Eventi tromboembolici nel paziente neoplastico

L'embolia polmonare: diagnosi e trattamento

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ESC GUIDELINES

2014 ESC Guidelines on the diagnosis and management of acute pulmonary embolism

The Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC)

Endorsed by the European Respiratory Society (ERS)

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L'embolia polmonare: diagnosi e trattamento

Relevant *new* aspects 2014

1. Recently identified predisposing factors for venous thromboembolism.
2. Simplification of clinical prediction rules
3. Age-adjusted D-dimer cut-offs
4. Sub-segmental pulmonary embolism (PE)
5. Incidental, clinically unsuspected PE
6. Advanced risk stratification of intermediate-risk PE
7. Initiation of treatment with vitamin K antagonists
8. Treatment and secondary prophylaxis of venous thromboembolism with non-Vitamin-K-dependent oral anticoagulants (NOACs)
9. Efficacy and safety of reperfusion treatment for patients at intermediate risk
10. Early discharge and home (outpatient) treatment of PE
11. Current diagnosis and treatment of CTEPH
12. Formal recommendations for the management of PE in pregnancy and of PE in patients with cancer

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EUROPEAN SOCIETY OF CARDIOLOGY®

F E

Strong risk factors (odds ratio >10)
Fracture of lower limb
Hospitalization for heart failure or atrial fib previous 3 months)
Hip or knee replacement
Major trauma
Myocardial infarction (within previous 3 mo
Previous venous thromboembolism
Spinal cord injury

Moderate risk factors (odds ratio 2–9)
Arthroscopic knee surgery
Auto-immune diseases
Blood transfusion
Central venous lines
Chemotherapy
Congestive heart or respiratory failure
Erythropoiesis-stimulating agents
Hormone replacement therapy (depends on formulation
In vitro fertilization
Infection (specifically pneumonia, urinary tract infection
Inflammatory bowel disease
Cancer (highest risk in metastatic disease)
Oral contraceptive therapy
Paralytic stroke
Postpartum period
Superficial vein thrombosis
Thrombophilia

Weak risk factors (odds ratio <2)
Bed rest >3 days
Diabetes mellitus
Hypertension
Immobility due to sitting (e.g. prolonged car or air travel)
Increasing age
Laparoscopic surgery (e.g. cholecystectomy)
Obesity
Pregnancy
Varicose veins

Nel 30% dei pazienti con EP non fattori predisponenti EHJ 2014;34:3033-3080

Caratteristiche cliniche

Feature	PE confirmed (n = 1880)	PE not confirmed (n = 528)
Dyspnoea	58%	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%

JACC 2011;57:700-706

Test routinari

EGA

Ipossiemia/Ipocapnia

40% dei pz normossiemico

RX torace

Alterazioni aspecifiche

Permette di escludere altre cause di dispnea
o dolore toracico

ECG

Inversione T V1-V4
S1Q3T3
P polmonare
BBdx

D-dimero

Probabilità clinica pre-test

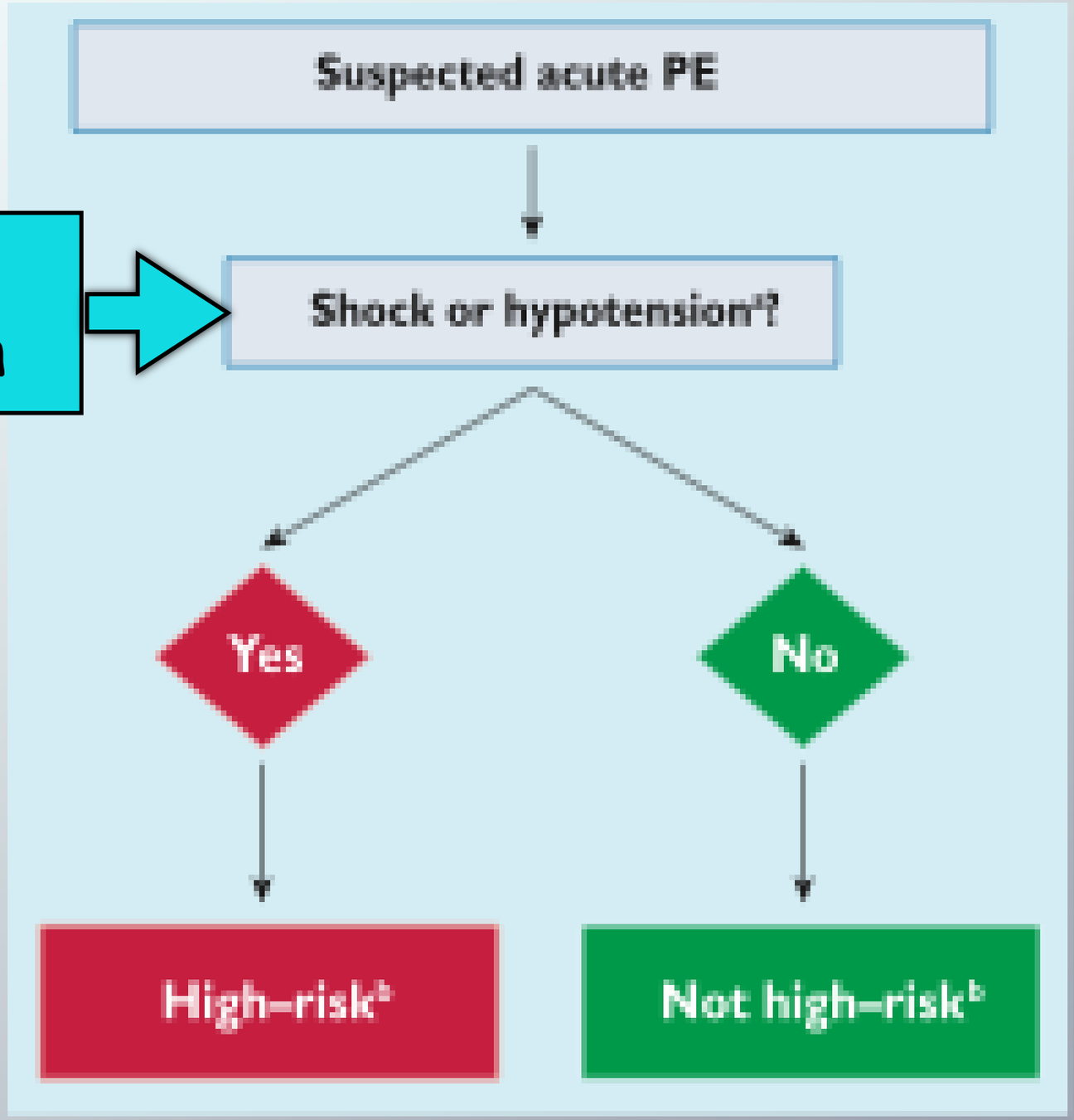
Items	Clinical decision rule points	
Wells rule	**Original version[41]**	**Simplified version[42]**
Previous PE or DVT	1.5	1
Heart rate ≥100 b.p.m.	1.5	1
Surgery or immobilization within the past four weeks	1.5	1
Haemoptysis	1	1
Active cancer	1	1
Clinical signs of DVT	3	1
Alternative diagnosis less likely than PE	3	1
Clinical probability		
Two-level score		
PE unlikely	0–4	0–1
PE likely	≥5	≥2

