Embolia polmonare e TVP: trattamento in acuto secondo le linee guida ESC

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20 MINUTI PER…

Linee guida ESC 2014 FASE ACUTA alto rischio e non alto rischio

Linee guida CHEST 2016

Come scegliere la terapia? Teoria e pratica

Quando scegliere è difficile:
TEP subsegmentaria, TVP distale isolata

Quando scegliere sembra troppo facile:
il pz a basso rischio

European Heart Journal (2014) **35**, 3033–3080
doi:10.1093/eurheartj/ehu283

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)

[Evidence-Based Medicine]

CHEST

Antithrombotic Therapy for VTE Disease

CHEST Guideline and Expert Panel Report

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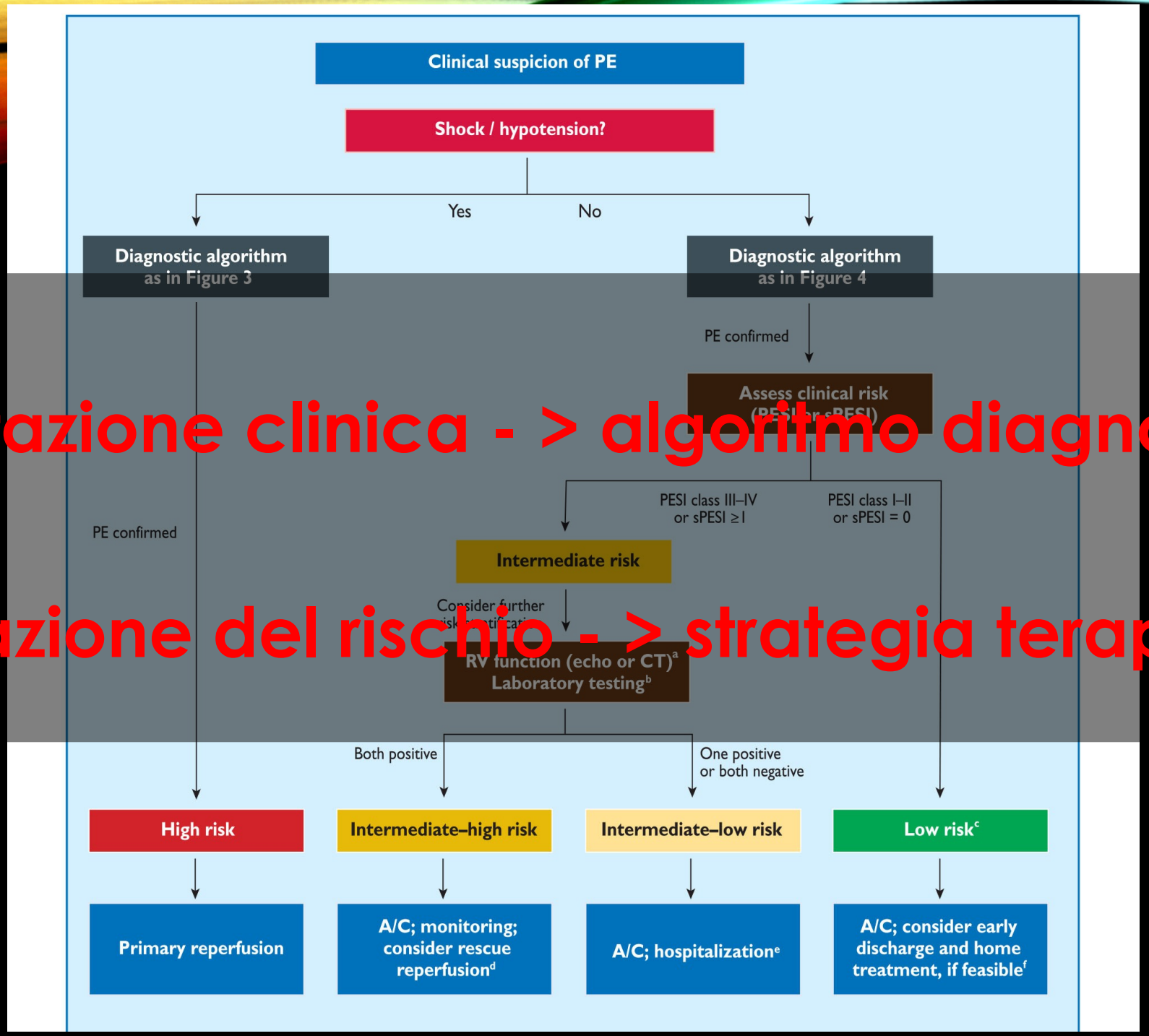
PODCAST



Presentazione clinica - > algoritmo diagnostico

Stratificazione del rischio - > strategia terapeutica

Table 7 Original and simplified PESI

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
	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%) **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%)

b.p.m. = beats per minute; PESI = Pulmonary embolism severity index.
[a]based on the sum of points.

Table 9 Classification of patients with acute PE based on early mortality risk

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]	

PE = pulmonary embolism; PESI = Pulmonary embolism severity index; RV = right ventricular; sPESI = simplified Pulmonary embolism severity index.

[a]PESI Class III to V indicates moderate to very high 30-day mortality risk; sPESI ≥1 point(s) indicate high 30-day mortality risk.

[b]Echocardiographic criteria of RV dysfunction include RV dilation and/or an increased end-diastolic RV–LV diameter ratio (in most studies, the reported threshold value was 0.9 or 1.0); hypokinesia of the free RV wall; increased velocity of the tricuspid regurgitation jet; or combinations of the above. On computed tomographic (CT) angiography (four-chamber views of the heart), RV dysfunction is defined as an increased end-diastolic RV/LV (left ventricular) diameter ratio (with a threshold of 0.9 or 1.0).

[c]Markers of myocardial injury (e.g. elevated cardiac troponin I or -T concentrations in plasma), or of heart failure as a result of (right) ventricular dysfunction (elevated natriuretic peptide concentrations in plasma).

[d]Neither calculation of the PESI (or sPESI) nor laboratory testing are considered necessary in patients with hypotension or shock.

[e]Patients in the PESI Class I–II, or with sPESI of 0, and elevated cardiac biomarkers or signs of RV dysfunction on imaging tests, are also to be classified into the intermediate-low-risk category. This might apply to situations in which imaging or biomarker results become available before calculation of the clinical severity index.

FASE ACUTA

ALTO RISCHIO

Supporto emodinamico e respiratorio

Trombolisi primaria

UFH

Embolectomia chirurgica e trattamenti percutanei

NON ALTO RISCHIO

EBPM/fondaparinux/VKA/NAO

Trombolisi rescue ?

FASE ACUTA
ALTO RISCHIO

Recommendations for acute phase treatment

Recommendations	Class[a]	Level[b]	Ref[c]
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	168
Surgical pulmonary embolectomy is recommended for patients in whom thrombolysis is contraindicated or has failed.[d]	I	C	313
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	

Systemic Thrombolytic Therapy for PE

21. In patients with acute PE associated with hypotension (eg, systolic BP <90 mm Hg) who do not have a high bleeding risk, we suggest systemically administered thrombolytic therapy over no such therapy (Grade 2B).

FASE ACUTA:
NON ALTO RISCHIO

Reperfusion treatment			
Routine use of primary systemic thrombolysis is not recommended in patients not suffering from shock or hypotension.	III	B	253
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	253
Thrombolytic therapy should be considered for patients with intermediate-high-risk PE and clinical signs of haemodynamic decompensation.	IIa	B	252, 253
Surgical pulmonary embolectomy may be considered in intermediate-high-risk patients if the anticipated risk of bleeding under thrombolytic treatment is high.[g]	IIb	C	
Percutaneous catheter-directed treatment may be considered in intermediate-high-risk patients if the anticipated risk of bleeding under thrombolytic treatment is high.[g]	IIb	B	336

***22. In most patients with acute PE not associated with hypotension, we recommend against systemically administered thrombolytic therapy** (Grade 1B).

***23. In selected patients with acute PE who deteriorate after starting anticoagulant therapy but have yet to develop hypotension and who have a low bleeding risk, we suggest systemically administered thrombolytic therapy over no such therapy** (Grade 2C).

