VTE & PREGNANCY

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EPIDEMIOLOGY

VTE | DVT

PE

most common preventable cause of death among hospitalized patients.

complications :

- chronic thromboembolic pulmonary hypertension
- postthrombotic syndrome.

CLASSIFICATION OF PULMONARY EMBOLISM AND DEEP VENOUS THROMBOSIS

- ✓ **Pulmonary Embolism**

Massive PE : 5–10%

Submassive PE : 20–25%

Low-risk PE : 65–75%

CLASSIFICATION OF PULMONARY EMBOLISM AND DEEP VENOUS THROMBOSIS

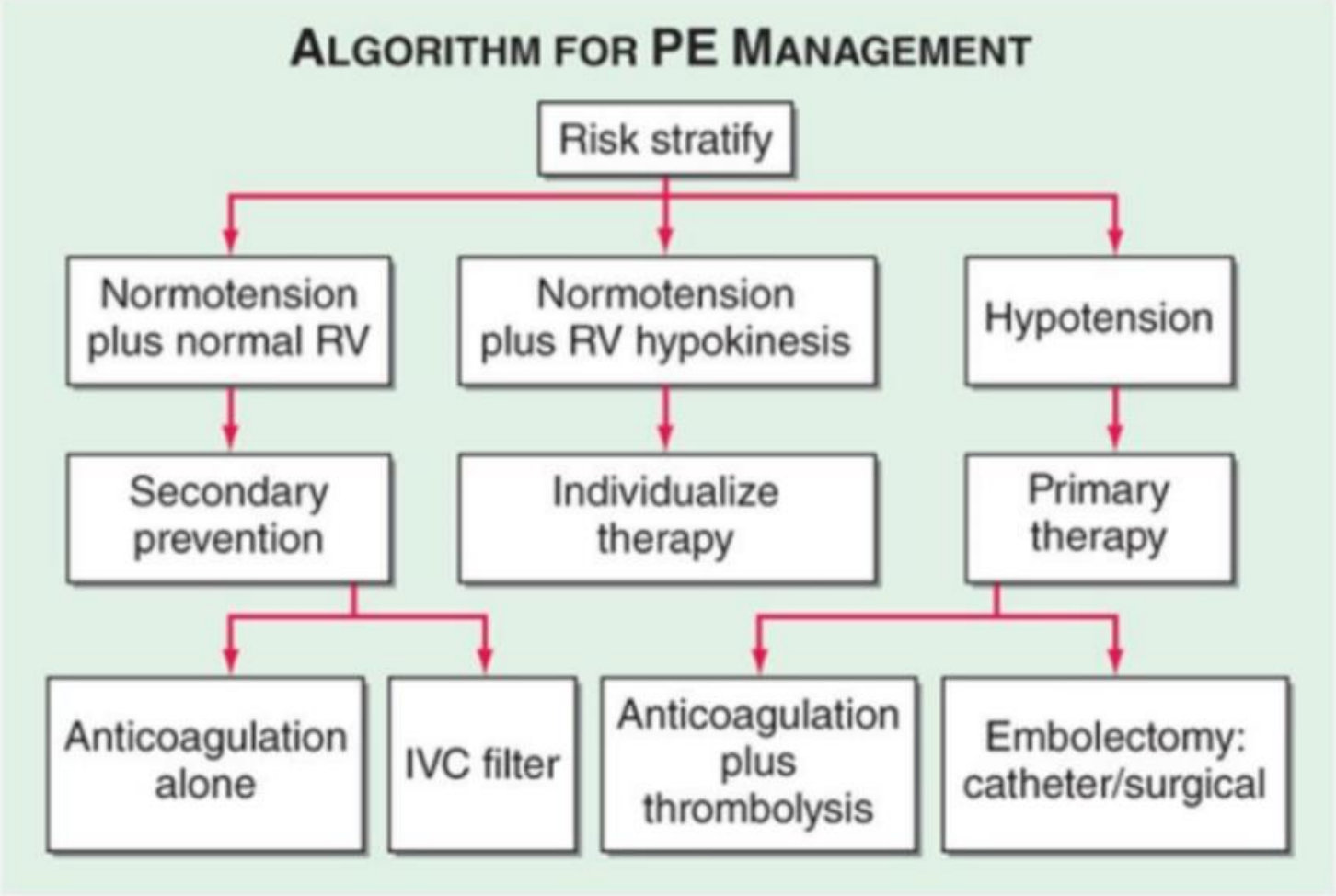
- ✓ Deep Venous Thrombosis

Lower extremity DVT

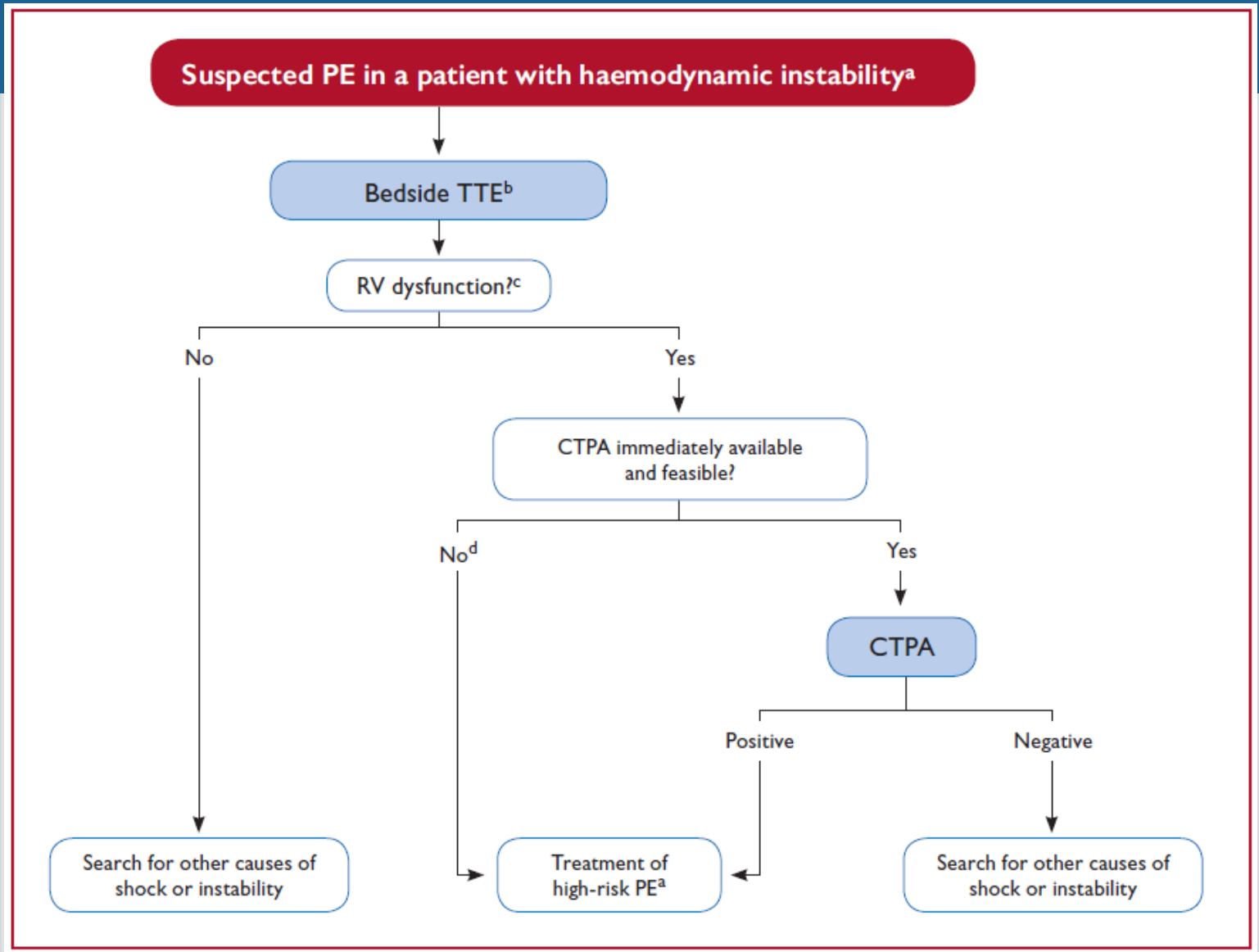
upper extremity DVT

Superficial venous thrombosis

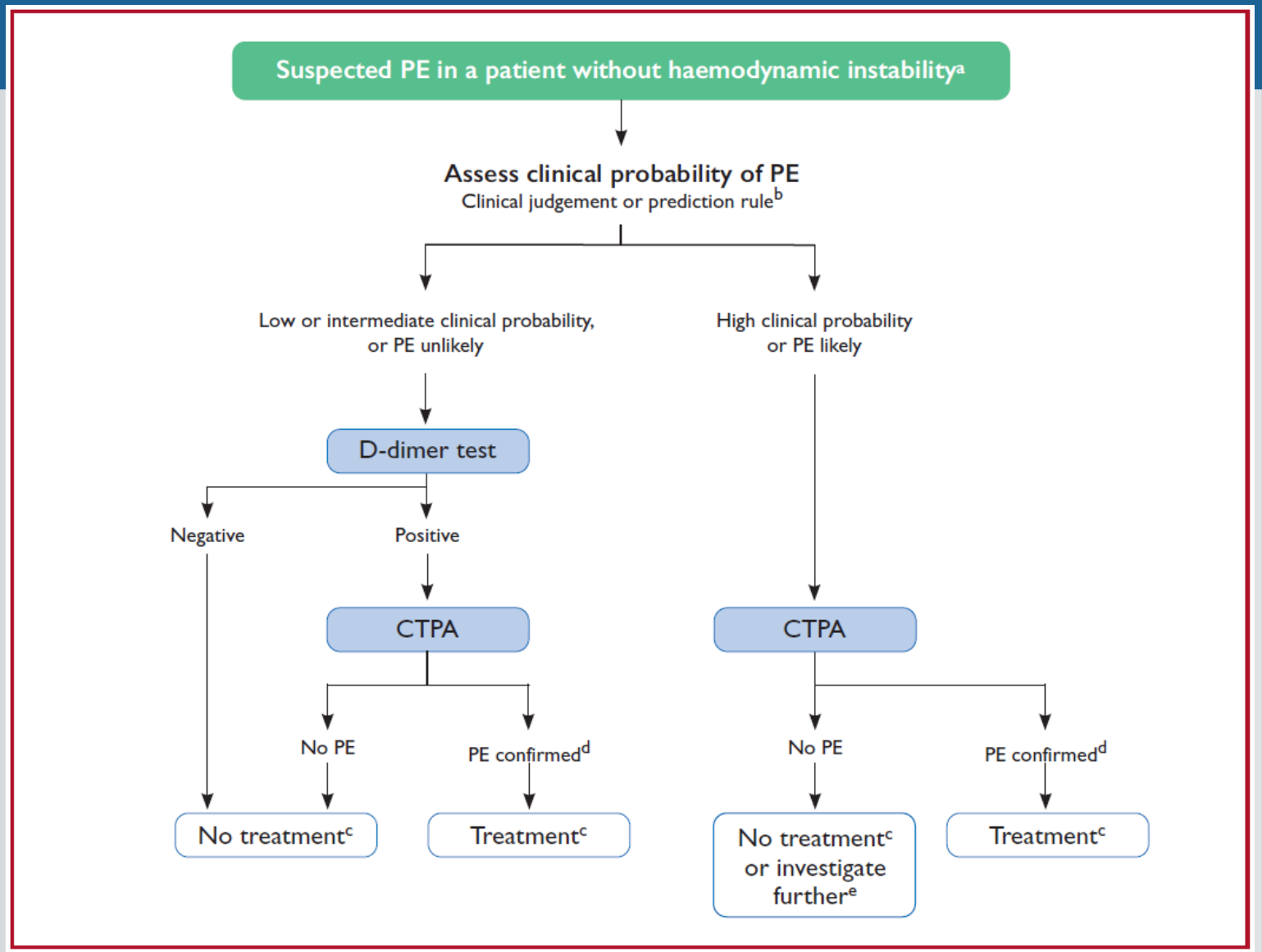
Acute management of pulmonary thromboembolism. RV, right ventricular; IVC, inferior vena cava.



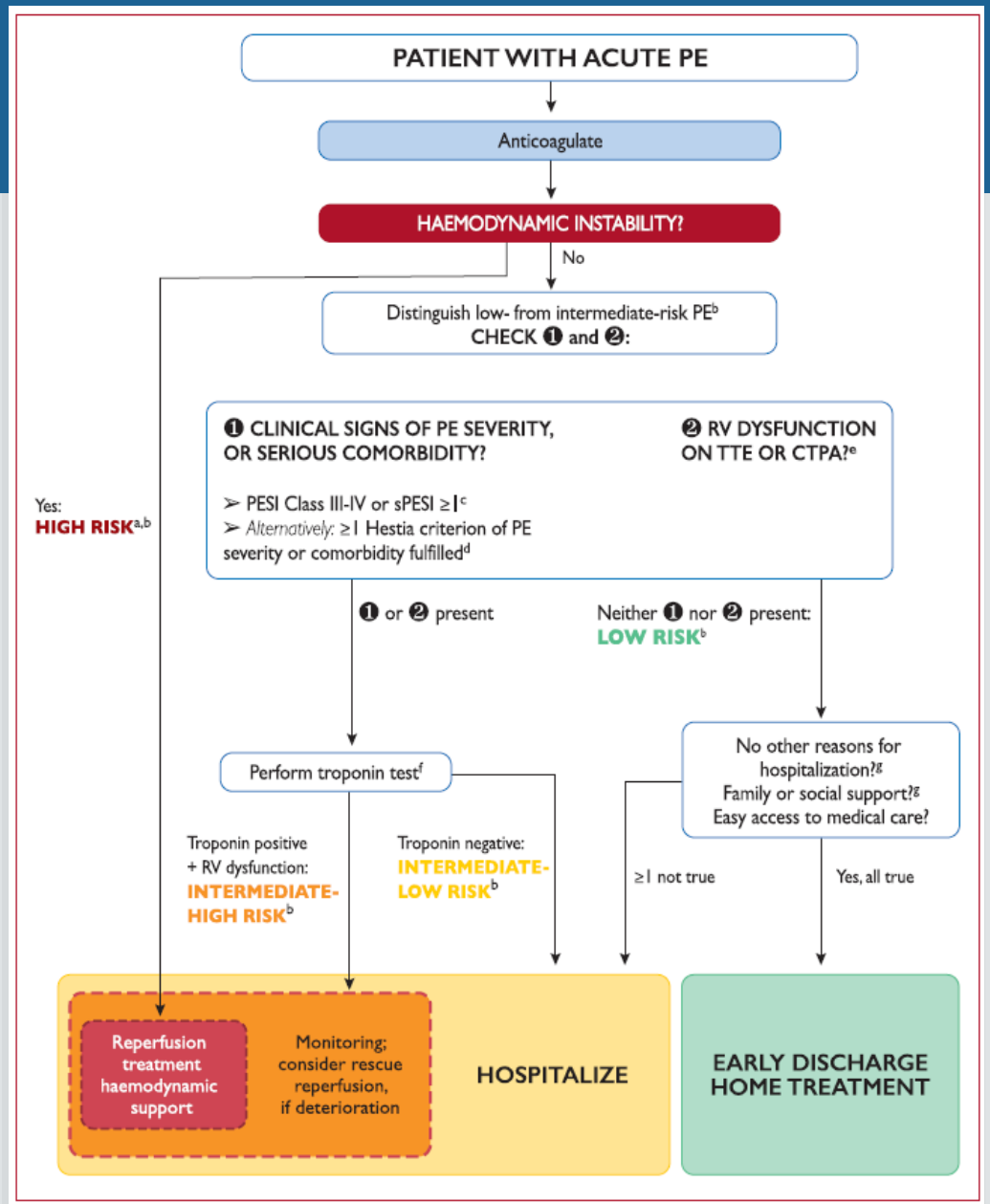
Diagnostic algorithmfor patients with suspected high-risk pulmonary embolism presenting with haemodynamic instability.



