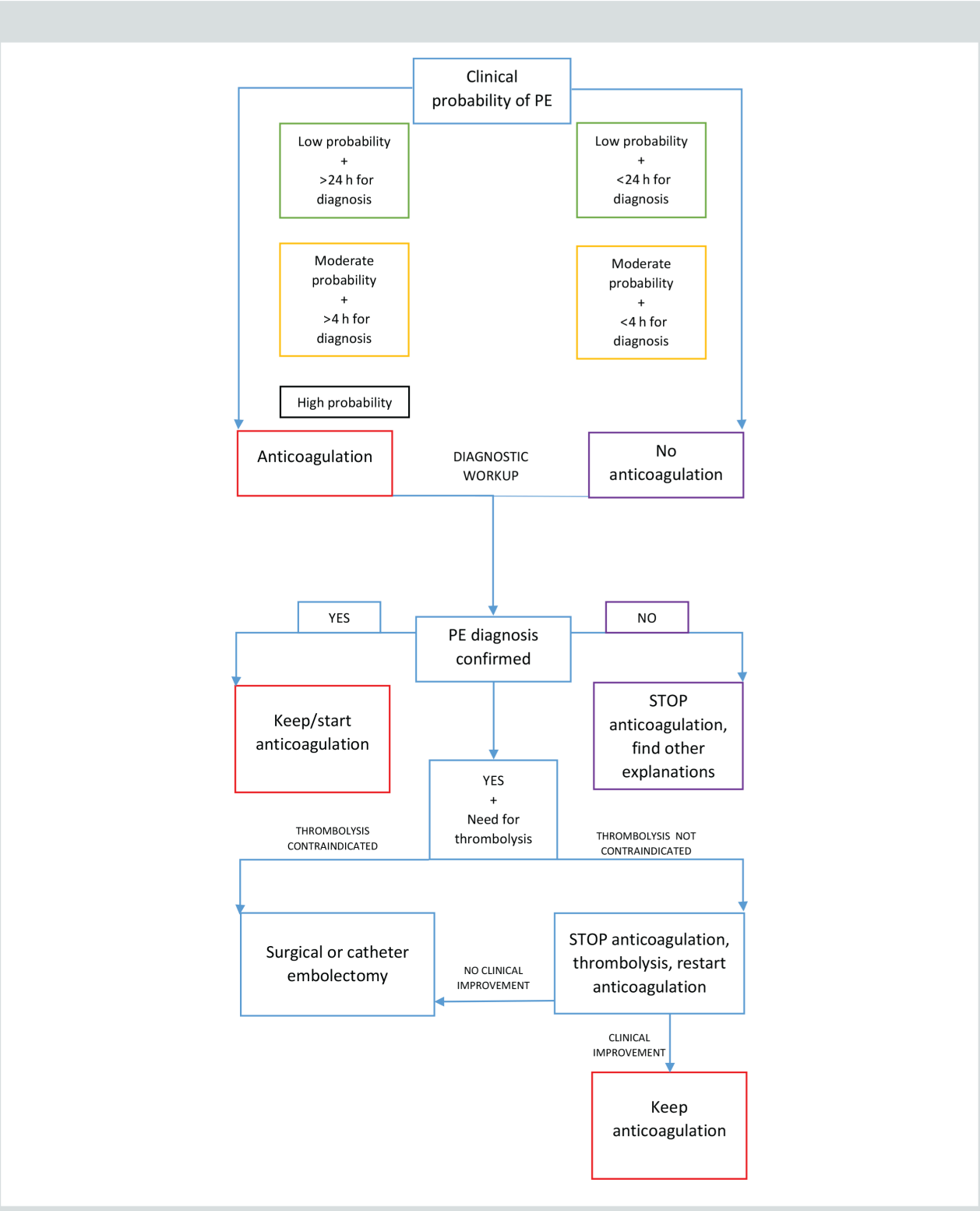

Figure 3. Diagnostic algorithm in pulmonary embolism.
PE: pulmonary embolism.

anticoagulation, as compared with anticoagulation alone, did not reduce the incidence of recurrent PE in the short term (3 months).

