EMBOLIA POLMONARE

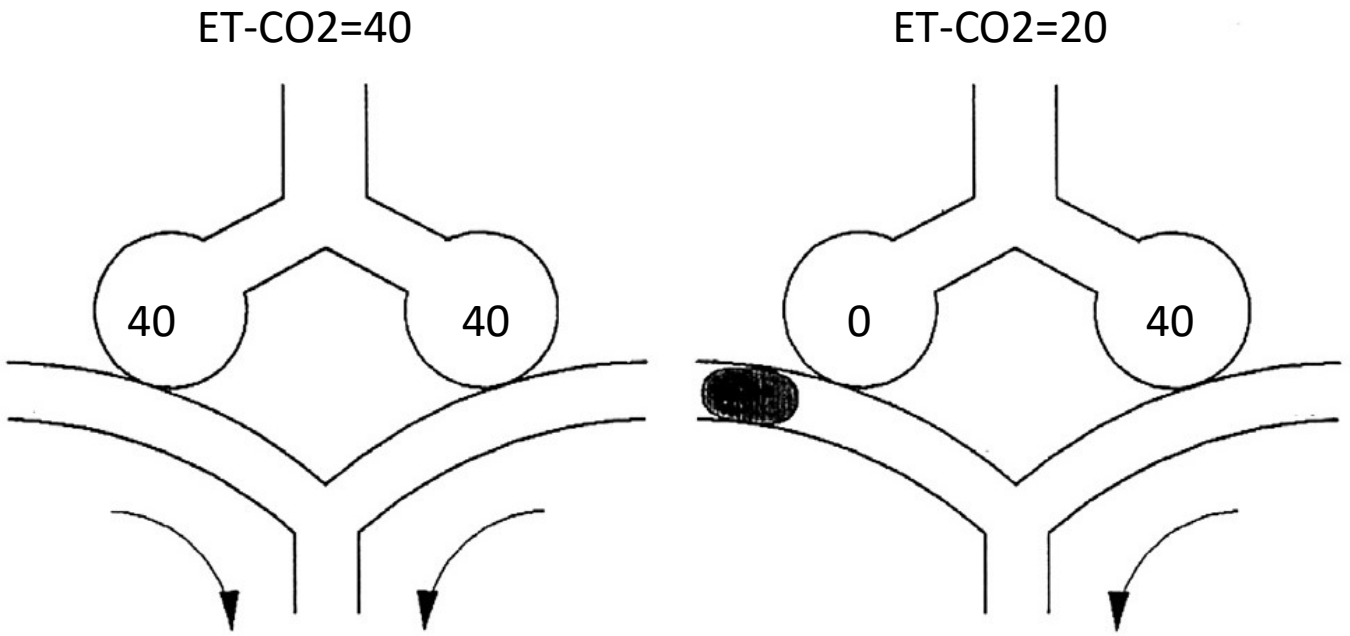
Modena 11 Marzo 2017

Pulmonary embolism is the third greatest cause of mortality from cardiovascular disease, after myocardial infarction and cerebrovascular stroke.

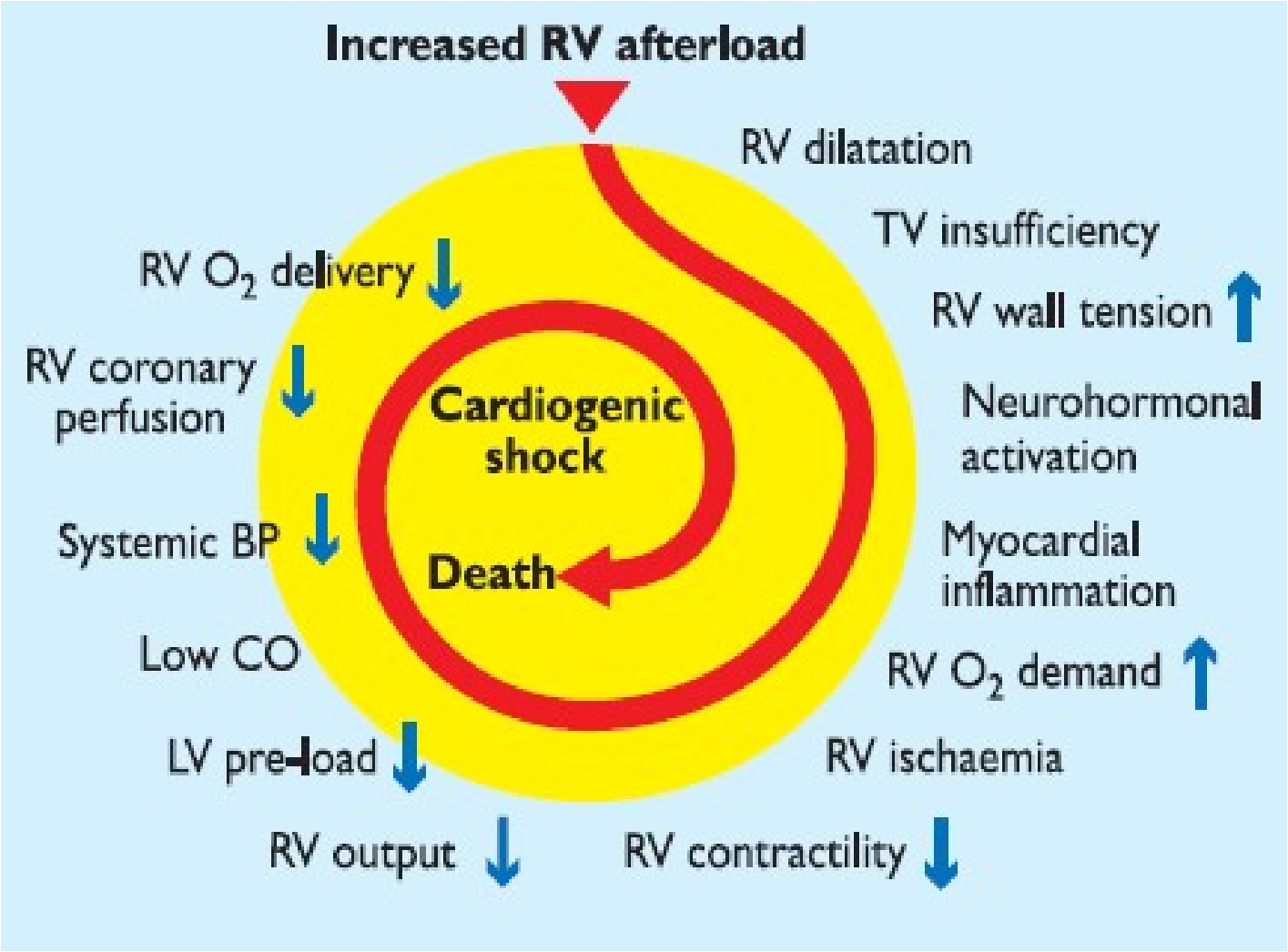
From hospital epidemiological data it has been calculated that the incidence of PE in the USA is 1 per 1,000 annually.