FASE ACUTA: NON ALTO RISCHIO

Recommendations for acute phase treatment

Recommendations	Class[a]	Level[b]	Ref[c]
PE without shock or hypotension (intermediate-or low-risk)[d]			
Anticoagulation: combination of parenteral treatment with VKA			
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	352
LMWH or fondaparinux is the recommended form of acute phase parenteral anticoagulation for most patients.	I	A	273, 274, 281, 353
In parallel to parenteral anticoagulation, treatment with a VKA is recommended, targeting an INR of 2.5 (range 2.0–3.0).	I	B	352, 354

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

FASE ACUTA:
NON ALTO RISCHIO

Anticoagulation: new oral anticoagulants			
As an alternative to the combination of parenteral anticoagulation with a VKA, anticoagulation with rivaroxaban (15 mg twice daily for 3 weeks, followed by 20 mg once daily) is recommended.	I	B	296
As an alternative to the combination of parenteral anticoagulation with a VKA, anticoagulation with apixaban (10 mg twice daily for 7 days, followed by 5 mg twice daily) is recommended.	I	B	297
As an alternative to VKA treatment, administration of dabigatran (150 mg twice daily, or 110 mg twice daily for patients ≥80 years of age or those under concomitant verapamil treatment) is recommended following acute-phase parenteral anticoagulation.	I	B[e]	293, 294
As an alternative to VKA treatment, administration of edoxaban* is recommended following acute-phase parenteral anticoagulation.	I	B	298

***2. In patients with DVT of the leg or PE and no cancer, as long-term (first 3 months) anticoagulant therapy, we suggest dabigatran, rivaroxaban, apixaban, or edoxaban over vitamin K antagonist (VKA) therapy** (all Grade 2B).

For patients with DVT of the leg or PE and no cancer who are not treated with dabigatran, rivaroxaban, apixaban, or edoxaban, we suggest VKA therapy over low-molecular weight heparin (LMWH) (Grade 2C).

Table 11 Overview of phase III clinical trials with non-vitamin K-dependent new oral anticoagulants (NOACs) for the acute-phase treatment and standard duration of anticoagulation after VTE

Drug	Trial	Design	Treatments and dosage	Duration	Patients	Efficacy outcome (results)	Safety outcome (results)
Dabigatran	RE-COVER[293]	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[294]	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[295]	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[296]	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[297]	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[298]	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

b.i.d. = bis in die (twice daily); CRNM = clinically relevant non-major; DVT= deep vein thrombosis; o.d. = omni die (once daily); PE= pulmonary embolism; UFH = unfractionated heparin; VTE = venous thromboembolism.

[a] Approved doses of dabigatran are 150 mg b.i.d. and 110 mg b.i.d.

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Direct oral anticoagulants compared with vitamin K antagonists for acute venous thromboembolism: evidence from phase 3 trials

Nick van Es, Michiel Coppens, Sam Schulman, Saskia Middeldorp and Harry R. Büller

In the last 4 years, 6 phase 3 trials including a total of 27 023 patients with venous thromboembolism (VTE) compared a direct oral anticoagulant (DOAC) with vitamin K antagonists (VKAs). To aid the clinician in assessing the amount of information, we address frequently raised clinical questions in a review of combined trial results. We included the phase 3 trials that compared dabigatran etexilate, rivaroxaban, apixaban, or edoxaban with VKA therapy in patients with acute symptomatic VTE. Recurrent VTE occurred in 2.0% of DOAC recipients compared with 2.2% in VKA recipients (relative risk [RR] 0.90, 95% confidence interval [CI] 0.77-1.06). Treatment with a DOAC significantly reduced the risk of major bleeding (RR 0.61, 95% CI 0.45-0.83). In parallel, intracranial bleeding, fatal bleeding, and clinically relevant nonmajor bleeding occurred significantly less in DOAC recipients. The efficacy and safety of DOACs were consistent in patients with pulmonary embolism, deep venous thrombosis, a body weight ≥100 kg, moderate renal insufficiency, an age ≥75 years, and cancer. In conclusion, DOACs and VKAs have similar efficacy in the treatment of acute symptomatic VTE, a finding that is consistent in key clinical subgroups. Treatment with a DOAC significantly reduces the risks of major bleeding. (*Blood*. 2014;124(12):1968-1975)

TRATTAMENTO: INIZIALE – LONG TERM- EXTENDED

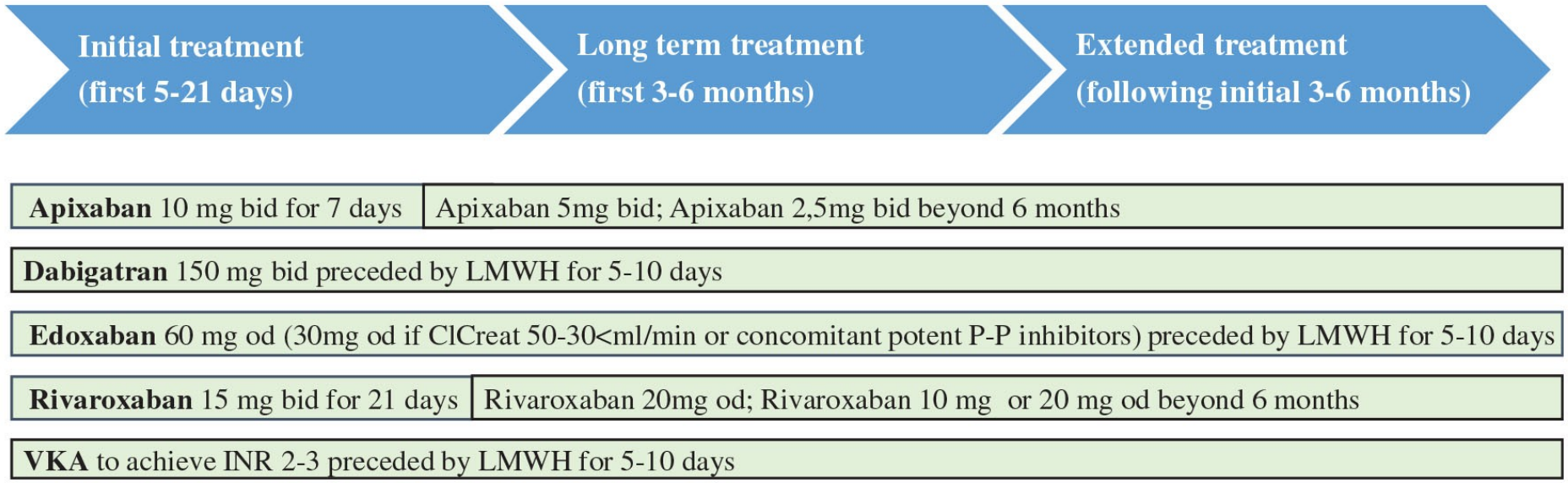


Figure 3 Deep vein thrombosis treatment phases. ClCreat: creatinine clearance; LMWH: low molecular weight heparin; P-P inhibitors: proton pump inhibitors; VKA: vitamin K antantagonist.

Recommendations for duration of anticoagulation after pulmonary embolism

Recommendations	Class[a]	Level[b]	Ref[c]
For patients with PE secondary to a transient (reversible) risk factor, oral anticoagulation is recommended for 3 months.	I	B	358
For patients with unprovoked PE, oral anticoagulation is recommended for at least 3 months.	I	A	363, 372–374
Extended oral anticoagulation should be considered for patients with a first episode of unprovoked PE and low bleeding risk .	IIa	B	375
Anticoagulation treatment of indefinite duration is recommended for patients with a second episode of unprovoked PE.	I	B	360

Duration of Anticoagulant Therapy

5. In patients with a proximal DVT of the leg or PE provoked by surgery, we recommend treatment with anticoagulation for 3 months over (i) treatment of a shorter period (Grade 1B), **(ii) treatment of a longer time-limited period (eg, 6, 12, or 24 months)** (Grade 1B), **or (iii) extended therapy (no scheduled stop date)** (Grade 1B).

6. In patients with a proximal DVT of the leg or PE provoked by a nonsurgical transient risk factor, we recommend treatment with anticoagulation for 3 months over (i) treatment of a shorter period (Grade 1B) **and (ii) treatment of a longer time-limited period (eg, 6, 12, or 24 months)** (Grade 1B). **We suggest treatment with anticoagulation for 3 months over extended therapy if there is a low or moderate bleeding risk** (Grade 2B), **and recommend treatment for 3 months over extended therapy if there is a high risk of bleeding** (Grade 1B).

