Understanding thrombosis in venous thromboembolism

João Morais

Head of Cardiology Division and Research Centre

Leiria Hospital Centre

Portugal

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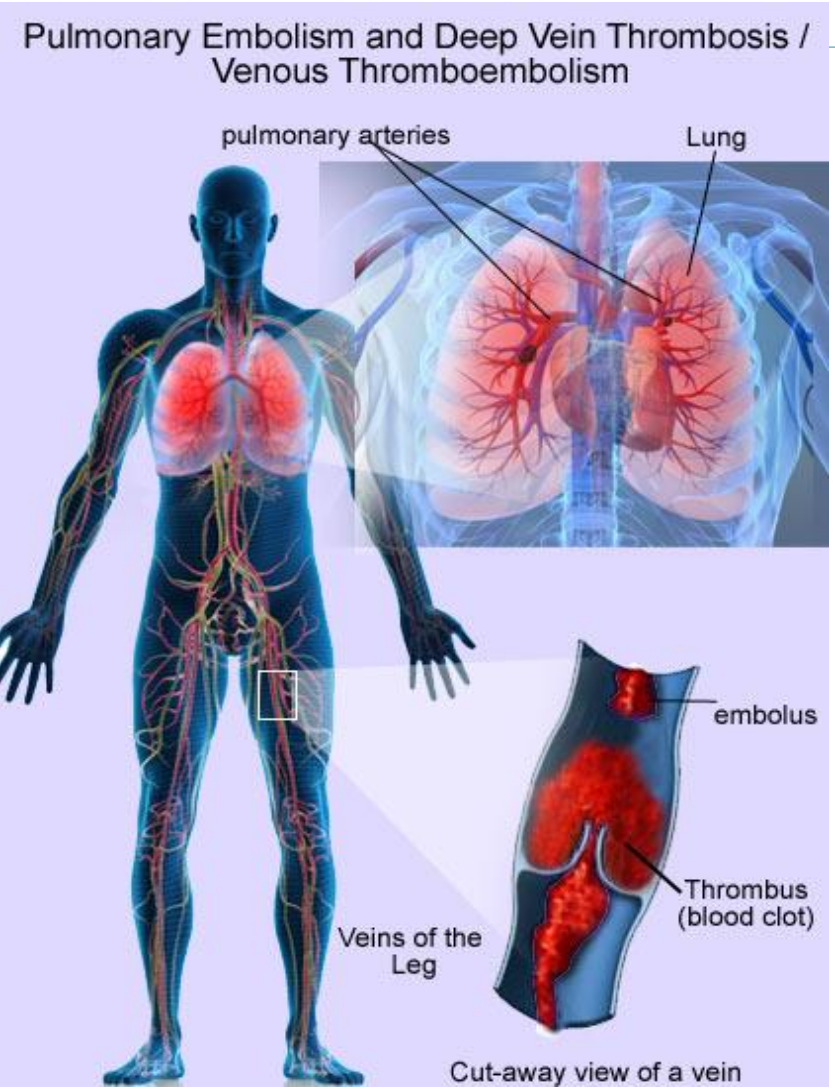
Disclosures

João Morais

On the last year JM received honoraria for consultant activities and invited speaker for pharmaceutical and device's companies

- Astra Zeneca
- Bayer Healthcare
- BMS / Pfizer
- Boehringher Ingelheim
- Boston Scientific
- Daiichi Sankyo
- Merck Sharp and Dhome

Background



Venous thrombosis

Yearly incidence
1/1000 person-years

1/3 of DVT complicate with a clot in the lungs

Recurrence at 5 years - 28%

Case-fatality rate (recurrence) 3% - 6%

Habson PO et al. Arch Intern Med 2000;160:769
Carrier M et al. Ann Intern Med 2010;152:578

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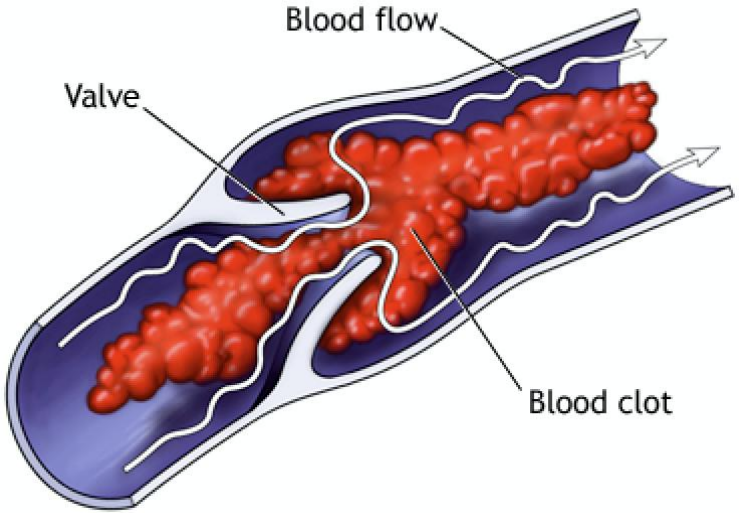
DVT by the numbers

96% arise in the **lower extremities**

4% arise in the **upper extremities**.

Chest 2008 Jan;133(1):143-8



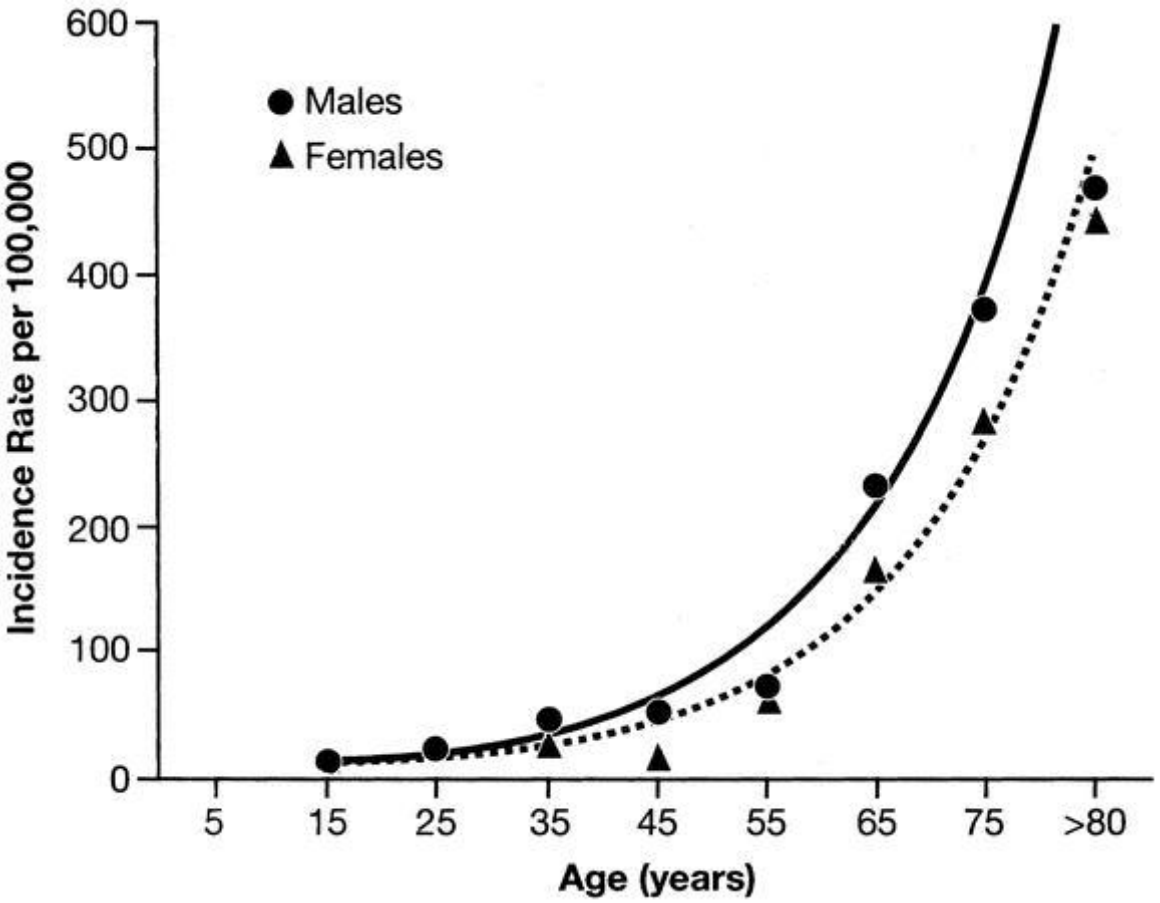
Of **symptomatic** lower-extremity DVTs, 88% involve the **proximal veins**; the rest only involve the **calf veins**.