Relative indications include the following:

- Free-floating thrombus in the IVC or iliofemoral segments.
- PE and limited cardiac reserve.
- Prophylaxis in patients with severe trauma, spinal cord injury, or paraplegia[60,61].
- Prophylaxis before surgery[62,63].
- Poor compliance with anticoagulation.
- Protection during DVT thrombolysis.

These are devices that mechanically prevent venous clots from impairing pulmonary circulation and they are placed percutaneously under angiographic guidance[10,40]. Placing and maintaining IVC filters is not risk-free, as complications are reported: device embolization, strut penetration, risk of DVT, access site hematoma, and failure to retrieve the IVC filter[6,32]. That is why, whenever the contraindication to anticoagulation is removed, it is recommended to retrieve the IVC filter and start anticoagulation[6]. Similar recommendations may be considered for PE in pregnancy[45].

CONCLUSIONS

Starting from what VTE is, how often it presents, and which is its clinical picture, we went through literature regarding the treatment options of PE in hemodynamic stable patients.

For intermediate–high risk PE, it seems that the best strategy is starting with anticoagulation, then reassessment after 24 h, and deciding whether to continue with anticoagulation or switch to other pathways (such as reperfusion therapy, systemic thrombolysis, etc.)[29,64].

New data from recent literature propose a treatment algorithm that summarizes the procedures that can be followed in hemodynamically stable patients (Fig. 3). It refers to patients in whom anticoagulation is not contraindicated; otherwise in such patients, if PE is confirmed, the only possibility is positioning an IVC filter.

ETHICAL DISCLOSURES

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article. Furthermore, they have acknowledged and followed the recommendations as per the SAGER guidelines depending on the type and nature of the study.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