8. In patients with an unprovoked DVT of the leg (isolated distal or proximal) or PE, we recommend treatment with anticoagulation for at least 3 months over treatment of a shorter duration (Grade 1B), **and we recommend treatment with anticoagulation for 3 months over treatment of a longer time-limited period (eg, 6, 12, or 24 months)** (Grade 1B).

9. In patients with a first VTE that is an unprovoked proximal DVT of the leg or PE and who have a (i) low or moderate bleeding risk (see text), we suggest extended anticoagulant therapy (no scheduled stop date) over 3 months of therapy (Grade 2B), **and (ii) high bleeding risk (see text), we recommend 3 months of anticoagulant therapy over extended therapy (no scheduled stop date)** (Grade 1B).

10. In patients with a second unprovoked VTE and who have a (i) low bleeding risk (see text), we recommend extended anticoagulant therapy (no scheduled stop date) over 3 months (Grade 1B); **(ii) moderate bleeding risk (see text), we suggest extended anticoagulant therapy over 3 months of therapy** (Grade 2B); **or (iii) high bleeding risk (see text), we suggest 3 months of anticoagulant therapy over extended therapy (no scheduled stop date)** (Grade 2B).

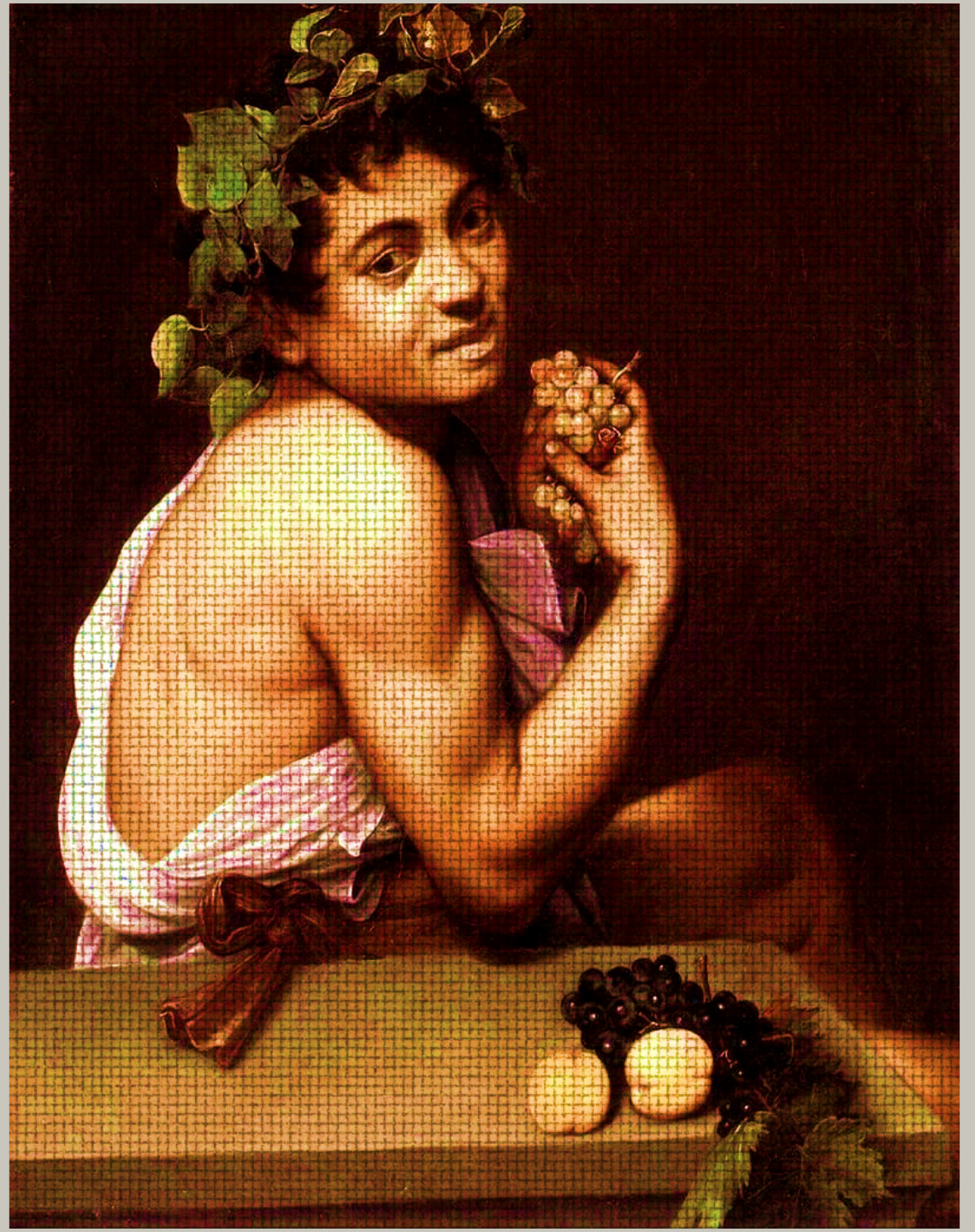
Come scegliere?

Scelta del farmaco
Scelta della dose

Teoria

Pratica

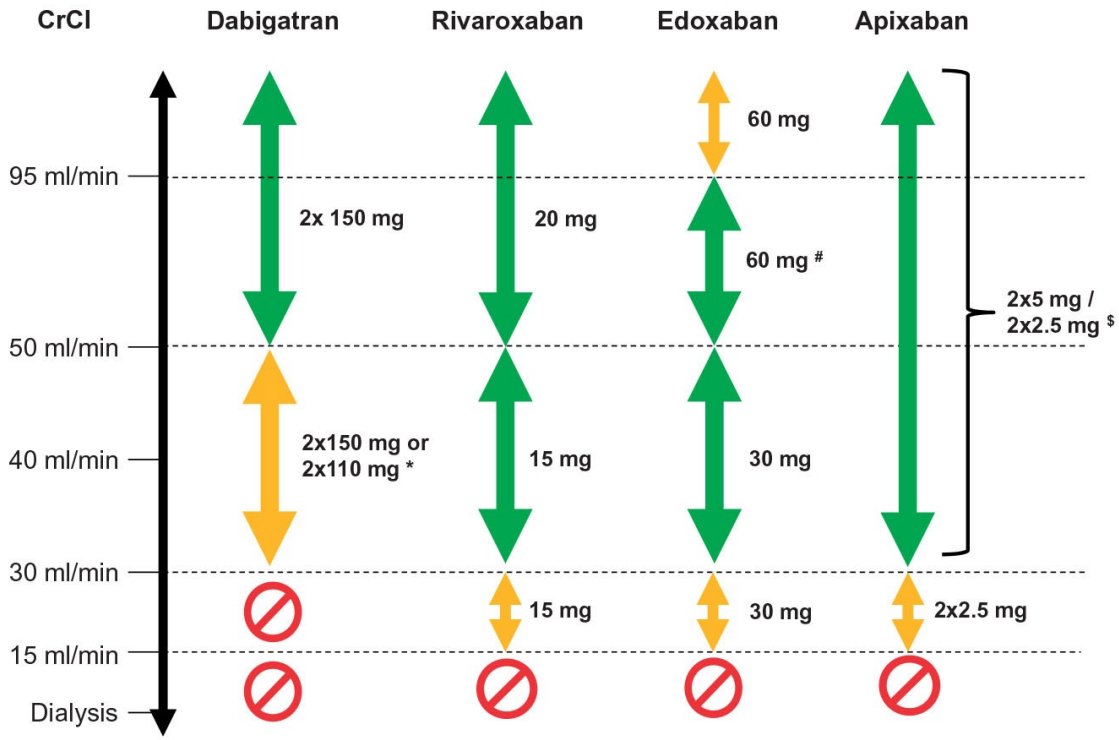
Visione d’insieme e cosa non scegliere



Età

Funzione renale?

New oral anticoagulants (rivaroxaban, apixaban, dabigatran, edoxaban) are not recommended in patients with severe renal impairment.[f]	III	A	293, 295–298



Funzione epatica?

