ESC European Society of Cardiology

European Heart Journal (2019) **00**, 1–19
doi:10.1093/eurheartj/ehz405

ESC GUIDELINES

2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS): supplementary data

The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC)

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Keywords Guidelines • pulmonary embolism • venous thrombosis • shock • dyspnoea • heart failure • right ventricle • diagnosis • risk assessment • echocardiography • biomarkers • treatment • anticoagulation • thrombolysis • pregnancy • venous thromboembolism • embolectomy

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1 Supplementary Tables and Supplementary Figure

Supplementary Table 1 The Wells clinical prediction rule for pulmonary embolism

Items	Clinical decision rule points	
	Original version[1]	Simplified version[2]
Previous PE or DVT	1.5	1
Heart rate >100 b.p.m.	1.5	1
Surgery or immobilization within the past 4 weeks	1.5	1
Haemoptysis	1	1
Active cancer	1	1
Clinical signs of DVT	3	1
Alterative diagnosis less likely than PE	3	1
Clinical probability		
Three-level score		
Low	0–1	N/A
Intermediate	2–6	N/A
High	≥7	N/A
Two-level score		
PE unlikely	0–4	0–1
PE likely	≥5	≥2

b.p.m. = beats per minute; DVT = deep vein thrombosis; N/A = not applicable; PE = pulmonary embolism.

Supplementary Table 2 Findings of pre-existing chronic thromboembolic pulmonary hypertension on computed tomography pulmonary angiography

Direct vascular signs
Eccentric wall-adherent filling defect(s), which may calcify; different from the central filling defects within a distended lumen, which are the hallmark of acute PE
Abrupt tapering and truncation
Complete occlusion and pouch defects
Intimal irregularity
Linear intraluminal filling defects (intravascular webs and bands)
Stenosis and post-stenotic dilatation
Vascular tortuosity
Indirect vascular signs
Significant RV hypertrophy, RA dilatation
Pericardial effusion
Dilatation of pulmonary artery (>29 mm in men and >27 mm in women) and/or calcifications of pulmonary artery
Systemic collateral arterial supply (bronchial arterial collaterals towards pulmonary post-obstructive vessels)
Parenchymal changes
Mosaic attenuation of the lung parenchyma resulting in geographical variation in perfusion

The above findings suggest pre-existing CTEPH on CTPA (adapted from Ruggiero and Screaton[3] and Gopalan *et al.*[4]).
CTEPH = chronic thromboembolic pulmonary hypertension; CTPA = computed tomography pulmonary angiography; PE = pulmonary embolism; RA = right atrial; RV = right ventricular.

Supplementary Table 3 **Prognostic value and cut-off levels of imaging parameters**

Parameter	*n*	Study design	Cut-off value	Study outcome[a]	OR or HR (95% CI)	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	NPV (%) (95% CI)	PPV (%) (95% CI)
TTE									
RV dysfunction	1249	Meta-analysis[5]	Various criteria	All-cause mortality	2.4 (1.3–4.3)	74 (61–84)	54 (51–56)	98 (96–99)	8 (6–10)
RV/LV diameter ratio	782[b]	Prospective cohort[6]	≥1.0	All-cause mortality	35.7 (3.4–381.0)	21 (10–39)	83 (80–86)	96 (94–97)	6 (2–11)
				PE-related mortality	8.9 (1.1–74.7)	50 (20–80)	83 (80–86)	99 (98–100)	4 (2–9)
	411[b]	Prospective cohort[7]	≥1.0	PE-related mortality or rescue thrombolysis	3.9 (1.5–10.2)	61 (39–84)	73 (68–78)	97 (91–99)	13 (5–20)
TAPSE	782[b]	Prospective cohort[6]	≤16 mm	All-cause mortality	2.4 (1.2–4.7)	34 (21–52)	82 (79–85)	96 (95–98)	8 (5–14)
				PE-related mortality	4.4 (1.3–15.3)	50 (24–76)	82 (79–84)	99 (98–100)	3 (1–8)
	411[b]	Prospective cohort[7]	<16 mm	PE-related mortality or rescue thrombolysis	27.9 (6.2–124.6)	82 (59–100)	86 (81–90)	99 (98–100)	21 (9–33)
McConnell sign	411[b]	Prospective cohort[7]	Present	PE-related mortality or rescue thrombolysis	3.6 (1.5–8.7)	45 (23–67)	82 (78–86)	97 (95–99)	12 (5–19)
Right heart thrombi	15 220	Meta-analysis[8]	Present	All-cause mortality	3.0 (2.2–4.1)	13 (11–16)	97 (96–97)	96 (95–96)	17 (14–20)
	12 955			PE-related mortality	4.8 (2.0–11.3)	26 (20–33)	97 (96–97)	99 (99–99)	10 (8–13)
CTPA									
RV/LV diameter ratio	4395	Meta-analysis[9]	≥1.0	All-cause mortality	2.5 (1.8–3.5)	—	—	—	—
	2698			PE-related mortality	5.0 (2.7–9.2)	—	—	—	—
RV/LV volume ratio	260	Prospective cohort[10]	>1.2	All-cause mortality	6.5 (1.8–23.8)	85 (64–95)	45 (39–51)	97 (92–99)	11 (7–18)
RA/LA volume ratio	636	Retrospective cohort[11]	>1.2	All-cause mortality	2.1 (1.3–3.4)	64 (54–74)	52 (48–56)	91 (87–93)	17 (13–21)
Contrast reflux into the IVC	1649	Meta-analysis[9]	Present	All-cause mortality	2.2 (1.5–3.2)	—	—	—	—

Validation of the prognostic value and respective cut-off levels of specific imaging parameters in acute pulmonary embolism.
CI = confidence interval; CTPA = computed tomography pulmonary angiography; HR = hazard ratio; IVC = inferior vena cava; LA = left atrium/atrial; LV = left ventricle/ventricular; NPV = negative predictive value; OR = odds ratio; PE = pulmonary embolism; PPV = positive predictive value; RA = right atrium/atrial; RV = right ventricle/ventricular; TAPSE = tricuspid annulus plane systolic excursion; TTE = transthoracic echocardiography.
[a]During hospital stay or within the first 30 days after PE diagnosis.
[b]Normotensive patients with PE.