Probabilità clinica pre-test

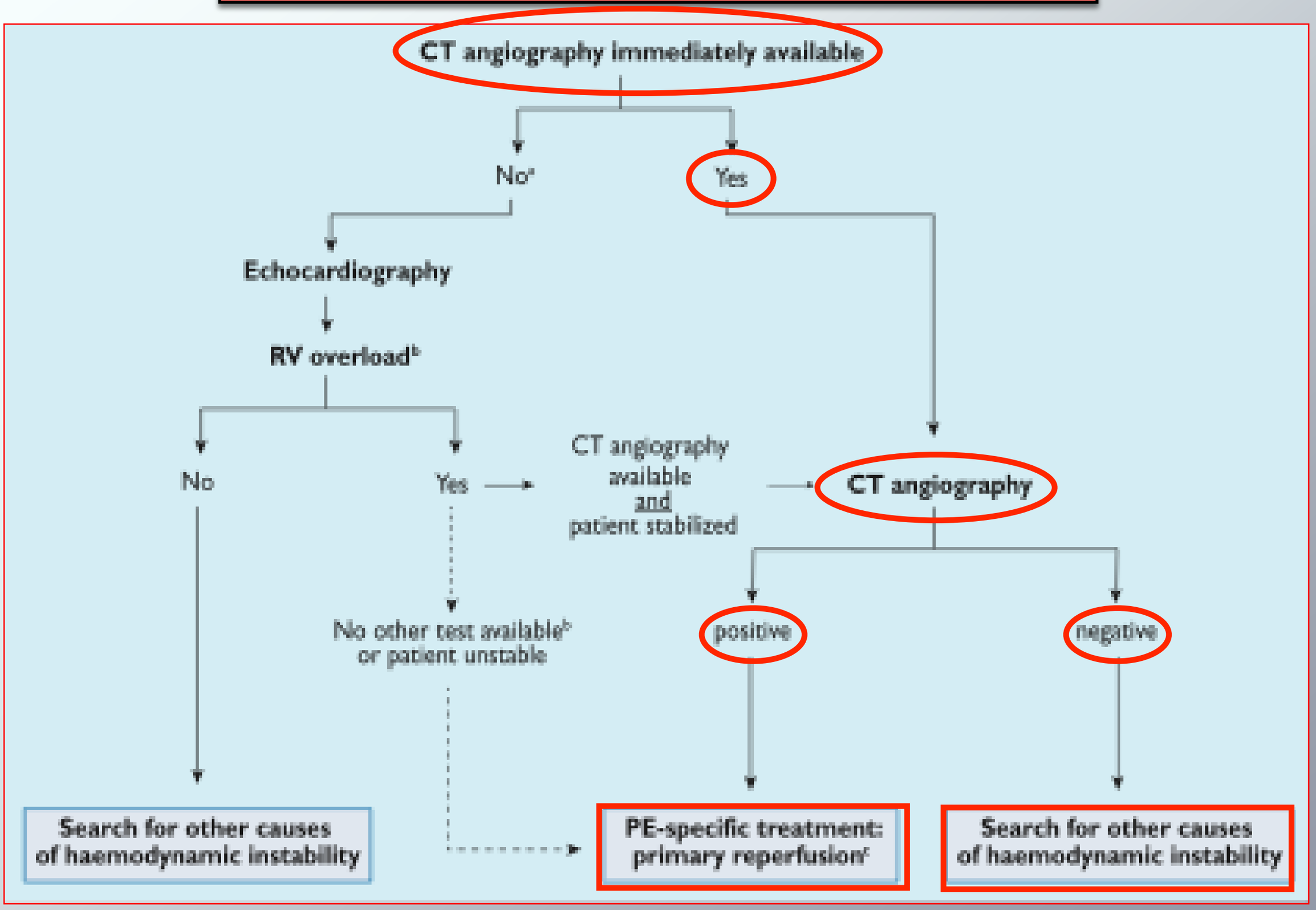
Revised Geneva score	Original version[17]	Simplified version[18]
Previous PE or DVT	3	1
Heart rate		
75–94 b.p.m.	3	1
≥95 b.p.m.	5	2
Surgery or fracture within the past month	2	1
Haemopysis	2	1
Active cancer	2	1
Unilateral lower limb pain	3	1
Pain on lower limb deep venous palpation and unilateral oedema	4	1
Age >65 years	1	1
Clinical probability		
Two-level score		
PE unlikely	0–5	0–2
PE likely	≥6	≥3