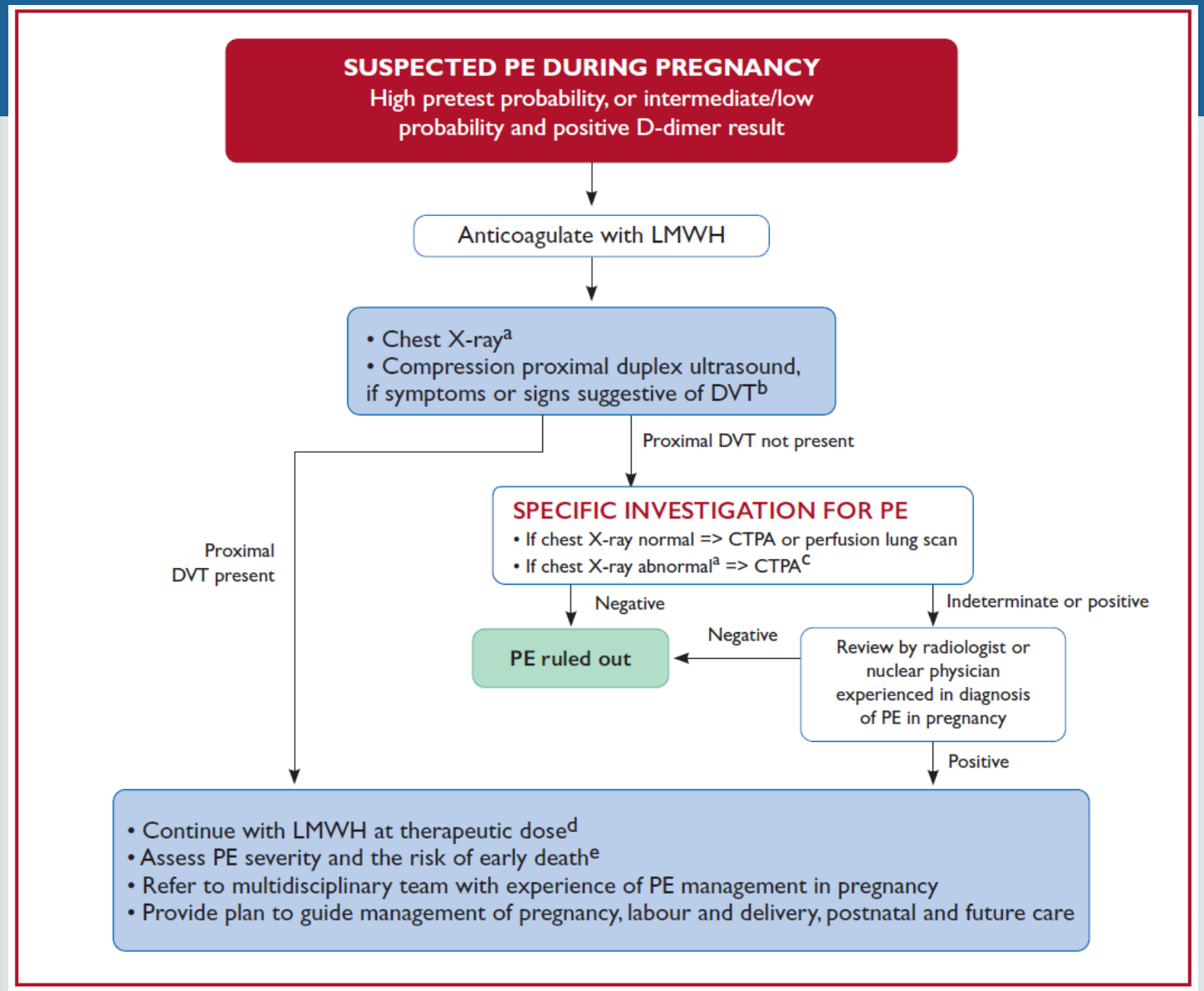
Diagnostic algorithmfor patients with suspected pulmonary embolism without haemodynamic instability.



Central Illustration. Risk-adjustedmanagement strategy for acute pulmonary mbolism.



Diagnostic workup andmanagement of suspected pulmonary embolismduring pregnancy, and up to 6 weeks post-partum.