Supplementary Table 4 Scores for advanced risk stratification

	Bova score[12–15]		FAST score[13,16,17]	
	Parameter	**Score points**	**Item**	**Score points**
	Elevated cardiac troponin	2	H-FABP ≥6 ng/mL or elevated cardiac troponin	1.5
	RV dysfunction (TTE or CTPA)[a]	2	Syncope	1.5
	Heart rate ≥110 b.p.m.	1	Heart rate ≥100 b.p.m.	2
	Systolic BP 90–100 mmHg	2		
Risk classes				
Low risk	0–2 points	≤4 points[b]	<3 points	
Intermediate-low risk	3–4 points			
Intermediate-high risk	>4 points	>4 points[b]	≥3 points	

Scores for advanced stratification of PE-related risk in patients presenting without haemodynamic instability.
BP = blood pressure; b.p.m. = beats per minute; CTPA = computed tomography pulmonary angiography; FAST = H-FABP (or high-sensitivity troponin T), Syncope, Tachycardia; H-FABP = heart-type fatty acid-binding protein; PE = pulmonary embolism; RV = right ventricular; TTE = transthoracic echocardiography.
[a]Parameters and cut-off values varied among studies from which the Bova score was derived; see *Figure 3* and *Supplementary Table 3*.
[b]If the Bova score is dichotomized.[13,14]

Supplementary Table 5 Low-molecular weight heparins and fondaparinux

	Dosage	Interval
Enoxaparin	1.0 mg/kg	Every 12 h
	or	
	1.5 mg/kg[a]	Once daily[a]
Tinzaparin	175 U/kg	Once daily
Dalteparin	100 IU/kg[b]	Every 12 h[b]
	or	
	200 IU/kg[b]	Once daily[b]
Nadroparin[c]	86 IU/kg	Every 12 h
	or	
	171 IU/kg	Once daily
Fondaparinux	5 mg (body weight <50 kg);	Once daily
	7.5 mg (body weight 50–100 kg);	
	10 mg (body weight >100 kg)	

Low-molecular weight heparins and pentasaccharide (fondaparinux) approved for the treatment of PE. All regimens administered subcutaneously.
IU = international units; PE = pulmonary embolism; U = units.
[a]Once-daily injection of enoxaparin at a dosage of 1.5 mg/kg is approved for inpatient (hospital) treatment of PE in the USA and in some, but not all, European countries.
[b]In patients with cancer, dalteparin is given at a dose of 200 IU/kg body weight (maximum, 18 000 IU) once a day over a period of 1 month, followed by 150 IU/kg once a day for 5 months.[18]
[c]Nadroparin is approved for treatment of PE in some, but not all, European countries.

Supplementary Table 6 Non-vitamin K antagonist oral anticoagulants

Characteristics[a]	Apixaban	Dabigatran	Edoxaban	Rivaroxaban
Target	Factor Xa	Factor IIa	Factor Xa	Factor Xa
Time to peak effect	1–2 h	1–3 h	1–2 h	2–4 h
Half-life	8–14 h	14–17 h	5–11 h	7–11 h
Renal elimination	27%	80%	50%	33%
Caveats due to interactions with concomitant medication[b]	Not recommended in patients receiving concomitant systemic treatment with strong inhibitors of both CYP3A4 and P-gp (azole antimycotics, HIV protease inhibitors). Concomitant use with strong CYP3A4 and P-gp inducers (rifampicin, phenytoin, carbamazepine, phenobarbital, or St John's Wort) may lead to an ~50% reduction in apixaban exposure.	Strong P-gp inhibitors (systemic ketoconazole, cyclosporine, itraconazole, and dronedarone) are contraindicated. Concomitant treatment with tacrolimus is not recommended. Concomitant administration of P-gp inducers (rifampicin, St John's wort, carbamazepine, and phenytoin) is expected to result in decreased dabigatran plasma concentrations and should be avoided.	In patients concomitantly taking edoxaban and the P-gp inhibitors cyclosporine, dronedarone, erythromycin, or ketoconazole, the recommended dose is 30 mg edoxaban o.d.	Not recommended in patients receiving concomitant systemic treatment with strong inhibitors of both CYP3A4 and P-gp (azole antimycotics, HIV protease inhibitors)
Further conditions in which NOACs are contraindicated or not recommended[c]	CrCl <15 mL/min. Severe hepatic impairment (Child–Pugh C) or hepatic disease associated with coagulopathy.	CrCl <30 mL/min. Concomitant treatment with P-gp inhibitors in patients with CrCl <50 mL/min.	CrCl <15 mL/min. Moderate or severe hepatic impairment. (Child–Pugh B and C) or hepatic disease associated with coagulopathy.	CrCl <30 mL/min (FDA); CrCl <15 mL/min (EMA). Moderate or severe hepatic impairment. (Child–Pugh B and C) or hepatic disease associated with coagulopathy.
Reversal agent	Andexanet	Idarucizumab	Andexanet	Andexanet

CrCl = creatinine clearance; CYP3A4 = cytochrome 3A4; EMA = European Medicines Agency; FDA = US Food and Drug Administration; HIV = human immunodeficiency virus; NOAC(s) = non-vitamin K antagonist oral anticoagulant(s); o.d. = omni die (once a day); P-gp = P-glycoprotein.
[a]For more detailed information on the characteristics and the use of NOACs, the reader is referred to the 2018 European Heart Rhythm Association Practical Guide.[19]
[b]Based on each drug's summary of product characteristics (http://www.ema.europa.eu/ema/index.jsp?curl=pages/includes/medicines/medicines_landing_page.jsp&mid).
[c]All these drugs should also be avoided in patients: (i) for whom thrombolysis or pulmonary embolectomy may be required, (ii) requiring dialysis, (iii) at significant risk of bleeding, (iv) receiving a concomitant anticoagulant, (v) with known hypersensitivity to the agent, and (vi) during pregnancy or breastfeeding.

Supplementary Table 7 Adjustment of unfractionated heparin dosage

Activated partial thromboplastin time	Change of dosage
<35 s (<1.2 × control)	80 U/kg bolus, increase infusion rate by 4 U/kg/h
35–45 s (1.2–1.5 × control)	40 U/kg bolus, increase infusion rate by 2 U/kg/h
46–70 s (1.5–2.3 × control)	No change
71–90 s (2.3–3.0 × control)	Reduce infusion rate by 2 U/kg/h
>90 s (>3.0 × control)	Stop infusion for 1 h, then reduce infusion rate by 3 U/kg/h

Weight-based adjustment of UFH dosage based on the activated partial thromboplastin time (adapted from Raschke *et al.*[20]).
U = units; UFH = unfractionated heparin.

