EUROPEAN SOCIETY OF CARDIOLOGY®

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ESC CONGRESS
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L'embolie pulmonaire, quoi de neuf?

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SMIG, HUG

Formation continue MFGe, 20 novembre 2014

HUG
Hôpitaux Universitaires de Genève

Embolie pulmonaire: nouveautés

- Algorithmes diagnostiques inchangés, mais
  - Nouvelles données sur la probabilité clinique et les D-dimères
- Stratification du risque
  - Nouvel algorithme incorporant le score clinique PESI/sPESI
- Traitement
  - Place des nouveaux anticoagulants
  - Durée du traitement anticoagulant

- NB: EP à haut risque ou "massive" pas abordée

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)

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European Heart Journal (2014) 35, 3033–3080

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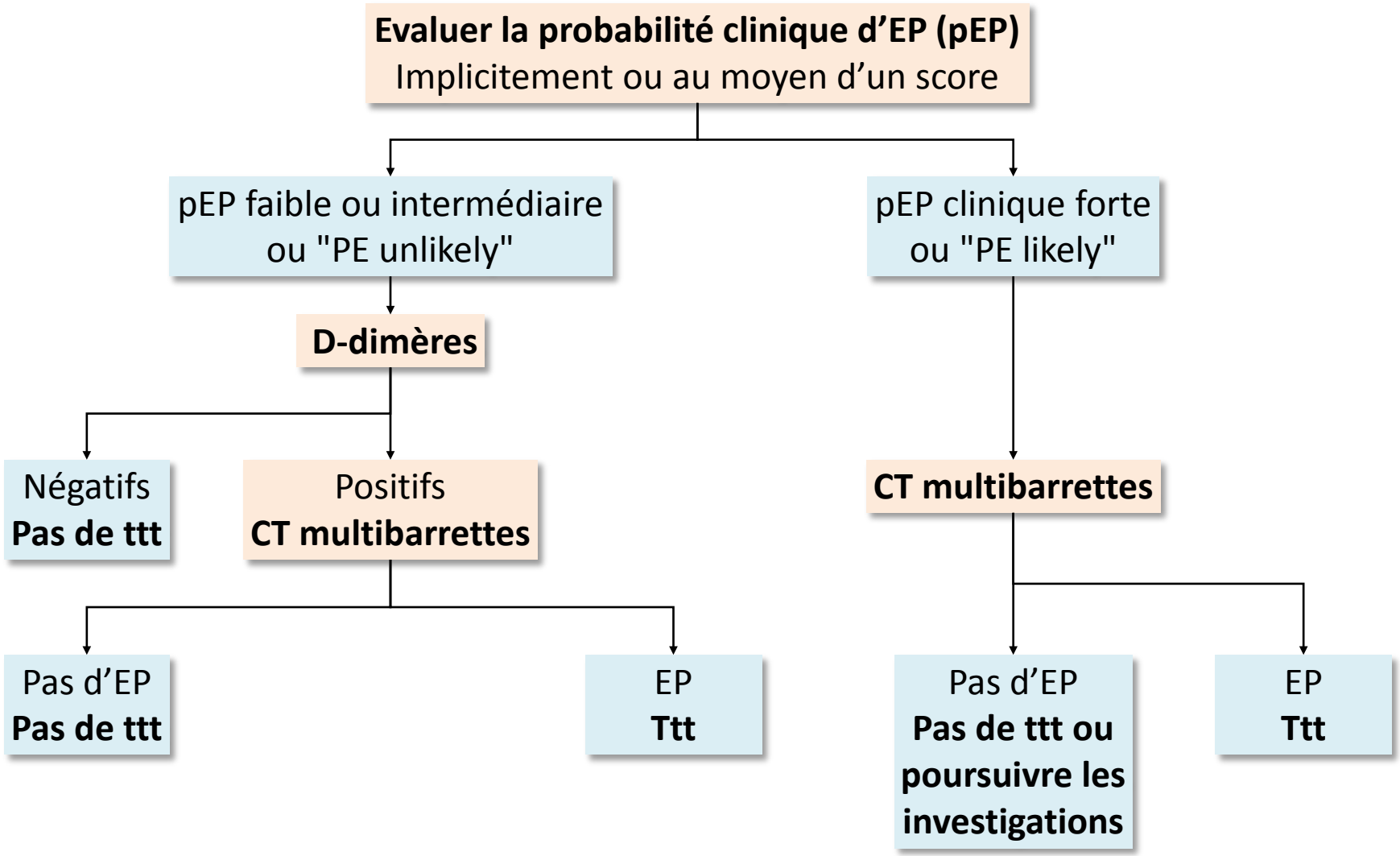
Suspicion d'EP non massive



Score de Wells

Clinical prediction rules for pulmonary embolism		
	Clinical decision rule points	
Wells rule	Original version	Simplified version
Previous PE or DVT	1.5	1
Heart rate ≥100 b.p.m.	1.5	1
Surgery or immobilization within the past 4 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		
Three-level score		
Low	0–1	N/A
Intermediate	2–6	N/A
High	≥7	N/A
Two-level score		
PE unlikely	0–4	0–1
PE likely	≥5	≥2

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Score de Genève révisé

	Clinical decision rule points	
Revised Geneva score	**Original version**	**Simplified version**
Previous DVT or PE	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

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Comparaison de 4 scores cliniques