The real number is likely to be larger, since the condition goes unrecognised in many patients. Mortality due to PE has been estimated to exceed 15%

Goldhaber SZ Lancet 1999;



Acute PE interferes with both the circulation and gas exchange. Right ventricular (RV) failure due to pressure overload is considered the primary cause of death in severe PE.
Pulmonary **artery pressure increases** only if more than 30–50% of the total cross-sectional area of the pulmonary arterial bed is occluded by thromboemboli.
PE-induced vasoconstriction, mediated by the release of thromboxane A2 and serotonin, contributes to the initial increase in pulmonary vascular resistance after PE, an effect that can be reversed by vasodilators.
Anatomical obstruction and vasoconstriction lead to an increase in pulmonary vascular resistance and a proportional decrease in arterial compliance.



The extent of immediate adaptation is limited, since a non-preconditioned, thin-walled right ventricle(RV) is unable to generate a mean pulmonary artery pressure above 40 mm Hg.

Clinical characteristics of patients with suspected PE in the emergency department

Feature	PE confirmed (*n* = 1880)	PE not confirmed (*n* = 528)
Dyspnoea	50%	51%
Pleuritic chest pain	39%	28%
Cough	23%	23%
Substernal chest pain	15%	17%
Fever	10%	10%
Haemoptysis	8%	4%
Syncope	6%	6%
Unilateral leg pain	6%	5%
Signs of DVT (unilateral extremity swelling)	24%	18%

Pollack CV, J Am Coll Cardiol 2011;

Differential diagnosis of pulmonary embolism

Pneumonia or bronchitis
Asthma
Exacerbation of chronic obstructive pulmonary disease
Myocardial infarction
Pulmonary oedema
Anxiety-hysteria
Aortic dissection
Lung cancer
Primary pulmonary hypertension
Rib fractures
Pneumothorax
Musculoskeletal pain

Kostadima E. HJC 2007

RISK FACTORS FOR DVT AND PE

Various **inherited** conditions increase a patient's risk for venous thromboembolism (VTE)

the most common of which are **factor V Leiden** and **prothrombin** gene mutation (G20210A) with population prevalences of approximately 4% to 5% and 2% to 4%, respectively.

in patients with factor V Leiden, the increased risk of VTE is 2- to 7-fold in heterozygous individuals and up to 40-fold in those who are homozygous.

Clin Exp Emerg Med 2016

The most common **acquired risk factors** for VTE include:

- *increasing age*
- *venous insufficiency*
- *Obesity*
- *Smoking*
- *rheumatologic conditions*
- *cardiovascular disease*
- *previous VTE*
- *antiphospholipid antibody syndrome*

The mechanism behind **increasing age** appears to be that naturally circulating anticoagulants (protein C and protein S) decrease more than procoagulation factors over time, creating an increased prothrombotic state.

Obesity is a known risk factor for VTE,
among the most obese subjects (body mass index >35), there was a 6-fold increase in risk when compared to normal-weight subjects.

Clin Exp Emerg Med 2016

provoking factors include:

Cancer

exogenous hormone use (in particular, recent initiation of estrogen)

pregnancy/postpartum state

limb immobility

recent trauma or surgical procedure

indwelling catheters.

Cancer is considered a provoking factor because the risk of VTE is elevated in patients with active cancer, but a history of treated cancer in remission is not associated with increased VTE.