Table 8 Calculation of the Child-Turcotte-Pugh score and use of NOACs in hepatic insufficiency

Parameters	1 point	2 points	3 points
Encephalopathy	No	Grade 1–2 (suppressed with medication)	Grade 3–4 (refractory/chronic)
Ascites	No	Mild (diuretic-responsive)	Moderate–severe (diuretic-refractory)
Bilirubin	<2 mg/dL	2–3 mg/dL	>3 mg/dL
	<34 µmol/L	34–50 µmol/L	>50 µmol/L
Albumin	>3.5 g/dL	2.8–3.5 g/dL	<2.8 g/dL
	>35 g/L	28–35 g/L	<28 g/dL
INR	<1.7	1.71–2.30	>2.30

Child–Pugh category	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
A (5–6 points)	No dose reduction	No dose reduction	No dose reduction	No dose reduction
B (7–9 points)	Use with caution	Use cautiously	Use cautiously	Do not use
C (10–15 points)	Do not use	Do not use	Do not use	Do not use

Table 3 Effect of drug–drug interactions and clinical factors on NOAC plasma levels ('area under the curve')

	Via	Dabigatran etexilate	Apixaban	Edoxaban	Rivaroxaban
P-gp substrate		Yes	Yes	Yes	Yes
CYP3A4 substrate		No	Yes (≈25%)	No (<4%)	Yes (≈18%)[131]
Antiarrhythmic drugs					
Amiodarone	moderate P-gp competition	+12 to 60%[SmPC]	No PK data[a]	+40%[132–134]	Minor effect[a]
Digoxin	P-gp competition	No effect[SmPC]	No effect[135]	No effect	No effect[SmPC]
Diltiazem	P-gp competition and weak CYP3A4 inhibition	No effect[SmPC]	+40%[136]	No data yet	No effect
Dronedarone	P-gp competition and CYP3A4 inhibition	+70 to 100% (US: 2 × 75 mg if CrCl 30–50 mL/min)	No PK or PD data: caution	+85%[b]	Moderate effect, should be avoided
Quinidine	P-gp competition	+53%[SMPC]	No data yet	+77%[137] (no dose reduction required by label)	Extent of increase unknown
Verapamil	P-gp competition (and weak CYP3A4 inhibition)	+12 to 180%[SmPC] (if taken simultaneously)	No PK data	+53% (SR)[137,142] (no dose reduction required by label)	No effect
Other cardiovascular drugs					
Atorvastatin	P-gp competition and CYP3A4 inhibition	No relevant interaction	No data yet	No effect	No effect
Ticagrelor	P-gp competition	+25%[SmPC] (give loading dose 2h after dabigatran)[d]	No data	No data	No data
Antibiotics					
Clarithromycin; Erythromycin	Moderate P-gp competition and strong CYP3A4 inhibition	+15 to 20%	+60% AUC +30% C_{max}	+90%[SmPC]	+34% (Erythromycin)/ +54% (Clarithromycin) SmPC129
Rifampicin	P-gp/BCRP and CYP3A4/ CYP2J2 inducers	Minus 66%[SmPC]	Minus 54%[138]	Minus 35%, but with compensatory increase of active metabolites	Up to minus 50%[SmPc]
Antiviral drugs					
HIV protease inhibitors (e.g. ritonavir)	P-gp and BCRP competition or inducer; CYP3A4 inhibition	No data yet	Strong increase[SmPC]	No data yet	Up to +153%[129]
Fungostatics					
Fluconazole	Moderate CYP3A4 inhibition	No data yet	No data yet	No data yet	+42% (if systemically administered)[SmPC]
Itraconazole; Ketoconazole; Voriconazole	potent P-gp and BCRP competition; CYP3A4 inhibition	+140 to 150% (US: 2 x 75 mg if CrCl 30–50 mL/min)	+100%[136]	+87 to 95%[132] (reduce NOAC dose by 50%)	Up to +160%[SmPc]
Posaconasole	Mild to moderate P-gp inhibition	SmPC	SmPC		SmPC
Others					
Naproxen	P-gp competition; pharmacodynamically increased bleeding time	No data yet	+55%[139]	No effect	No data yet
H2B; PPI; Al-mg-hydroxide	GI absorption	Minus 12–30%	No effect	No effect[SmPc]	No effect[140]
St. John's wort	P-gp/BCRP and CYP3A4/ CYP2J2 inducers				
Other factors					
Age ≥80 years	Potential for Increased plasma levels		b	c	
Age ≥75 years	Potential for Increased plasma levels			c	
Weight ≤60 kg	Potential for Increased plasma levels		b	b	
Renal function	Increased plasma level	See *Figure 4*			
Other increased bleeding risk		• Concomitant antiplatelet drugs; NSAID; systemic steroid therapy; other anticoagulants • History of GI bleeding • Recent surgery on critical organ (brain; eye) • Frailty/falls risk • St.p bleeding or predisposition (anaemia, thrombocytopenia)			

The hatched colour coding indicates no clinical or PK data available, and recommendations are based on the respective NOAC SmPC (where available) or expert opinion.
White: No relevant drug–drug interaction anticipated.
Yellow: Consider dose adjustment or different NOAC if 2 or more 'yellow' factors are present (see *Figure 3*).
Orange: Consider dose adjustment or different NOAC (see *Figure 3*).
Red: contraindicated/not recommended.
Brown: Contraindicated due to *reduced* NOAC plasma levels.
Blue: The label for edoxaban mentions that co-administration is possible in these cases, despite a decreased plasma level, which are deemed not clinically relevant. Since not tested prospectively, however, such concomitant use should be used with caution, and avoided when possible.
BCRP, breast cancer resistance protein; NSAID, non-steroidal anti-inflammatory drugs; H2B, H2-blockers; PPI, proton pump inhibitors; P-gp, P-glycoprotein; GI, gastrointestinal.
[a]Based on *in vitro* investigations, comparing the IC_{50} for P-gp inhibition to maximal plasma levels at therapeutic dose, and/or on interaction analysis of efficacy and safety endpoints in the Phase-3 clinical trials.[29,30] No direct PK interaction data available.
[b]Dose reduction based on published criteria (see *Table 13*, *Figure 3*).
[c]Age had no significant effect after adjusting for weight and renal function.
[d]Data from Phase I study. Evidence from Re-DUAL PCI indicate safety in the (small) subgroup on dabigatran and ticagrelor.[141]

Controlli?
Antidoti?