Diagnosis of Suspected Pulmonary Embolism in Pregnancy

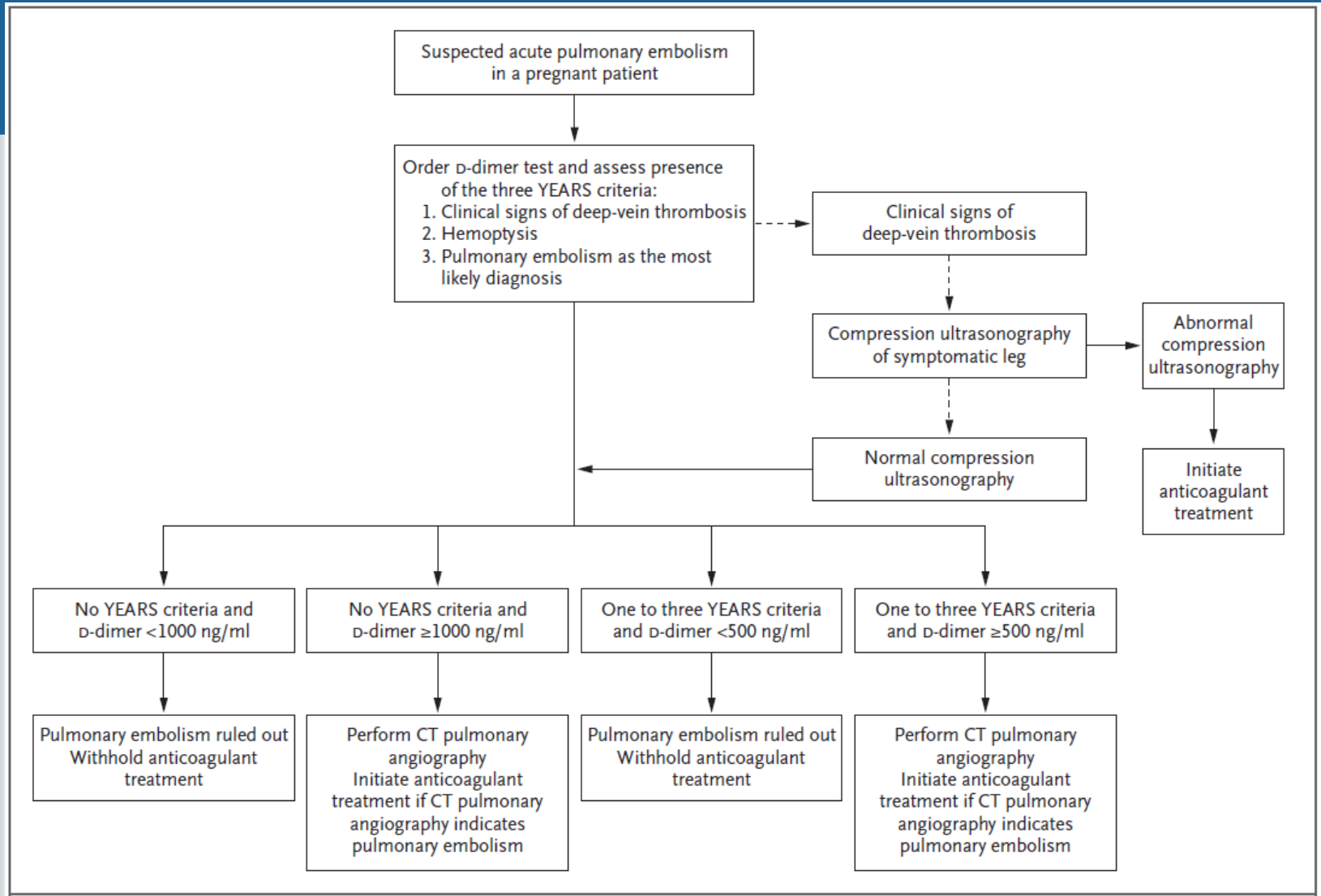


Figure 1. Pregnancy-Adapted YEARS Algorithm for the Management of Suspected Acute Pulmonary Embolism in Pregnant Patients.
CT denotes computed tomography.

Estimated amounts of radiation absorbed in procedures used to diagnose pulmonary embolism (based on various references385,392–398)

Test	Estimated foetal radiation exposure (mGy)[a]	Estimated maternal radiation exposure to breast tissue (mGy)[a]
Chest X-ray	<0.01	<0.1
Perfusion lung scan with technetium-99m-labelled albumin		
Low dose: ~40 MBq	0.02–0.20	0.16–0.5
High dose: ~200 MBq	0.20–0.60	1.2
Ventilation lung scan	0.10–0.30	<0.01
CTPA	0.05–0.5	3–10

Recommendations for pulmonary embolismin pregnancy

Recommendations	Class[a]	Level[b]
Diagnosis		
Formal diagnostic assessment with validated methods is recommended if PE is suspected during pregnancy or in the post-partum period.[388,391]	I	B
D-dimer measurement and clinical prediction rules should be considered to rule out PE during pregnancy or the post-partum period.[388,391]	IIa	B
In a pregnant patient with suspected PE (particularly if she has symptoms of DVT), venous CUS should be considered to avoid unnecessary irradiation.[388]	IIa	B
Perfusion scintigraphy or CTPA (with a low-radiation dose protocol) should be considered to rule out suspected PE in pregnant women; CTPA should be considered as the first-line option if the chest X-ray is abnormal.[385,386]	IIa	C
Treatment		
A therapeutic, fixed dose of LMWH based on early pregnancy body weight is the recommended therapy for PE in the majority of pregnant women without haemodynamic instability.[408,410]	I	B
Thrombolysis or surgical embolectomy should be considered for pregnant women with high-risk PE.[421]	IIa	C
Insertion of a spinal or epidural needle is not recommended, unless ≥24 h have passed since the last therapeutic dose of LMWH.	III	C
Administration of LMWH is not recommended within 4 h of removal of an epidural catheter.	III	C
NOACs are not recommended during pregnancy or lactation.	III	C

Recommendations for pulmonary embolismin pregnancy

Amniotic fluid embolism		
Amniotic fluid embolism should be considered in a pregnant or post-partum woman with otherwise unexplained cardiac arrest, sustained hypotension, or respiratory deterioration, especially if accompanied by disseminated intravascular coagulation.[422,425,426]	IIa	C

Recommendations for acute-phase treatment of intermediate or low-risk pulmonary embolism

Recommendations	Class[a]	Level[b]
Initiation of anticoagulation		
Initiation of anticoagulation is recommended without delay in patients with high or intermediate clinical probability of PE,[c] while diagnostic workup is in progress.	I	C
If anticoagulation is initiated parenterally, LMWH or fondaparinux is recommended (over UFH) for most patients.[262,309–311]	I	A
When oral anticoagulation is started in a patient with PE who is eligible for a NOAC (apixaban, dabigatran, edoxaban, or rivaroxaban), a NOAC is recommended in preference to a VKA.[260,261,312–314]	I	A
When patients are treated with a VKA, overlapping with parenteral anticoagulation is recommended until an INR of 2.5 (range 2.0–3.0) is reached.[315,316]	I	A
NOACs are not recommended in patients with severe renal impairment,[d] during pregnancy and lactation, and in patients with antiphospholipid antibody syndrome.[260,261,312–314]	III	C

Reperfusion treatment		
Rescue thrombolytic therapy is recommended for patients with haemodynamic deterioration on anticoagulation treatment.[282]	I	B
As an alternative to rescue thrombolytic therapy, surgical embolectomy[e] or percutaneous catheter-directed treatment[e] should be considered for patients with haemodynamic deterioration on anticoagulation treatment.	IIa	C
Routine use of primary systemic thrombolysis is not recommended in patients with intermediate- or low-risk PE.[c,f 179]	III	B

Recommendations for multidisciplinary pulmonary embolism teams

Recommendation	Class[a]	Level[b]
Set-up of a multidisciplinary team and a programme for the management of high- and (in selected cases) intermediate-risk PE should be considered, depending on the resources and expertise available in each hospital.	IIa	C

Recommendations for inferior vena cava filters

Recommendations	Class[a]	Level[b]
IVC filters should be considered in patients with acute PE and absolute contraindications to anticoagulation.	IIa	C
IVC filters should be considered in cases of PE recurrence despite therapeutic anticoagulation.	IIa	C
Routine use of IVC filters is not recommended.[302–304]	III	A

Recommendations for early discharge and home treatment

Recommendation	Class[a]	Level[b]
Carefully selected patients with low-risk PE should be considered for early discharge and continuation of treatment at home, if proper outpatient care and anticoagulant treatment can be provided.[c] 178,206,317–319	IIa	A

➢Management of massive PE

Treatment of right ventricular failure in acute high-risk pulmonary embolism

Strategy	Properties and use	Caveats
Volume optimization		
Cautious volume loading, saline, or Ringer's lactate, ≤500 mL over 15–30 min	Consider in patients with normal–low central venous pressure (due, for example, to concomitant hypovolaemia)	Volume loading can over-distend the RV, worsen ventricular interdependence, and reduce CO[239]
Vasopressors and inotropes		
Norepinephrine, 0.2–1.0 μg/kg/min[a] [240]	Increases RV inotropy and systemic BP, promotes positive ventricular interactions, and restores coronary perfusion gradient	Excessive vasoconstriction may worsen tissue perfusion
Dobutamine, 2–20 μg/kg/min[241]	Increases RV inotropy, lowers filling pressures	May aggravate arterial hypotension if used alone, without a vasopressor; may trigger or aggravate arrhythmias
Mechanical circulatory support		
Veno–arterial ECMO/extracorporeal life support[251,252,258]	Rapid short-term support combined with oxygenator	Complications with use over longer periods (>5–10 days), including bleeding and infections; no clinical benefit unless combined with surgical embolectomy; requires an experienced team