Almost all lower-extremity DVTs arise from the calf veins and extend proximally.

Arch Intern Med 1993;153(24):2777-80

Epidemiology

Incidence of DVT by age



♂ > ♀

P < 0,005

USA data (Worcester Massachusets)

380.000 inhabitants

Anderson FA et al. Arch Intern Med 1991; 151: 933

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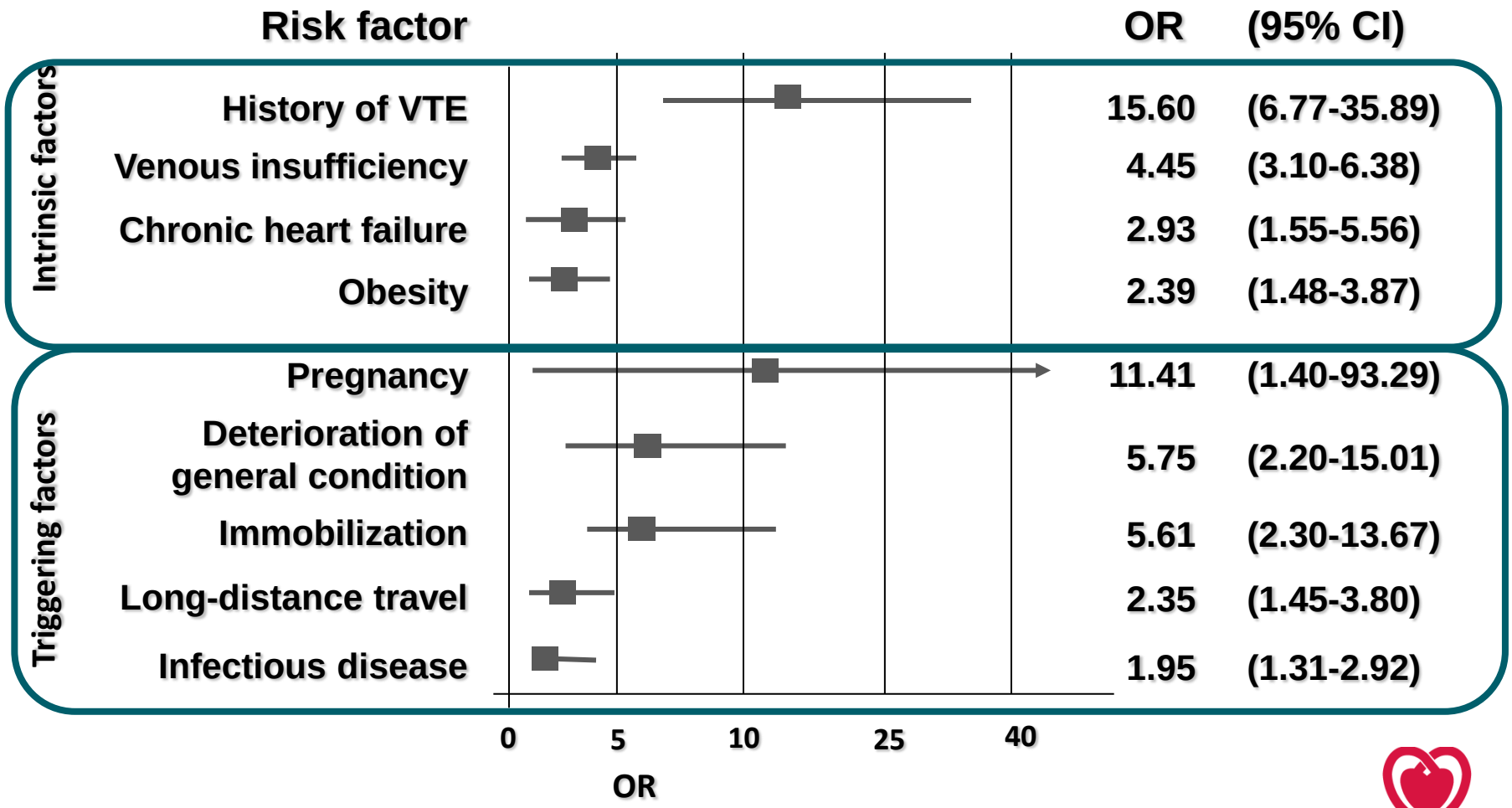
Risk factors

medical outpatients presenting with DVT



Samama MM. Arch Intern Med. 2000;160: 3415

Recurrence after withdrawal of AC

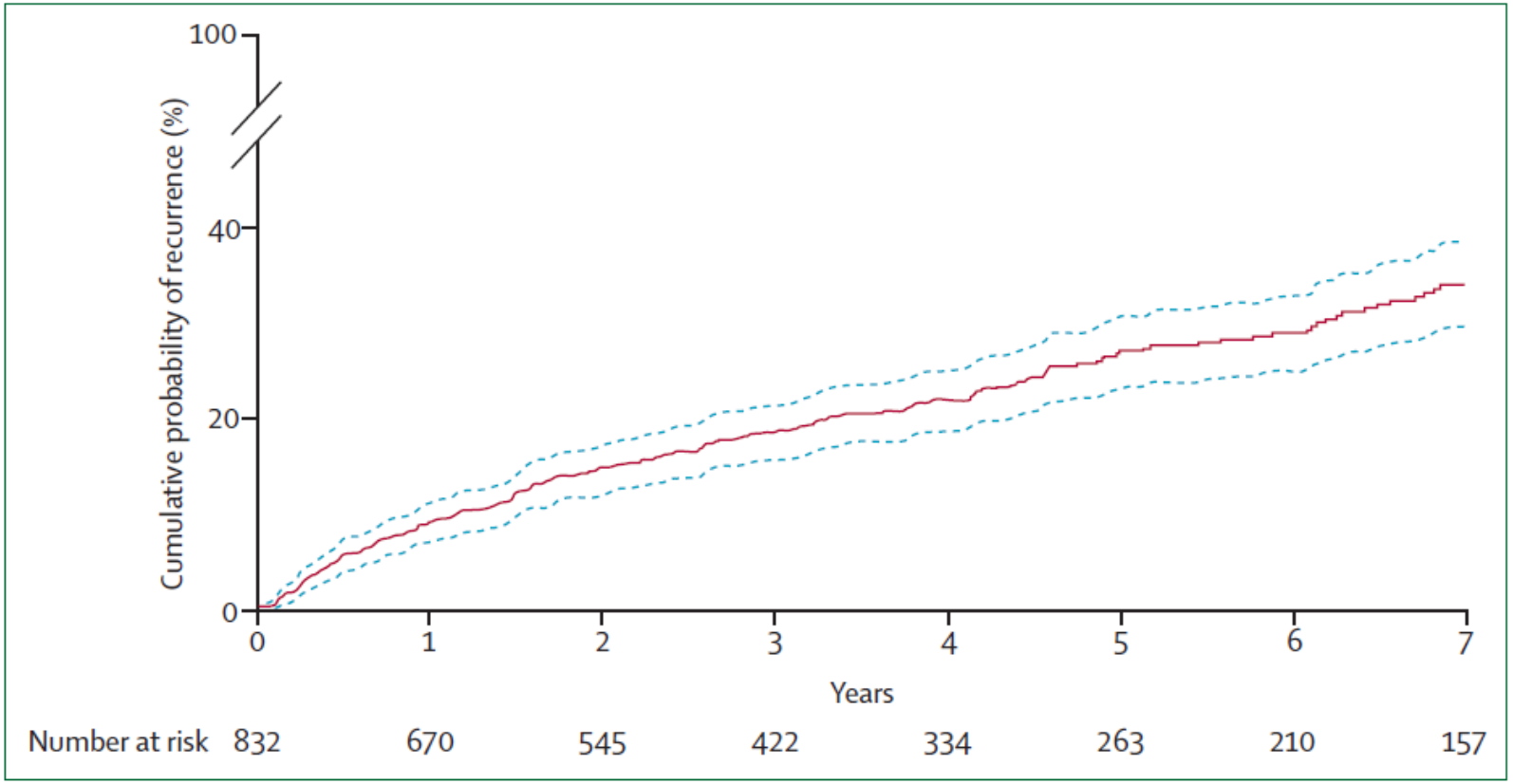
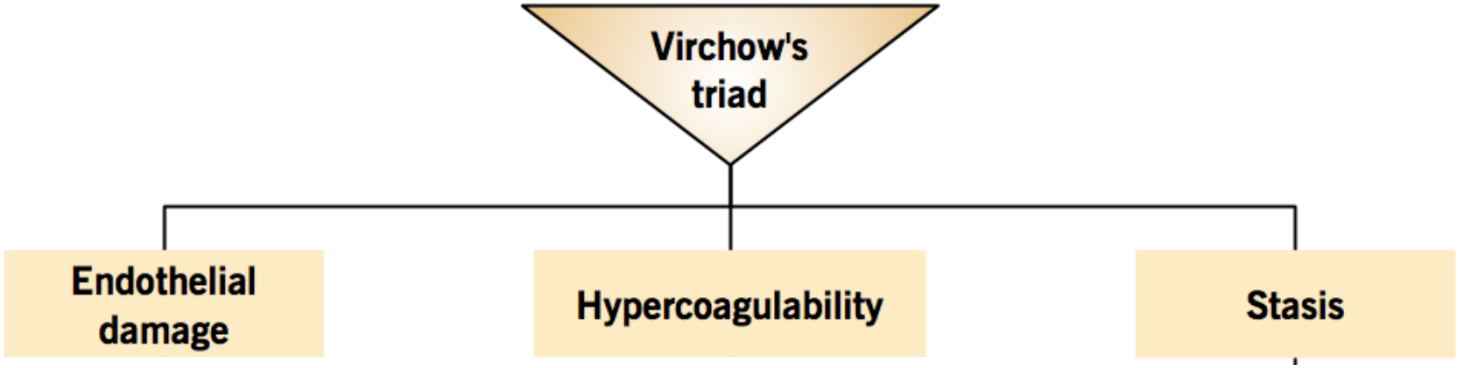