Supplementary Table 8 **Trials of non-vitamin K antagonist oral anticoagulants in venous thromboembolism**

Drug	Trial	Design	Treatment arms (drug regimens)	Duration	Patients	Main exclusion criteria	Efficacy outcome results	Safety outcome results
Dabigatran	RE-COVER[21]	Double-blind, double-dummy	Parenteral anticoagulant for ≥5 days followed by dabigatran 150 mg b.i.d. vs. parenteral anticoagulant/warfarin.	6 months	2539; acute VTE	PE with haemodynamic instability or requiring thrombolysis. Recent unstable cardiovascular disease. High risk of bleeding, liver disease with aminotransferase level ≥2 × ULN. CrCl <30 mL/min. Pregnancy. Long-term antiplatelet therapy.	Recurrent VTE or fatal PE: 2.4% on dabigatran 2.1% on warfarin.	Major bleeding: 1.6% on dabigatran 1.9% on warfarin.
	RE-COVER II[22]	Double-blind, double-dummy	Parenteral anticoagulant for ≥5 days followed by dabigatran 150 mg b.i.d. vs. parenteral anticoagulant/warfarin.	6 months	2589; acute VTE	Same as above, except aminotransferase ≥3 × ULN.	Recurrent VTE or fatal PE: 2.3% on dabigatran 2.2% on warfarin.	Major bleeding: 1.2% on dabigatran 1.7% on warfarin.
Rivaroxaban	EINSTEIN-DVT[23]	Open-label	Rivaroxaban (15 mg b.i.d. for 3 weeks, then 20 mg o.d.) vs.enoxaparin/warfarin.	3, 6, or 12 months	3449; acute DVT	Thrombectomy, cava filter, fibrinolysis CrCl <30 mL/min. Acute or chronic active hepatitis, cirrhosis, ALT ≥3 × ULN. Active bleeding or high risk of bleeding. Systolic BP >180 mmHg, diastolic BP >110 mmHg. Childbearing potential without contraception, pregnancy, breastfeeding.	Recurrent VTE or fatal PE: 2.1% on rivaroxaban 3.0% on warfarin.	Major or CRNM bleeding 8.1% on rivaroxaban 8.1% on warfarin.
	EINSTEIN-PE[24]	Open-label	Rivaroxaban (15 mg b.i.d. for 3 weeks, then 20 mg o.d.) vs. enoxaparin/warfarin.	3, 6, or 12 months	4832; acute PE	Same as in EINSTEIN-DVT	Recurrent VTE or fatal PE: 2.1% on rivaroxaban 1.8% on warfarin.	Major or CRNM bleeding: 10.3% on rivaroxaban 11.4% on warfarin.
Apixaban	AMPLIFY[25]	Double-blind, double-dummy	Apixaban (10 mg b.i.d. for 7 days, then 5 mg	6 months	5395; acute DVT or PE	Active bleeding, high risk of bleeding.	Recurrent VTE or fatal PE:	Major bleeding: 0.6% on apixaban

Continued

Supplementary Table 8 *Continued*

Drug	Trial	Design	Treatment arms (drug regimens)	Duration	Patients	Main exclusion criteria	Efficacy outcome results	Safety outcome results
			b.i.d.) vs. enoxaparin/ warfarin.			Dual antiplatelet therapy, aspirin >165 mg daily. Haemoglobin <9 mg/dL, platelet count <100 000 per mm^3, CrCl <25 mL/min.	2.3% on apixaban 2.7% on warfarin.	1.8% on warfarin.
Edoxaban	Hokusai−VTE[26]	Double-blind, double-dummy	Enoxaparin or UFH for ≥5 days followed by edoxaban (60 mg o.d.; 30 mg o.d. if CrCl 30−50 mL/min or body weight <60 kg) vs. enoxaparin or UFH/warfarin.	Variable, 3−12 months	8240; acute DVT and/or PE	Aspirin >100 mg daily, or dual anti-platelet therapy. CrCl <30 mL/min.	Recurrent VTE or fatal PE: 3.2% under edoxa-ban vs. 3.5% under warfarin.	Major or CRNM bleeding: 8.5% on edoxaban 10.3% on warfarin.

Phase III trials comparing NOACs with LMWH and VKAs in patients with VTE.
AMPLIFY = Apixaban for the Initial Management of Pulmonary Embolism and Deep-Vein Thrombosis as First-line Therapy; ALT = alanine aminotransferase; b.i.d. = bis in die (twice a day); BP = blood pressure; CrCl = creatinine clearance; CRNM = clinically relevant non-major; DVT = deep vein thrombosis; LMWH = low-molecular-weight heparin; NOAC(s) = non-vitamin K antagonist oral anticoagulant(s); o.d. = omni die (once a day); PE = pulmonary embolism; UFH = unfractionated heparin; ULN = upper limit of the normal range; VKA(s) = vitamin K antagonist(s); VTE = venous thromboembolism.

Supplementary Table 9 Management of pulmonary embolism in specific clinical situations

