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EGYPTIAN SOCIETY OF CARDIOLOGY

Acute pulmonary embolism

A case-based concept learning

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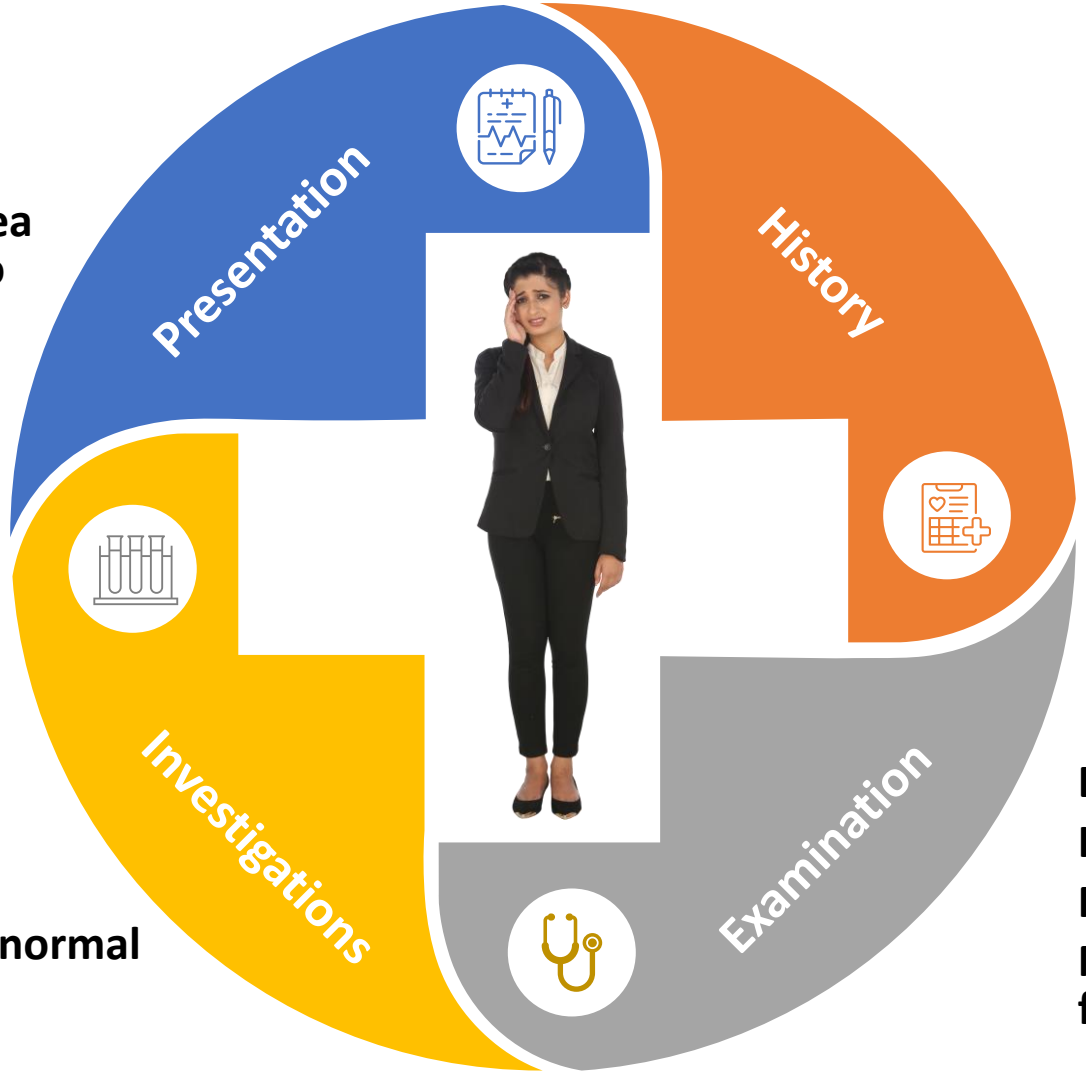
Scan Me

Clinical data – Mrs. Hala

35-years old female

Recurrent attacks of dyspnea & palpitations few days ago



No significant past medical or surgical history except for oral contraceptives 4 years ago

ECG: Sinus tachycardia

Echo: normal

CBC, TSH, electrolytes are normal

BP 110/70 mmHg

HR 100 bpm & regular

PO_2 sat= 96%

No other positive examination findings

Question #1

Best next step for management is…?

a) CT pulmonary angiography (CTPA)

b) Assessment of the pre-test likelihood of pulmonary embolism (PE)

c) Assurance and discharge

The revised Geneva clinical prediction rule for PE

Items	Clinical decision rule points	
	Original version[91]	Simplified version[87]
Previous PE or DVT	3	1
Heart rate		
75–94 b.p.m.	3	1
≥95 b.p.m.	5	2
Surgery or fracture within the past month	2	1
Haemoptysis	2	1
Active cancer	2	1
Unilateral lower-limb pain	3	1
Pain on lower-limb deep venous palpation and unilateral oedema	4	1
Age >65 years	1	1
Clinical probability		
Three-level score		
Low	0–3	0–1
Intermediate	4–10	2–4
High	≥11	≥5
Two-level score		
PE-unlikely	0–5	0–2
PE-likely	≥6	≥3

b.p.m. = beats per minute; DVT = deep vein thrombosis; PE = pulmonary embolism.

Konstantinides, Stavros V., et al. "2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS) The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC)." European heart journal 41.4 (2020): 543-603.