Figure 1: Kaplan-Meier estimates of cumulative rate of recurrence in 832 patients with a first unprovoked venous thrombosis after withdrawal of anticoagulant treatment
Dotted lines show 95% CIs.

Eichinger S, et al. Circulation 2010;121:1630

Pathophysiology

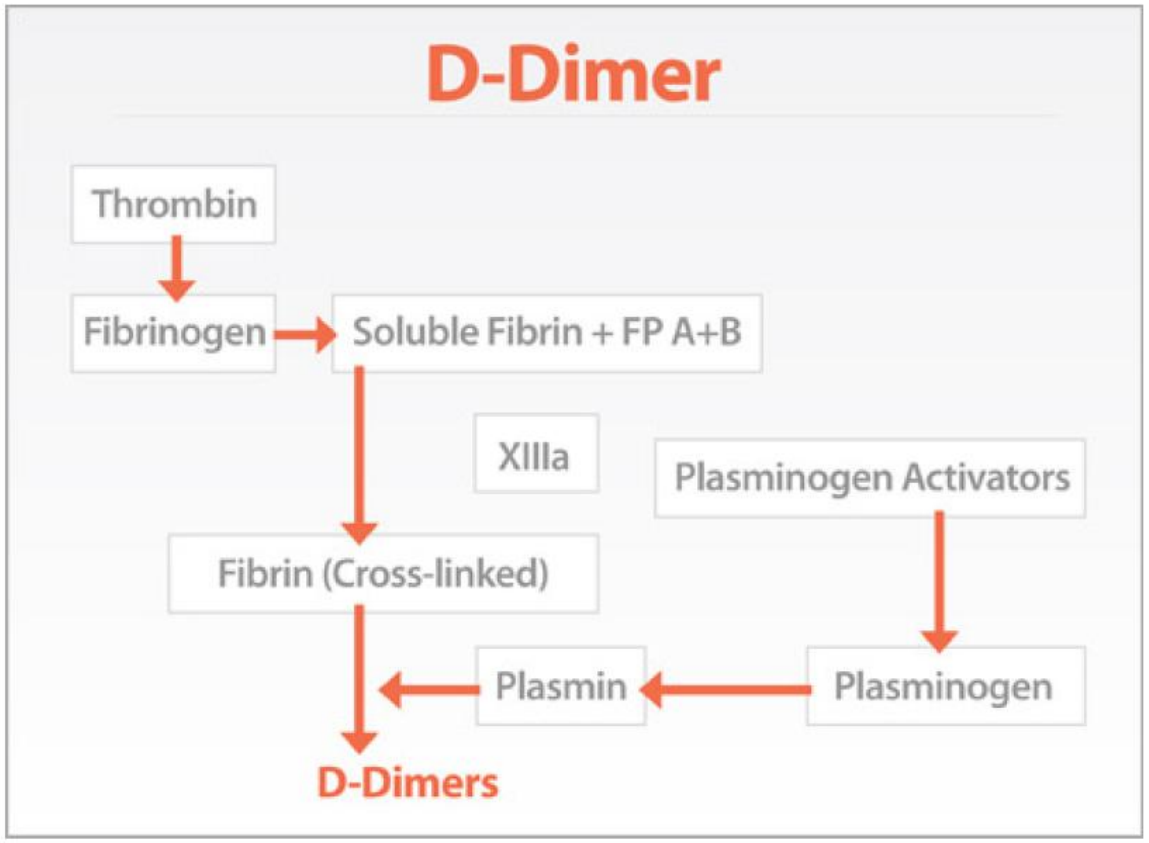


Arterial versus venous thrombosis

	Arterial thrombosis	**Venous thrombosis (VTE)**
Mechanism	Typically from rupture of atherosclerotic plaques.	Typically from a combination of factors from Virchow's triad.
Location	Left heart chambers, arteries	Venous sinusoids of muscles and valves in veins
Diseases	**Acute coronary syndrome** **Ischemic stroke** **Limb claudication/ischemia**	**Deep venous thrombosis** **Pulmonary embolism**
Composition	Mainly platelets	Mainly fibrin
Treatment	Mainly antiplatelet agents (ASA, clopidogrel)	Mainly anticoagulants (heparins, warfarin)

Thromb Haemost 2011 Apr;105(4):586-96.

Diagnosis (indirect thrombus evidence)

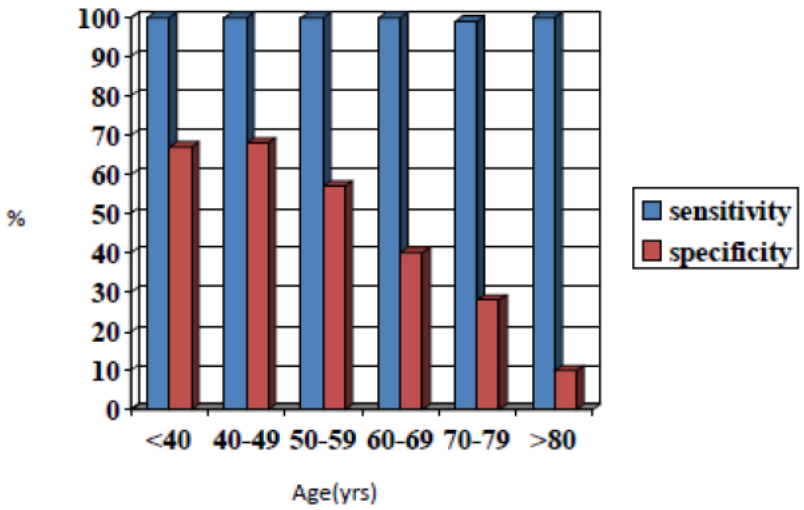


- Fibrin D-dimer is a degradation product of cross-linked fibrin, and its concentration increases in patients with VTE.