Strategie diagnostiche

- PAS: <90mmHg
- ↓40mmHg >15min



Sospetta EP con shock o ipotensione



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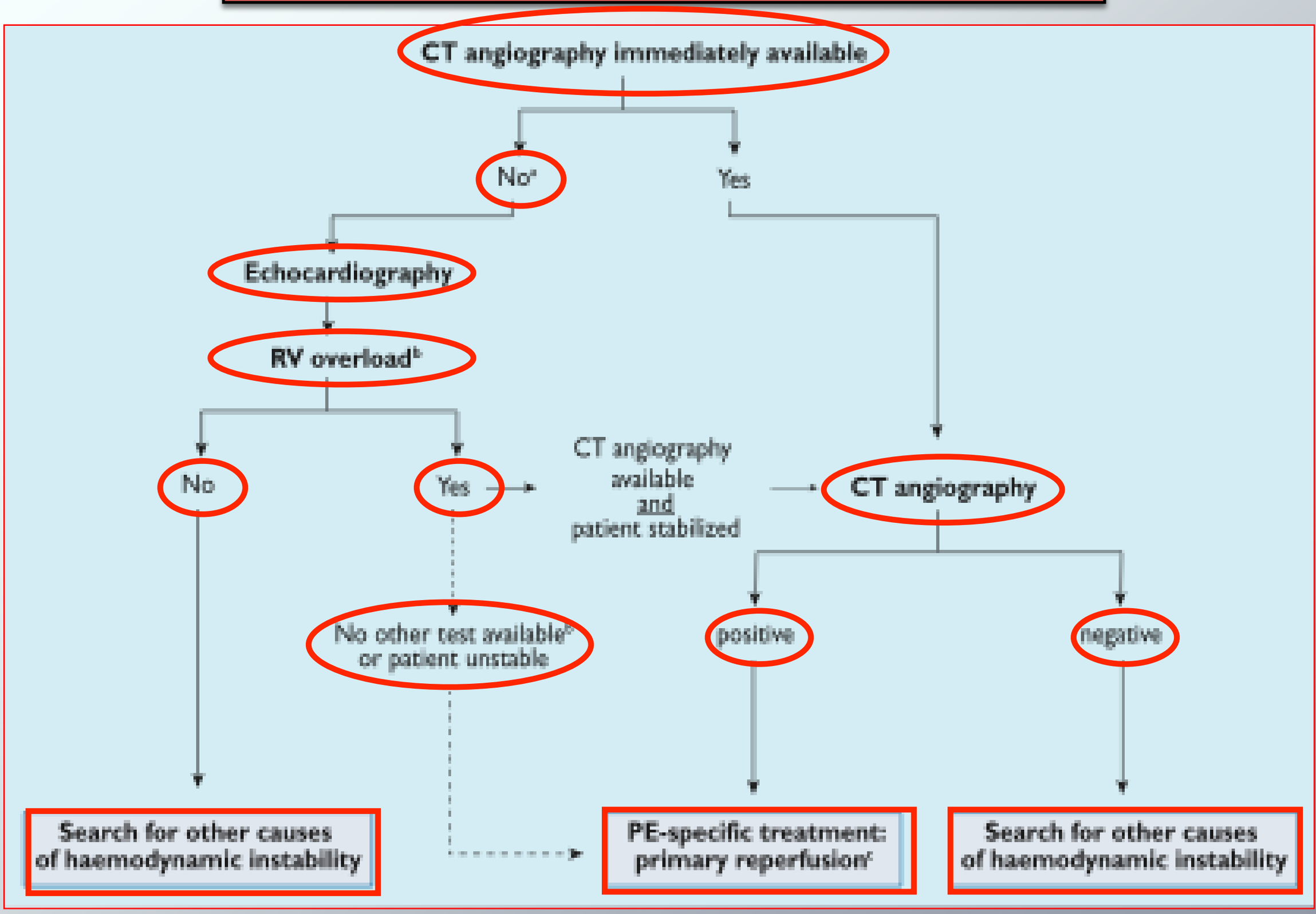
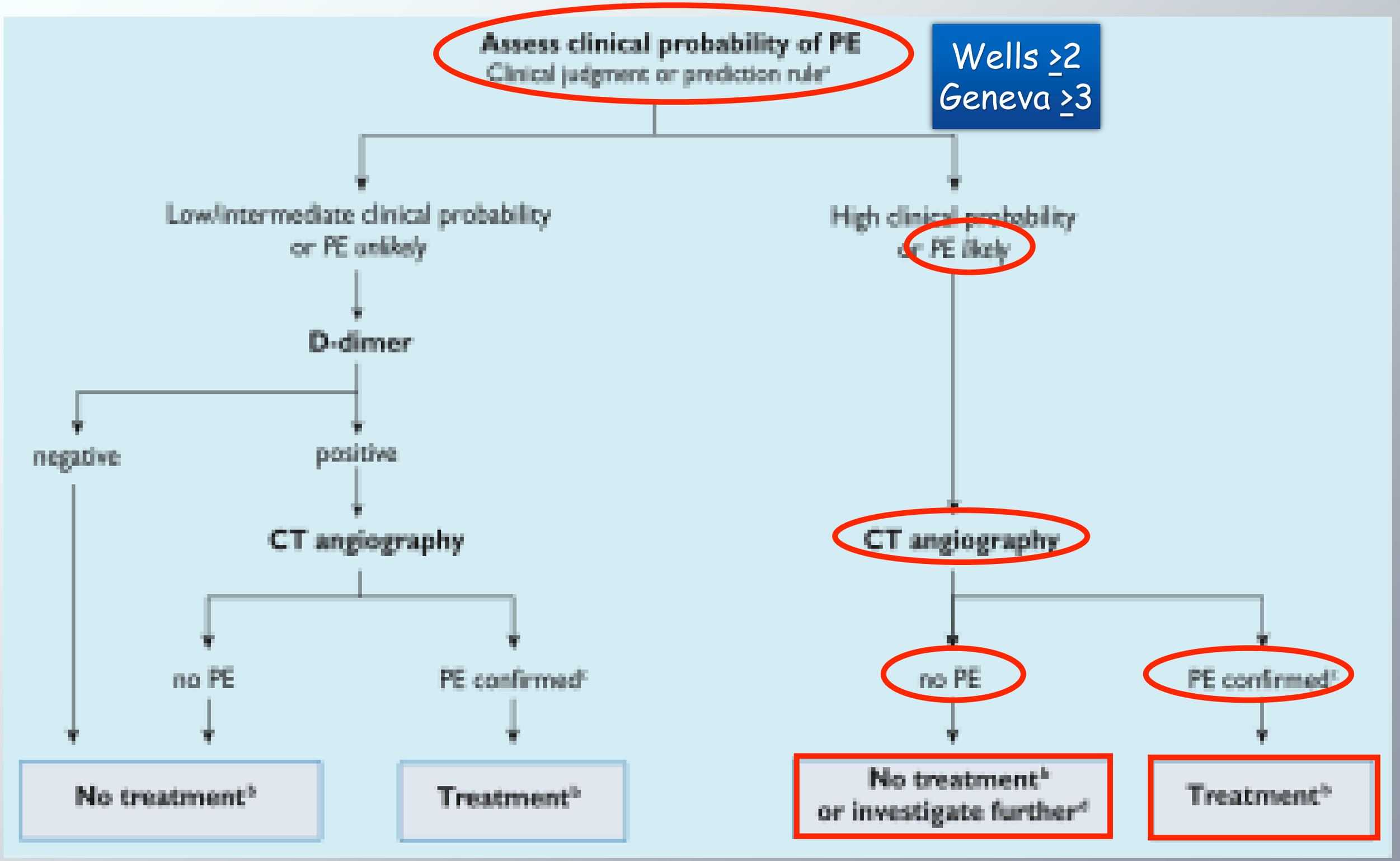
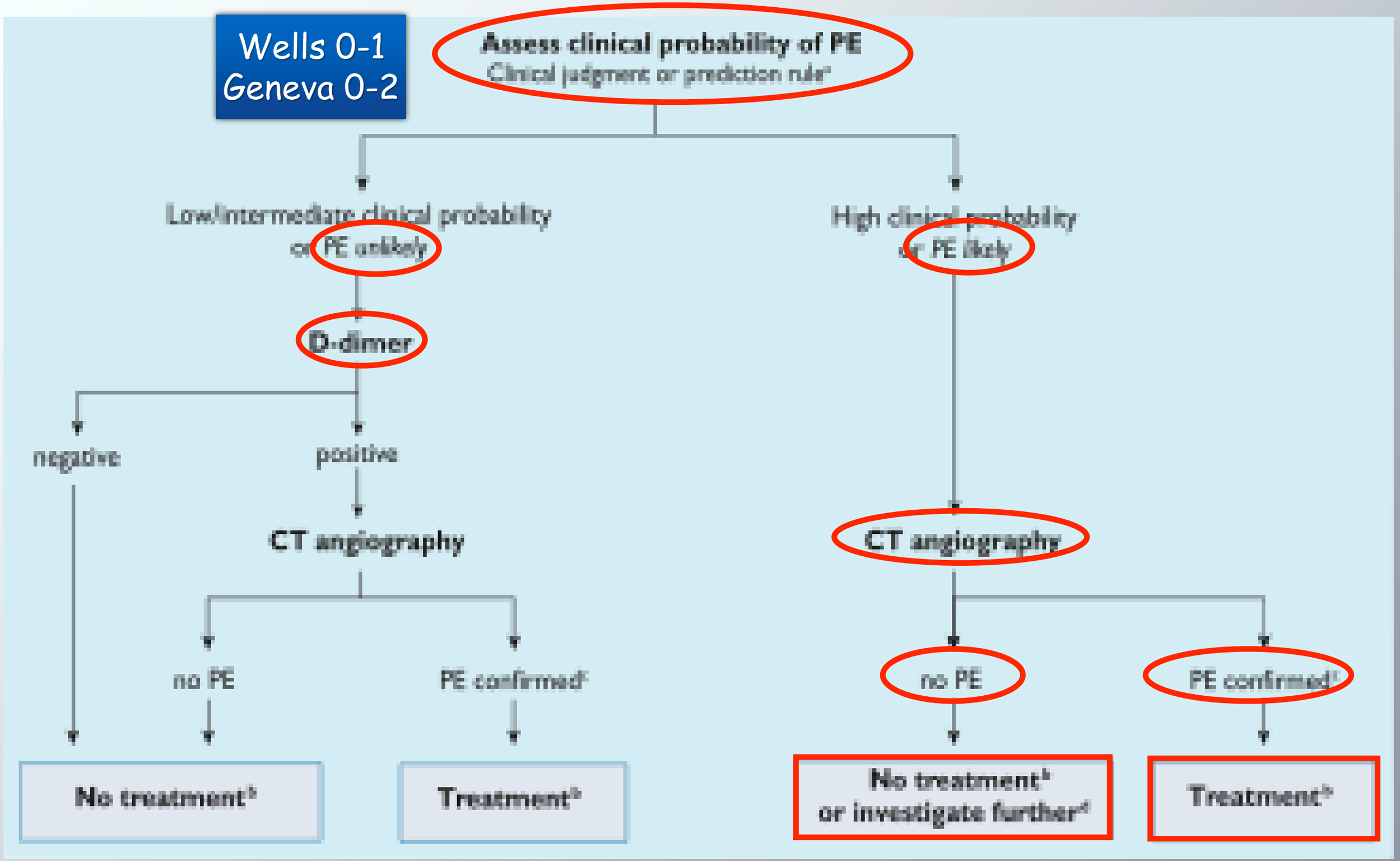