Question #1

Best next step for management is…?

a) CT pulmonary angiography (CTPA)

b) Assessment of the pre-test likelihood of pulmonary embolism (PE)

c) Assurance and discharge

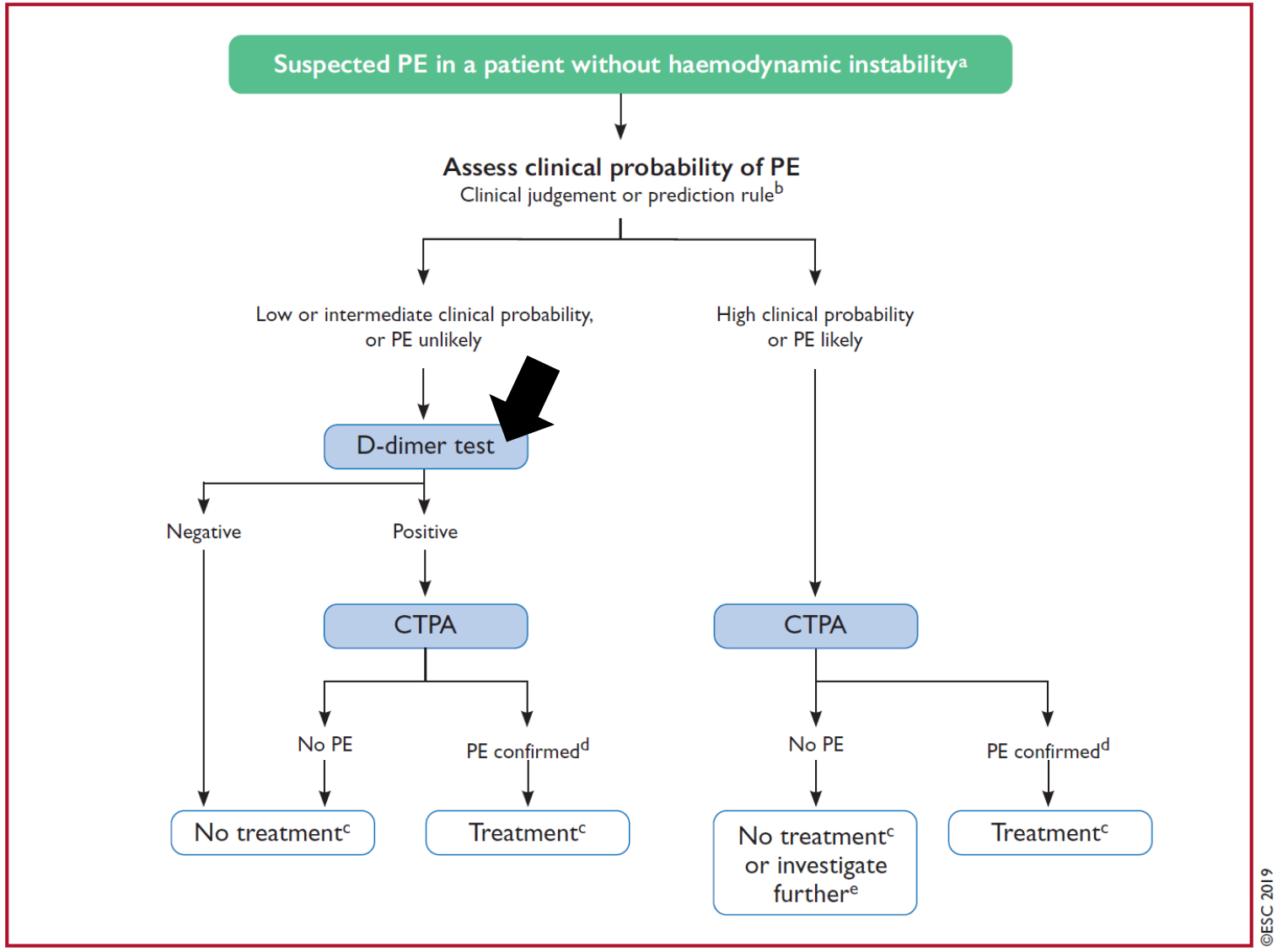
Question #2

The patient was found to be PE unlikely, should we stop?