D-dimer is highly sensitive (more than 95%) in excluding DVT, usually below a threshold of 500 µg/L

Age-adjusted D-dimers levels

Effects of age on D-dimer performance



Righini et al, Presse Med. 2001

age	Cut-off
≤ 50 yrs	500 µg/L
> 50 yrs	Age x 10 µg/L

ESC guidelines 2014

Table 3. Study Results According to D-Dimer Assays

D-Dimer Assay	Low/Intermediate or Unlikely Clinical Probability, No. of Patients	D-Dimer <500 µg/L	3-mo Thromboembolism Risk		D-Dimer ≥500 µg/L and <Age-Adjusted Cutoff	3-mo Thromboembolism Risk	
			No. of Events/ Total Patients	% (95% CI)		No. of Events/ Total Patients	% (95% CI)
VIDAS D-Dimer Exclusion	1345	423	0/417	0.0 (0.0-0.9)	130	0/127	0.0 (0.0-2.9)
Innovance D-Dimer	838	202	1/202	0.5 (0.1-2.8)	103	1/103	1.0 (0.2-5.3)
STA-Liatest D-Dimer	389	132	0/132	0.0 (0.0-2.8)	49	0/47	0.0 (0.0-7.6)
D-Dimer HS 500	185	32	0/31	0.0 (0.0-11.0)	23	0/23	0.0 (0.0-14.3)
Second-generation Tina-quant	128	26	0/26	0.0 (0.0-12.9)	32	0/31	0.0 (0.0-11.0)
Cobas h 232	13	2	0/2	0.0 (0.0-65.8)	0		
Total	2898	817	1/8	0 0.1 (0.0-0.7)	337	1/331	0.3 (0.1-1.7)

Righini et al., JAMA 2014

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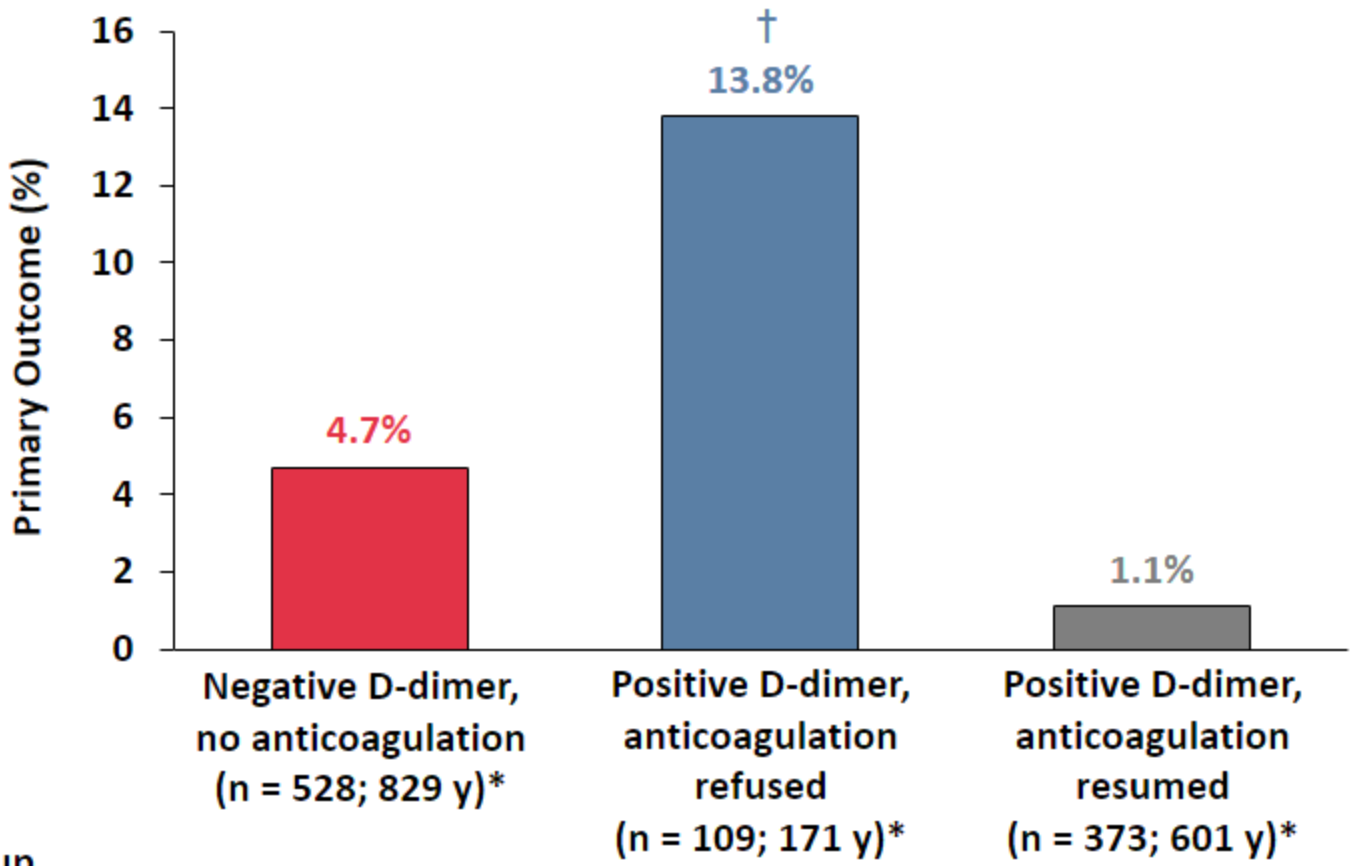
DULCIS: D-dimer Use in Determining Anticoagulant Treatment Duration for VTE