Exogenous hormone use has long been known to be associated with increased risk of VTE. In patients taking oral contraceptives there is a 3- to 4-fold increased risk of VTE, and those using “third-generation” progesterone formulations are especially at risk.

The **increased risk of VTE** during pregnancy starts in the first trimester and continues through the postpartum period, with the greatest risk during the first 2 weeks postpartum.

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INITIATING THE DIAGNOSTIC WORKUP: PRE-TEST PROBABILITY ASSESSMENT

Wells score for PE

Variable		Points
Previous PE or DVT		+1.5
Heart rate > 100 bpm		+1.5
Recent surgery or immobilization		+1.5
Clinical signs of DVT		+3
Hemoptysis		+1
Cancer		+1
Alternative diagnosis less likely than PE		+3
Probability of PE	**Score**	**Prevalence of PE**
Low	≤ 4	7.8%
High	> 6	61%

Clin Exp Emerg Med 2016

INITIATING THE DIAGNOSTIC WORKUP: PRE-TEST PROBABILITY ASSESSMENT

Revised Geneva score for PE

Variable		Points
Age > 65 yr		+1
Previous venous thromboembolism		+3
Surgery requiring anesthesia or fracture of lower limb in the past month		+2
Active malignancy		+2
Unilateral leg pain		+3
Hemoptysis		+2
Unilateral leg edema		+4
Heart rate 75-94 bpm		+3
Heart rate > 95 bpm		+5
Probability of PE	**Score**	**Prevalence of PE**
Low	≤ 3	8%
High	> 11	74%