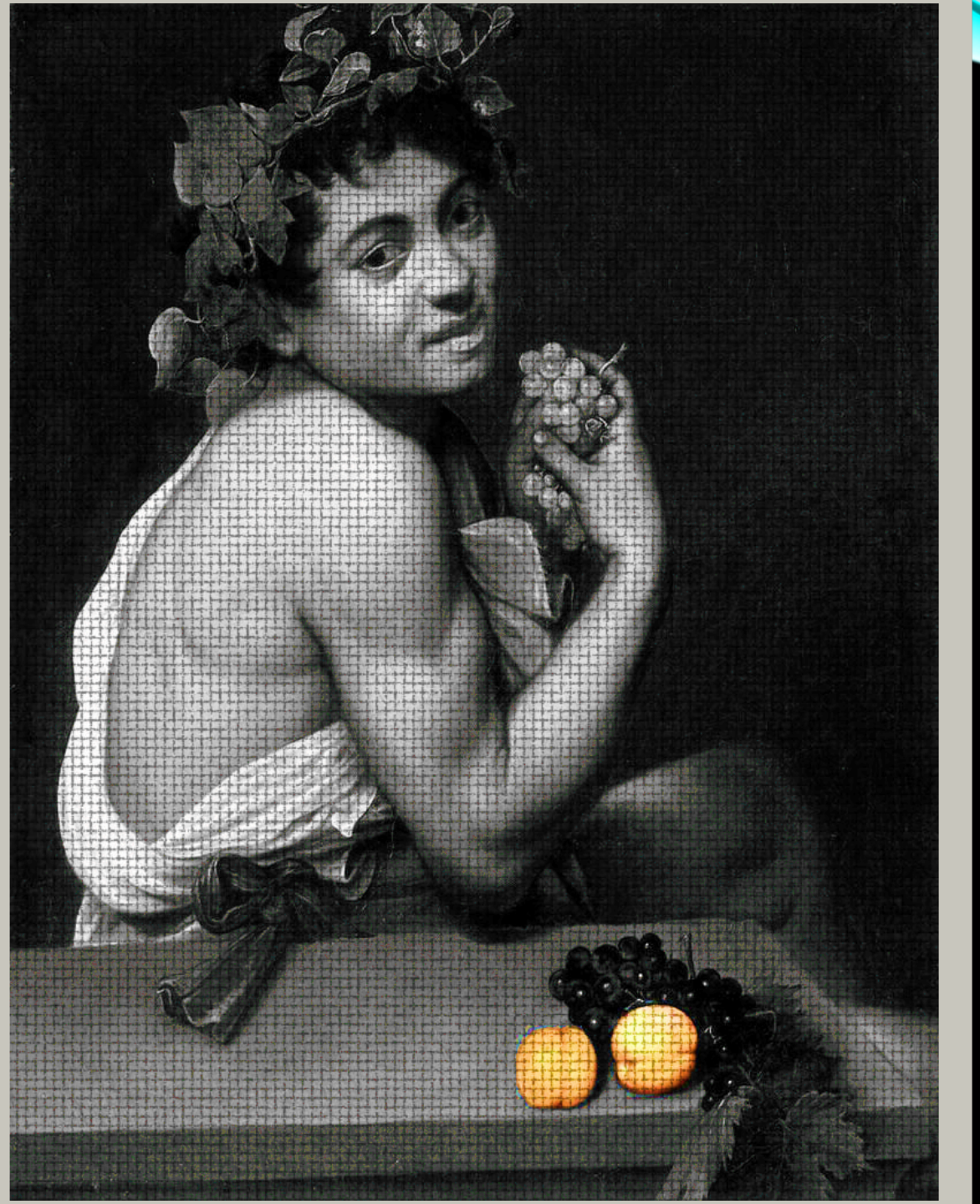


Table 9 Plasma levels and coagulation assays in patients treated with non-vitamin K antagonist oral anticoagulants

	Dabigatran[229,230]	Apixaban[231], SmPc	Edoxaban[184,232]	Rivaroxaban[131,186]
Expected plasma levels of NOACs in patients treated for AF (based on dTT/ECA for dabigatran and anti-FXa activity for Xa inhibitors)				
Expected range of plasma levels *at peak* for standard dose (ng/mL)[a]	64–443	69–321	91–321	184–343
Expected range of plasma levels *at trough* for standard dose (ng/mL)[a]	31–225	34–230	31–230	12–137
Expected impact of NOACs on routine coagulation tests				
PT	↑	(↑)	↑(↑)	↑↑ (↑)
aPTT	↑↑(↑)	(↑)	↑	↑
ACT	↑(↑)	↑	↑	↑
TT	↑↑↑↑	—	—	—

Ranges indicate the P5/95 percentiles for dabigatran, rivaroxaban, and apixaban, and the interquartile ranges for edoxaban.
The reagents influence the sensitivity of the PT for FXa inhibitors and of the aPTT for dabigatran. When a sensitive assay is used, normal aPTT excludes above on-therapy levels in dabigatran-treated patients, and normal PT excludes above on-therapy levels in rivaroxaban and edoxaban, but not apixaban treated patients. Point-of-care INR devices developed to monitor vitamin K antagonists do not accurately reflect the anticoagulant status of NOAC treated patients.
ACT, activated clotting time; aPTT, activated partial thromboplastin time; dTT, diluted thrombin time; ECA, ecarin clotting assay; INR, international normalized ratio; PT, prothrombin time.

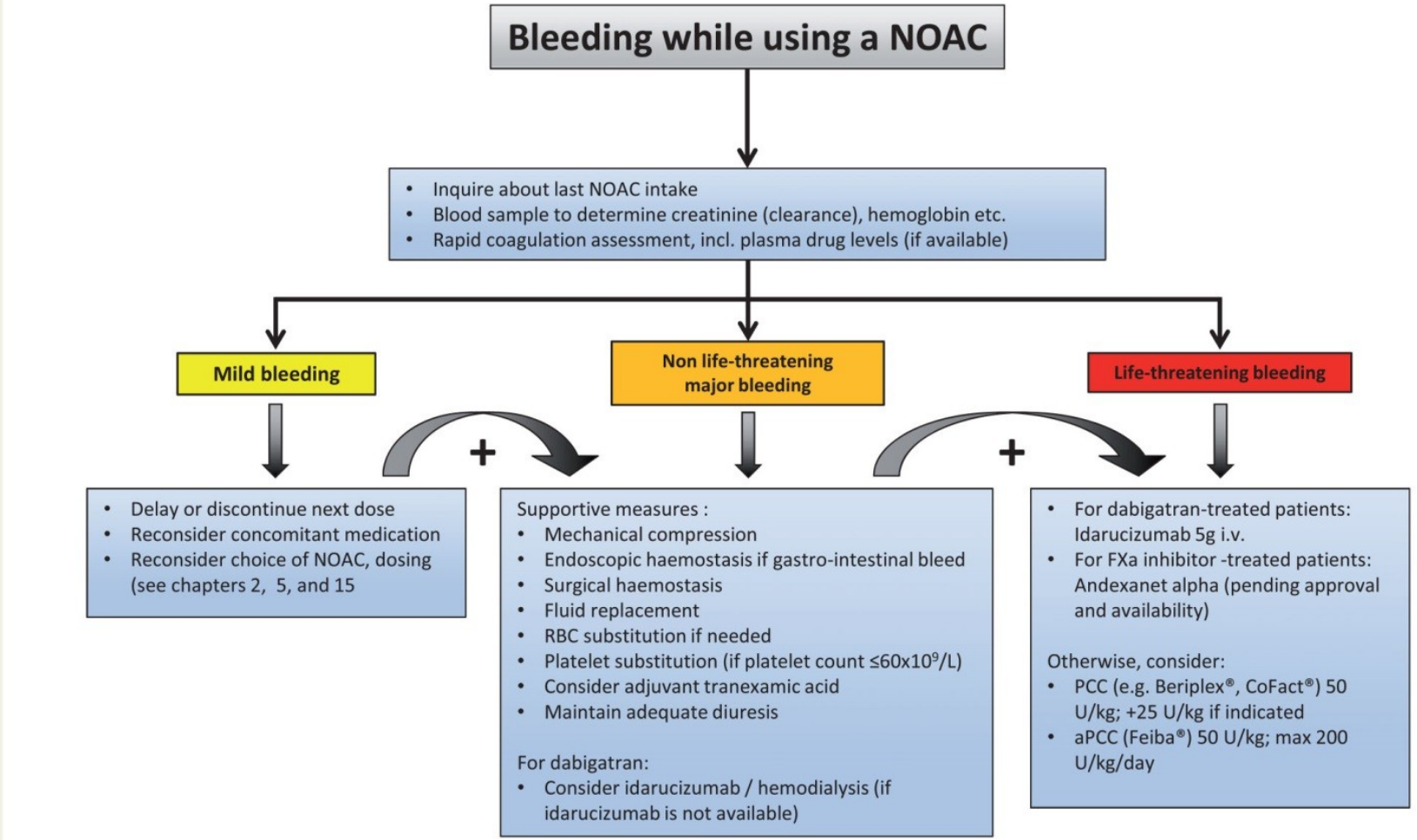


Figure 5 Management of bleeding in patients taking non-vitamin K antagonist oral anticoagulants.

The NEW ENGLAND JOURNAL of MEDICINE

Agosto 2015

ORIGINAL ARTICLE

Idarucizumab for Dabigatran Reversal

Charles V. Pollack, Jr., M.D., Paul A. Reilly, Ph.D., John Eikelboom, M.B., B.S., Stephan Glund, Ph.D., Peter Verhamme, M.D., Richard A. Bernstein, M.D., Ph.D., Robert Dubiel, Pharm.D., Menno V. Huisman, M.D., Ph.D., Elaine M. Hylek, M.D., Pieter W. Kamphuisen, M.D., Ph.D., Jörg Kreuzer, M.D., Jerrold H. Levy, M.D., Frank W. Sellke, M.D., Joachim Stangier, Ph.D., Thorsten Steiner, M.D., M.M.E., Bushi Wang, Ph.D., Chak-Wah Kam, M.D., and Jeffrey I. Weitz, M.D.