Clinical setting	Suggested management[a]	Comments
Subsegmental PE	Single subsegmental PE in an outpatient without cancer and without proximal DVT: • Clinical surveillance. Single subsegmental PE in a hospitalized patient, a patient with cancer, or if associated with confirmed proximal DVT: • Anticoagulant treatment. Multiple subsegmental PE: • Anticoagulant treatment.	• Poor interobserver agreement for the diagnosis of subsegmental PE; diagnosis to be confirmed by an experienced thoracic radiologist. • Suggestion based on indirect evidence, only limited data available.
Incidental PE	If single subsegmental PE: • Proceed as above. In all other cases: • Anticoagulant treatment.	• Suggestion based on retrospective cohort data.
Management of acute PE in a patient with active bleeding	• Insert inferior vena cava filter (preferably retrievable). • Reassess the possibility of anticoagulation as soon as the bleeding has ceased and the patient is stabilized, and remove the filter as soon as anticoagulant treatment is resumed.	
PE diagnosis and anticoagulation in the elderly, frail patients, and patients with polypharmacy	• Assess clinical probability of PE as in the non-frail patient, but caution needed in the nursing home setting as clinical prediction rules may be unreliable.[27] • Generally prefer NOACs over VKAs in elderly and frail patients, but observe the following: a. Avoid NOACs in patients with severe renal impairment.[b] b. Consult the drugs' summary of product characteristics and the updated European Heart Rhythm Association guide[19] for possible interactions between NOACs and the patient's concomitant medication. • Reassess, at regular intervals, drug tolerance and adherence, hepatic and renal function, and the patient's bleeding risk (*Supplementary Table 14*).	• Number of diseases mimicking PE symptoms increases with age, making diagnostic delay more common. • These patients have been poorly represented in clinical trials. Whatever the treatment (VKAs or NOACs), these patients are at high risk of bleeding.
Management of acute PE in a patient with signs of chronic pulmonary hypertension on TTE,[c] or findings suggesting pre-existing CTEPH on CTPA[d] (suspected 'acute-on-chronic' PE)	• If the diagnosis of *acute* PE has been confirmed, as described in *section 5* (the diagnostic strategies, depending on the patient's clinical and haemodynamic status, are summarized in *Figures 5*), focus on the patient's acute problem and proceed to risk-adjusted acute-phase treatment of PE, as described in *section 6* and summarized in *Figure 6*. • Perform a TTE upon discharge, and document any signs of persisting pulmonary hypertension or RV dysfunction. • Continue anticoagulation for ≥3 months and schedule the patient for a 3 month follow-up visit. • At the 3 month follow-up visit, assess the presence of persisting or worsening symptoms, or functional limitation, and consider further tests and possible referral to a PH/CTEPH expert centre, as summarized in *Figure 8*.	
Initial anticoagulation in a patient with acute PE and end-stage renal disease	• Administer UFH; consider anti-Xa (rather than aPTT) monitoring.[28]	• No truly safe anticoagulation option available, although LMWH with anti-Xa monitoring is also used in clinical practice.
Duration of anticoagulation in a young female patient suffering acute PE while on oral contraceptives	If patient was taking an oestrogen-containing contraceptive, and especially if PE occurred in the first 3 months of initiation of contraception: • Discontinue hormonal contraceptives after discussing alternative methods of contraception; consider discontinuing anticoagulation after 3 months.	• The risk of VTE attributable to oestrogen–progestin contraception (or hormonal treatment) depends on the specific compound and the presence of concomitant thrombophilia, and is associated with the time interval

Continued

Supplementary Table 9 ***Continued***

Clinical setting	Suggested management[a]	Comments
	All other cases: ● Manage chronic anticoagulation as after acute PE occurring in the absence of identifiable risk factors. ● Consider using a validated prediction model for quantification of the risk for VTE recurrence (*Supplementary Table 14*); for example, the HERDOO2 score: a. hyperpigmentation, oedema, or redness in either leg; b. D-dimer level ≥250 μg/L; c. obesity with body mass index ≥30; d. older age (essentially 0 in this case). A score of 0 or 1 may help identify young women who can safely discontinue anticoagulant treatment. ● Advise patient on the need for prophylaxis with LMWH in case of pregnancy.	between the initiation of hormonal treatment and the occurrence of acute PE.[29,30]
Long-term management of a patient who suffered PE during pregnancy	● Anticoagulant treatment with LMWH throughout pregnancy and >6 weeks post-partum. ● No NOACs during pregnancy or lactation! ● Advise patient on the need for prophylaxis with LMWH in case of future pregnancies.	
Anticoagulation in the patient with PE and cancer, after the first 6 months	If cancer still active:[e] ● Continue anticoagulation LMWH or, alternatively, edoxaban or rivaroxaban, as recommended in *section 8.4* If cancer in remission: ● Continue oral anticoagulation (NOAC or VKA); alternatively, consider discontinuing if the bleeding risk is high. ● In either case, periodically reassess the risk–benefit ratio of continuing/resuming anticoagulation.	● In the absence of conclusive evidence, the decision to continue or stop after the first 6 months of anticoagulation should be made on a case-by-case basis after considering the success of anticancer therapy, the estimated overall risk of VTE recurrence (*Supplementary Table 13*), the bleeding risk (*Supplementary Table 14*), and the preference of the patient.

aPTT = activated partial thromboplastin time; CrCl = creatinine clearance; CTEPH = chronic thromboembolic pulmonary hypertension; CTPA = computed tomography pulmonary angiography; DVT = deep vein thrombosis; HERDOO2 = Hyperpigmentation, Edema, or Redness in either leg; D-dimer level ≥250 μg/L; Obesity with body mass index ≥30; or Older age, ≥65 years; LMWH = low-molecular-weight heparin; NOAC(s) = non-vitamin K antagonist oral anticoagulant(s); PE = pulmonary embolism; PH = pulmonary hypertension; RV = right ventricular; TTE = transthoracic echocardiography/echocardiogram; UFH = unfractionated heparin; VKA(s) = vitamin K antagonist(s); VTE = venous thromboembolism.
[a]Mostly based on indirect evidence and expert opinion due to limited data.
[b]Dabigatran is not recommended in patients with CrCl <30 mL/min. Edoxaban should be given at a dose of 30 mg once daily in patients with CrCl of 15 - 50 mL/min and is not recommended in patients with CrCl <15 mL/min. Rivaroxaban and apixaban are to be used with caution in patients with creatinine clearance 15 - 29 mL/min, and their use is not recommended in patients with CrCl <15 mL/min.
[c]Increased RV wall thickness or tricuspid insufficiency jet velocity beyond values compatible with acute RV pressure overload (>3.8m/s or a tricuspid valve peak systolic gradient >60 mmHg).
[d]See *Supplementary Table 2*.
[e]Recurrent, regionally advanced, or metastatic cancer; cancer for which treatment has been administered in the past 6 months; or haematological cancer that is not in complete remission.