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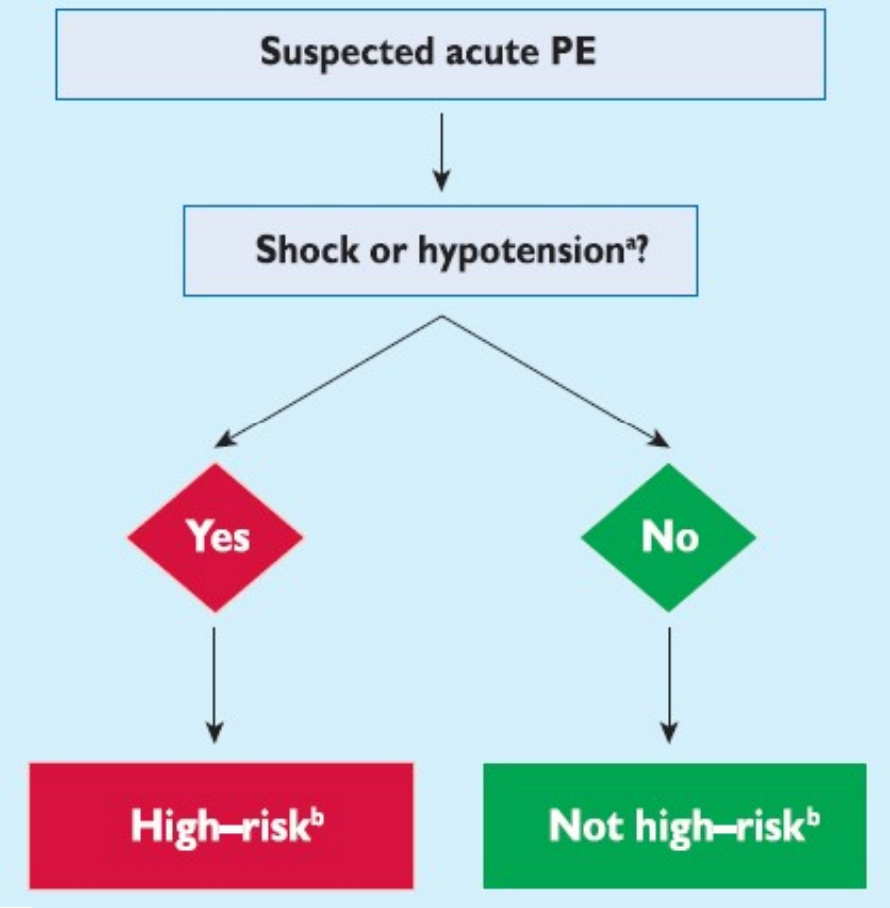
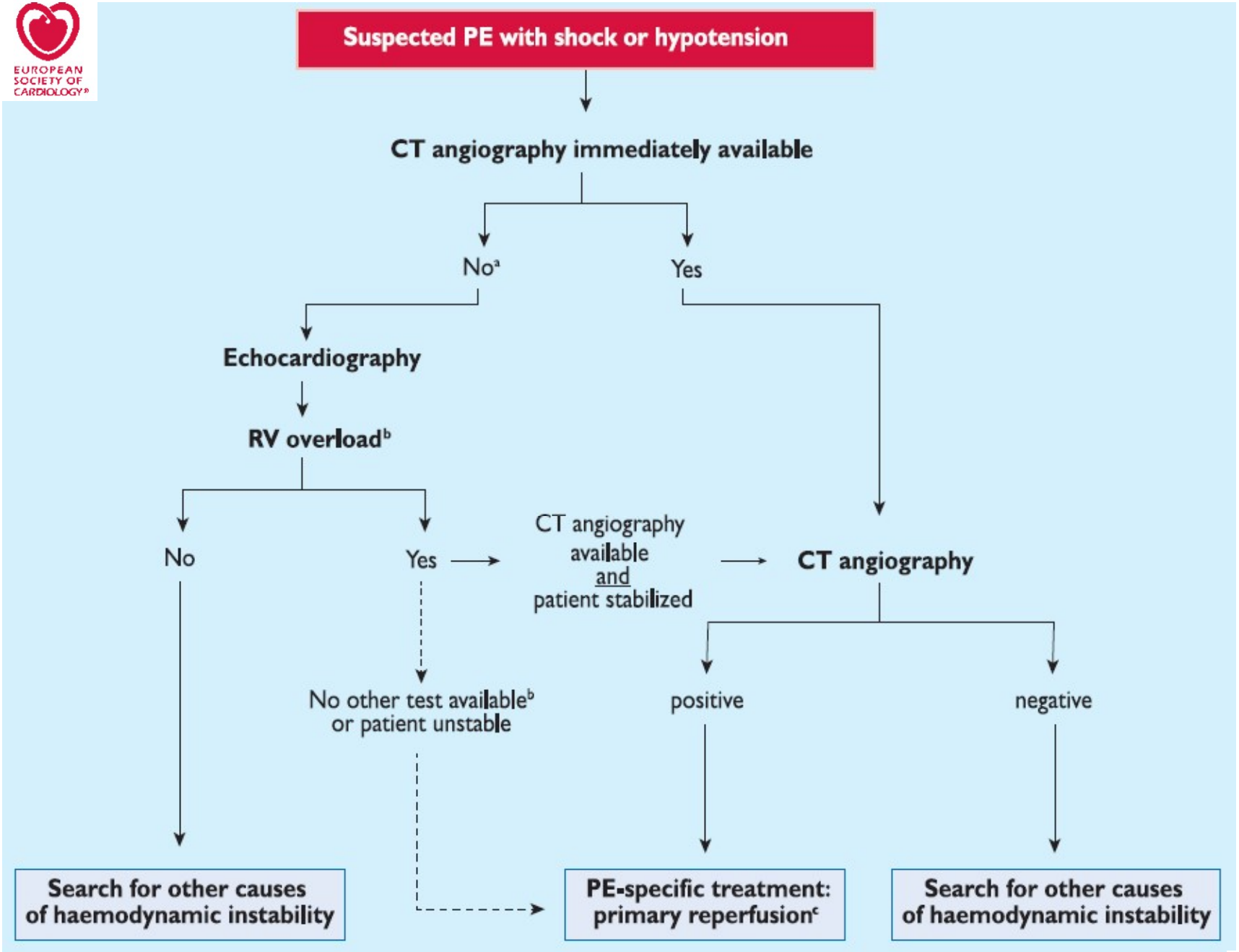
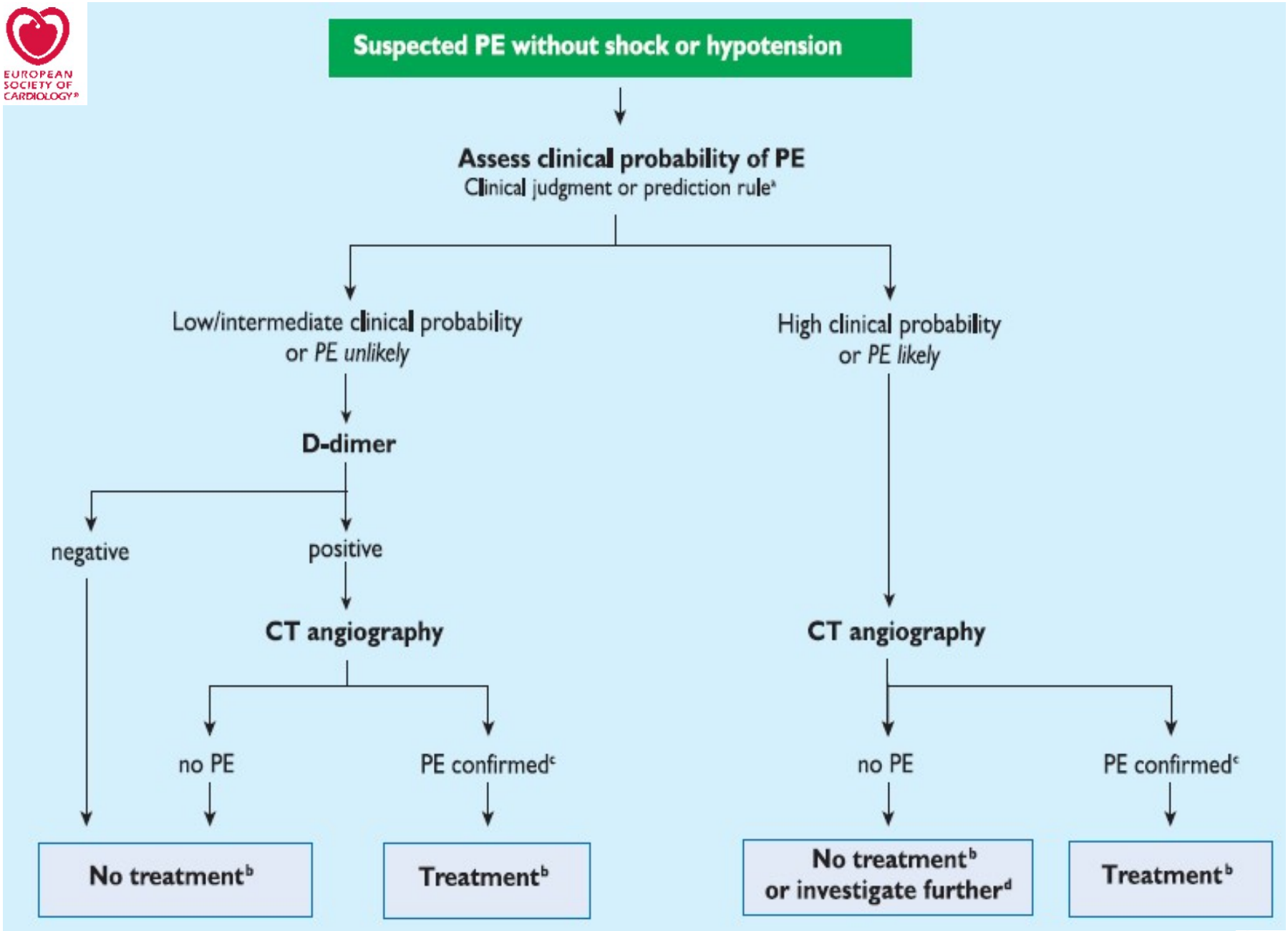
The clinical classification of the severity of an episode of acute PE is based on the estimated PE-related early mortality risk defined by in-hospital or 30-day mortality