Composite of Confirmed Recurrent VTE and Death Caused by VTE



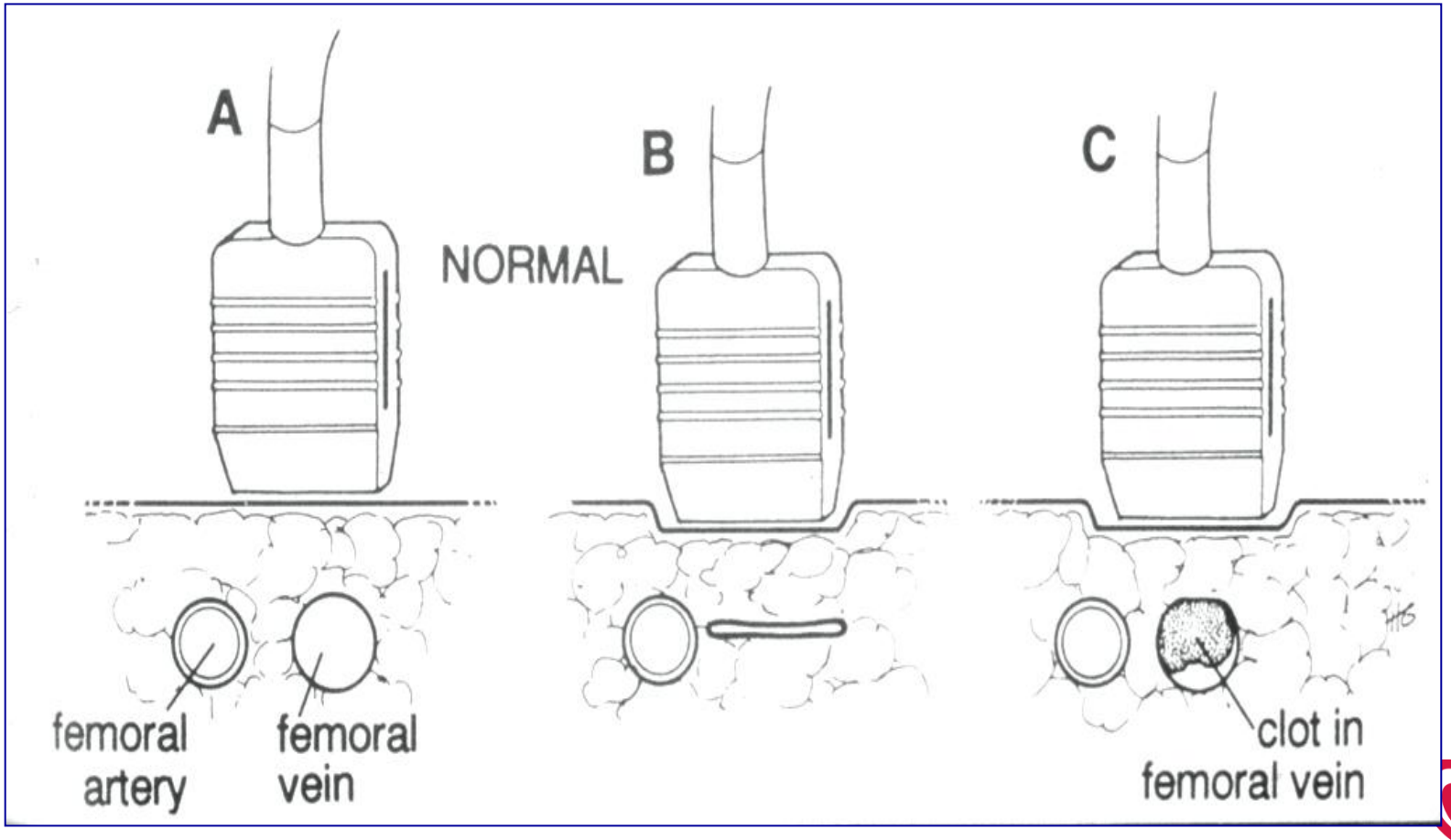
*Total follow-up

†*P*=.0008 vs patients with negative D-dimer

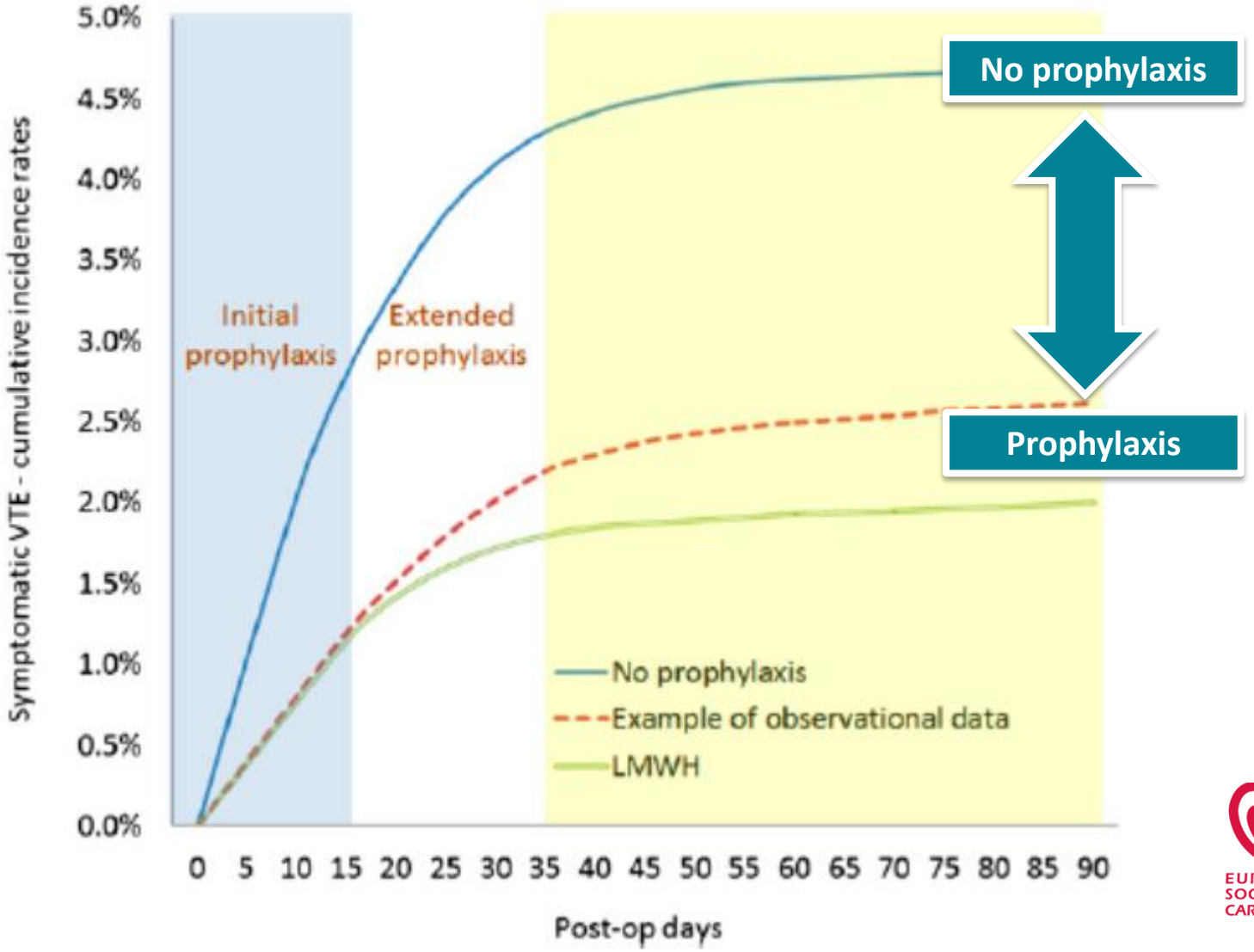
DULCIS = D-dimer and ULtrasonography in Combination Italian Study

Palareti G, et al. *Blood*. 2014;124:196-203.

Compression Doppler Ultrasound



Major orthopaedic surgery



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Major orthopaedic surgery

The success of thromboprophylaxis

Meta-analysis of randomized clinical trials and observational studies that reported rates of postoperative symptomatic VTE in patients who received recommended VTE prophylaxis after undergoing TPHA or TPKA.

44 844 cases provided by 47 studies

The pooled rates of symptomatic postoperative VTE before hospital discharge

1.09% (95% CI, 0.85% - 1.33%) for patients undergoing TPKA
0.53% (95% CI, 0.35% - 0.70%) for those undergoing TPHA
0.63% (95% CI, 0.47% - 0.78%) for knee arthroplasty
0.26% (95% CI, 0.14% - 0.37%) for hip arthroplasty

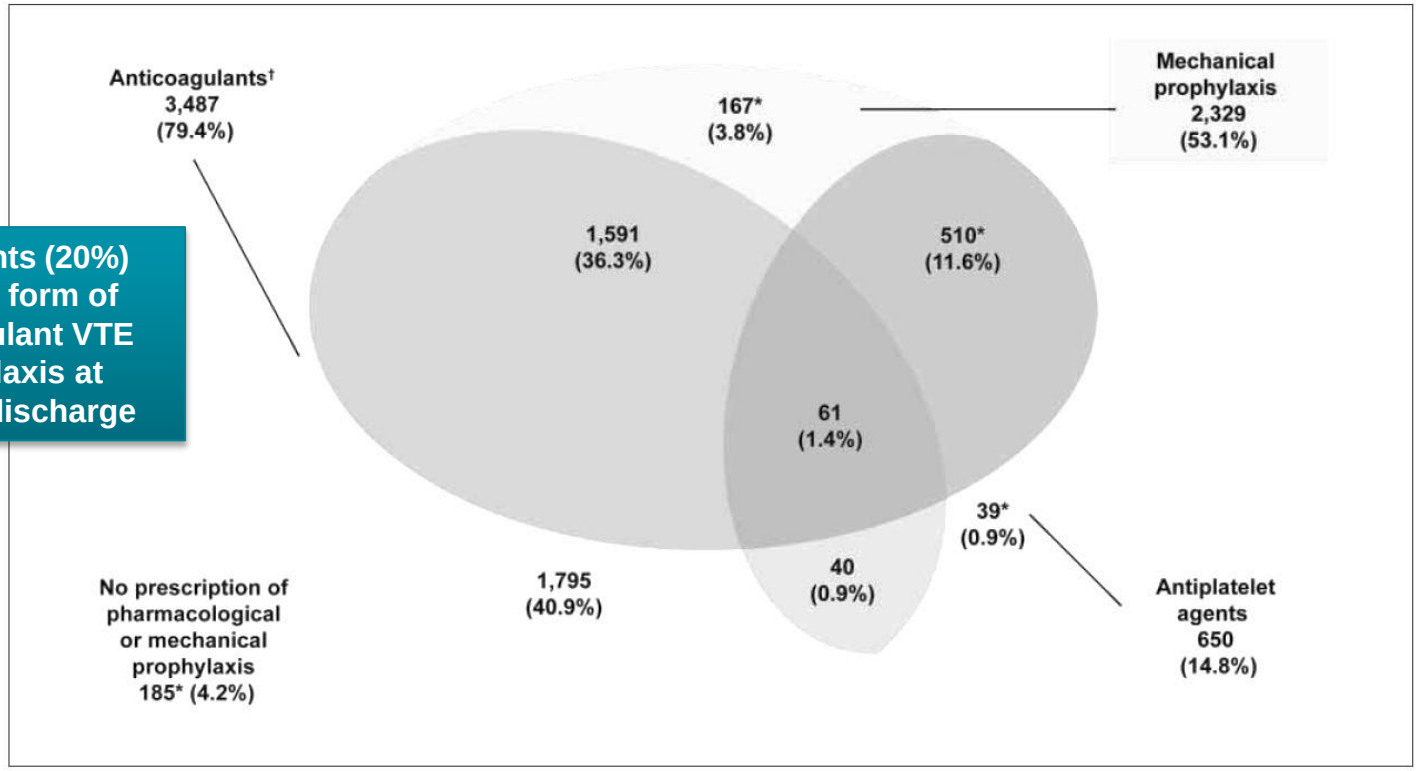
Major orthopaedic surgery

ETHOS observational study

17 European countries

4,388 eligible and assessable patients for the analysis of VTE prophylaxis prescribed