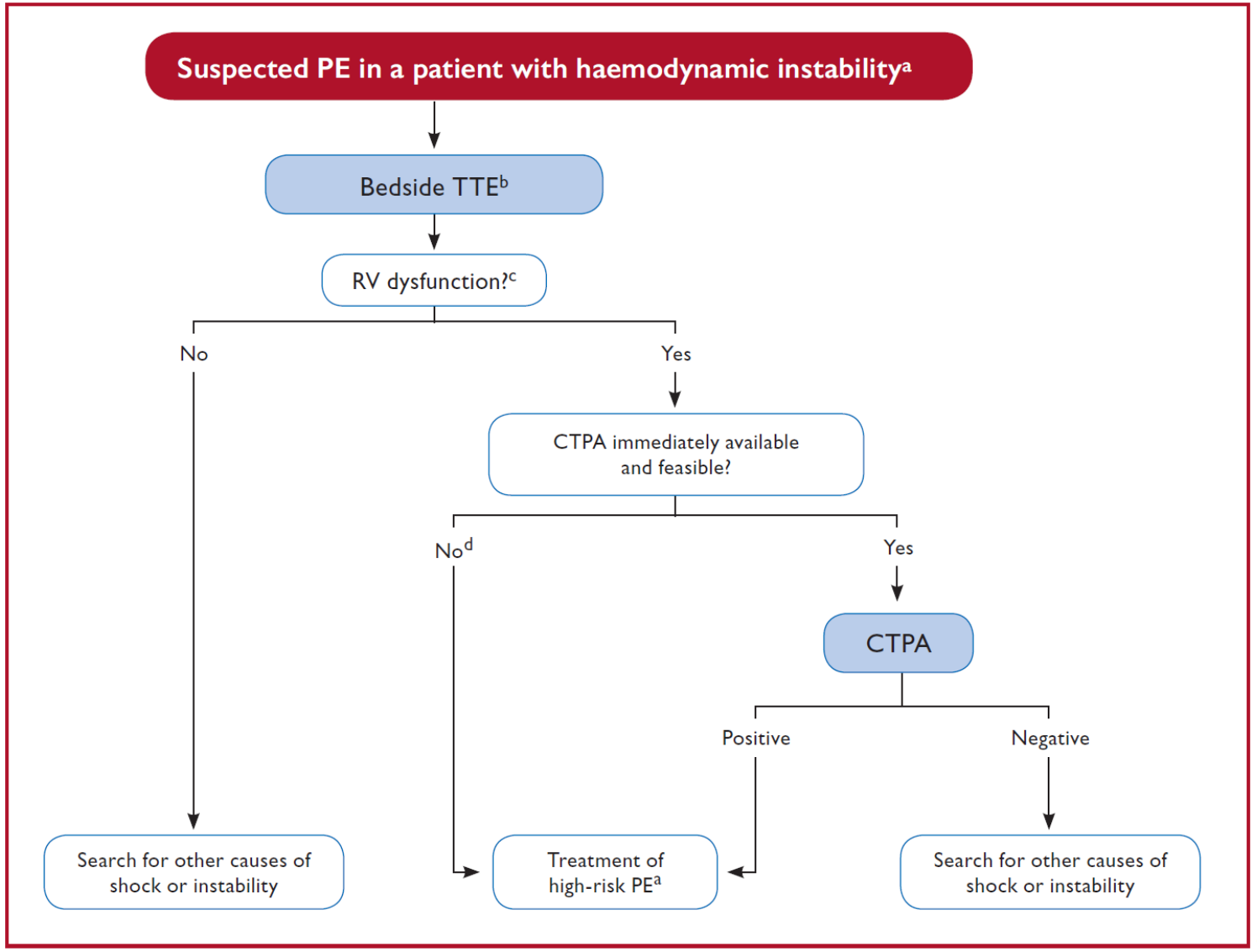
a) No, further testing is required!

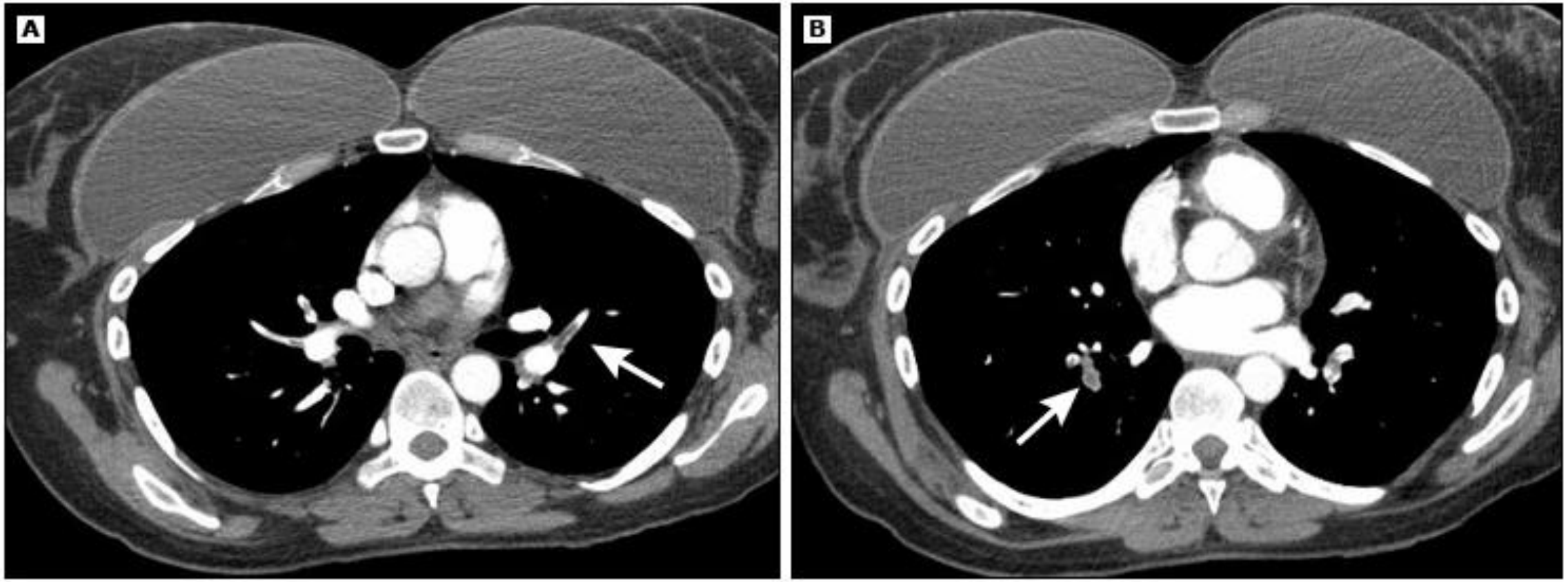
b) Yes, assurance and discharge.

Diagnosis of PE in patients without hemodynamic instability



Diagnosis of PE in patients with hemodynamic instability





The patient’s CTPA after a highly +ve D-Dimer test

Question #2

The patient was found to be PE unlikely, should we stop?

a) **No, further testing is required!**

b) Yes, assurance and discharge.