The NEW ENGLAND JOURNAL of MEDICINE

Dicembre 2015

ORIGINAL ARTICLE

Andexanet Alfa for the Reversal of Factor Xa Inhibitor Activity

Deborah M. Siegal, M.D., John T. Curnutte, M.D., Ph.D., Stuart J. Connolly, M.D., Genmin Lu, Ph.D., Pamela B. Conley, Ph.D., Brian L. Wiens, Ph.D., Vandana S. Mathur, M.D., Janice Castillo, B.S., Michele D. Bronson, Ph.D., Janet M. Leeds, Ph.D., Florie A. Mar, Ph.D., Alex Gold, M.D., and Mark A. Crowther, M.D.

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Agosto 2017

ORIGINAL ARTICLE

Idarucizumab for Dabigatran Reversal — Full Cohort Analysis

Charles V. Pollack, Jr., M.D., Paul A. Reilly, Ph.D., Joanne van Ryn, Ph.D., John W. Eikelboom, M.B., B.S., Stephan Glund, Ph.D., Richard A. Bernstein, M.D., Ph.D., Robert Dubiel, Pharm.D., Menno V. Huisman, M.D., Ph.D., Elaine M. Hylek, M.D., Chak-Wah Kam, M.D., Pieter W. Kamphuisen, M.D., Ph.D., Jörg Kreuzer, M.D., Jerrold H. Levy, M.D., Gordon Royle, M.D., Frank W. Sellke, M.D., Joachim Stangier, Ph.D., Thorsten Steiner, M.D., Peter Verhamme, M.D., Bushi Wang, Ph.D., Laura Young, M.D., and Jeffrey I. Weitz, M.D.

The NEW ENGLAND JOURNAL of MEDICINE

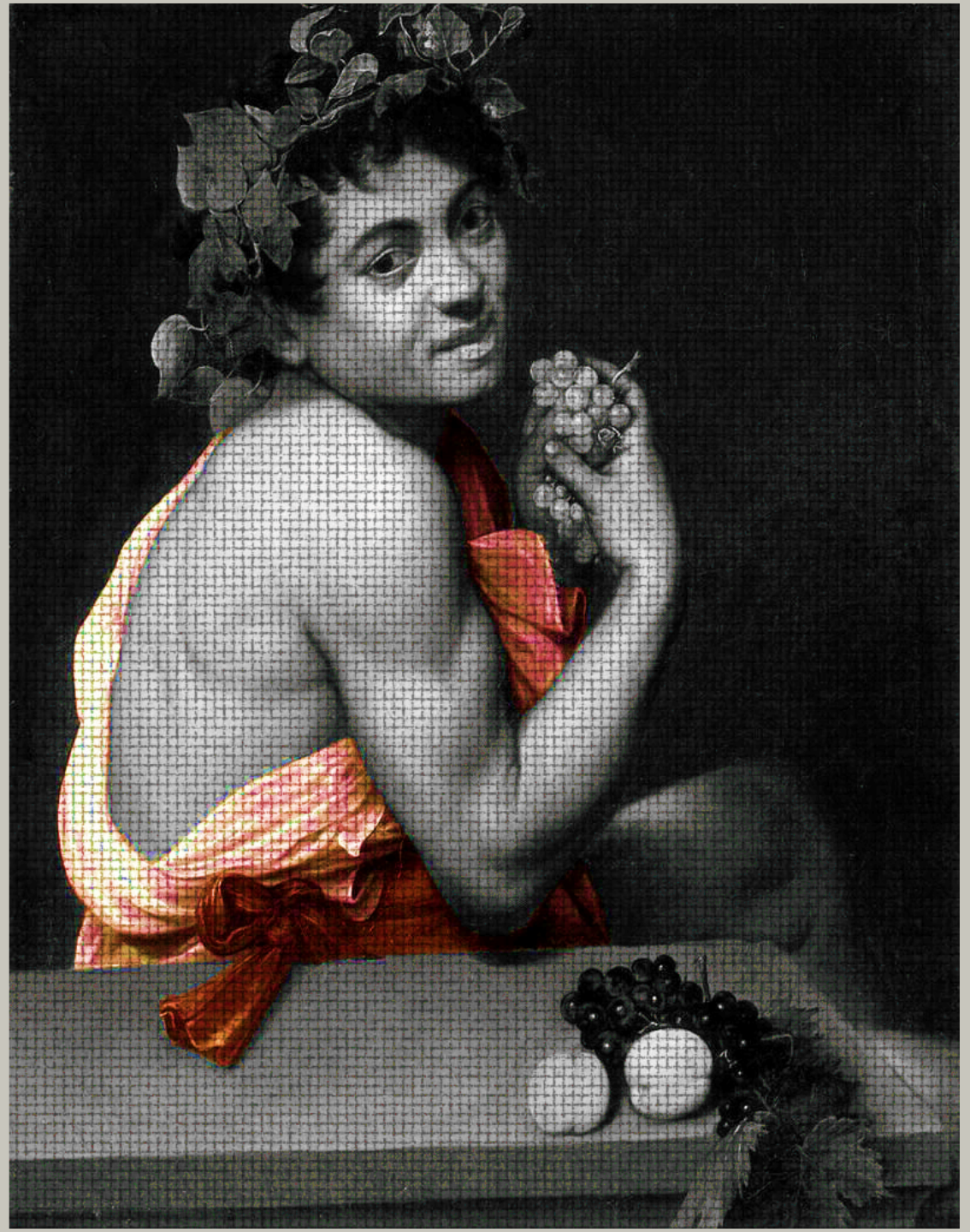
Settembre 2016

ORIGINAL ARTICLE

Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors

Stuart J. Connolly, M.D., Truman J. Milling, Jr., M.D., John W. Eikelboom, M.D., C. Michael Gibson, M.D., John T. Curnutte, M.D., Ph.D., Alex Gold, M.D., Michele D. Bronson, Ph.D., Genmin Lu, Ph.D., Pamela B. Conley, Ph.D., Peter Verhamme, M.D., Ph.D., Jeannot Schmidt, M.D., Saskia Middeldorp, M.D., Alexander T. Cohen, M.D., Jan Beyer-Westendorf, M.D., Pierre Albaladejo, M.D., Jose Lopez-Sendon, M.D., Shelly Goodman, Ph.D., Janet Leeds, Ph.D., Brian L. Wiens, Ph.D., Deborah M. Siegal, M.D., Elena Zotova, Ph.D., Brandi Meeks, B.Eng., Juliet Nakamya, Ph.D., W. Ting Lim, M.Sc., and Mark Crowther, M.D., for the ANNEXA-4 Investigators*

Gravida?



- EBPM sicure, dosaggio corretto per peso, eventuale monitoraggio attività antiXa (pesi estremi, IRC). LOE IB
- UFH con monitoraggio aPTT
- Fondaparinux: meno dati, seconda linea
- VKA controindicati in gravidanza, non controindicati in allattamento
- NAO controindicati
- Trombolisi: critical case

Neoplasia?

Recommendations for pulmonary embolism in cancer

Recommendations	Class[a]	Level[b]	Ref[c]
Incidental PE in patients with cancer should be managed in the same manner as symptomatic PE.	IIa	C	447–449, 463
Negative D-dimer levels have the same negative diagnostic value as in non-cancer patients.	IIa	B	98, 443
For patients with PE and cancer, weight-adjusted subcutaneous LMWH should be considered for the first 3–6 months.	IIa	B	278, 376, 377
For patients with PE and cancer, extended anticoagulation (beyond the first 3–6 months) should be considered for an indefinite period or until the cancer is cured.	IIa	C	

***3. In patients with DVT of the leg or PE and cancer ("cancer-associated thrombosis"), as long-term (first 3 months) anticoagulant therapy, we suggest LMWH over VKA therapy** (Grade 2B), **dabigatran** (Grade 2C), **rivaroxaban** (Grade 2C), **apixaban** (Grade 2C), **or edoxaban** (Grade 2C).

11. In patients with DVT of the leg or PE and active cancer ("cancer-associated thrombosis") and who (i) do not have a high bleeding risk, we recommend extended anticoagulant therapy (no scheduled stop date) over 3 months of therapy (Grade 1B), **or (ii) have a high bleeding risk, we suggest extended anticoagulant therapy (no scheduled stop date) over 3 months of therapy** (Grade 2B).

BACKGROUND

Direct oral anticoagulants (DOAs) have been shown to be as effective and at least as safe as conventional anticoagulation for the prevention of recurrences in patients with VTE. Whether this is the case in patients with cancer-associated VTE remains undefined.