Thrombolytic regimens, doses, and contraindications

Molecule	Regimen	Contraindications to fibrinolysis
rtPA	100 mg over 2 h	**Absolute**
	0.6 mg/kg over 15 min (maximum dose 50 mg)[a]	History of haemorrhagic stroke or stroke of unknown origin
Streptokinase	250 000 IU as a loading dose over 30 min, followed by 100 000 IU/h over 12–24 h	Ischaemic stroke in previous 6 months
	Accelerated regimen: 1.5 million IU over 2 h	Central nervous system neoplasm
Urokinase	4400 IU/kg as a loading dose over 10 min, followed by 4400 IU/kg/h over 12–24 h	Major trauma, surgery, or head injury in previous 3 weeks
	Accelerated regimen: 3 million IU over 2 h	Bleeding diathesis
		Active bleeding
		Relative
		Transient ischaemic attack in previous 6 months
		Oral anticoagulation
		Pregnancy or first post-partum week
		Non-compressible puncture sites
		Traumatic resuscitation
		Refractory hypertension (systolic BP >180 mmHg)
		Advanced liver disease
		Infective endocarditis
		Active peptic ulcer

Recommendations for acute-phase treatment of high-risk pulmonary embolism

Recommendations	Class[b]	Level[c]
It is recommended that anticoagulation with UFH, including a weight-adjusted bolus injection, be initiated without delay in patients with high-risk PE.	I	C
Systemic thrombolytic therapy is recommended for high-risk PE. [282]	I	B
Surgical pulmonary embolectomy is recommended for patients with high-risk PE, in whom thrombolysis is contraindicated or has failed.[d] [281]	I	C
Percutaneous catheter-directed treatment should be considered for patients with high-risk PE, in whom thrombolysis is contraindicated or has failed.[d]	IIa	C
Norepinephrine and/or dobutamine should be considered in patients with high-risk PE.	IIa	C
ECMO may be considered, in combination with surgical embolectomy or catheter-directed treatment, in patients with PE and refractory circulatory collapse or cardiac arrest.[d] [252]	IIb	C

PHARMACOMECHANICAL CATHETER-DIRECTED THERAPY

- Many patients have relative contraindications to full-dose thrombolysis.
- Pharmacomechanical catheter-directed therapy usually combines physical fragmentation or pulverization of thrombus with catheter-directed low-dose thrombolysis.
- Mechanical techniques include catheter maceration and intentional embolization of clot more distally, suction thrombectomy, rheolytic hydrolysis, and low energy ultrasound-facilitated thrombolysis.
- The dose of alteplase can be markedly reduced, usually to a range of 20–25 mg, instead of the peripheral intravenous systemic dose of 100 mg.

- In 2014, the FDA approved ultrasound-facilitated catheter-directed thrombolysis for acute massive and submassive PE.
- Using a total tPA dose of 24 mg, this approach decreased RV dilation, reduced pulmonary hypertension, decreased anatomic thrombus burden, and minimized intracranial hemorrhage. Lower doses and durations of TPA are currently being studied.

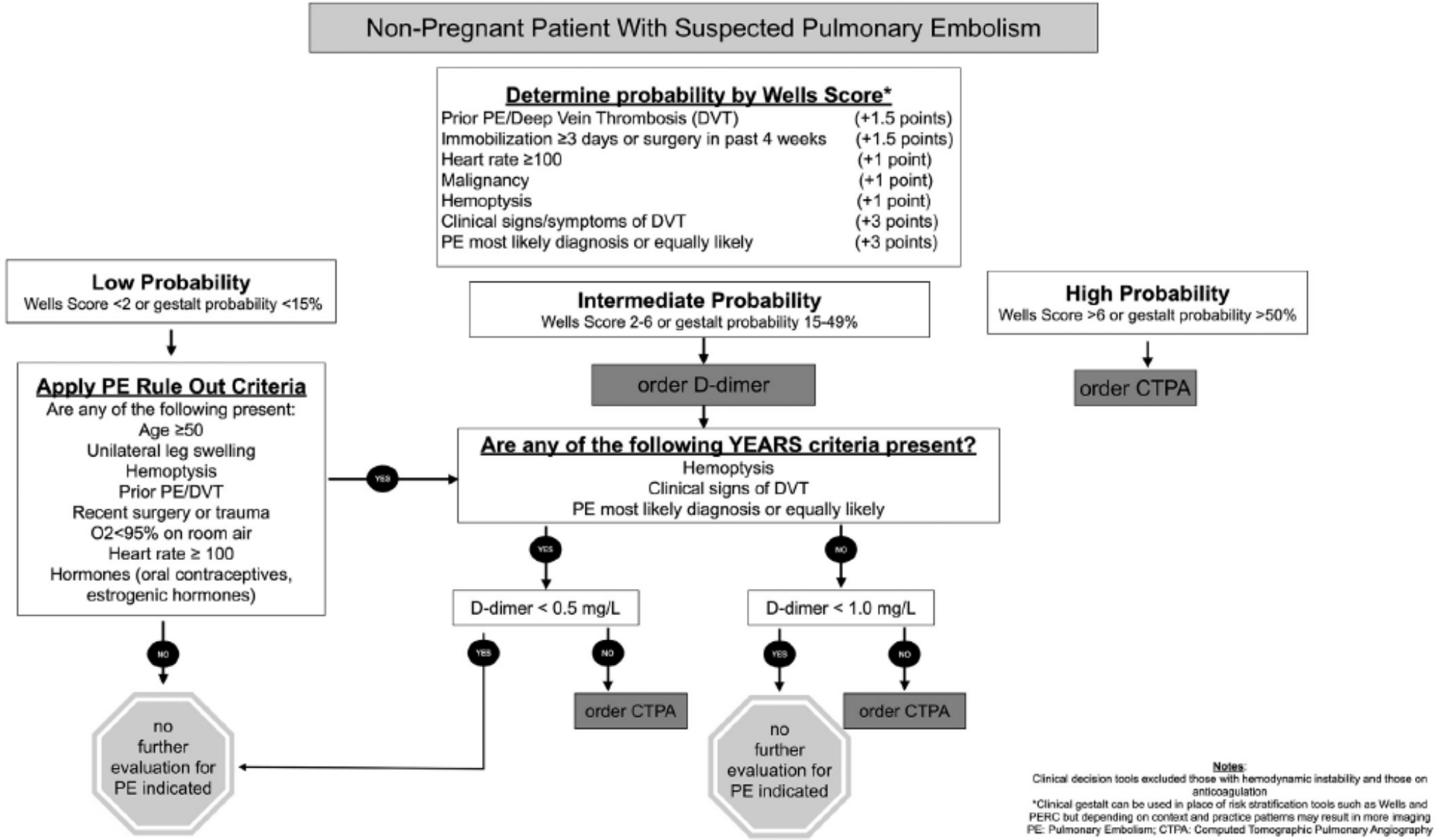


Figure 1. Possible diagnostic algorithm for nonpregnant patients with suspected PE. *CTPA*, computed tomography pulmonary angiography; *DVT*, deep venous thrombosis; *RV*, right ventricular; *SBP*, systolic blood pressure.