Sospetta EP senza shock o ipotensione



Sospetta EP senza shock o ipotensione

Wells 0-1
Geneva 0-2



D-dimero

- prodotto dall'attivazione della coagulazione e fibrinolisi
- elevato valore predittivo negativo
- fibrina prodotta anche in molte altre situazione (neopasie, infiammazione, sanguinamenti, traumi, interventi chirurgici, ecc)
- aumenta con l'età

cut-off: 500ug/L
cut-off aggiustato per età >50aa (età x 10ug/L)

BMJ 2013;346:2492
JAMA 2014;311:117

JAMA 2014;311:117

Age-Adjusted D-Dimer Cutoff Levels to Rule Out Pulmonary Embolism
The ADJUST-PE Study

Marc Righini, MD; Josien Van Es, MD, PhD; Paul L. Den Exter, MD; Pierre-Marie Roy, MD, PhD; Franck Verschuren, MD; Alexandre Ghuysen, MD; Olivier T. Rutschmann, MD; Olivier Sanchez, MD; Morgan Jaffrelot, MD; Albert Trinh-Duc, MD; Catherine Le Gall, MD; Farès Moustafa, MD; Alessandra Principe, MD; Arja A. Van Houten, MD; Marije Ten Wolde, MD, PhD; Renée A. Douma, MD, PhD; Germa Hazelaar, MD; Petra M. G. Erkens, PhD; Klaas W. Van Kralingen, MD; Marco J. J. H. Grootenboers, MD, PhD; Marc F. Durian, MD; Y. Whitney Cheung, MD; Guy Meyer, MD; Henri Bounameaux, MD; Menno V. Huisman, MD, PhD; Pieter W. Kamphuisen, MD, PhD; Grégoire Le Gal, MD, PhD

OBJECTIVE To prospectively validate whether an age-adjusted D-dimer cutoff, defined as age × 10 in patients 50 years or older, is associated with an increased diagnostic yield of D-dimer in elderly patients with suspected PE.