European Heart Journal (2014)


Suspected PE with shock or hypotension
CT angiography immediately available
No[a]
Yes
Echocardiography
RV overload[b]
No
Yes
No other test available[b] or patient unstable
CT angiography available and patient stabilized
CT angiography
positive
negative
Search for other causes of haemodynamic instability
PE-specific treatment: primary reperfusion[c]
Search for other causes of haemodynamic instability


Suspected PE without shock or hypotension
Assess clinical probability of PE
Clinical judgment or prediction rule[a]
Low/intermediate clinical probability
or PE unlikely
High clinical probability
or PE likely
D-dimer
negative
positive
CT angiography
CT angiography
no PE
PE confirmed[c]
no PE
PE confirmed[c]
No treatment[b]
Treatment[b]
No treatment[b]
or investigate further[d]
Treatment[b]

D-dimer testing

D-dimer levels are elevated in plasma in the presence of acute thrombosis because of simultaneous activation of coagulation and fibrinolysis.

The negative predictive value of D-dimer testing is high and a normal D-dimer level renders acute PE or DVT unlikely.

On the other hand, fibrin is also produced in a wide variety of conditions such as

- Cancer
- Inflammation
- Trauma
- Surgery
- necrosis

The specificity of D-dimer in suspected PE decreases steadily with age, to almost 10% in patients 80 years. Recent evidence suggests using age-adjusted cut-offs to improve the performance of D-dimer testing in the elderly

J Thromb Haemost 2004;

Suspected PE without shock or hypotension

European Heart Journal (2014)

Plasma D-dimer measurement is recommended in outpatients/ emergency department patients with low or intermediate clinical probability, or PE-unlikely, to reduce the need for unnecessary imaging and irradiation, preferably using a highly sensitive assay.	I
In low clinical probability or PE-unlikely patients, normal D-dimer level using either a highly or moderately sensitive assay excludes PE.	I
Further testing may be considered in intermediate probability patients with a negative moderately sensitive assay.	IIb
D-dimer measurement is not recommended in patients with high clinical probability, as a normal result does not safely exclude PE, even when using a highly sensitive assay.	III

Computed tomographic pulmonary angiography

European Heart Journal (2014)

The **PIOPED II** trial observed a sensitivity of 83% and a specificity of 96% for MDCT

Stein PD N Engl J Med 2006

Whether patients with a negative CT and a high clinical probability should be further investigated is controversial.

MDCT showing PE at the segmental or more proximal level is adequate proof of PE in patients with a non-low clinical probability

The positive predictive value of MDCT is lower in patients with a low clinical probability of PE, and further testing may be considered, especially if the clots are limited to segmental or sub-segmental arteries.

Suspected PE without shock or hypotension

Normal CT angiography safely excludes PE in patients with low or intermediate clinical probability or PE-unlikely.	I	A
Normal CT angiography may safely exclude PE in patients with high clinical probability or PE-likely.	IIa	B
CT angiography showing a segmental or more proximal thrombus confirms PE.	I	B
Further testing to confirm PE may be considered in case of isolated sub-segmental clots.	IIb	C

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European Heart Journal (2014)

Lung scintigraphy

Ventilation–perfusion scintigraphy (V/Q scan) is an established diagnostic test for suspected PE. It is safe and few allergic reactions have been described.

Being a radiation- and contrast medium-sparing procedure, the V/Q scan may preferentially be applied in:

- outpatients with low clinical probability and a normal chest X-ray
- young (particularly female) patients
- pregnancy
- patients with history of contrast medium-induced anaphylaxis and strong allergic history
- severe renal failure
- patients with myeloma and paraproteinaemia

Reid JH, Eur J Nucl Med Mol Imaging 2009

Echocardiography

Acute PE may lead to RV pressure overload and dysfunction,which can be detected by echocardiography.