Table 1. Wells' Criteria for PE.

Consideration	No	Yes
Clinical signs and symptoms of DVT	0	+3
PE is #1 diagnosis or equally likely	0	+3
Pulse rate of >100 beats/min	0	+1.5
Immobilization at least 3 d or surgery in the previous 4 wk	0	+1.5
Previous, objectively diagnosed PE or DVT	0	+1.5
Hemoptysis	0	+1
Malignancy with treatment within 6 mo or palliative	0	+1

Score	
Three-tier model	Risk (prevalence of PE in the US studies)
0-1	Low risk (1%-3%).[79-81]
2-6	Intermediate risk (8.5%-15%).[79-81]
>6	High risk (37%-43%).[79,81]
Two-tier model	Risk (prevalence of PE in the US studies)
≤4	PE unlikely (1.8%-7.2%).[79]
≥5	PE likely (28%).[79]

Table 2. PERC rule for PE.

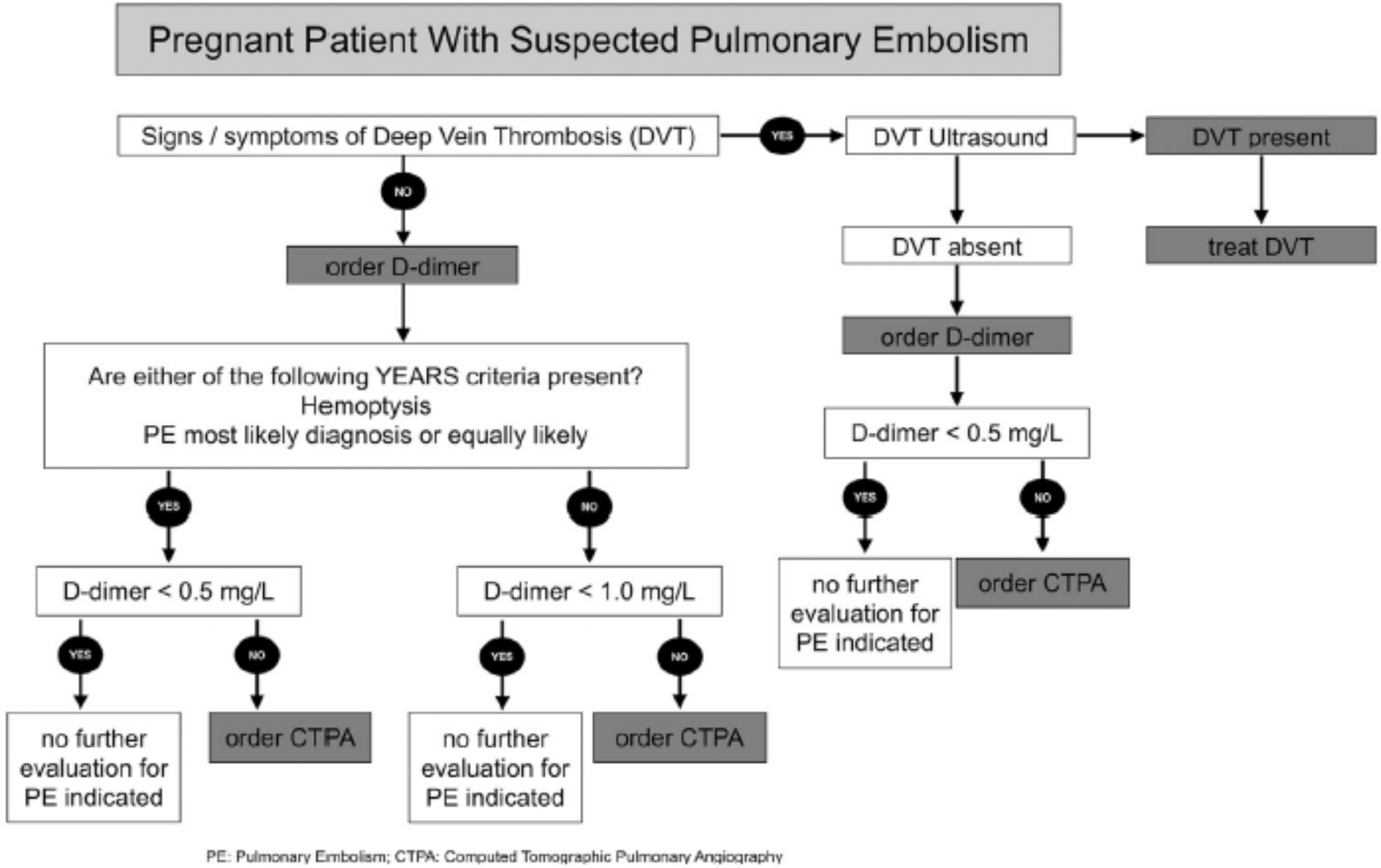
Consideration	No	Yes
Age of ≥50 y	0	+1
Pulse rate of ≥100 beats/min	0	+1
Oxygen saturation on room air of <95%	0	+1
Unilateral leg swelling	0	+1
Hemoptysis	0	+1
Recent surgery or trauma (≤4 wk ago, requiring general anesthesia)	0	+1
Prior PE or DVT	0	+1
Hormone use (eg, oral contraceptives, hormone replacement, or estrogenic hormone use in male or female patients)	0	+1

Score: if any criteria are positive, PE is not excluded

Table 3. YEARS algorithm for PE.

Consideration	No	Yes
Clinical signs of DVT	0	+1
Hemoptysis	0	+1
PE most likely diagnosis	0	+1

If no criteria present, use a FEU D-dimer threshold of 1,000 ng/mL.
If ≥1 criterion present, use a FEU D-dimer threshold of 500 ng/mL.
If the patient is pregnant and clinical signs of DVT are present, perform compression ultrasonography of the symptomatic leg; if normal, perform D-dimer testing.
FEU, fibrin-equivalent units.



PE: Pulmonary Embolism; CTPA: Computed Tomographic Pulmonary Angiography

Figure 2. Possible diagnostic algorithm for pregnant patients with suspected PE.

		Hemodynamic instability[1]	Right Ventricular (RV) Dysfunction (RV strain on echocardiography more predictive than CTPA)	Elevated cardiac troponin	Higher risk based on clinical parameters/comorbidities (PESI III/IV or sPESI ≥1)
High		**Present**	**Present**	**Not necessary**	**Not necessary**
Intermediate	**Intermediate-high**	**Absent**	**Present**	**Present**	**May be present** (elevated troponin or right ventricular dysfunction may be present in patients with calculated higher risk, but the implications for treatment of these patients is uncertain)
	Intermediate-low	**Absent**	**No more than one category positive** (e.g. right ventricular dysfunction present with a negative cardiac troponin)		**May be present** (elevated troponin or right ventricular dysfunction may be present in patients with calculated higher risk, but the implications for treatment of these patients is uncertain)
Low		**Absent**	**Absent**	**Optional assessment but negative if assessed**	**Absent**

CTPA: Computed Tomographic Pulmonary Angiography; PESI: Pulmonary Embolism Severity Index; sPESI: Simplified Pulmonary Embolism Severity Index
1. Hemodynamic instability: Cardiac arrest ***OR*** hypotension with systolic blood pressure (SBP) <90 mmHg or vasopressors required to achieve SBP ≥90 mmHg despite adequate filling status and signs of end organ dysfunction ***OR*** persistent SBP <90 mmHg or SBP drop >_40 mmHg, lasting longer than 15 min and not caused by new-onset arrhythmia, hypovolemia, or sepsis

Figure 3. PE risk stratification for mortality.