DESIGN, SETTINGS, AND PATIENTS A multicenter, multinational, prospective management outcome study in 19 centers in Belgium, France, the Netherlands, and Switzerland between January 1, 2010, and February 28, 2013.

INTERVENTIONS All consecutive outpatients who presented to the emergency department with clinically suspected PE were assessed by a sequential diagnostic strategy based on the clinical probability assessed using either the simplified, revised Geneva score or the 2-level Wells score for PE; highly sensitive D-dimer measurement; and computed tomography pulmonary angiography (CTPA). Patients with a D-dimer value between the conventional cutoff of 500 µg/L and their age-adjusted cutoff did not undergo CTPA and were left untreated and formally followed-up for a 3-month period.

MAIN OUTCOMES AND MEASURES The primary outcome was the failure rate of the diagnostic strategy, defined as adjudicated thromboembolic events during the 3-month follow-up period among patients not treated with anticoagulants on the basis of a negative age-adjusted D-dimer cutoff result.

Age-Adjusted D-Dimer Cutoff Levels to Rule Out Pulmonary Embolism
The ADJUST-PE Study

JAMA 2014;311:117

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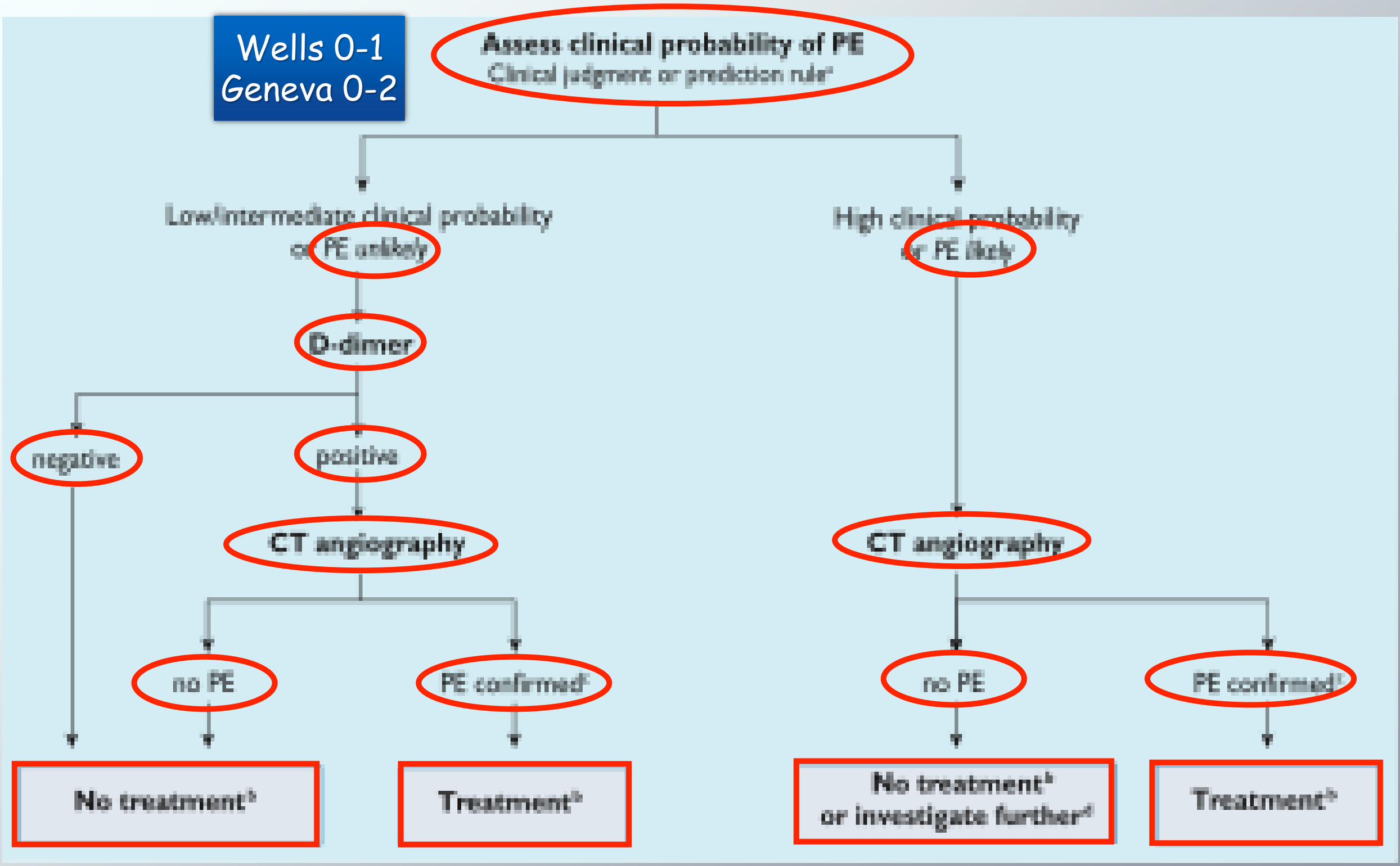
RESULTS Of the 3346 patients with suspected PE included, the prevalence of PE was 19%. Among the 2898 patients with a nonhigh or an unlikely clinical probability, 817 patients (28.2%) had a D-dimer level lower than 500 µg/L (95% CI, 26.6%-29.9%) and 337 patients (11.6%) had a D-dimer between 500 µg/L and their age-adjusted cutoff (95% CI, 10.5%-12.9%). The 3-month failure rate in patients with a D-dimer level higher than 500 µg/L but below the age-adjusted cutoff was 1 of 331 patients (0.3% [95% CI, 0.1%-1.7%]). Among the 766 patients 75 years or older, of whom 673 had a nonhigh clinical probability, using the age-adjusted cutoff instead of the 500 µg/L cutoff increased the proportion of patients in whom PE could be excluded on the basis of D-dimer from 43 of 673 patients (6.4% [95% CI, 4.8%-8.5%]) to 200 of 673 patients (29.7% [95% CI, 26.4%-33.3%]), without any additional false-negative findings.