REFERENCES

1. Lasica R, Asanin M, Djukanovic L, Radovanovic N, Savic L, Polovina M, et al. Dilemmas in the choice of adequate therapeutic treatment in patients with acute pulmonary embolism-from modern recommendations to clinical application. Pharmaceuticals (Basel). 2022;15(9).
2. Duffett L. Deep Venous Thrombosis. Ann Intern Med. 2022;175(9):ITC129–42.
3. Pastori D, Cormaci VM, Marucci S, Franchino G, Del Sole F, Capozza A, et al. A Comprehensive Review of Risk Factors for Venous Thromboembolism: From Epidemiology to Pathophysiology. Int J Mol Sci. 2023;24(4):3169.
4. Licha CRM, McCurdy CM, Maldonado SM, Lee LS. Current management of acute pulmonary embolism. Ann Thorac Cardiovasc Surg. 2020;26(2):65–71.
5. Becattini C, Agnelli G. Acute Treatment of Venous Thromboembolism. Blood. 2020;135(5):305–16.
6. Ortel TL, Neumann I, Ageno W, Beyth R, Clark NP, Cuker A, et al. American Society of Hematology 2020 guidelines for management of venous thromboembolism: treatment of deep vein thrombosis and pulmonary embolism. Blood Adv. 2020;4(19):4693–738.
7. Heit JA, Spencer FA, White RH. The epidemiology of venous thromboembolism. J Thromb Thrombol. 2016;41(1):3–14.
8. Wenger N, Sebastian T, Engelberger RP, Kucher N, Spirk D. Pulmonary embolism and deep vein thrombosis: similar but different. Thromb Res. 2021;206:88–98.
9. Carson JL, Kelley MA, Duff A, Weg JG, Fulkerson WJ, Palevsky HI, et al. The Clinical Course of Pulmonary Embolism. N Engl J Med. 1992;326(19):1240–5.
10. Konstantinides SV, Meyer G, Becattini C, Bueno H, Geersing GJ, Harjola VP, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European respiratory society (ERS). Eur Heart J. 2020;41(4):543–603.
11. Yamashita Y, Morimoto T, Kimura T. Venous thromboembolism: recent advancement and future perspective. J Cardiol. 2022;79(1):79–89.
12. Khan F, Tritschler T, Kahn SR, Rodger MA. Venous thromboembolism. The Lancet. 2021;398(10294):64–77.
13. Howard L. Acute Pulmonary Embolism. Clin Med. 2019;19(3):243–7.
14. Smulders YM. Pathophysiology and Treatment of Haemodynamic Instability in Acute Pulmonary Embolism: The Pivotal role of Pulmonary Vasoconstriction. Cardiovasc Res. 2000;48(1):23–33. Available from: www.elsevier.com/locate/cardioreswww.elsevier.nl/locate/cardiores
15. Goldhaber SZ, Elliott CG. Acute Pulmonary Embolism: Part I: Epidemiology, Pathophysiology, and Diagnosis. Circulation. 2003;108(22):2726–9.
16. Prosperi-Porta G, Ronksley P, Kiamanesh O, Solverson K, Motazedian P, Weatherald J. Prognostic value of echocardiography-derived right ventricular dysfunction in haemodynamically stable pulmonary embolism: a systematic review and meta-analysis. Eur Respir Rev. 2022;31(166):220120.
17. Becattini C, Maraziti G, Vinson DR, Ng ACC, den Exter PL, Côté B, et al. Right ventricle assessment in patients with pulmonary embolism at low risk for death based on clinical models: an individual patient data meta-analysis. Eur Heart J. 2021;42(33):3190–9.