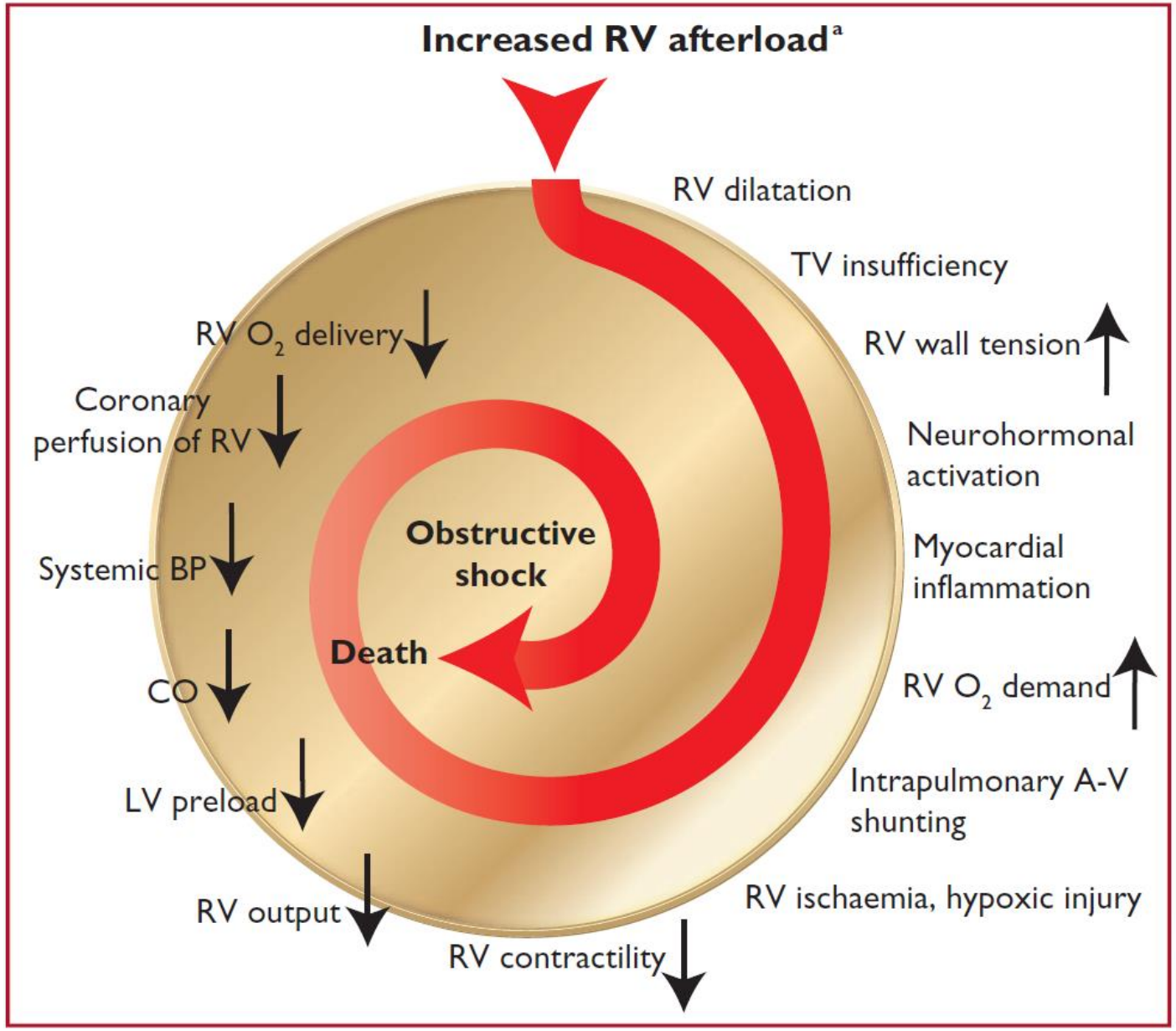
Question #3

Is this a low or a high-risk PE?

a) A high-risk patient of course

b) This is a low-risk PE patient!

How one dies from PE?



How can we define “high-risk” PE?

(1) Cardiac arrest	(2) Obstructive shock[68–70]	(3) Persistent hypotension
Need for cardiopulmonary resuscitation	Systolic BP < 90 mmHg or vasopressors required to achieve a BP ≥90 mmHg despite adequate filling status	Systolic BP < 90 mmHg or systolic BP drop ≥40 mmHg, lasting longer than 15 min and not caused by new-onset arrhythmia, hypovolaemia, or sepsis
	And	
	End-organ hypoperfusion (altered mental status; cold, clammy skin; oliguria/anuria; increased serum lactate)	

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Original and simplified Pulmonary Embolism Severity (PESI) Index

Parameter	Original version[226]	Simplified version[229]
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 BP <100 mmHg	+30 points	1 point
Respiratory rate >30 breaths per min	+20 points	–
Temperature <36°C	+20 points	–
Altered mental status	+60 points	–
Arterial oxyhaemoglobin saturation <90%	+20 points	1 point

	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%)

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Question #3

Is this a low or a high-risk PE?

a) A high-risk patient of course

b) **This is a low-risk PE patient!**

Question #4

Which anti-coagulants is the best for this patient?

a) LMWHs together with Warfarin (target INR 2-3)

b) DOACs if available would be a better option.

c) Thrombolytic therapy is indicated.