CONCLUSIONS AND RELEVANCE Compared with a fixed D-dimer cutoff of 500 µg/L, the combination of pretest clinical probability assessment with age-adjusted D-dimer cutoff was associated with a larger number of patients in whom PE could be considered ruled out with a low likelihood of subsequent clinical venous thromboembolism.

Sospetta EP senza shock o ipotensione

Wells 0-1
Geneva 0-2



Terapia

In base al rischio di mortalità

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

sPESI

Parametro	sPESI
Età	1 (se età >80aa)
Neoplasia	1
Scompenso cardiaco cronico o pneumopatia cronica	1
FC>110 bpm	1
PAS <100mmHg	1
Saturazione O2 <90%	1

Terapia

In base al rischio prognostico

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

EP con shock o ipotensione

Pz ad alto rischio

Streptokinase	250 000 IU as a loading dose over 30 minutes, followed by 100 000 IU/h over 12–24 hours
	Accelerated regimen: 1.5 million IU over 2 hours
Urokinase	4400 IU/kg as a loading dose over 10 min, followed by 4400 IU/kg per hour over 12–24 hours
	Accelerated regimen: 3 million IU over 2 hours
rtPA	100 mg over 2 hours; or
	0.6 mg/kg over 15 minutes (maximum dose 50 mg)

+ K/h

Controindicazioni a Trombolisi

Absolute contraindications:[a]

- Haemorrhagic stroke or stroke of unknown origin at any time
- Ischaemic stroke in the preceding 6 months
- Central nervous system damage or neoplasms
- Recent major trauma/surgery/head injury in the preceding 3 weeks
- Gastrointestinal bleeding within the last month
- Known bleeding risk

Relative contraindications

- Transient ischaemic attack in the preceding 6 months
- Oral anticoagulant therapy
- Pregnancy, or within one week postpartum
- Non-compressible puncture site
- Traumatic resuscitation
- Refractory hypertension (systolic blood pressure >180 mm Hg)
- Advanced liver disease
- Infective endocarditis
- Active peptic ulcer

rischio intermedio

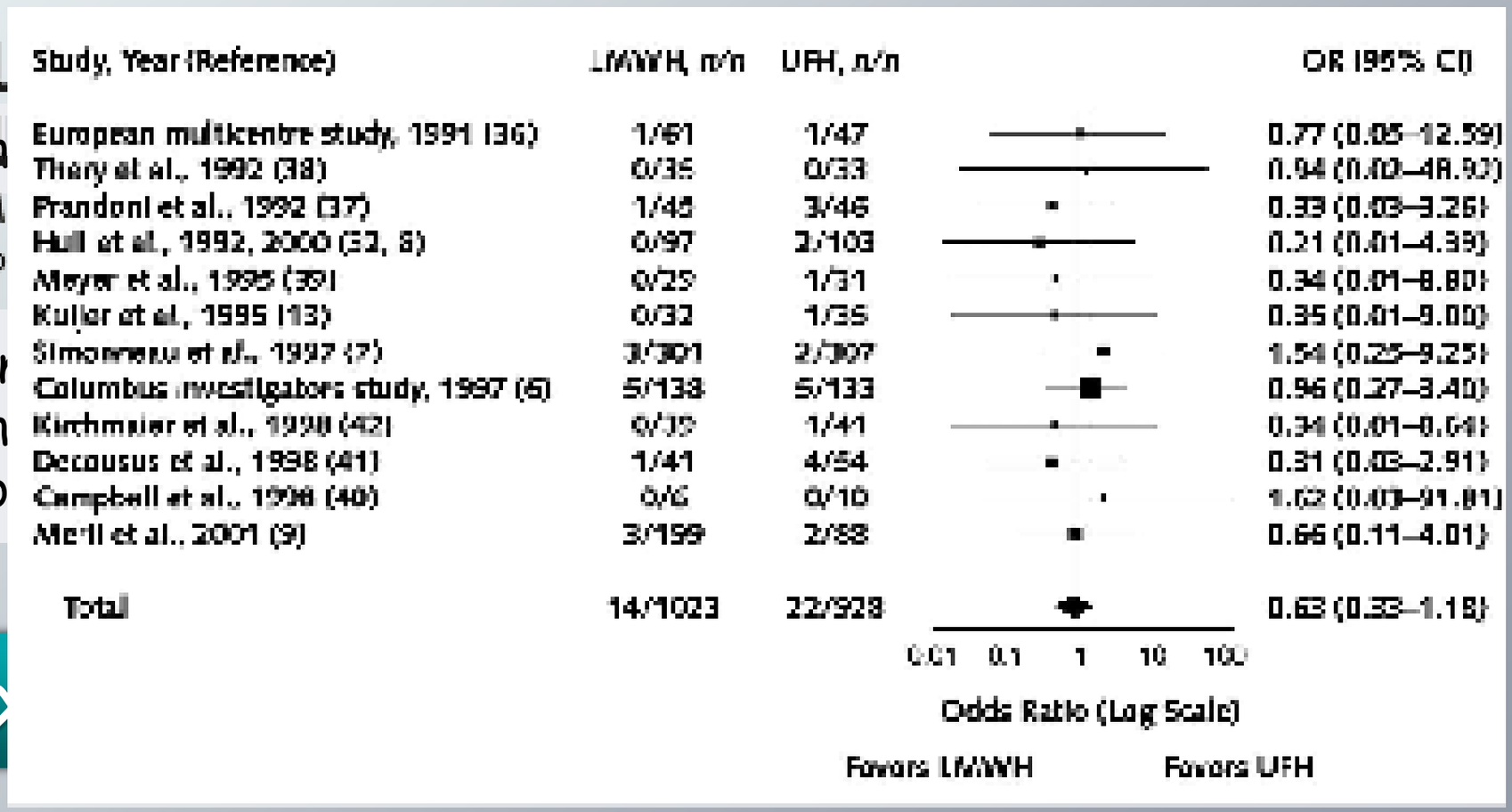
rischio basso

Anticoagulante parenterale

LMWEs

UFE

Fondaparinux



rischio intermedio

rischio basso

Anticoagulante parenterale

LMWEs

UFE

Fondaparinux

Table 10 Low molecular weight heparin and pentasaccharide (fondaparinux) approved for the treatment of pulmonary embolism