Supplementary Table 10 **Meta-analysis of thrombolysis trials**

	Studies including high-risk PE[a] OR (95% CI)	Intermediate-risk PE	Low or intermediate-risk PE	Between-group difference *P*-value
Mortality	0.48 (0.20–1.15)	0.42 (0.17–1.03)	0.96 (0.41–2.24)	0.36
PE-related mortality	0.15 (0.03–0.78)	0.17 (0.05–0.67)	0.63 (0.20–1.97)	0.23
Death or therapeutic escalation	0.18 (0.04–0.79)	0.37 (0.20–0.69)	0.35 (0.18–0.66)	0.67
Recurrent PE	0.97 (0.31–2.98)	0.25 (0.06–1.03)	0.46 (0.17–1.21)	0.33

Meta-analysis of RCTs comparing heparin alone with heparin and thrombolysis in a total of 2057 patients with acute PE.[31]
CI = confidence interval; OR = odds ratio; PE = pulmonary embolism; RCT = randomized controlled trial.
[a]These were not homogeneous populations, as patients without high-risk PE were also included in these studies.

Supplementary Table 11 Percutaneous catheter-directed treatment

Catheter interventions with thrombolysis		Catheter interventions without thrombolysis	
Technique	**Device examples**	**Technique**	**Device examples**
Catheter-directed thrombolysis	UniFuse® (AngioDynamics, Latham, NY) Cragg-McNamara® (ev3 Endovascular, Plymouth, MN) 4–5 F infusion catheters, with 10–20 cm infusion length	Aspiration thrombectomy	Aspirex® 8 F or 10 F catheter (Straub Medical, Switzerland): rotational thrombectomy[a]
			Angiovac suction cannula® (AngioDynamics, Latham, NY): veno-venous bypass system, with 26 F access for inflow and 16–20 F access for outflow
			Indigo® Mechanical Thrombectomy System (Penumbra, Alameda, CA): 8 F vacuum-assisted aspiration with mechanical clot engagement
			Sheath with detachable haemostatic valve 8–9 F (Argon Medical Devices, Athens, TX), multi-purpose guide catheter (8–9 F), aspiration syringe (60 mL)
Ultrasound-assisted catheter-directed thrombolysis	EkoSonic 5.2® F 12 cm treatment zone device (EKOS, Bothell, WA)	Mechanical thrombectomy	Flowtriever® (Inari Medical, Irvine, CA): 20 F device with three self-expanding nitinol discs entrapping the thrombus with simultaneous aspiration
Rheolytic thrombectomy plus catheter-directed thrombolysis	AngioJet 6 F PE® thrombectomy with Power Pulse™ thrombolysis (Boston Scientific, Minneapolis, MN)[a]	Rheolytic thrombectomy	AngioJet 6 F PE® catheter (Boston Scientific, Minneapolis, MN)[a]
Combined techniques	For example, pigtail fragmentation (5 F) plus AngioJet 6 F PE® thrombectomy with Power Pulse™ thrombolysis	Thrombus fragmentation	Pigtail catheter (5–6 F) or peripheral balloon catheters (6–7 F, balloon diameter 5–10 mm)
		Combined techniques	Pigtail fragmentation (5 F) plus thrombectomy with Aspirex® 8/10 F

Techniques and devices for percutaneous catheter-directed treatment of pulmonary embolism.
F = French (refers to catheter diameter); FDA = US Food and Drug Administration.
[a]Black box warning for use in pulmonary arteries by the FDA because of reports of asystole and haemodynamic collapse.

Supplementary Table 12 Hestia exclusion criteria for outpatient management

Criterion/question
Is the patient haemodynamically unstable?[a]
Is thrombolysis or embolectomy necessary?
Active bleeding or high risk of bleeding?[b]
More than 24 h of oxygen supply to maintain oxygen saturation >90%?
Is PE diagnosed during anticoagulant treatment?
Severe pain needing i.v. pain medication for more than 24 h?
Medical or social reason for treatment in the hospital for >24 h (infection, malignancy, or no support system)?
Does the patient have a CrCl of <30 mL/min?[c]
Does the patient have severe liver impairment?[d]
Is the patient pregnant?
Does the patient have a documented history of heparin-induced thrombocytopenia?

Hestia exclusion criteria for outpatient management of pulmonary embolism (from Zondag *et al.*[32]). If the answer to one or more of the questions is 'yes', then the patient cannot be treated at home.
BP = blood pressure; b.p.m. = beats per minute; CrCl = creatinine clearance; i.v. = intravenous; PE = pulmonary embolism.
[a]Include the following criteria but leave them to the discretion of the investigator: systolic BP <100 mmHg with heart rate >100 b.p.m.; condition requiring admission to an intensive care unit.
[b]Gastrointestinal bleeding in the preceding 14 days, recent stroke (<4 weeks ago), recent operation (<2 weeks ago), bleeding disorder or thrombocytopenia (platelet count $<75 \times 10^9$/L), or uncontrolled hypertension (systolic BP >180 mmHg or diastolic BP >110 mmHg).
[c]Calculated CrCl according to the Cockroft–Gault formula.
[d]Left to the discretion of the physician.

Supplementary Table 13 **Validated prediction models for quantification of the risk of recurrent venous thromboembolism**

Prediction model	Parameters	Points	Categories of recurrence risk	Risk group (for VTE recurrence) studied	Type of studies	Number of PE patients included	Remarks
Vienna prediction model[33–35]	• Male sex • Proximal DVT • Pulmonary embolism • D-dimer (continuous value)	n.a.	Continuous (nomogram)	Unprovoked VTE	Cohorts database (derivation, validation)	Derivation study: 438 (47% of cohort) Validation study: 291 (32%)	
HERDOO2[36,37]	• Hyperpigmentation, oedema or leg redness • D-dimer ≥250 μg/L (on VKAs) • Body mass index ≥30 kg/m^2 • Age ≥65 years	1 1 1 1	0–1 points: low risk; ≥2 points: high risk	Unprovoked VTE (derivation); unprovoked VTE, or with minor risk factors (validation)	Management study (derivation, internal validation)	Derivation study: 327 (49%) Management study: 1634 (59%)	Only applicable in women
DASH tool[38,39]	• D-dimer (post-VKA; normal or abnormal) • Age <50 years • Male sex • Hormonal therapy	2 1 1 −2	≤1 points: low risk; ≥2 points: high risk	Unprovoked VTE, or minor risk factors	Cohorts database (derivation, external validation)	Not reported	
DAMOVES[40,41]	• Age (continuous) • Sex • Obesity • Abnormal D-dimer • Factor VIII (continuous) • Genetic thrombophilia • Varicose veins	n.a.	Continuous (nomogram)	Unprovoked VTE	Prospective cohort (derivation) Retrospective cohort (external validation)	Derivation study: 270 (68%) Validation study: not reported	