Given the peculiar geometry of the RV, there is no individual echocardiographic parameter that provides fast and reliable information on RV size or function. This is why echocardiographic criteria for the diagnosis of PE have differed between studies.

Because of the reported negative predictive value of 40–50%, a negative result cannot exclude PE.

On the other hand, signs of RV overload or dysfunction may also be found in the absence of acute PE and be due to concomitant cardiac or respiratory disease.

RV dilation is found in at least 25% of patients with PE, and its detection, either by echocardiography or CT**, is useful for risk stratification of the disease**

Compression venous ultrasonography

Positive and Negative Predictive Values of Venous Ultrasonography

	Sensitivity % (95% CI)	Specificity % (95% CI)	Positive likelihood ratio (95 % CI)
All patients	39 (32 to 46)	99 (97 to 100)	42 (13 to 132)
Patients without clinical symptoms of DVT	38 (21 to 36)	99 (97 to 100)	39 (12–130)
Patients with clinical symptoms of DVT	72 (58 to 83)	100 (83 to 100)	+ ∞

a positive proximal CUS result has a high positive predictive value for PE

Most proximal level of PE at MSCT	Proportion of patients with positive CUS
Multiple subsegmental	7.1% (1/14)
Segmental	14.6% (7/48)
Lobar	47.7% (31/65)
Main pulmonary arteries	56.7% (34/60)

Grégoire Le Gal. Thromb Haemost 2006

Suspected PE without shock or hypotension

Lower-limb CUS in search of DVT may be considered in selected patients with suspected PE, to obviate the need for further imaging tests if the result is positive.	IIb	B
CUS showing a proximal DVT in a patient with clinical suspicion of PE confirms PE.	I	B
If CUS shows only a distal DVT, further testing should be considered to confirm PE.	IIa	B

European Heart Journal (2014)

ECG

Sinus Tachycardia

The presence of sinus tachycardia on ECG in the setting of PE is worth two points in the Daniel et al. prognostic score, however there is mixed evidence regarding the prognostic role of sinus tachycardia in this setting

RBBB is an ECG sign of acute RV strain and dilation affects peripheral branches of the right bundle branch. The incidence of incomplete or complete RBBB in association with PE has been reported in many studies with a variable range from 6% to 69%n with some overall estimates closer to 25%. The presence of the RBBB pattern has been noted to be more frequent in cases of massive trunk obstruction than peripheral embolism

T-Wave Inversion in anterior Leads. TWI is a repolarization abnormality that has been frequently reported to be associated with PE . The pathophysiology of T-wave changes in the precordial leads is not well established, but is thought to be the consequence of an ischemic phenomenon due to low cardiac output in the context of RV dilation and strain. Presence of TWI in anterior leads has been reported with variable frequency from 16% to 68%

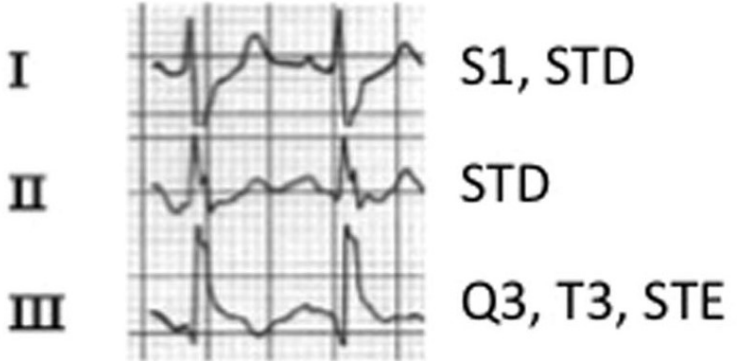
Ann Noninvasive Electrocardiol 2015

S1Q3T3 and S1Q3

Several studies have described the prevalence of the S1Q3T3 sign in PE, with variable rates from 11% to 52%.

it was recognized that the S1Q3T3 pattern was found more frequently in patients with severe PE presenting as syncope, with 47% of patients with syncope demonstrating the pattern compared to 8% of patients withoutsyncope ($P < 0.001$).

Is significantly more common in patients with elevated cardiac biomarkers (43% vs 21%, P=0.003) and is a predictor of mortality (58% dead vs 28% alive, P = 0.006



Ann Noninvasive Electrocardiol 2015

ST-Segment Depression(STD)

STD in leads V4– V6 was present in over 26% of all patients with acute PE

ST Elevation (STE)

Several patterns of STE have been described in terms of prognostic association with acute PE

STE of 1 mm or more in any lead except aVR has been reported in 16–48% of patients but has not been found to accurately prognosticate according to severity of PE on its own. STE in any lead also did not prognosticate for RV enlargement

Ann Noninvasive Electrocardiol 2015

Correlations between electrocardiogram and biomarkers in acute pulmonary embolism: Analysis of ZATPOL-2 Registry