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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

European Heart Journal (2020) 41, 543-603
doi:10.1093/eurheartj/ehz405

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

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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

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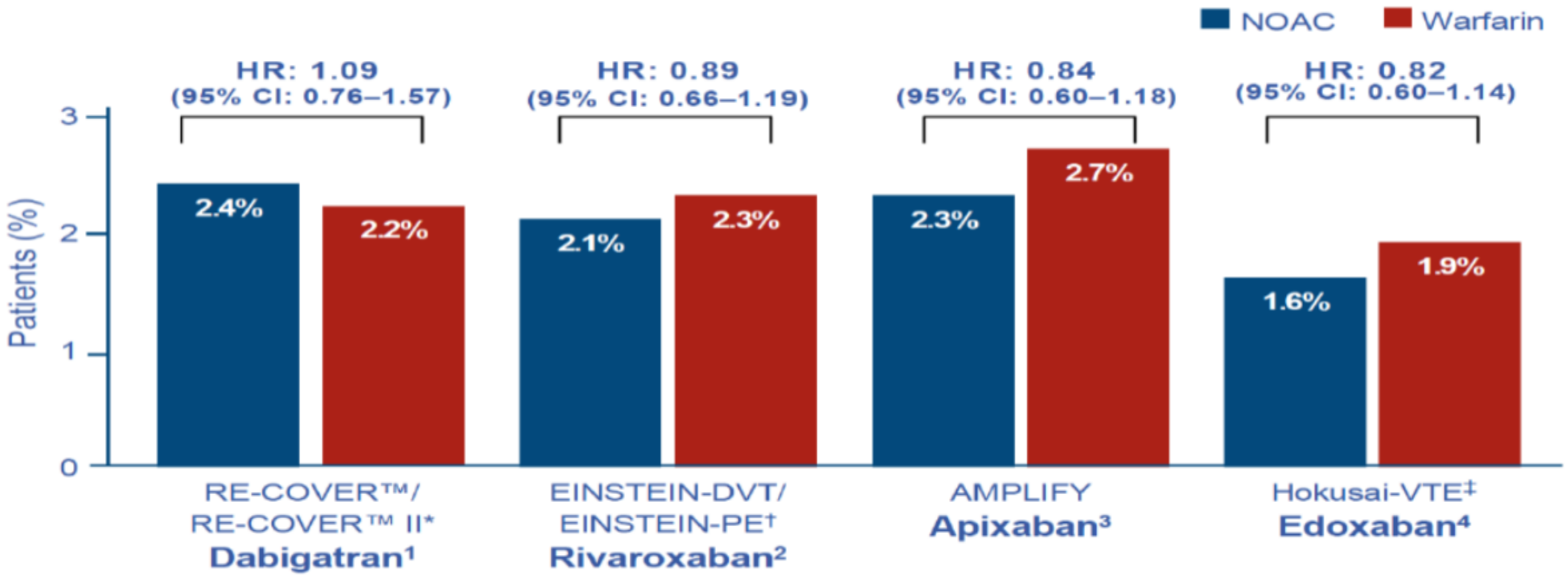
Recommendations for acute-phase treatment of intermediate- or low-risk pulmonary embolism

European Heart Journal (2020) 41, 543-603
doi:10.1093/eurheartj/ehz405

Treatment of acute DVT/PE: NOACs non-inferior to warfarin for prevention of recurrent DVT/PE in Phase III trials

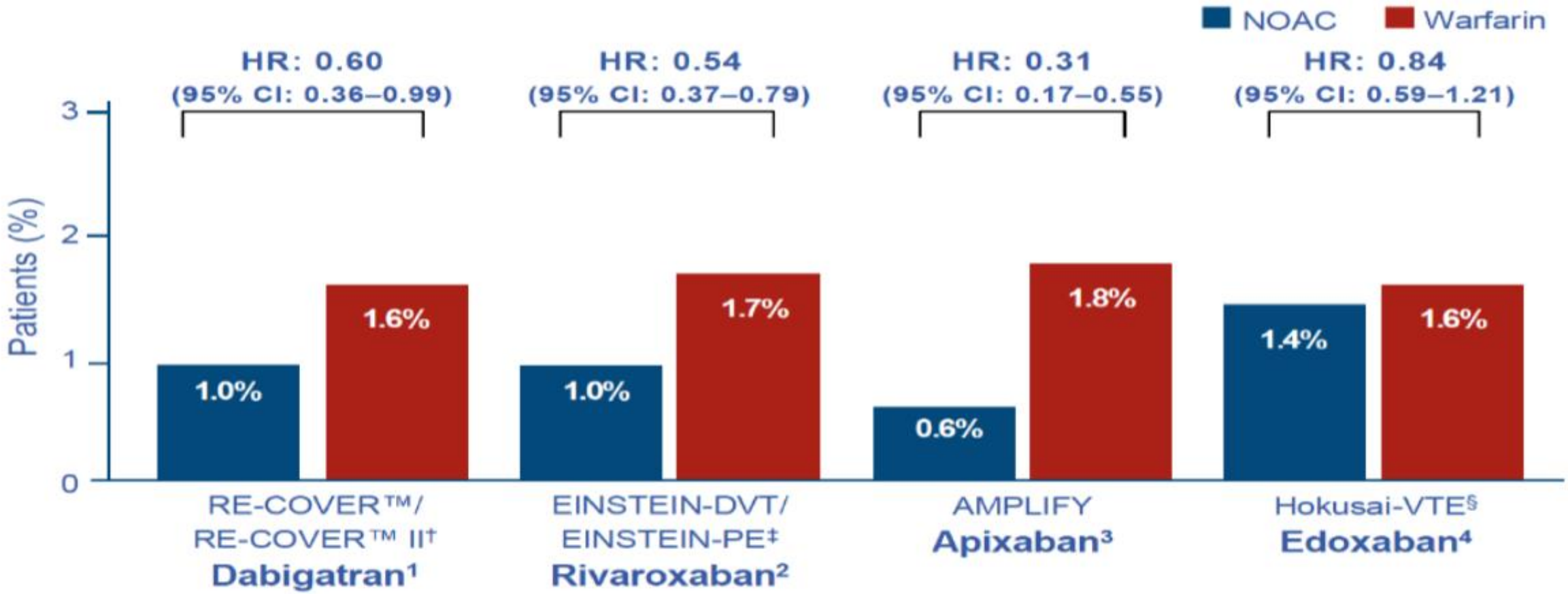


Direct comparisons cannot be made as no head-to-head data are available

*Pooled data from RE-COVER™ and RE-COVER™ II; †Pooled analysis; ‡On treatment

1. Schulman S et al. Circulation 2014;129:764–72; **2.** Prins MH et al. Thromb J 2013;11:21; **3.** Agnelli G et al. N Engl J Med 2013;369:799–808; **4.** The Hokusai-VTE Investigators. N Engl J Med 2013;369:1406–15