1,059 KA (24.1%) 2,217 THA (50.5%) 1,112 HFS (25.3%)



901patients (20%) with any form of anticoagulant VTE prophylaxis at hospital discharge

Thromb Haemost 2012; 107: 270–279

DVT in cancer patients

Symptomatic venous thromboembolism (VTE) occurs 4-7 times more frequently in cancer patients as compared to non-cancer patients

Patient-related factors

- Older age
- Gender (Female)
- Ethnic origin (higher in African Americans; lower in Asian-Pacific Islanders)
- Comorbidities (obesity, renal disease, pulmonary disease, neutropenia, infection)
- Prior history of venous thromboembolism
- Lower performance status
- Immobilisation
- Heritable prothrombotic mutations (Factor V Leiden, prothrombin gene mutation)

Cancer-related factors

- Primary tumour site (pancreatic, ovarian, kidney, lung, gastric, brain, and haematologic)
- Histologic subtype (adenocarcinoma > squamous cell carcinoma)
- Locally advanced tumours/ distant metastases
- Initial period after diagnosis

Thromb Haemost 2016; 116: 618–625

DVT in cancer patients

Symptomatic venous thromboembolism (VTE) occurs 4-7 times more frequently in cancer patients as compared to non-cancer patients

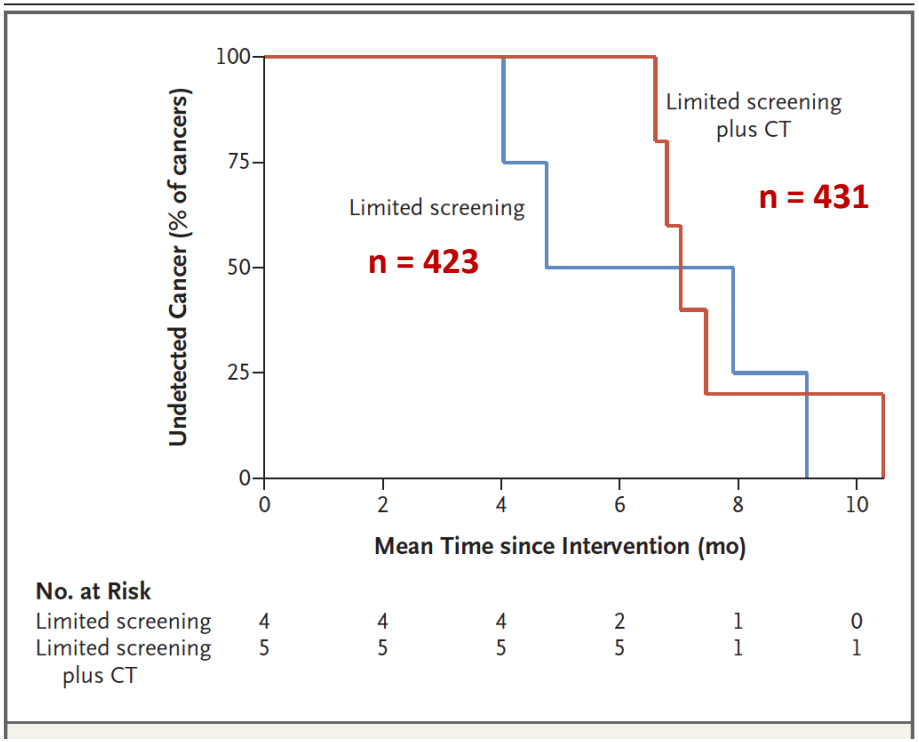
Treatment-related factors
• Recent major surgery
• Hospitalisation
• Central venous catheters
• Chemotherapy
• Antiangiogenic agents (bevacizumab, sunitunib, sorafenib)
• Immonomodulatory drugs (thalidomide, lenalidomide)
• Hormonal therapy (tamoxifen)
• Erythropoietin
• Transfusions (platelets, red blood cells)

Thromb Haemost 2016; 116: 618–625

Screening for occult cancer

ORIGINAL ARTICLE DOI: 10.1056/NEJMoa1506623

Screening for Occult Cancer in Unprovoked Venous Thromboembolism



ıer, M.D., Sudeep Shivakumar, M.D.,

CONCLUSIONS

The prevalence of occult cancer was low among patients with a first unprovoked venous thromboembolism. Routine screening with CT of the abdomen and pelvis did not provide a clinically significant benefit.

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Thrombophilia

Cause of death	Number of patients (%) (Total number n=78)
VTE, thereof:	∑ 4 (5 %)
Definite PE	3 (3.8 %)
Possible PE	1 (1.3 %)
Bleedings	4 (5 %)
Other causes	
Cardiovascular causes/heart failure	20 (26 %)
Malignancies	27 (35 %)
Trauma / accident /suicide	7 (9 %)
Others (e.g. pulmonary, renal causes, infection, long-term consequences of diabetes mellitus)	16 (21 %)

VTE – venous thromboembolism; PE – pulmonary embolism.

1905 with VTE
944 with thrombophilia
78 died (4.1%)

Thrombosis and Haemostasis 109.1/2013

Thrombophilia

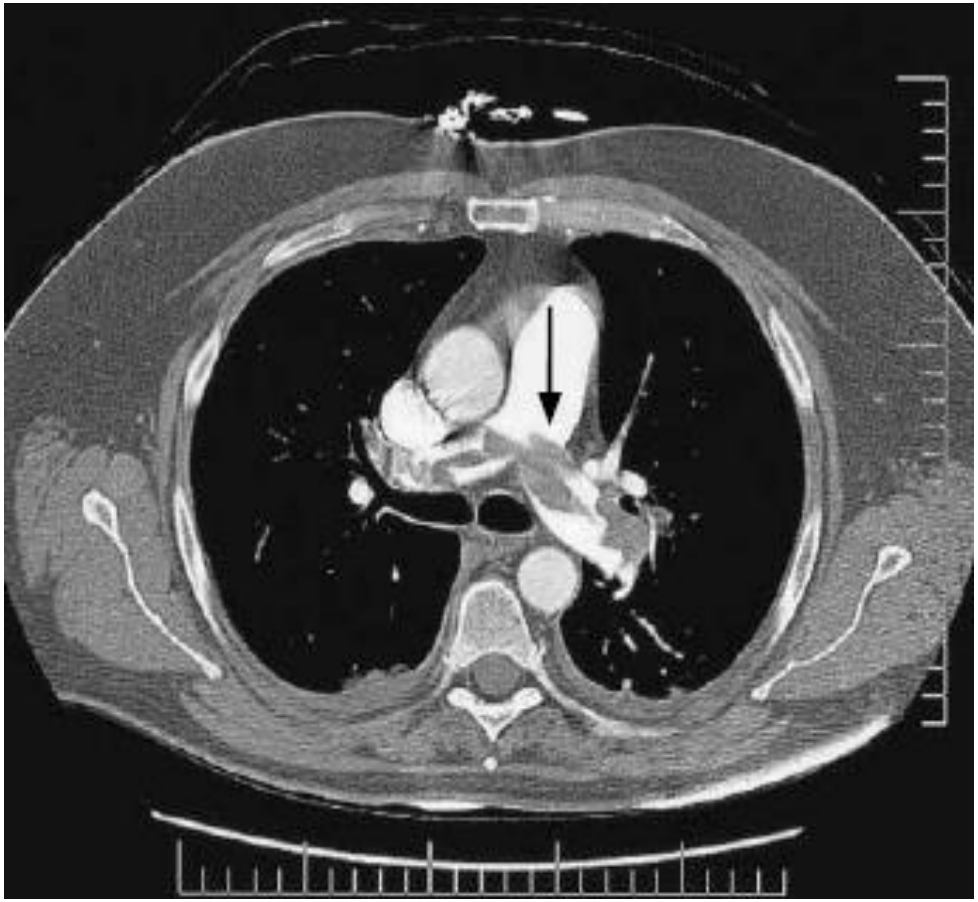
Table 4: Hazard ratios and 95 % confidence intervals for death (corrected for sex and age) regarding thrombophilia risk factors.