Ottawa[a] [42,43]	• Female sex
	• Primary tumour site:
	  • lung
	  • breast
	• Tumour Node Metastasis stage I
	• History of VTE
		1
		1
		−1
		−2
		1
			≤0: low risk;
			≥1: high risk
				Patients with cancer	Retrospective cohort (derivation)
					Two RCTs (external validation)
						Not reported	Only applicable in patients with cancer

DAMOVES = D-dimer, Age, Mutation, Obesity, Varicose veins, Eight [coagulation factor VIII], Sex; DASH = D-dimer, Age, Sex, Hormonal therapy; DVT = deep vein thrombosis; HERDOO2 = Hyperpigmentation, Edema, or Redness in either leg; D-dimer level ≥250 μg/L; Obesity with body mass index ≥30; or Older age, ≥65 years; n.a. = not available; PE = pulmonary embolism; RCT(s) = randomized controlled trial(s); VKA(s) = vitamin K antagonist(s); VTE = venous thromboembolism.

[a]The Ottawa score applies only to patients with cancer and refers to the risk of VTE recurrence during (and not after discontinuation of) anticoagulation.

Supplementary Table 14 Prediction models for quantifying bleeding risk

Prediction model	Parameters	Points	Categories of bleeding risk	Validation status
OBRI[44]	Age ≥65 years History of stroke History of gastrointestinal bleeding Recent myocardial infarction, renal insufficiency, diabetes, or anaemia	1 1 1 1	0: low 1–2: intermediate 3–4: high	Validation showed modest accuracy in VKA cohorts (reviewed in Klok *et al.*[45]) No data in patients treated with NOACs
Kuijer *et al.*[46]	Age ≥60 years Female sex Malignancy	1.6 1.3 2.2	0: low 1–3: intermediate >3: high	
RIETE[47]	Age >75 years Recent bleeding Cancer Creatinine >1.2 mg/dL Anaemia PE (vs. DVT) index event	1 2 1 1.5 1.5 1	0: low 1–4: intermediate >4: high	
HAS-BLED[48,49]	Uncontrolled hypertension Abnormal liver/renal function Previous stroke Bleeding history or predisposition Labile INR (time in therapeutic range <60%) Age >65 years Concomitant drugs or alcohol	1 1 1 1 1 1 1	0–2: low ≥3: high	
VTE-BLEED[50]	Active cancer Male patient with uncontrolled hypertension Anaemia History of bleeding Age ≥60 years Renal dysfunction (CrCl 30–60 mL/min)	1.5 2 1 1.5 1.5 1.5	0–1: low ≥2: high	Validated in *post hoc* analysis of RCTs testing NOACs vs. VKAs after initial LMWH treatment[50,51]

Prediction models (clinical scores) for quantification of the bleeding risk in patients receiving oral anticoagulation treatment.
CrCl = creatinine clearance; DVT = deep vein thrombosis; HAS-BLED = Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (>65 years), Drugs/alcohol concomitantly; INR = international normalized ratio; LMWH = low-molecular weight heparin; NOAC(s) = non-vitamin K antagonist oral anticoagulant(s); OBRI = Outpatient Bleeding Risk Index; PE = pulmonary embolism; RCT(s) = randomized controlled trial(s); RIETE = Registro Informatizado de la Enfermedad Thromboembolica venosa; VKA(s) = vitamin K antagonist(s); VTE-BLEED = actiVe cancer, male with uncontrolled hyperTension at baseline, anaEmia, history of BLeeding, agE ≥60 years, rEnal Dysfunction.

Supplementary Table 15 **Trials on extended anticoagulant treatment**

Active[a]	Study	Comparison	Design	No. patients enrolled	Patients with index PE	Treatment duration	VTE rate in control group	Risk reduction for recurrent VTE (HR; 95% CI)	Major or CRNM bleeding in active[a] group (HR; 95% CI)
Dabigatran	RE-SONATE[52]	Placebo vs. D 150 mg b.i.d.	Superiority	1343	33%	6 months	5.6%	92% (0.08; 0.02–0.25)	5.3% (2.92; 1.52 - 5.60)
	RE-MEDY[52]	Warfarin (INR 2–3) D 150 mg b.i.d.	Non-inferiority	2856	35%	18–36 months	1.3%	Risk difference, 0.38% vs. VKA (1.44; 0.78–2.64)	5.6% (0.54; 0.41 - 0.71)
Rivaroxaban	EINSTEIN Extension[23]	Placebo R 20 mg o.d.	Superiority	1196	38%	6–12 months	7.1%	82% (0.18; 0.09–0.39)	6.0% (5.19; 2.3 - 11.7)
	EINSTEIN Choice[53]	Aspirin 100 mg o.d. R 20 mg o.d. R 10 mg o.d.	Superiority	3365	49%	12 months	4.4%	66% (0.34; 0.20–0.59; R 20 mg vs. aspirin)	3.3% (1.59; 0.94 - 2.69)
								74% (0.26; 0.14–0.47; R 10 mg vs. aspirin)	2.4% (1.16; 0.67 - 2.03)
Apixaban[b]	AMPLIFY Extension[54]	Placebo vs. A 5 mg b.i.d. vs. A 2.5 mg b.i.d.[b]	Superiority	2486	35%	12 months	8.8%	80%[d] (0.36; 0.25–0.53; A 5 mg vs. placebo)	4.3% (1.62; 0.96 - 2.73)
								81% (0.33; 0.22–0.48; A 2.5 mg vs. placebo)	3.2% (1.20; 0.69 - 2.10)
Aspirin	WARFASA[55]	Placebo vs. ASA 100 mg daily	Superiority	402	40%	≥24 months	11.2%[c]	40% (0.58; 0.36–0.93)	1.0% (0.98; 0.24–3.96)
	ASPIRE[56]	Placebo vs. ASA 100 mg daily	Superiority	822	30%	Between 2 and 4 years (actual, 27 months)	6.5%[c]	26% (0.74; 0.52 - 1.05)	1.1%
Sulodexide	SURVET[57]	Placebo vs. S 2 cp 250 mg b.i.d.	Superiority	617	8%	24 months	9.7%	51% (0.49; 0.27 - 0.92)	0.6% (0.97; 0.14 - 6.88)