Ann Noninvasive Electrocardiol. 2017

ECG

	Total	ECHO RVO (−)	ECHO RVO (+)	*p*
Sinus rhythm	408 (85.2%)	291 (88.2%)	117 (78.5%)	.009
AF[a]	78 (16.2%)	46 (13.9%)	32 (21.3%)	.057
Right axis deviation	51 (10.6%)	31 (9.4%)	20 (13.4%)	.245
Left axis deviation	164 (34.2%)	115 (34.8%)	49 (32.7%)	.716
$S_1Q_3T_3$ sign	106 (22.1%)	50 (15.2%)	56 (37.3%)	<.001
Incomplete RBBB	45 (9.4%)	26 (7.9%)	19 (12.7%)	.134
Complete RBBB	49 (10.3%)	29 (8.8%)	20 (13.4%)	.169
ST depression V_4–V_6	63 (13.2%)	39 (11.9%)	24 (16.0%)	.277
ST depression lead I	35 (7.3%)	19 (5.8%)	16 (10.7%)	.084
Negative T wave V_1–V_3	162 (33.8%)	94 (28.5%)	68 (45.3%)	<.001
Negative T wave V_4–V_6	104 (21.7%)	65 (19.8%)	39 (26.0%)	.156
Negative T wave II, III, aVF	109 (22.7%)	70 (21.2%)	39 (26.0%)	.297
ST elevation lead aVR	43 (9.0%)	25 (7.6%)	18 (12.0%)	.164
ST elevation lead III	28 (5.8%)	19 (5.8%)	9 (6.0%)	1.000
ST elevation lead V_1	24 (5.0%)	15 (4.6%)	9 (6.0%)	.645
Clockwise axis rotation	58 (12.2%)	40 (12.3%)	18 (12.2%)	1.000
Normal ECG	91 (19.0%)	79 (23.9%)	12 (8.0%)	<.001

Correlations between electrocardiogram and biomarkers in acute pulmonary embolism: Analysis of ZATPOL-2 Registry

Ann Noninvasive Electrocardiol. 2017

ECG

	Total	cTnT (−)	cTnT (+)	*p*
Sinus rhythm	396 (85.0%)	124 (91.9%)	272 (82.2%)	.012
AF[a]	77 (16.5%)	11 (8.1%)	66 (19.9%)	.003
Right axis deviation	48 (10.3%)	7 (5.2%)	41 (12.4%)	.031
Left axis deviation	161 (34.5%)	43 (31.9%)	118 (35.5%)	.514
$S_1Q_3T_3$ sign	105 (22.5%)	13 (9.6%)	92 (27.7%)	<.001
Incomplete RBBB	44 (9.4%)	10 (7.4%)	34 (10.2%)	.438
Complete RBBB	47 (10.1%)	5 (3.7%)	42 (12.7%)	.006
ST depression V_4–V_6	62 (13.3%)	8 (6.0%)	54 (16.3%)	.005
ST depression lead I	34 (7.3%)	4 (3.0%)	30 (9.0%)	.036
Negative T wave V_1–V_3	159 (34.0%)	23 (17.0%)	136 (41.0%)	<.001
Negative T wave V_4–V_6	100 (21.5%)	18 (13.3%)	82 (24.8%)	.009
Negative T wave II, III, aVF	108 (23.1%)	21 (15.6%)	87 (26.2%)	.019
ST elevation lead aVR	43 (9.2%)	4 (3.0%)	39 (11.7%)	.005
ST elevation lead III	28 (6.0%)	3 (2.2%)	25 (7.6%)	.048
ST elevation lead V_1	23 (4.9%)	3 (2.2%)	20 (6.0%)	.140
Clockwise axis rotation	57 (12.4%)	10 (7.5%)	47 (14.4%)	.059
Normal ECG	88 (18.8%)	53 (39.3%)	35 (10.5%)	<.001

Prognostic assessment

Various prediction rules based on clinical parameters have been shown to be helpful in the prognostic assessment of patients with acute PE. Of those, **the pulmonary embolism severity index (PESI)** is the most extensively validated score to date.

Parameter	Original version[214]	Simplified version[218]
Age	Age in years	1 point (if age >80 years)
Male sex	+10 points	–
Cancer	+30 points	1 point
Chronic heart failure	+10 points	1 point
Chronic pulmonary disease	+10 points	
Pulse rate ≥110 b.p.m.	+20 points	1 point
Systolic blood pressure <100 mm Hg	+30 points	1 point
Respiratory rate >30 breaths per minute	+20 points	–
Temperature <36 °C	+20 points	–
Altered mental status	+60 points	–
Arterial oxyhaemoglobin saturation <90%	+20 points	1 point

pulmonary embolism severity index

0riginal version	Simplified vesion
Risk strata[a]	
Class I:≤65 points very low 30-day mortality risk (0–1.6%) **Class II: 66–85 points** low mortality risk (1.7–3.5%)	**0 points**= 30-day mortality risk 1.0% (95% CI 0.0%–2.1%)
Class III: 86–105 points moderate mortality risk (3.2–7.1%) **Class IV: 106–125 points** high mortality risk (4.0–11.4%) **Class V: >125 points** very high mortality risk (10.0–24.5%)	**≥1 point(s)**= 30-day mortality risk 10.9% (95% CI 8.5%–13.2%)