Parameter	HR	95 % CI
ATIII-, PC-, PS-deficiency (binary)	2.03	0.71 – 4.56
Factor V Leiden (binary)	0.81	0.46 – 1.35
Hyperhomocysteinaemia (linear)	1.02	0.98 – 1.05
Hyperhomocysteinaemia (binary)	1.98	1.08 – 3.48
Elevated FVIII (linear)	1.00	1.00 – 1.01
Elevated FVIII (binary)	1.27	0.78 – 2.05

ATIII – antithrombin III; PC – protein C; PS – protein S; FVIII – factor VIII; HR – hazard ratio; CI – confidence interval.

Thrombosis and Haemostasis 109.1/2013

DVT and pulmonary embolism



1/3
of DVT
complicate with
a clot in the
lungs

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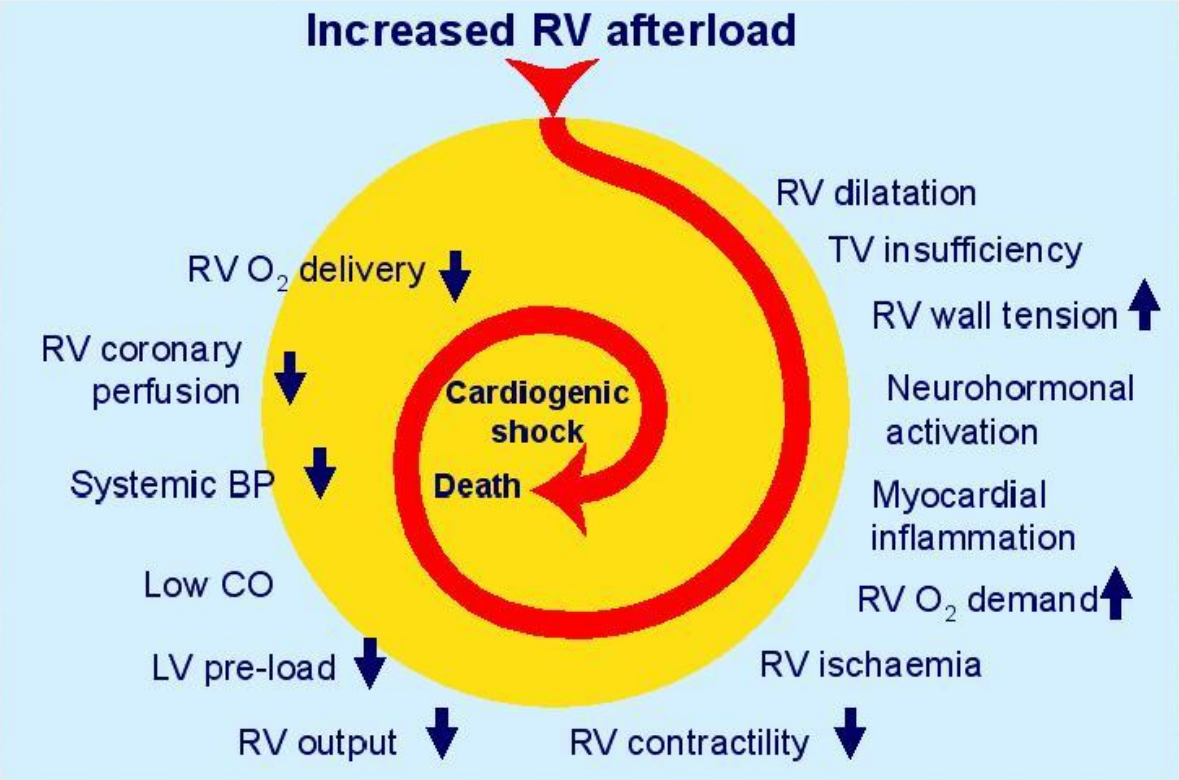
Key factors contributing to haemodynamic collapse in acute pulmonary embolism



BP = blood pressure; CO = cardiac output; LV = left ventricular; RV = right ventricular; TV = tricuspid valve.

www.escardio.org/guidelines

European Heart Journal (2014):doi:10.1093/eurheartj/ehu283

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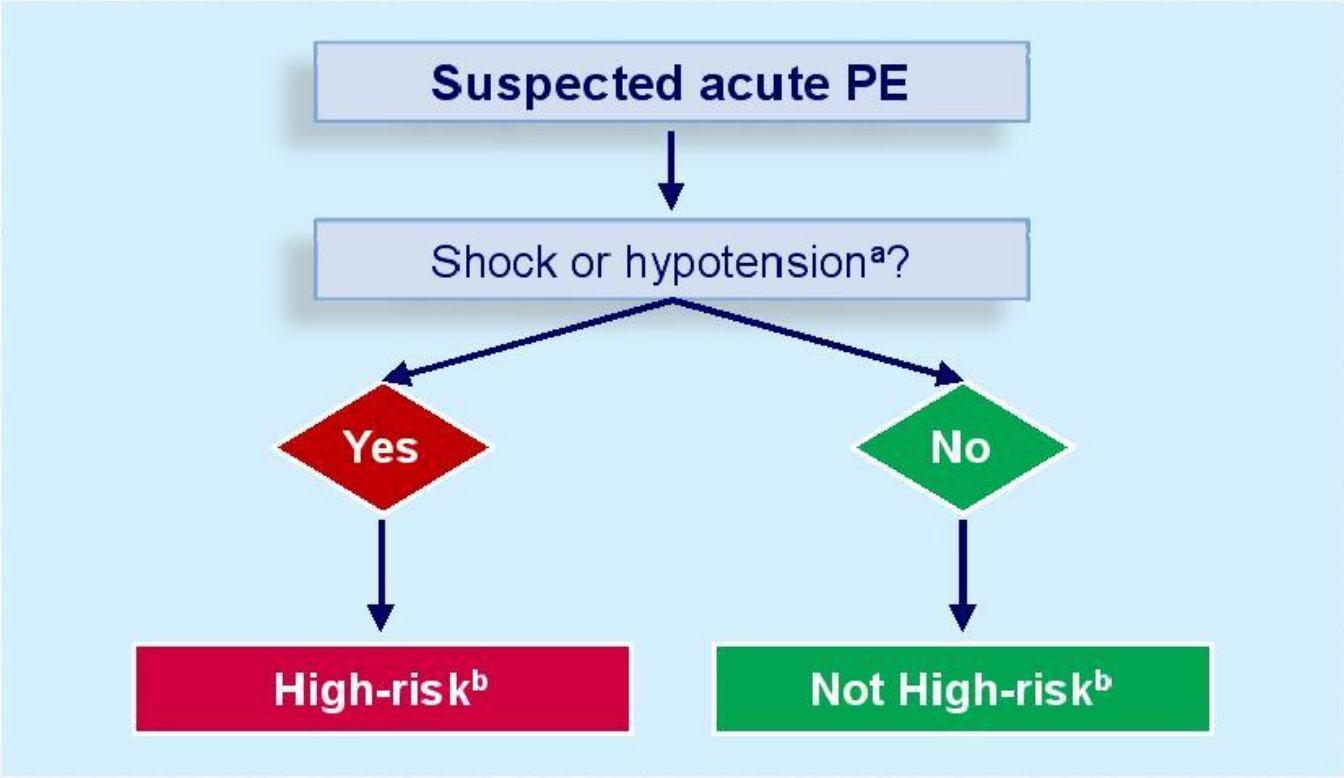
Initial risk stratification of acute PE



[a] Defined as systolic blood pressure <90 mmHg, or a systolic pressure drop by ≥40 mmHg, for >15 minutes, if not caused by new-onset arrhythmia, hypovolaemia, or sepsis.
[b] Based on the estimated PE-related in-hospital or 30-day mortality.