18. Meyer G, Vicaut E, Danays T, Agnelli G, Becattini C, Beyer-Westendorf J, et al. Fibrinolysis for patients with intermediate-risk pulmonary embolism. N Engl J Med. 2014;370(15):1402–11.
19. Martin KA, Beyer-Westendorf J, Davidson BL, Huisman MV, Sandset PM, Moll S. Use of direct oral anticoagulants in patients with obesity for treatment and prevention of venous thromboembolism: updated communication from the ISTH SSC Subcommittee on Control of Anticoagulation. J Thromb Haemost. 2021;19(8):1874–82.
20. Malik A, Ha NB, Barnes GD. Choice and Duration of Anticoagulation for Venous Thromboembolism. J Clin Med. 2024;13(1):301.
21. Kimmerle AR, Noflatscher M, Raggam RB. Optimal long-term anticoagulation after acute pulmonary embolism: Current state of the art and a look into the near future. Curr Opin Pulm Med. 2024;30(5):421–8.
22. Robertson L, Broderick C, Yeoh SE, Stansby G. Effect of testing for cancer on cancer- or venous thromboembolism (VTE)-related mortality and morbidity in people with unprovoked VTE. Cochrane Database Syst Rev. 2021;10(10).
23. Freund Y, Cohen-Aubart F, Bloom B. Acute Pulmonary Embolism: A review. JAMA. 2022;328(13):1336–45.
24. Trott T, Bowman J. Diagnosis and Management of Pulmonary Embolism. Emerg Med Clin North Am. 2022;40(3):565–81.
25. Roy PM, Douillet D, Penaloza A. Contemporary management of acute pulmonary embolism. Trends Cardiovasc Med. 2022;32(5):259–68.
26. van der Hulle T, Kooiman J, den Exter PL, Dekkers OM, Klok FA, Huisman MV. Effectiveness and safety of novel oral anticoagulants as compared with vitamin K antagonists in the treatment of acute symptomatic venous thromboembolism: A systematic review and meta-analysis. J Thromb Haemost. 2014;12(3):320–8.
27. Wang X, Ma Y, Hui X, Li M, Li J, Tian J, et al. Oral direct thrombin inhibitors or oral factor Xa inhibitors versus conventional anticoagulants for the treatment of deep vein thrombosis. Cochrane Database Syst Rev. 2023;4(4):CD010956.
28. Connors JM. Testing and Monitoring Direct Oral Anticoagulants. Blood. 2018;132(19):2009–15.
29. Pastré J, Sanchis-Borja M, Benlounes M. Risk stratification and treatment of pulmonary embolism with intermediate-risk of mortality. Curr Opin Pulm Med. 2022;28(5):375–83.
30. Klok FA, Toenges G, Mavromanoli AC, Barco S, Ageno W, Bouvaist H, et al. Early switch to oral anticoagulation in patients with acute intermediate-risk pulmonary embolism (PEITHO-2): a multinational, multicentre, single-arm, phase 4 trial. Lancet Haematol. 2021;8(9):e627–36.
31. Duffett L, Castellucci LA, Forgie MA. Pulmonary embolism: Update on management and controversies. BMJ. 2020;370:m2177.
32. Martins MA, Silva TF, Fernandes CJ. An Update in Anticoagulant Therapy for Patients with Cancer-Associated Venous Thromboembolism. Curr Oncol Rep. 2023;25(5):425–32.
33. Leentjens J, Peters M, Esselink AC, Smulders Y, Kramers C. Initial anticoagulation in patients with pulmonary embolism: thrombolysis, unfractionated heparin, LMWH, fondaparinux, or DOACs? Br J Clin Pharmacol. 2017;83(11):2356–66.