Prognostic assessment

A meta-analysis found that 51% of 1132 unselected patients with acute PE had **elevated BNP or NT-proBNP** concentrations on admission. These patients had a 10% risk of early death (95% CI 8.0–13) and a 23% risk of an adverse clinical outcome

Elevated **plasma troponin** concentrations on admission have been reported in connection with PE and were associated with worse prognosis

The reported positive predictive value of troponin elevation for PE-related early mortality ranges from 12–44%

Elevated **serum creatinine** levels and a decreased (calculated) glomerular filtration rate are related to 30-day all-cause mortality inacute PE.
Elevated neutrophil gelatinase-associated lipocalin (NGAL) and cystatin C, both indicating acute kidney injury, have also been found to be of prognostic value

Treatment in the acute phase

Aggressive **volume expansion** is of no benefit and may even worsen RV function by causing mechanical overstretch,
On the other hand, modest (500 mL) fluid challenge may help to increase cardiac index in patients with PE, low cardiac index, and normal BP

Use of **vasopressors** is often necessary, in parallel with (or while waiting for) pharmacological, surgical, or interventional reperfusion treatment.
Norepinephrine appears to improve RV function via a direct positive inotropic effect, while also improving RV coronary perfusion by peripheral vascular alpha-receptor stimulation and the increase in systemic BP.
Its use should probably be limited to hypotensive patients.

Based on the results of small series, the use of **dobutamine and/or dopamine** may be considered for patients with PE, low cardiac index, and normal BP

Treatment in the acute phase

Vasodilators decrease pulmonary arterial pressure and pulmonary vascular resistance, but the main concern is the lack of specificity of these drugs for the pulmonary vasculature after systemic (intravenous) administration

Hypoxaemia and hypocapnia are frequently encountered in patients with PE, but they are of moderate severity in most cases. A patent foramen ovale may aggravate hypoxaemia due to shunting when right atrial- exceeds left atrial pressure.

Treatment in the acute phase

PE with shock or hypotension (high-risk)		
It is recommended that intravenous anticoagulation with UFH be initiated without delay in patients with high-risk PE.	I	C
Thrombolytic therapy is recommended.	I	B
Surgical pulmonary embolectomy is recommended for patients in whom thrombolysis is contraindicated or has failed.[d]	I	C
Percutaneous catheter-directed treatment should be considered as an alternative to surgical pulmonary embolectomy for patients in whom full-dose systemic thrombolysis is contraindicated or has failed.[d]	IIa	C

Treatment in the acute phase

PE without shock or hypotension (intermediate-or low-risk)		
Initiation of parenteral anticoagulation is recommended without delay in patients with high or intermediate clinical probability of PE while diagnostic work-up is in progress.	I	C
LMWH or fondaparinux is the recommended form of acute phase parenteral anticoagulation for most patients.	I	A
In parallel to parenteral anticoagulation, treatment with a VKA is recommended, targeting an INR of 2.5 (range 2.0–3.0).	I	B

Treatment in the acute phase

Anticoagulation: new oral anticoagulants

Rivaroxaban Dabigratan Apixaban Edoxaban	I	B

New oral anticoagulants (rivaroxaban, apixaban, dabigatran, edoxaban) are not recommended in patients with severe renal impairment.[f]	III	A

Treatment in the acute phase

Reperfusion treatment		
Routine use of primary systemic thrombolysis is not recommended in patients not suffering from shock or hypotension.	III	B
Close monitoring is recommended in patients with intermediate-high risk PE to permit early detection of haemodynamic decompensation and timely initiation of 'rescue' reperfusion therapy.	I	B
Thrombolytic therapy should be considered for patients with intermediate-high-risk PE and clinical signs of haemodynamic decompensation.	IIa	B

Non-thrombotic pulmonary embolism

Different cell types can cause non-thrombotic embolization, including adipocytes, 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.

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

- intravenous drug abuse
- infected indwelling catheters or pacemaker wires.
- septic thrombophlebitis from the tonsils and the jugular, dental, and pelvic regions.

Non-thrombotic pulmonary embolism

Foreign-material pulmonary embolism

Examples of foreign material include

- Silicone
- broken catheters
- guide wires
- vena cava filters
- coils for embolization
- and endovascular stent components

If possible, intravascular foreign objects should be removed, since the material may cause further thrombosis and sepsis

Fat embolism

Embolization of fat occurs in almost all patients with

- pelvic or longbone fractures
- in those undergoing endomedullary nailing or placement of knee and hip prostheses during lipid and propofol infusion
- intra-osseous infusion and bone marrow harvest
- 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, thus explaining why some patients with fat embolism develop acute respiratory distress syndrome.

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 is estimated to range from 100 to 500 mL.

Amniotic fluid embolism

is a rare but catastrophic complication unique to pregnancy.
Estimated incidences range between 1.9 and 2.5 cases per 100 000 maternities.
The most likely mechanism is that amniotic fluid is forced into the uterine veins during normal labouror when the placenta is disrupted by surgery or trauma.

Mortality is high—up to 21%,

Tumour embolism

Pulmonary intravascular tumour emboli are seen in up to 26% of autopsies
of patients with solid malignancies, although the diagnosis is rarely made before death.
Carcinoma

- prostate
- Gland
- Digestive system
- Liver
- breast

are most commonly implicated.