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Classification of early mortality risk

Early mortality risk		Risk parameters and scores			
		Shock or hypotension	PESI Class III-V or sPESI ≥1	Signs of RV dysfunction on an imaging test	Cardiac laboratory biomarkers
High		+	(+)	+	(+)
Intermediate	Intermediate-high	–	+	Both positive	
	Intermediate-low	–	+	Either one (or none) positive	
Low		–	–	Assessment optional; if assesed, both negative	

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European Heart Journal (2014):doi:10.1093/eurheartj/ehu283

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Original and simplified pulmonary embolism severity index (PESI)

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

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European Heart Journal (2014):doi:10.1093/eurheartj/ehu283

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Original and simplified pulmonary embolism severity index (PESI)

Parameter	Original version	Simplified version
	Risk strata	
	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%) **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%)	**0 points** = 30-day mortality risk 1.0% (95% CI 0.0%-2.1%) **≥1 point(s)** = 30-day mortality risk 10.9% (95% CI 8.5%-13.2%)

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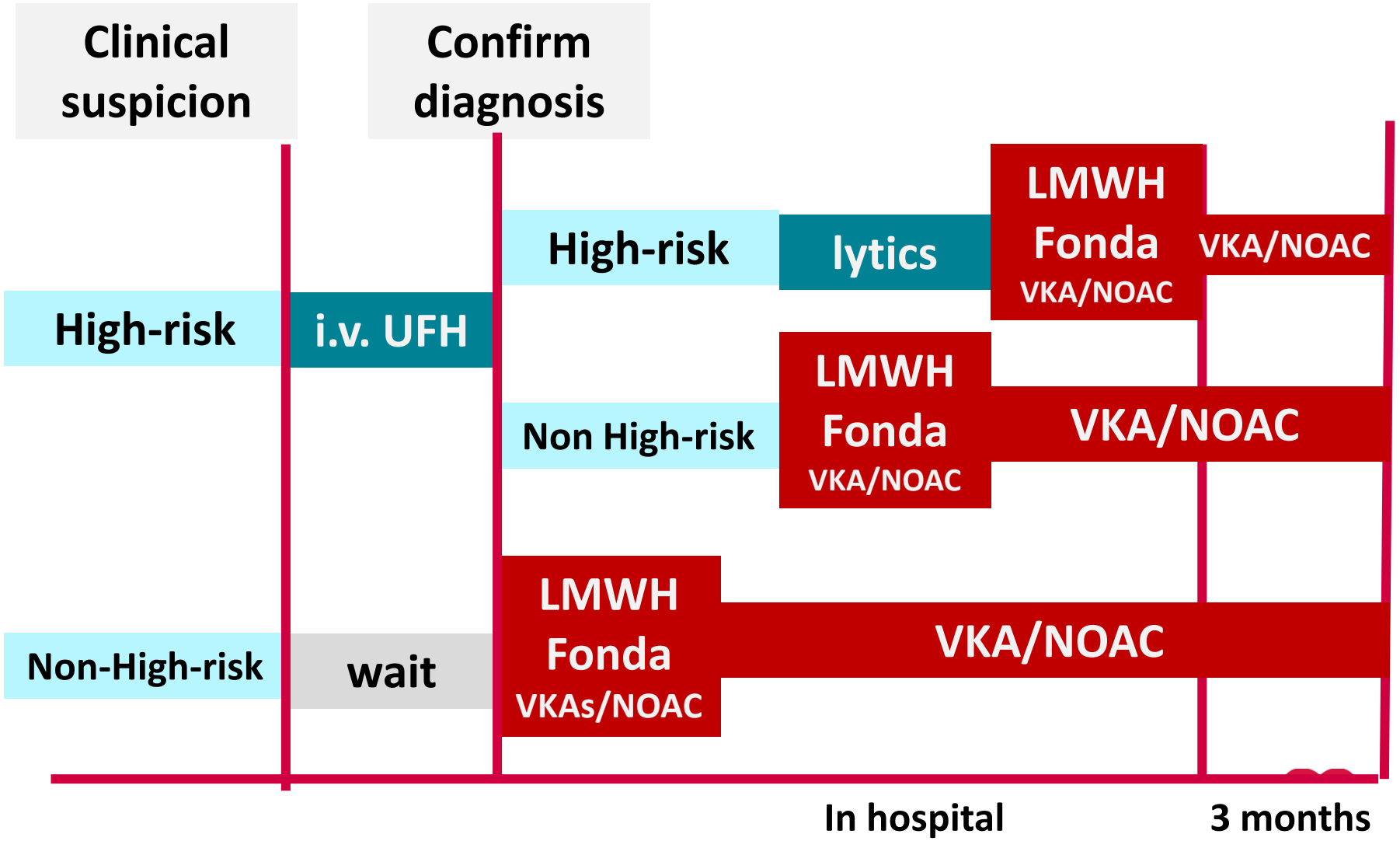
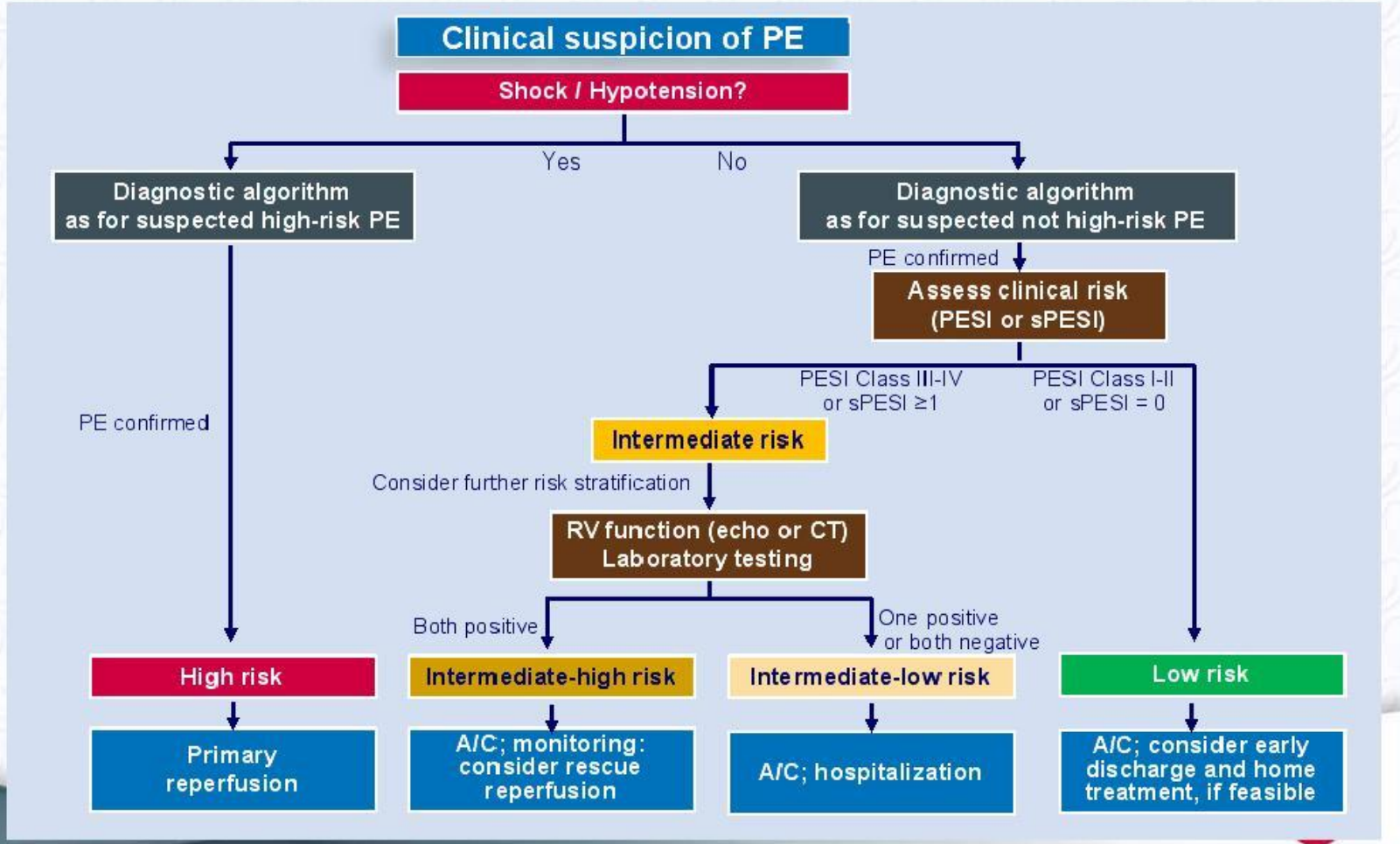
Standard of care for PE



Risk-adjusted management algorithm



European Heart Journal (2014):doi:10.1093/eurheartj/ehu283

Key messages

- **Prophylaxis and early recognition are the keys to change the prognosis in patients with DVT**
- **The workflow is based on the risk stratification. The higher the risk more aggressive pharmacological treatment should be**
- **Antithrombotics mostly anticoagulants are very effective not only for prevention but also for treatment**
- **Pulmonary embolism should be prevented. The acute management is based on the level of risk**

Many thanks

Understanding thrombosis in venous thromboembolism

João Morais

Head of Cardiology Division and Research Centre

Leiria Hospital Centre

Portugal

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