Treatment of acute DVT/PE: NOACs associated with less major bleeding than warfarin in Phase III trials*



Direct comparisons cannot be made as no head-to-head data are available

*Statistically significant reductions for dabigatran, rivaroxaban, and apixaban vs warfarin, numerical reduction for edoxaban vs warfarin; †Pooled data from RE-COVER™ and RE-COVER™ II; oral drug treatment period only; ‡Pooled analysis; §On treatment

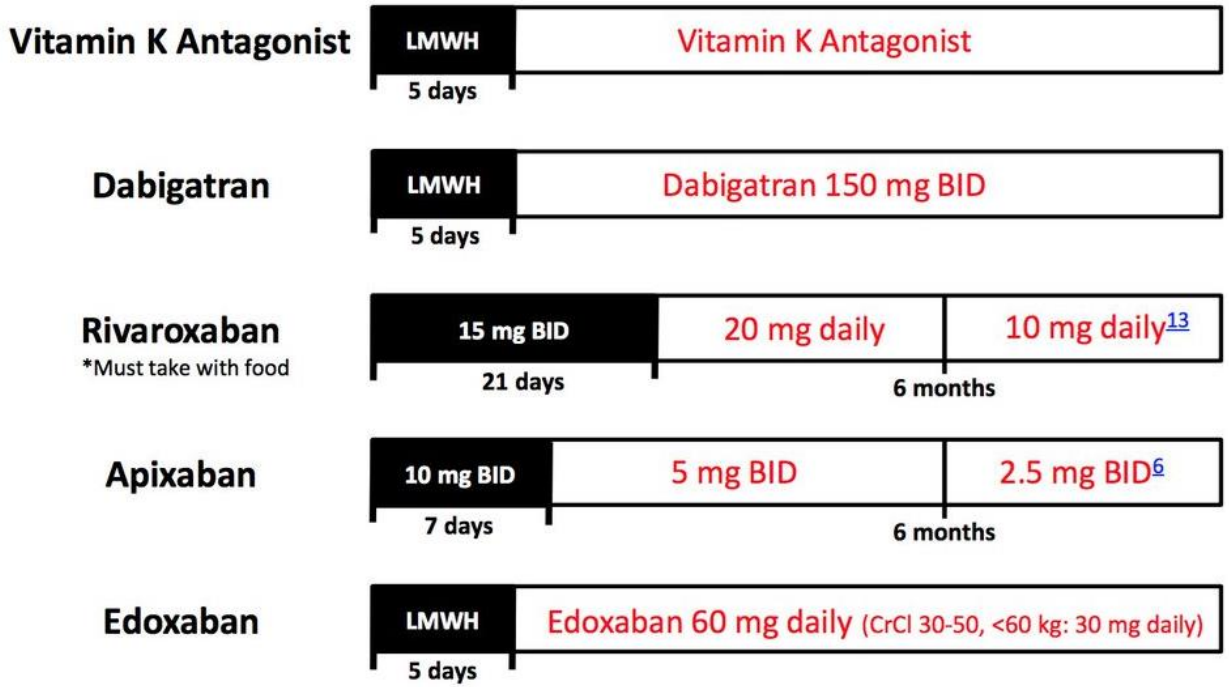
1. Schulman S et al. Circulation 2014;129:764–72; **2.** Prins MH et al. Thromb J 2013;11:21; **3.** Agnelli G et al. N Engl J Med 2013;369:799–808; **4.** The Hokusai-VTE Investigators. N Engl J Med 2013;369:1406–15

Pharmacological properties of oral anticoagulants

	VKA	Dabigatran etexilate	Apixaban	Edoxaban	Rivaroxaban
Target	Vitamin K dependent clotting factors (II, VII, IX, X)	Thrombin (IIa)	Factor Xa	Factor Xa	Factor Xa
Prodrug	No	Yes	No	No	No
Dosing	o.d. (INR adjusted)	b.d.	10 mg b.d. for first 7 d followed by 5 mg b.d.	60 mg o.d.	15 mg b.d. for inital three w, followed by 20 mg o.d.
Reduced dosing for extended therapy	NA	NA	2.5 mg b.d. after six mo	NA	10 mg o.d. after six mo
Bioavailability – %	100	≈6	50	60	80–100*
Time to peak – h	1.5	1.5–3.0	1.5–3.5	1–2	2–4
Half life – h	36–42	12–17	12–15	10–14	5–13
Renal elimination – %	Negligible	80	≈ 27	≈50	≈ 35
Plasma protein binding – %	99	35	87	55	95
Drug–drug interactions	Multiple	P-gp inhibitors	CYP3A4 and P-gp inhibitors	P-gp inhibitors	CYP3A4 and P-gp inhibitors
Routine coagulation monitoring	Yes	No	No	No	No

* Bioavailability of rivaroxaban calculated for 10 mg dose.

Regimens of VKA and different NOACS in PE



- Patients with CrCl <30 mL/min, obesity with BMI >40 or >120 kg, and advanced age were **excluded** from major clinical trials
- Unlike in atrial fibrillation, FDA labels make no recommendations for DOAC dose-reductions for VTE treatment with any of the above patient characteristics. **Use caution in these settings, consider measuring drug levels, and consult hematology for assistance.**

Question #4

Which anti-coagulants is the best for this patient?

a) LMWHs together with Warfarin (target INR 2-3)

b) **DOACs if available would be a better option.**

c) Thrombolytic therapy is indicated.