Clinical trials on extended treatment of VTE with anticoagulants and other antithrombotic agents.
A = apixaban; AMPLIFY = Apixaban for the Initial Management of Pulmonary Embolism and Deep-Vein Thrombosis as First-line Therapy; ASA = acetylsalicylic acid; ASPIRE = Aspirin to Prevent Recurrent Venous Thromboembolism trial; b.i.d. = bis in die (twice a day); CI = confidence interval; CRNM = clinically relevant non-major; cp = capsules; D = dabigatran; HR = hazard ratio; INR = international normalized ratio; o.d. = omni die (once a day); PE = pulmonary embolism; R = rivaroxaban; S = sulodexide; SURVET = Sulodexide in Secondary Prevention of Recurrent Deep Vein Thrombosis study; VKA = vitamin K antagonists; VTE = venous thromboembolism; WARFASA = Warfarin and Aspirin study.
[a]'Active' denotes the anticoagulant tested in the table; the comparator arm also received anticoagulation (a VKA) in some of the studies.
[b]This is the approved dose of apixaban for extended treatment.
[c]Incidence per patient-year.

Supplementary Table 16 Assessment of the severity of dyspnoea

Grade/ functional class	Medical Research Council scale	World Health Organization functional class
1	Not troubled by breathlessness except on strenuous exercise	No limitation of physical activity; ordinary physical activity does not cause undue dyspnoea or fatigue, chest pain, or near syncope
2	Short of breath when hurrying or walking up a slight hill	Slight limitation of physical activity, but comfortable at rest; ordinary physical activity causes undue dyspnoea or fatigue, chest pain, or near syncope
3	Walks slower than contemporaries on level ground because of breathlessness or has to stop for breath when walking at own pace	Marked limitation of physical activity, but comfortable at rest; less than ordinary activity causes undue dyspnoea or fatigue, chest pain, or near syncope
4	Stops for breath after walking ~100 m or after a few minutes on level ground	Inability to carry out any physical activity without symptoms; manifest signs of right heart failure; dyspnoea and/or fatigue may even be present at rest; discomfort is increased by any physical activity
5	Too breathless to leave the house, or becomes breathless while dressing or undressing	

Scales used for assessment of the severity of dyspnoea.[58,59]

Supplementary Table 17 Echocardiographic probability of pulmonary hypertension

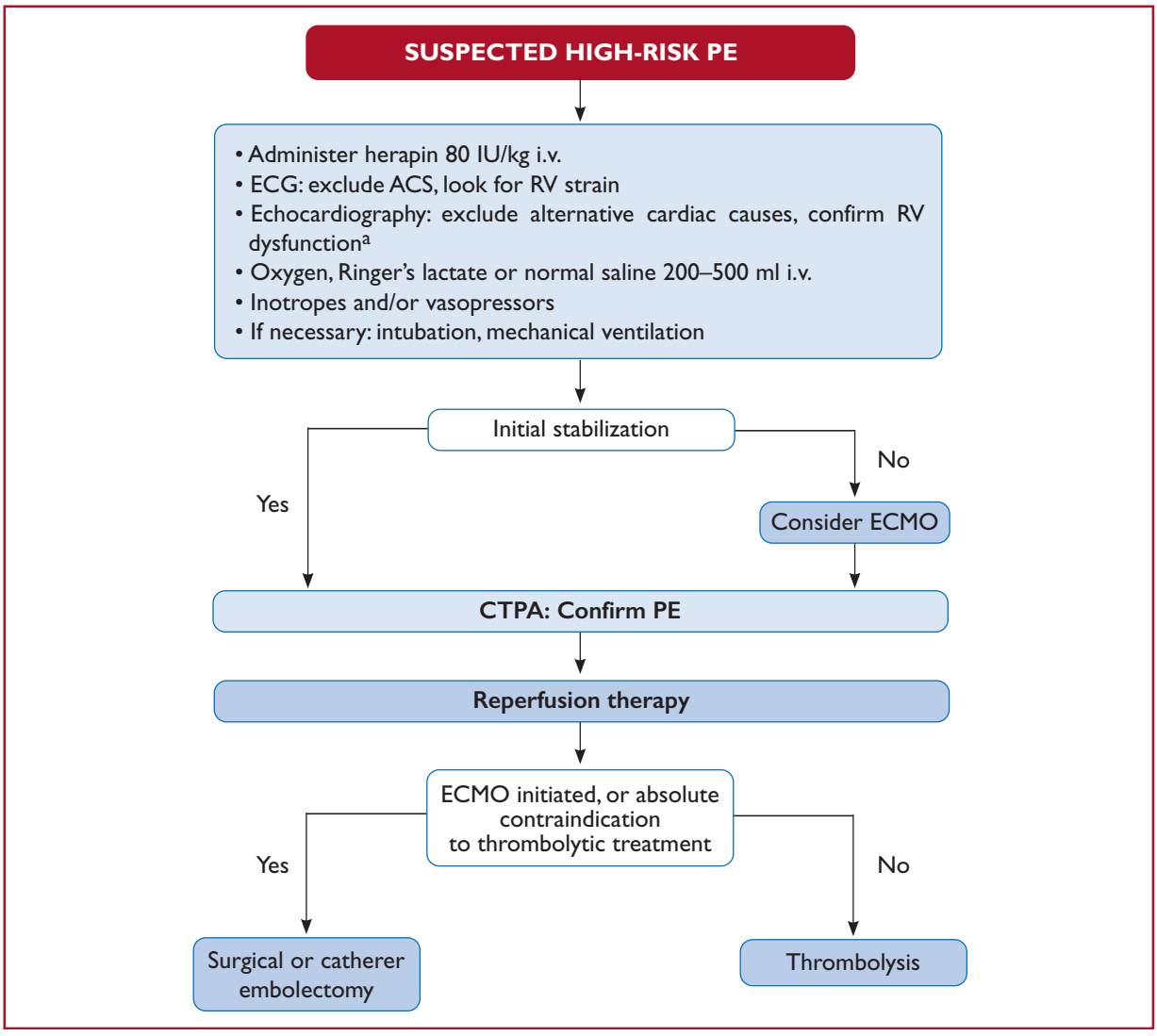
Peak tricuspid regurgitation velocity (m/s)	Presence of other echocardiographic PH signs[a]	Echocardiographic probability of PH
≤2.8 or not measurable	**No**	**Low**
≤2.8 or not measurable	Yes	**Intermediate**
2.9–3.4	No	
2.9–3.4	**Yes**	**High**
>3.4	**Not required**	

Echocardiographic probability of PH in symptomatic patients with a suspicion of pulmonary hypertension.[59]
PH = pulmonary hypertension.
[a]See *Supplementary Table 18*.