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

rischio intermedio

rischio basso

Anticoagulante parenterale

Anticoagulante orale

LMWEs

UFE

Fondaparinux

AVK

NAO

Apixaban
Dabigatran
Rivaroxaban

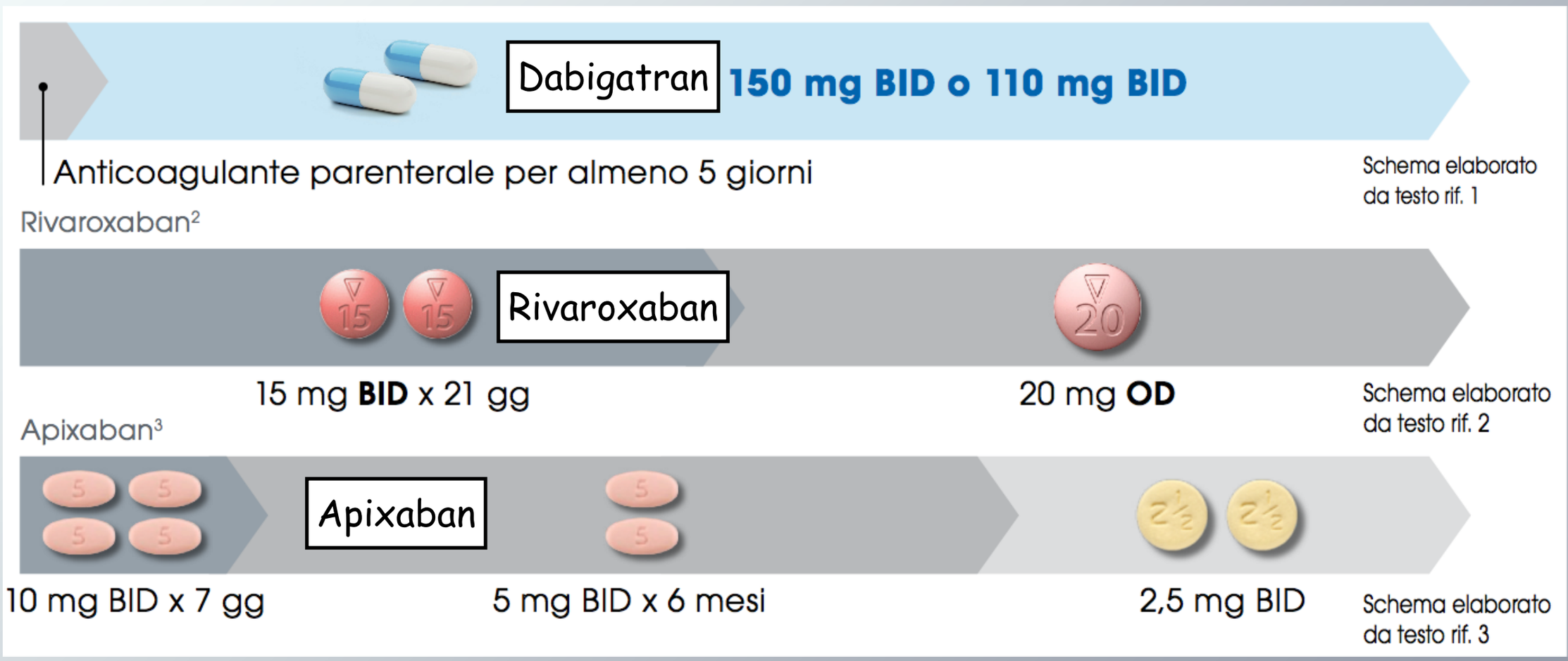
Quando iniziare l'anticoagulante orale

AVK

- L'anticoagulante orale dovrebbe essere iniziato il prima possibile
- Anticoagulante parenterale dovrebbe essere continuato fino a quando non è stato raggiunto e mantenuto range terapeutico PT INR per almeno 2 giorni

Quando iniziare l'anticoagulante orale

NAO



NAO

Drug	Trial	Design	Treatments and dosage	Duration	Patients	Efficacy outcome (results)	Safety outcome (results)
Dabigatran	RE-COVER[93]	Double-blind, double-dummy	Enoxaparin/dabigatran (150 mg b.i.d.)[a] vs. enoxaparin/warfarin	6 months	2539 patients with acute VTE	Recurrent VTE or fatal PE: 2.4% under dabigatran vs. 2.1% under warfarin	Major bleeding: 1.6% under dabigatran vs. 1.9% under warfarin
	RE-COVER II[94]	Double-blind, double-dummy	Enoxaparin/dabigatran (150 mg b.i.d.)[a] vs. enoxaparin/warfarin	6 months	2589 patients with acute VTE	Recurrent VTE or fatal PE: 2.3% under dabigatran vs. 2.2% under warfarin	Major bleeding: 15 patients under dabigatran vs. 22 patients under warfarin
Rivaroxaban	EINSTEIN-DVT[95]	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 patients with acute DVT	Recurrent VTE or fatal PE: 2.1% under rivaroxaban vs. 3.0% under warfarin	Major or CRNM bleeding: 8.1% under rivaroxaban vs. 8.1% under warfarin
	EINSTEIN-PE[96]	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 patients with acute PE	Recurrent VTE or fatal PE: 2.1% under rivaroxaban vs. 1.8% under warfarin	Major or CRNM bleeding: 10.3% under rivaroxaban vs. 11.4% under warfarin
Apixaban	AMPLIFY[97]	Double-blind, double-dummy	Apixaban (10 mg b.i.d. for 7 days, then 5 mg b.i.d.) vs. enoxaparin/warfarin	6 months	5395 patients with acute DVT and/or PE	Recurrent VTE or fatal PE: 2.3% under apixaban vs. 2.7% under warfarin	Major bleeding: 0.6% under apixaban vs. 1.8% under warfarin
Edoxaban	Hokusai-VTE[98]	Double-blind, double-dummy	LMWH/edoxaban (60 mg o.d.; 30 mg o.d. if creatinine clearance 30–50 ml/min or body weight <60 kg) vs. UFH or LMWH/warfarin	Variable, 3–12 months	8240 patients with acute DVT and/or PE	Recurrent VTE or fatal PE: 3.2% under edoxaban vs. 3.5% under warfarin	Major or CRNM bleeding: 8.5% under edoxaban vs. 10.3% under warfarin