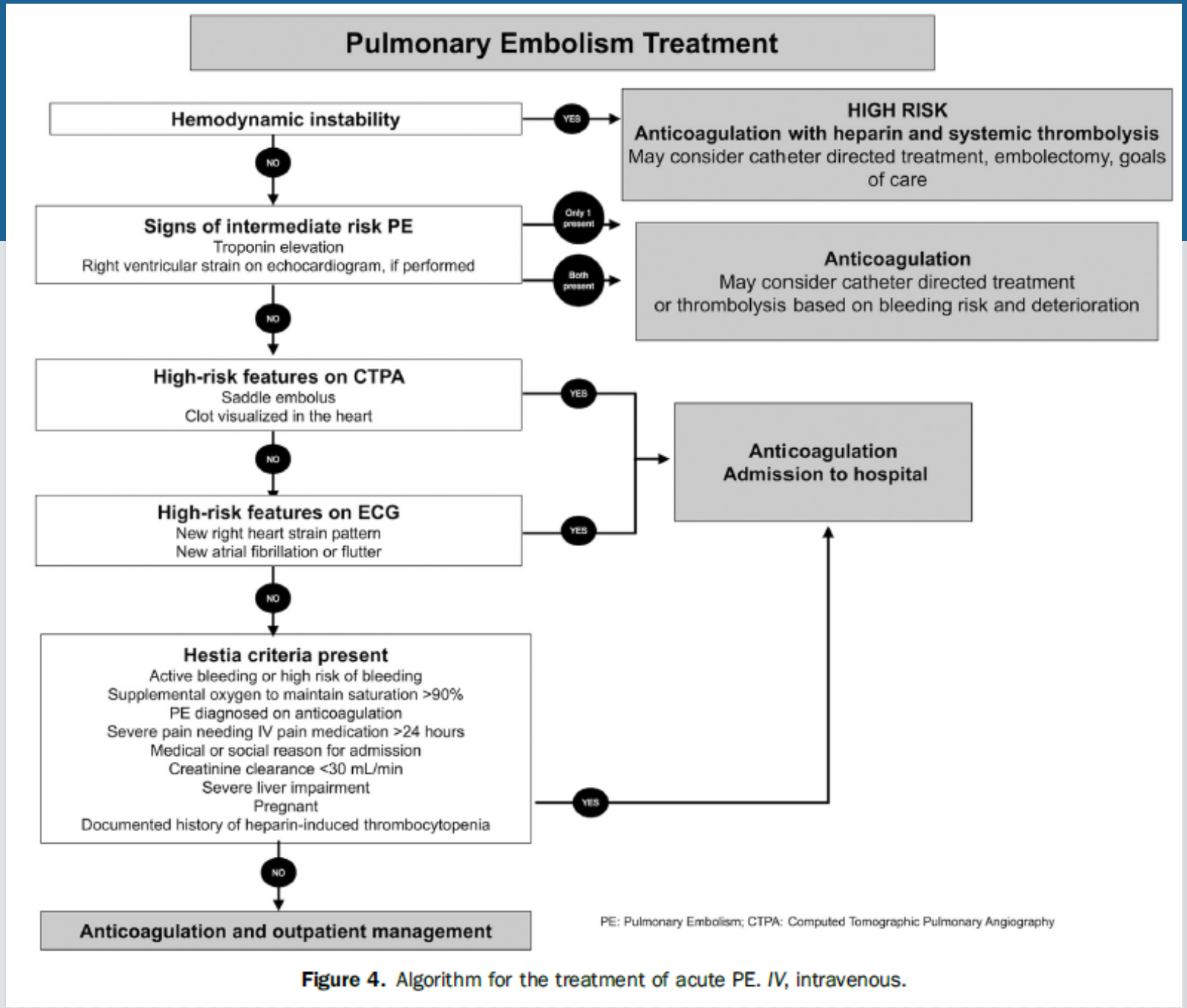


Figure 4. Algorithm for the treatment of acute PE. *IV*, intravenous.

	Dose	Concurrent Anticoagulation	Notes
Alteplase	**100 mg infusion over 2 hours*** **OR** **In emergent situations such as impending cardiac arrest: a bolus, quick infusion, or 20 mg bolus followed by 2 hour infusion for remaining 80 mg may be used although these are not US FDA approved** **Or** **Reduced-dose thrombolysis (0.5 mg/kg up to 50 mg) alteplase has been studied in**	**Hold unfractionated heparin (UFH) infusion and restart near or at the completion of the alteplase infusion when the partial thromboplastin time or thrombin time returns to less than or equal to twice normal**	*Currently, only the 100 mg infusion is approved by the United States Food and Drug Administration (US FDA) for this use at this dose.
Tenecteplase	**Weight-based intravenous push of 30-50 mg**** (30 mg: ≤60 kg, 35 mg: 61-69 kg, 40 mg: 70 -79 kg, 45 mg: 80-89, 50 mg: ≥90 kg	**Full-dose low-molecular weight heparin (LMWH): enoxaparin 1 mg/kg or weight-based dalteparin prior to bolus and throughout hospital stay** **OR** **Unfractionated heparin bolus and infusion** (no need to hold UFH unless patient received LMWH or fondaparinaux in which case bolus should not administered the infusion should be held for 12 hours after LMWH or 24 hours after fondaprinaux)	**Not official approved for this indication by the US FDA

Figure 5. Possible thrombolytic doses for acute PE. *FDA*, Food and Drug Administration; *LMWH*, low–molecular-weight heparin; *UFH*, unfractionated heparin.

Table 4. Hestia criteria for outpatient PE treatment.

Consideration	No	Yes
Hemodynamically unstable—SBP of <100 mmHg and PR of >100, requires ICU care, or clinician judgment	0	+1
Thrombolysis or embolectomy needed—for reasons other than hemodynamic instability	0	+1
Active bleeding or high risk of bleeding—GI bleeding or surgery <2 wk ago, stroke <1 mo ago, bleeding disorder or platelet disorder $<75\times10^9$/L, uncontrolled HTN (SBP of >180 mmHg or DBP of >100 mmHg), or clinician judgment	0	+1
>24 h on supplemental oxygen required to maintain an SaO_2 of >90%	0	+ 1
PE diagnosed while on anticoagulation	0	+1
Severe pain needing IV pain medication required >24 h	0	+1
Medical or social reason for admission >24 h (infection, malignancy, no support system)	0	+1
Creatinine clearance of <30 mL/min by Cockcroft-Gault	0	+1
Severe liver impairment by clinician judgment	0	+1
Pregnant	0	+1
Documented history of heparin-induced thrombocytopenia	0	+1

RECOMMENDATION 1

For pregnant women with acute VTE, the ASH guideline panel recommends antithrombotic therapy compared with no antithrombotic therapy (strong recommendation, high certainty in evidence about effects).

RECOMMENDATION 2

For pregnant women with acute VTE, the ASH guideline panel recommends LMWH over UFH (strong recommendation, moderate certainty in evidence about effects).

RECOMMENDATION 3

For pregnant women with proven acute superficial vein thrombosis, the ASH guideline panel suggests that LMWH be used over not using any anticoagulant (conditional recommendation, low certainty in evidence about effects).

RECOMMENDATION 4

For pregnant women with acute VTE treated with LMWH, the ASH guideline panel suggests either once-per-day or twice-per-day dosing regimens (conditional recommendation, very low certainty in evidence about effects).