34. Robertson L, Jones LE. Fixed dose subcutaneous low molecular weight heparins versus adjusted dose unfractionated heparin for the initial treatment of venous thromboembolism. Cochrane Database Syst Rev. 2017;2(2):CD001100.
35. Renner E, Barnes GD. Antithrombotic Management of Venous Thromboembolism: JACC Focus Seminar. J Am Coll Cardiol. 2020;76(18):2142–54.
36. Costantino G, Ceriani E, Rusconi AM, Podda GM, Montano N, Duca P, et al. Bleeding Risk during Treatment of Acute Thrombotic Events with Subcutaneous LMWH Compared to Intravenous Unfractionated Heparin; A Systematic Review. PLoS ONE. 2012;7(9):e44553.
37. Cohen AT, Benson G, Bradbury CA, Choudhuri S, Hutchinson Jones N, Maraveyas A, et al. A consensus viewpoint on the role of direct factor xa inhibitors in the management of cancer-associated venous thromboembolism in the UK. Curr Med Res Opin. 2023;39(3):483–95.
38. Young AM, Marshall A, Thirlwall J, Chapman O, Lokare A, Hill C, et al. Comparison of an Oral Factor xa Inhibitor With Low Molecular Weight Heparin in Patients with Cancer with Venous Thromboembolism: Results of a Randomized Trial (SELECT-D). J Clin Oncol. 2018;36(20):2017–23.
39. Tirandi A, Preda A, Carbone F, Montecucco F, Liberale L. Pulmonary embolism in patients with cancer: An updated and operative guide for diagnosis and management. Int J Cardiol. 2022;358:95–102.
40. Stevens SM, Woller SC, Kreuziger LB, et al. Antithrombotic Therapy for VTE Disease: Second Update of the CHEST Guideline and Expert Panel Report. Guideline Expert Panel Rep Chest. 2021;160:e545–608.
41. Westafer LM, Long B, Gottlieb M. Managing Pulmonary Embolism. Ann Emerg Med. 2023;82(3):394–402.
42. Tatsumi K. The pathogenesis of cancer-associated thrombosis. Int J Hematol. 2024;119(5):495–504.
43. Lyman GH, Carrier M, Ay C, Di Nisio M, Hicks LK, Khorana AA, et al. American Society of Hematology 2021 guidelines for management of venous thromboembolism: Prevention and treatment in patients with cancer. Blood Adv. 2021;5(4):927–74.
44. Tran VN, Varfolomeev I, Hill G. Prophylactic Enoxaparin Dosing in Obese Orthopedic Patients: A Literature Search. Hosp Pharm. 2020;55(6):366–72. .
45. Lao TT. Pulmonary embolism in pregnancy and the puerperium. Best Pract Res Clin Obstet Gynaecol. 2022;85:96–106. .
46. Saheb Sharif-Askari F, Syed Sulaiman SA, Saheb Sharif-Askari N. Anticoagulation therapy in patients with chronic kidney disease. Adv Exp Med Biol. 2017;906:101–14.
47. Bauersachs RM. Fondaparinux Sodium: Recent Advances in the Management of Thrombosis. J Cardiovasc Pharmacol Ther. 2023;28:10742484221145010.
48. Tan CW, Balla S, Ghanta RK, Sharma AM, Chatterjee S. Contemporary Management of Acute Pulmonary Embolism. Semin Thorac Cardiovasc Surg. 2020;32(3):396–403.
49. Yang J, Madani MM, Mahmud E, Kim NH. Evaluation and Management of Chronic Thromboembolic Pulmonary Hypertension. Chest. 2023;164(2):490–502.
50. Humbert M, Kovacs G, Hoeper MM, Badagliacca R, Berger RMF, Brida M, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J. 2022;43(38):3618–731.
51. Altiok E, Marx N. Oral Anticoagulation. Dtsch Arztebl Int 2018;115(46):776–83.
52. Lapostolle F, Siguret V, Martin AC, Pailleret C, Vigué B, Zerbib Y, et al. Vitamin K antagonists and emergencies. Eur J Emerg Med. 2018;25(6):378–86.
53. Wang M, Zeraatkar D, Obeda M, Lee M, Garcia C, Nguyen L, et al. Drug-drug interactions with warfarin: A systematic review and meta-analysis. Br J Clin Pharmacol. 2021;87(11):4051–100.
54. Kasperkiewicz K, Ponczek MB, Owczarek J, Guga P, Budzisz E. Antagonists of vitamin K-popular coumarin drugs and new synthetic and natural coumarin derivatives. Molecules. 2020 Mar 24;25(6):1465.
55. van Rein N, Biedermann JS, van der Meer FJM, Cannegieter SC, Wiersma N, Vermaas HW, et al. Major bleeding risks of different low-molecular-weight heparin agents: a cohort study in 12 934 patients treated for acute venous thrombosis. J Thromb Haemost. 2017;15(7):1386–91.
56. Venous thromboembolic diseases: diagnosis, management and thrombophilia testing. Published online. 2023 Aug 2.
57. Lei K, DiCaro MV, Tak N, Turnbull S, Abdallah A, Cyrus T, et al. Contemporary Management of Pulmonary Embolism: Review of the Inferior Vena Cava filter and Other Endovascular Devices. Int J Angiol. 2024;33(2):112–22.
58. Van Ha TG, Chien AS, Funaki BS, Lorenz J, Piano G, Shen M, et al. Use of retrievable compared to permanent inferior vena cava filters: A single-institution experience. Cardiovasc Intervent Radiol. 2008;31(2):308–15.
59. Jiang J, Jiao Y, Zhang X. The short-term efficacy of vena cava filters for the prevention of pulmonary embolism in patients with venous thromboembolism receiving anticoagulation: Meta-analysis of randomized controlled trials. Phlebology. 2017;32(9):620–7.
60. Giannoudis PV, Pountos I, Pape HC, Patel JV. Safety and efficacy of vena cava filters in trauma patients. Injury. 2007;38(1):7–18.
61. Farray D, Carman TL, Fernandez BB. The treatment and prevention of deep vein thrombosis in the preoperative management of patients who have neurologic diseases. Neurol Clin. 2004;22(2):423–39.
62. Kim H, Han Y, Ko GY, Jeong MJ, Choi K, Cho YP, et al. Clinical Outcomes of a Preoperative Inferior Vena Cava Filter in Acute Venous Thromboembolism Patients Undergoing Abdominal-Pelvic Cancer or Orthopedic Surgery. Vasc Spec Int. 2018;34(4):103–8.
63. Makary MS, Koso M, Yoder M. Inferior vena cava filter thromboprophylaxis in surgical cancer patients. J Surg Oncol. 2024;130(2):257–64.
64. Jiang C, Xie M. Clinical Outcomes of Intermediate-Risk Pulmonary Embolism Across a Northeastern Health System: A Multi-Center Retrospective Cohort Study. Cureus. 2021;13(6):e15888.