concludendo … EP nel paziente oncologico

Diagnosi

- La presenza di neoplasia rientra nella valutazione della probabilità clinica di EP

    - D-DIMERO
- stesso significato predittivo negativo
- solitamente più elevato nel paziente neoplastico
- un unico studio ha proposto cut-off di 700ug/L o cut-off aggiustato per età

Thromb Haemost 2010;104:831-836

concludendo … EP nel paziente oncologico

Terapia

Figure 2. Forest plot of comparison: 1 Low molecular weight heparin (LMWH) versus unfractionated heparin (UFH), outcome: 1.1 Mortality at 3 months.

Anticoagulation for the initial treatment of venous

Study or Subgroup	LMWH Events	LMWH Total	UHH Events	UHH Total	Weight	Risk Ratio M H, Random, 95% CI
Columbus 1997	20	119	27	113	38.5%	0.70 [0.42, 1.18]
Dulcux 1991	0	6	2	12	1.2%	0.37 [0.02, 6.71]
Gallel 2004	3	76	5	80	5.3%	0.63 [0.16, 2.55]
Hull 1992	7	48	14	49	15.6%	0.53 [0.24, 1.20]
Kackman 1996	3	34	3	35	4.4%	1.06 [0.23, 4.68]
Levine 1996	11	48	14	57	21.8%	0.97 [0.49, 1.94]
Lindmarker 1994	2	7	2	9	3.6%	1.29 [0.24, 6.99]
Lopaciuk 1997	0	7	0	2		Not estimable
Prandoni 1992	1	15	6	13	2.8%	0.20 [0.03, 1.46]
Simonneau 1993	2	7	1	2	3.1%	0.57 [0.09, 3.51]
Simonneau 1997	2	26	4	34	3.9%	0.65 [0.13, 3.30]
Total (95% CI)		**389**		**412**	**100.0%**	**0.71 [0.52, 0.98]**
Total events	51		70			

Heterogeneity: Tau² = 0.00; Chi² = 3.88, df = 9 (P = 0.92); I² = 0%
Test for overall effect: Z = 2.07 (P = 0.04)

Risk Ratio M H, Random, 95% CI

0.01 0.1 1 10 100
Favors LMWH Favors UFH

- In questa review sistematica, i dati ricavati da 13 studi suggeriscono che LMWE è superiore rispetto all'UFE nel ridurre la mortalità a 3 mesi. Per contro non vi è sufficiente evidenza di una superiorità nel ridurre recidive di eventi tromboembolici.

concludendo … EP nel paziente oncologico

Terapia

Anticoagulation for the long-term treatment of venous thromboembolism in patients with cancer

Elie A Akl[1], Lara A Kahale[2], Maddalena Barba[3], Ignacio Neumann[4], Nawman Labedi[5], Irene Terrenato[6], Francesca Sperati[6], Paola Muti[7], Holger Schünemann[8]

- Nel lungo termine, la terapia con LMWE rispetto a VKA si è dimostrata in grado di ridurre gli eventi tromboembolici mentre non ha dimostrato vantaggi sulla mortalità.

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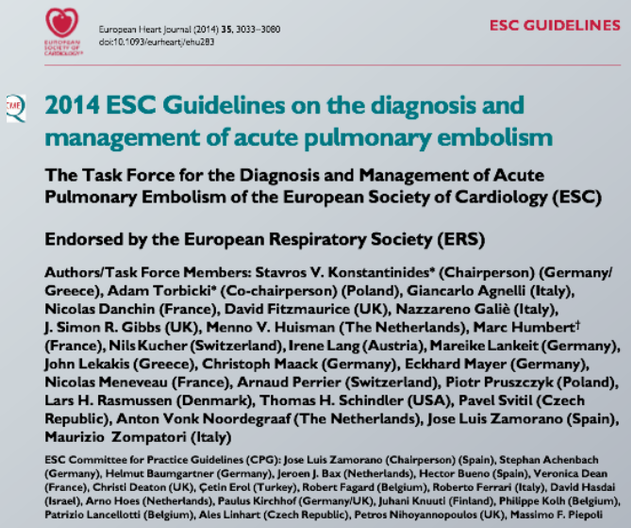
Editorial group: Cochrane Gynaecological Cancer Group.
Publication status and date: Edited (no change to conclusions), published in Issue 2, 2015.
Review content assessed as up-to-date: 9 February 2013.

Citation: Akl EA, Kahale LA, Barba M, Neumann I, Labedi N, Terrenato I, Sperati F, Muti P, Schünemann H. Anticoagulation for the long-term treatment of venous thromboembolism in patients with cancer. *Cochrane Database of Systematic Reviews* 2014, Issue 7. Art. No.: CD006650. DOI: 10.1002/14651858.CD006650.pub4.

concludendo … EP nel paziente oncologico

Terapia



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Endorsed by the European Respiratory Society (ERS)

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- LMWH in fase acuta e per il proseguimento della terapia dovrebbe essere la terapia anticoagulante nel paziente oncologico

Eventi tromboembolici nel paziente neoplastico

Grazie per l'attenzione

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Ospedale Sacro Cuore - Don Calabria
Negrar

Ospedale
Sacro Cuore - Don Calabria
Negrar (Verona)