RECOMMENDATION 5

For pregnant women receiving therapeutic LMWH for the treatment of VTE, the ASH guideline panel suggests against routine monitoring of anti-FXa levels to guide dosing (conditional recommendation, low certainty in evidence about effects).

RECOMMENDATION 6

For pregnant women with acute lower-extremity DVT, the ASH guideline panel suggests against the addition of catheter-directed thrombolysis therapy to anticoagulation (conditional recommendation, low certainty in evidence about effects).

RECOMMENDATION 7

In pregnant women with acute pulmonary embolism and right ventricular dysfunction in the absence of hemodynamic instability, the ASH guideline panel suggests against the addition of systemic thrombolytic therapy to anticoagulation, compared with anticoagulation alone (conditional recommendation, low certainty in evidence about effects).

RECOMMENDATION 8

In pregnant women with acute pulmonary embolism and life threatening hemodynamic instability, the ASH guideline panel suggests administering systemic thrombolytic therapy in addition to anticoagulant therapy (conditional recommendation, very low certainty in evidence about effects).

RECOMMENDATION 9

In pregnant women with low-risk acute VTE, the ASH guideline panel suggests initial outpatient therapy over hospital admission(conditional recommendation, low certainty in evidence about effects).

RECOMMENDATION 10

For pregnant women receiving therapeutic-dose LMWH for the management of VTE, the ASH guideline panel suggests scheduled delivery with prior discontinuation of anticoagulant therapy (conditional recommendation, very low certainty in evidence about effects).

RECOMMENDATION 11

In pregnant women receiving prophylactic-dose LMWH, the ASH guideline panel suggests against scheduled delivery with discontinuation of prophylactic anticoagulation compared with allowing spontaneous labor (conditional recommendation, very low certainty in evidence about effects).

RECOMMENDATION 12

In breastfeeding women who have an indication for anticoagulation, the ASH guideline panel recommends using UFH, LMWH, warfarin, acenocoumarol, fondaparinux, or danaparoid as safe options (strong recommendation, low certainty in evidence about effects).

RECOMMENDATION 13

In breastfeeding women who have an indication for anticoagulation, the ASH guideline panel recommends against using direct-acting oral anticoagulants (strong recommendation, very low certainty in evidence about effects).

RECOMMENDATION 14

In unselected women undergoing assisted reproductive therapy, the ASH guideline panel suggests against prophylactic antithrombotic therapy to prevent VTE (conditional recommendation, low certainty in evidence about effects).

RECOMMENDATION 15

For women undergoing assisted reproductive therapy who develop severe ovarian hyperstimulation syndrome, the ASH guideline panel suggests prophylactic antithrombotic therapy to prevent VTE (conditional recommendation, low certainty in evidence about effects).

RECOMMENDATION 16

For women not already receiving long-term anticoagulant therapy who have a history of VTE that was unprovoked or was associated with a hormonal risk factor, the ASH guideline panel recommends antepartum anticoagulant prophylaxis over no anticoagulant prophylaxis (strong recommendation, low certainty in evidence about effects).

RECOMMENDATION 17

For women not already receiving long-term anticoagulant therapy who have a history of prior VTE associated with a nonhormonal temporary provoking risk factor and no other risk factors, the ASH guideline panel suggests against antepartum anticoagulant prophylaxis (conditional recommendation, low certainty in evidence about effects).

RECOMMENDATION 18

For women not already receiving long-term anticoagulant therapy who have a history of VTE, the ASH guideline panel recommends postpartum anticoagulant prophylaxis (strong recommendation, low certainty in evidence about effects).

RECOMMENDATION 19

For women who are heterozygous for the factor V Leiden or prothrombin mutation and in those who have protein C or protein S deficiency, regardless of family history of VTE, the ASH guideline panel suggests against using antepartum antithrombotic prophylaxis to prevent a first venous thromboembolic event (conditional recommendation, very low certainty in evidence about effects).

RECOMMENDATION 20

For women who have no family history of VTE but have antithrombin deficiency or are homozygous for the prothrombin gene mutation, the ASH guideline panel suggests against using antepartum antithrombotic prophylaxis to prevent a first venous thromboembolic event (conditional recommendation, very low certainty in evidence about effects).

RECOMMENDATION 21

For women with antithrombin deficiency who have a family history of VTE and in those who are homozygous for the factor V Leiden mutation or who have combined thrombophilias, regardless of family history of VTE, the ASH guideline panel suggests antepartum antithrombotic prophylaxis to prevent a first venous thromboembolic event (conditional recommendation, very low certainty in evidence about effects).

RECOMMENDATION 22

For women without a family history of VTE who are heterozygous for the factor V Leiden mutation or prothrombin mutation or who have antithrombin, protein C, or protein S deficiency, the ASH guideline panel suggests against antithrombotic prophylaxis in the postpartum period to prevent a first venous thromboembolic event (conditional recommendation, very low certainty in evidence about effects).

RECOMMENDATION 23

For women with a family history of VTE who are heterozygous for the factor V Leiden mutation or prothrombin mutation, the ASH guideline panel suggests against postpartum antithrombotic prophylaxis to prevent a first venous thromboembolic event (conditional recommendation, very low certainty in evidence about effects).

RECOMMENDATION 24

For women with a family history of VTE who have antithrombin deficiency, the ASH guideline panel recommends postpartum antithrombotic prophylaxis to prevent a first venous thromboembolic event (strong recommendation, moderate certainty in evidence about effects).

RECOMMENDATION 25

For women with a family history of VTE who have protein C or protein S deficiency, the ASH guideline panel suggests postpartum antithrombotic prophylaxis to prevent a first venous thromboembolic event (conditional recommendation, very low certainty in evidence about effects).

RECOMMENDATION 26

For women with combined thrombophilias or who are homozygous for the factor V Leiden mutation or prothrombin gene mutation, regardless of family history, the ASH guideline panel suggests postpartum antithrombotic prophylaxis to prevent a first venous thromboembolic event (conditional recommendation, very low certainty in evidence about effects).

RECOMMENDATION 27

For women with no or 1 clinical risk factor (excluding a known thrombophilia or history of VTE), the ASH guideline panel suggests against antepartum or postpartum prophylaxis (conditional recommendation, low certainty in evidence about effects).

RECOMMENDATION 28

In pregnant women who require prophylaxis, the ASH guideline panel suggests against intermediate-dose LMWH prophylaxis compared with standard-dose LMWH prophylaxis during the antepartum period (conditional recommendation, very low certainty in evidence about effects).

RECOMMENDATION 29

For women who require prophylaxis, the ASH Guideline panel suggests either standard- or intermediate-dose LMWH prophylaxis during the postpartum period (conditional recommendation, very low certainty in evidence about effects).

RECOMMENDATION 29

For women who require prophylaxis, the ASH Guideline panel suggests either standard- or intermediate-dose LMWH prophylaxis during the postpartum period (conditional recommendation, very low certainty in evidence about effects).

RECOMMENDATION 30

In pregnant women with suspected pulmonary embolism, the ASH guideline panel suggests V/Q lung scanning over CT pulmonary angiography (conditional recommendation, low certainty in evidence about effects).

RECOMMENDATION 31

In pregnant women with suspected DVT, the ASH guideline panel suggests additional investigations, including serial compression ultrasound or magnetic resonance venography compared with no further investigations after an initial negative ultrasound with imaging of the iliac veins (conditional recommendation, low certainty in evidence about effects).