For how long should we anti-coagulate?

Duration of anticoagulation

High risk: anticoagulation should not be stopped unless there is a strong contraindication. **Intermediate risk**: further factors should be considered, including specific risk factors for thrombosis, bleeding risk and patient preference. **Low risk**: anticoagulation can be stopped after three or a maximum of six months

Risk of recurrence	Duration of anticoagulation	Underlying risk factors
High	Indefinite anticoagulation, unless there is a high risk of bleeding	Active cancer, persistent major risk factor, e.g., chronic rheumatic disorder, severe thrombophilia*
Medium	Equipoise: consider extended anticoagulation, preferably with lowest bleeding risk	Recurrent venous thromboembolism
		Unprovoked event
		Minor, soft, and transient risk factor, e.g., travel
		Male sex, obesity, heart failure, chronic obstructive pulmonary disease/significant comorbidities
		Pulmonary embolism (more likely to continue) *vs.* deep vein thrombosis
Low	Stop anticoagulation (3 mo)	Clear and major transient risk factor (e.g., surgery, leg injury with a reduced mobility, confined to bed in hospital)
		Combined oral contraceptives or hormonal therapy – now discontinued; pregnancy†, puerperium
		Calf vein thrombosis

* Severe thrombophilia = antithrombin deficiency, antiphospholipid syndrome, homozygous FV Leiden or prothrombin 20210 mutation, combination thrombophilia. Definitions modified from Kearon *et al.*, 2016,[44] and Prins *et al.*, 2018.[122]

† Treatment should continue for three months and at least until the end of puerperium (6 weeks post partum).

Thrombophilias

Thrombophilia deficiency/ mutation	Prevalence in the general population – %	Prevalence in patients with VTE – %	Relative risk of first VTE *vs.* community controls
Heterozygous AT	0.02	1	10–30
Heterozygous PC	0.2–0.5	1–3	10
Homozygous PC			Very high risk
Heterozygous PS	0.1–0.7	1–2	8
Homozygous PS			Very high risk
FV Leiden heterozygous	2–15	10–20	3–7
FV Leiden homozygous	0.06–0.25	–	80
FII G20210A heterozygous	1–2	3–5	3–7
FII G20210A homozygous	Rare	Rare	10–20
Combined heterozygous in FV Leiden and FII G20210A or other genetic risk factor (two or more defects)	Rare	Rare	10–20
FVIII > 150%	11	25	2
MTHFR polymorphisms with hyperhomocysteinaemia	5	10	1.5
Antiphospholipid syndrome	2	4–15	7–10
JAK2 mutation	0.1–0.2	3.2 (mainly with splanchnic vein thrombosis)	2–3
Dysfibrinogenaemia	Rare	Rare	5–7
PNH	1–9/100 000	Rare	3–5

Question #5

The patient asked if she could be treated at home. The senior consultant ordered discharge of the patient from the hospital after 2 days! Do you agree with him?

a) Yes.

b) No.

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European Heart Journal (2020) **41**, 543–603
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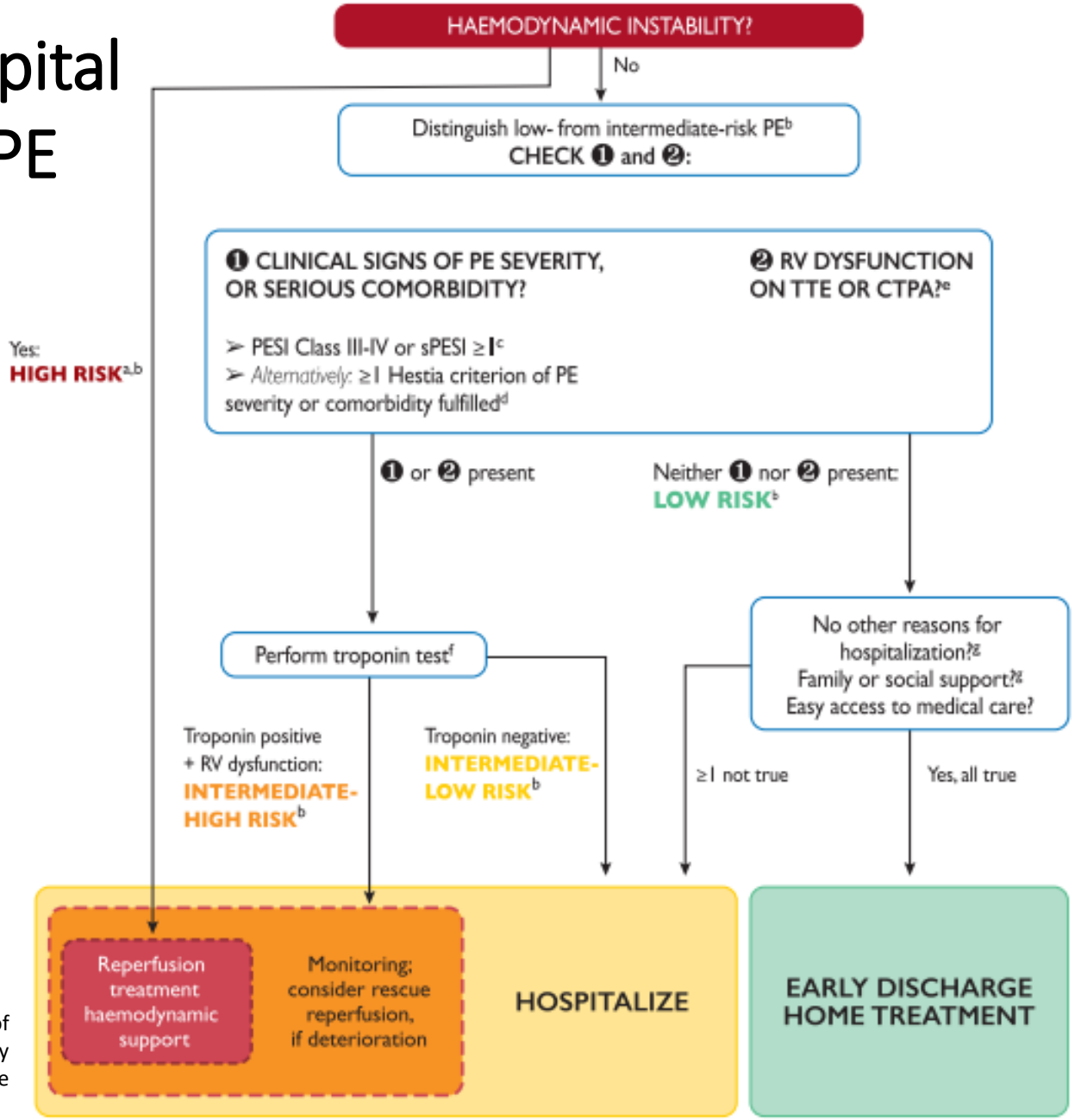
ESC GUIDELINES