METHODS

We performed a meta-analysis of randomized controlled trials with the aim of assessing the efficacy and safety of DOAs in patients with VTE and cancer. MEDLINE, EMBASE, and CENTRAL were searched up to December 2013 with no language restriction. The primary outcome of the analysis was recurrent VTE. Data on major bleeding (MB) and clinically relevant nonmajor bleeding were analyzed. Data were pooled and compared by ORs and 95% CIs.

RESULTS

Overall, 10 studies comparing DOAs with conventional anticoagulation for treatment of VTE including patients with cancer were included in the review. Six studies were included in the meta-analysis (two with dabigatran, two with rivaroxaban, one with edoxaban, and one with apixaban), accounting for a total of 1, 132 patients. VTE recurred in 23 of 595 (3.9%) and in 32 of 537 (6.0%) patients with cancer treated with DOAs and conventional treatment, respectively (OR, 0.63; 95% CI, 0.37-1.10; I^2, 0%). MB occurred in 3.2% and 4.2% of patients receiving DOAs and conventional treatment, respectively (OR, 0.77; 95% CI, 0.41-1.44; I^2, 0%).

CONCLUSIONS

DOAs seem to be as effective and safe as conventional treatment for the prevention of VTE in patients with cancer. Further clinical trials in patients with cancer-associated VTE should be performed to confirm these results.

CHEST® JOURNAL

Direct Oral Anticoagulants in Patients With VTE and Cancer

Maria Cristina Vedovati, MD, Federico Germini, MD, Giancarlo Agnelli, MD, Cecilia Becattini, MD, PhD

BACKGROUND

Low-molecular-weight heparin is the standard treatment for cancer-associated venous thromboembolism. The role of treatment with direct oral anticoagulant agents is unclear.

METHODS

In this open-label, noninferiority trial, we randomly assigned patients with cancer who had acute symptomatic or incidental venous thromboembolism to receive either low-molecular-weight heparin for at least 5 days followed by oral edoxaban at a dose of 60 mg once daily (edoxaban group) or subcutaneous dalteparin at a dose of 200 IU per kilogram of body weight once daily for 1 month followed by dalteparin at a dose of 150 IU per kilogram once daily (dalteparin group). Treatment was given for at least 6 months and up to 12 months. The primary outcome was a composite of recurrent venous thromboembolism or major bleeding during the 12 months after randomization, regardless of treatment duration.

RESULTS

Of the 1050 patients who underwent randomization, 1046 were included in the modified intention-to-treat analysis. A primary-outcome event occurred in 67 of the 522 patients (12.8%) in the edoxaban group as compared with 71 of the 524 patients (13.5%) in the dalteparin group (hazard ratio, 0.97; 95% confidence interval [CI], 0.70 to 1.36; P=0.006 for noninferiority; P=0.87 for superiority). Recurrent venous thromboembolism occurred in 41 patients (7.9%) in the edoxaban group and in 59 patients (11.3%) in the dalteparin group (difference in risk, −3.4 percentage points; 95% CI, −7.0 to 0.2). Major bleeding occurred in 36 patients (6.9%) in the edoxaban group and in 21 patients (4.0%) in the dalteparin group (difference in risk, 2.9 percentage points; 95% CI, 0.1 to 5.6).

CONCLUSIONS

Oral edoxaban was noninferior to subcutaneous dalteparin with respect to the composite outcome of recurrent venous thromboembolism or major bleeding. The rate of recurrent venous thromboembolism was lower but the rate of major bleeding was higher with edoxaban than with dalteparin. (Funded by Daiichi Sankyo; Hokusai VTE Cancer ClinicalTrials.gov number, NCT02073682.)

The NEW ENGLAND JOURNAL *of* MEDICINE

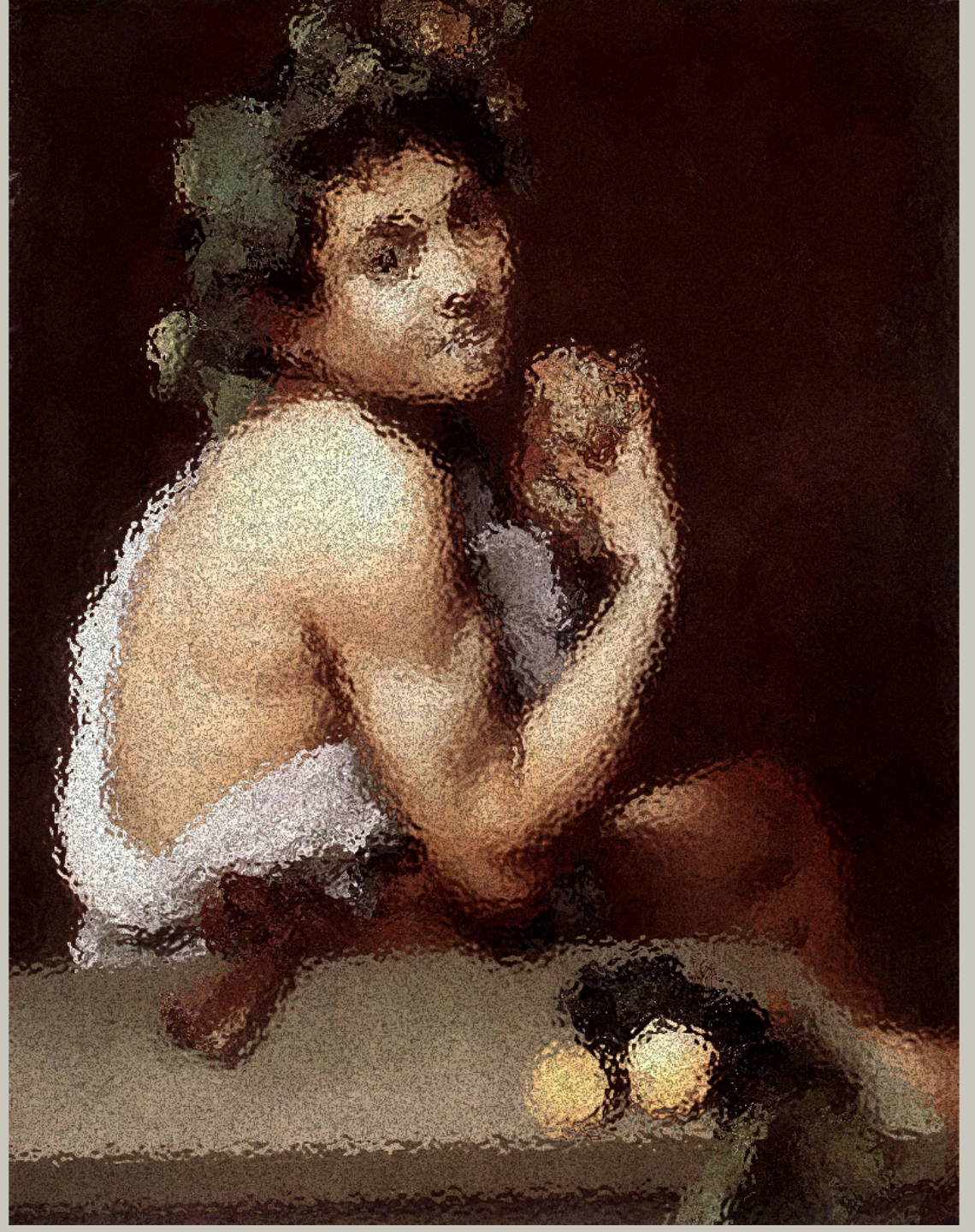
ORIGINAL ARTICLE

Edoxaban for the Treatment of Cancer-Associated Venous Thromboembolism

Gary E. Raskob, Ph.D., Nick van Es, M.D., Peter Verhamme, M.D., Marc Carrier, M.D., Marcello Di Nisio, M.D., David Garcia, M.D., Michael A. Grosso, M.D., Ajay K. Kakkar, M.B., B.S., Michael J. Kovacs, M.D., Michele F. Mercuri, M.D., Guy Meyer, M.D., Annelise Segers, M.D., Minggao Shi, Ph.D., Tzu-Fei Wang, M.D., Erik Yeo, M.D., George Zhang, Ph.D., Jeffrey I. Zwicker, M.D., Jeffrey I. Weitz, M.D., and Harry R. Büller, M.D., for the Hokusai VTE Cancer Investigators*

Febbraio 2018

L’intoccabile?