Supplementary Table 18 Echocardiographic signs of pulmonary hypertension

A: the ventricles[a]	B: pulmonary artery[a]	C: IVC and RA[a]
RV/LV basal diameter ratio >1.0	AcT <105 ms and/or mid-systolic notching	Inferior vena cava diameter >21 mm with decreased respiratory collapse (<50% with a sniff or <20% with quiet inspiration)
Flattening of the interventricular septum (LV eccentricity index >1.1 in systole and/or diastole)	Early diastolic pulmonary regurgitation velocity >2.2 m/s	Right atrial area (end-systole) >18 cm^2
	PA diameter >25 mm	

Echocardiographic signs suggesting PH used to assess the probability of PH in addition to tricuspid regurgitation velocity measurement.[59]
AcT = right ventricular outflow Doppler acceleration time; IVC = inferior vena cava; LV = left ventricular; PA = pulmonary artery; PH = pulmonary hypertension; RA = right atrium; RV = right ventricular.
[a]Echocardiographic signs from at least two different categories (A/B/C) from the list should be present to alter the echocardiographic probability of PH.



Supplementary Figure 1 Emergency management of patients with suspected high-risk pulmonary embolism. ACS = acute coronary syndrome; CTPA = computed tomography pulmonary angiography; ECG = electrocardiogram; ECMO = extracorporeal membrane oxygenation; IU = international units; i.v. = intravenous; PE = pulmonary embolism; RV = right ventricular.
[a]See *Figure 3* and *Supplementary Table 3*.

2 Non-thrombotic pulmonary embolism (*section 11* in Full Text)

Different cell types can cause non-thrombotic embolization, including adipocytes, and haematopoietic, amniotic, trophoblastic, and tumour cells. In addition, bacteria, fungi, parasites, foreign materials, and gas can lead to PE. Symptoms are similar to those of acute VTE and include dyspnoea, tachycardia, chest pain, cough, and occasionally haemoptysis, cyanosis, and syncope.

Diagnosis of non-thrombotic PE can be a challenge. In the case of small particles, microemboli cannot be detected on CT images. Given the rarity of this disease, clinical evidence is limited and based mainly on small case series.

2.1 Septic embolism

Septic embolism to the pulmonary circulation is a relatively rare clinical event and is commonly associated with right-sided endocarditis. Risk factors include i.v. drug abuse, and infected indwelling catheters or pacemaker wires. Other causes include septic thrombophlebitis from the tonsils and the jugular, dental, and pelvic regions. Septic embolism usually manifests as multiple lung nodules, infiltrates, or abscesses in an infectious context. With the exception of infected pacemaker wires, septic embolism is not associated with PH. The diagnosis is based on identifying the source of septic emboli, positive blood culture tests, and chest X-ray or CT after considering the clinical context; there are no filling contrast defects on CTPA. Although *Staphylococcus aureus* is the most common bacterial pathogen, the

increasing number of immunocompromised patients—and those with indwelling catheters and vascular prostheses—has led to a rise in the incidence of anaerobic Gram-positive and Gram-negative bacteria, bacterioidae species, and fungi.[60] Specific treatment of the responsible bacterial or fungal microorganism is necessary.

2.2 Foreign-material pulmonary embolism

The increasing use of interventional techniques in modern medicine has drastically increased the incidence of foreign-material PE.[61] Examples of foreign material include silicone, broken catheters, guide wires, vena cava filters, coils for embolization, cement from vertebroplasty, and endovascular stent components. If possible, intravascular foreign objects should be removed as the material may cause further thrombosis and sepsis.

2.3 Fat embolism

Embolization of fat occurs in almost all patients with pelvic or long-bone fractures, and in those undergoing endomedullary nailing or placement of knee and hip prostheses. It also occurs during lipid and propofol infusion, intraosseous infusion, and bone marrow harvest, and in sickle cell disease, fatty liver disease, pancreatitis, and after liposuction. Pulmonary involvement is not only due to vascular obstruction but also to the release of substances triggering an inflammatory cascade, explaining why some patients with fat embolism develop acute respiratory distress syndrome.[62]

The classical triad of fat embolization is characterized by altered mental status, respiratory distress, and petechial rash occurring typically 12–36 h after injury. Fat globules can be found in the blood, urine, sputum, broncho-alveolar lavage, and cerebrospinal fluid.[63] In most cases, the condition is self-limiting. Treatment should be supportive. Although the successful use of high doses of methyl prednisolone has been reported in humans, along with the positive effects of phorbol myristate acetate and sivelestat in animals, there is no evidence that these drugs alter the course of the disease.[64]

2.4 Air embolism

Although air embolism can occur in both the venous and arterial systems, venous emboli are more common. Venous air embolization is often an iatrogenic complication of the manipulation of central venous and haemodialysis catheters. The lethal volume of air after injection in humans is estimated to range from 100–500 mL.[65] The major effect of venous air embolism is the obstruction of the RV outflow tract or of the pulmonary arterioles, by a mixture of air bubbles and fibrin. Although the diagnosis can be made by X-ray or echocardiography, CT scanning may be the most sensitive diagnostic test, showing a unique picture of round or mirror-shaped densities localized ventrally in the supine patient.[66] Treatment includes maintenance of the circulation, the prevention of further entry of gas, high-flow oxygen, and volume expansion. The patient should be placed in the left lateral decubitus position to prevent RV outflow obstruction by airlock.[67] In the case of large amounts of central air, aspiration via the use of a central venous catheter might be an option.

2.5 Tumour embolism

Pulmonary intravascular tumour emboli are seen in ≤26% of autopsies of patients with solid malignancies, although the diagnosis is rarely made before death.[68] Carcinomas of the prostate, digestive system, liver, kidney, and breast are most commonly implicated. Radiologically, tumour microembolism may mimic many lung conditions, including pneumonia, tuberculosis, and interstitial lung disease, whereas tumour macroembolism is indistinguishable from VTE. Treatment should target the underlying malignant disease. Anticoagulant treatment is often prescribed in this context because tumour embolism and VTE are difficult to distinguish.

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