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

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]	IIa	A

Algorithm for deciding on hospital discharge for patients with PE



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Question #5

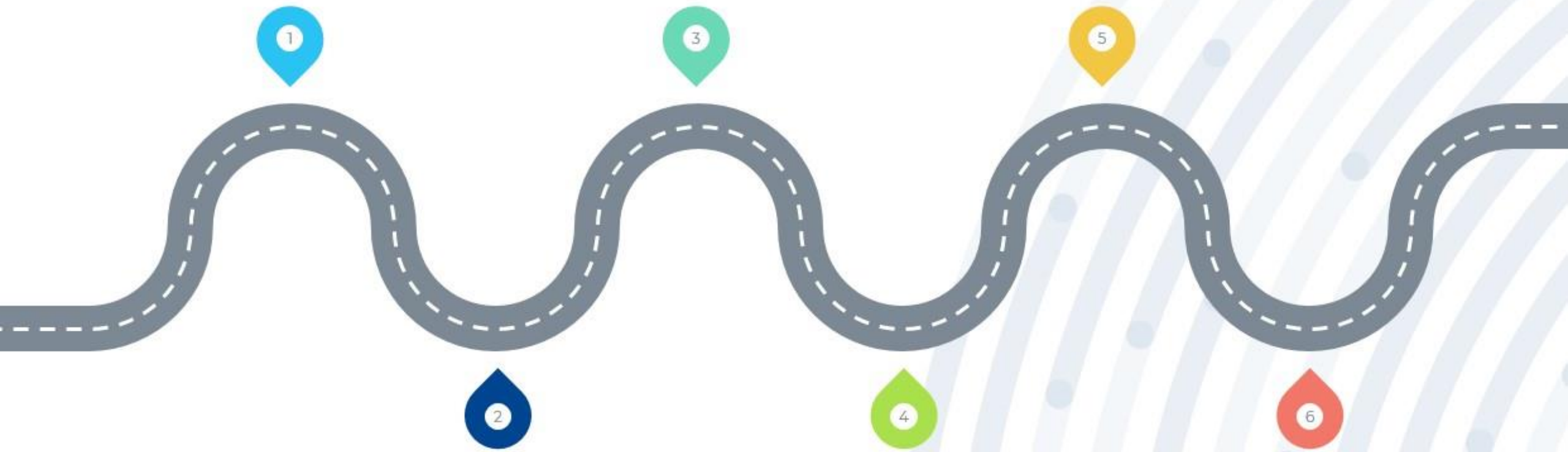
The patient asked if she could be treated at home. The senior consultant ordered discharge of the patient from the hospital after 2 days! Do you agree with him?

a) **Yes.**

b) No.

What about cancer-associated thrombosis (CAT)?

Trial Roadmap (CAT)



Cancer-associated thrombosis (CAT)

For patients with cancer associated deep vein thrombosis, a low molecular weight heparin is recommended for initial and principal phase anticoagulation.

Class	Level	Reference
I	A	Kirkilesis *et al.* (2019)[365]

For patients with active cancer associated deep vein thrombosis, switching from a low molecular weight heparin to an oral anticoagulant is recommended after three to six months of treatment for extended treatment.

Class	Level	Reference
I	C	Consensus

In selected patients with cancer associated deep vein thrombosis, with the malignancy not located in the gastrointestinal or genitourinary systems, an approved direct oral anticoagulant for initial, principal, and extended treatment should be considered.

Class	Level	References
IIa	A	Posch *et al.* (2015),[364] Kirkilesis *et al.* (2019),[365] Kraaijpoel *et al.* (2018),[367] McBane *et al.* (2020),[369] Agnelli *et al.* (2020)[370]

CHEST

Antithrombotic Therapy for VTE Disease

Second Update of the CHEST Guideline and Expert Panel Report

16. In patients with acute VTE in the setting of cancer (cancer-associated thrombosis) we recommend an oral Xa inhibitor (apixaban, edoxaban, rivaroxaban) over low molecular weight heparin (LMWH) for the initiation and treatment phases of therapy (strong recommendation, moderate-certainty evidence).

Remark: Edoxaban and rivaroxaban appear to be associated with a higher risk of GI major bleeding than LMWH in patients with cancer-associated thrombosis (CAT) and a luminal GI malignancy, while apixaban does not. Apixaban or LMWH may be the preferred option in patients with luminal GI malignancies.

CHEST 2021; 160(6):e545-e608


Thank you!