Recommendations for venous filters

Recommendations	Class[a]	Level[b]	Ref[c]
IVC filters should be considered in patients with acute PE and absolute contraindications to anticoagulation.	IIa	C	
IVC filters should be considered in case of recurrence of PE, despite therapeutic levels of anticoagulation.	IIa	C	
Routine use of IVC filters in patients with PE is not recommended.	III	A	341, 355

QUANDO SCEGLIERE È DIFFICILE: TEP SUBSEGMENTARIA

We suggest that a diagnosis of subsegmental PE is more likely to be correct (ie, a true positive) if: (1) the CT pulmonary angiogram is of high quality with good opacification of the distal pulmonary arteries; (2) there are multiple intraluminal defects; (3) defects involve more proximal subsegmental arteries (ie, are larger); (4) defects are seen on more than one image; (5) defects are surrounded by contrast rather than appearing to be adherent to the pulmonary artery walls; (6) defects are seen on more than one projection; (7) patients are symptomatic, as opposed to PE being an incidental finding; (8) there is a high clinical pretest probability for PE; and (9) D-dimer level is elevated, particularly if the increase is marked and otherwise unexplained.

C'è
o
non c'è?

QUANDO SCEGLIERE È DIFFICILE: TEP SUBSEGMENTARIA

Ricercare TVP
Rischio ricorrenza
Rischio emorragico
Preferenze del pz

Whether to Anticoagulate Subsegmental PE

***19. In patients with subsegmental PE (no involvement of more proximal pulmonary arteries) and no proximal DVT in the legs who have a (i) low risk for recurrent VTE (see text), we suggest clinical surveillance over anticoagulation** (Grade 2C) **or (ii) high risk for recurrent VTE (see text), we suggest anticoagulation over clinical surveillance** (Grade 2C).

Rischio di recidiva
Alto (1 o più fattori di rischio) • 2 o più episodi di TEV unprovoked (idiopatico) • TVP iliaco-femorale • Residuo trombotico > 4 mm • Neoplasia attiva • Trombofilia severa • D-dimero > 500 ng/ml (0,5 µg/ml) (1-3 mesi dopo la sospensione dell'anticoagulazione) • EP severa (a rischio di fatalità) • IBD (malattia cronica intestinale)
Moderato (1 fattore di rischio) • TVP isolata unprovoked • Maschio • Obesità (BMI >30)
Basso (1 fattore di rischio transitorio) • Post-chirurgia maggiore • Allettamento (>4gg) • Post-gesso o immobilizzazione • Post-trauma maggiore • Terapia estrogenica (contracettiva o sostitutiva)

TABLE 11] Risk Factors for Bleeding with Anticoagulant Therapy and Estimated Risk of Major Bleeding in Low-, Moderate-, and High-Risk categories[a]

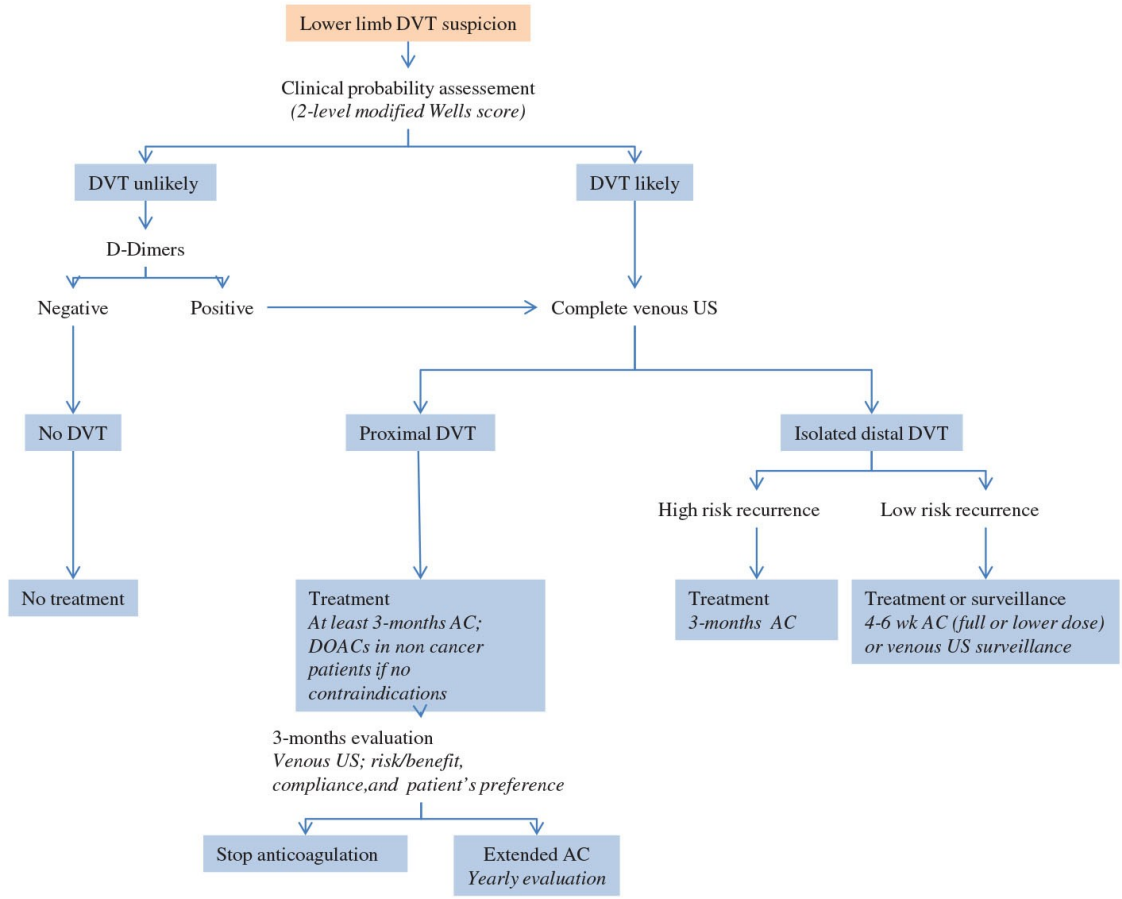
Risk Factors[b]
Age >65 y[184-193]
Age >75 y[184-188,190,192,194-202]
Previous bleeding[185,191-193,198,201-204]
Cancer[187,191,195,198,205]
Metastatic cancer[181,204]
Renal failure[185,191-193,196,199,201,206]
Liver failure[186,189,195,196]
Thrombocytopenia[195,204]
Previous stroke[185,192,195,207]
Diabetes[185,186,196,200,202]
Anaemia[185,189,195,198,202]
Antiplatelet therapy[186,195,196,202,208]
Poor anticoagulant control[189,196,203]
Comorbidity and reduced functional capacity[191,196,204]
Recent surgery[189,209,c]
Frequent falls[195]
Alcohol abuse[191,192,195,202]
Nonsteroidal anti-inflammatory drug[210]

QUANDO SCEGLIERE È DIFFICILE: TVP DISTALE ISOLATA

Previous VTE events

Males

Age >50 years
Cancer
Unprovoked isolated distal DVT
Secondary isolated distal DVT with persistently hampered mobilization
Isolated distal DVT involving the popliteal trifurcation
Isolated distal DVT involving >1 calf vein
Isolated distal DVT present in both legs
Presence of predisposing diseases (e.g. inflammatory bowel diseases)
Known thrombophilic alterations
Axial vs Muscular isolated distal DVT



d deep vein thrombosis diagnostic and management algorithm. AC, anticoagulation; DOAC, direct oral anticoagulant.

Isolated distal DVT secondary to surgery or other transient risk factors (plasters, immobilization, trauma, long trip, etc.), provided complete mobilization is achieved

Isolated distal DVT occurring during contraceptive or replacement hormonal therapy (provided therapy has been interrupted)

PZ A BASSO RISCHIO SCEGLIERE È FACILE?

Early discharge and home treatment			
Patients with acute 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.	IIa	B	217, 237, 347, 349

Treatment of Acute PE Out of the Hospital

***20. In patients with low-risk PE and whose home circumstances are adequate, we suggest treatment at home or early discharge over standard discharge (eg, after the first 5 days of treatment)** (Grade 2B).

PZ A BASSO RISCHIO SCEGLIERE È FACILE?

Quale terapia in ospedale?
Quando a casa? Con quale terapia?
Chi prescrive?
Con quali controlli? Dove?


Grazie