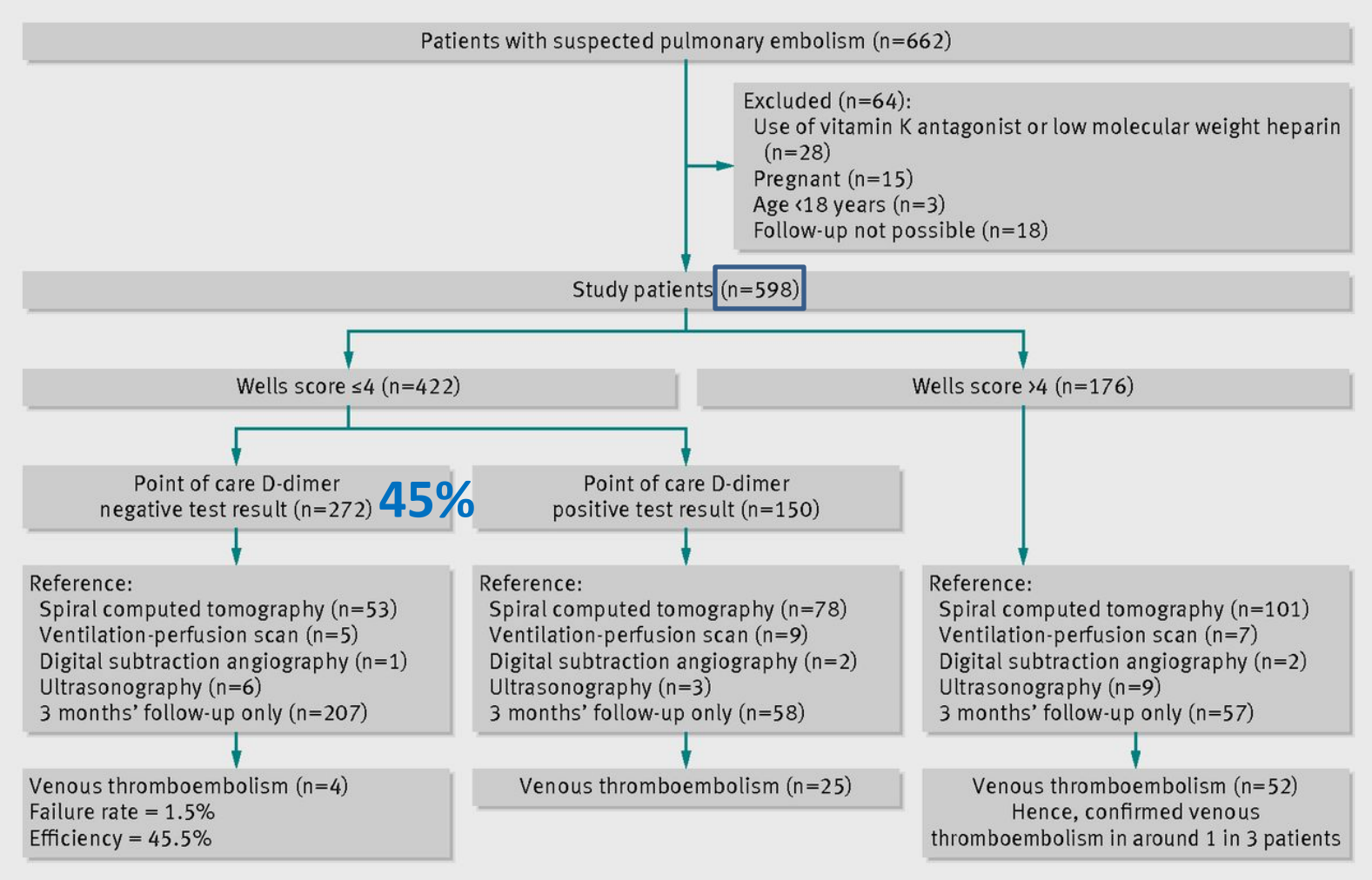
Variable	Original Wells Rule % (95% CI)	Simplified Wells Rule % (95% CI)	Original Revised Geneva Score % (95% CI)	Simplified Revised Geneva Score % (95% CI)
PE unlikely	72 (69–76)	62 (59–65)	69 (65–72)	71 (68–75)
Prevalence of PE, PE unlikely	15 (13–18)	13 (10–16)	16 (13–19)	17 (14–20)
Prevalence of PE, PE likely	43 (36–49)	39 (34–44)	38 (32–44)	39 (32–45)
PE unlikely and normal D-dimer	23 (20–26)	22 (19–25)	23 (20–26)	24 (21–27)
Global VTE risk in PE unlikely and normal D-dimer	0.5 (0.0–3.0)	0.6 (0.0–3.1)	0.5 (0.0–3.0)	0.5 (0.0–2.9)

807 patients, D-dimères très sensibles c/o tous les patients, CT si patient classé dans la catégorie "EP probable" par un ou plusieurs scores

Même capacité de classification, rendement Dx et sécurité

Douma et al. Ann Intern Med. 2011;154:709-718

L'étude AMUSE-2: exclusion de l'EP en médecine de premier recours (score de Wells et Simplify D-dimer®)



Prévalence de l'EP 12.2%. Taux d'échec 1.5% (0.4 to 3.7)

BMJ 2012;345:e6564

Probabilité clinique: recommandations

Suspected PE without shock or hypotension		
The use of validated criteria for diagnosing PE is recommended.	I	B
Clinical evaluation		
It is recommended to base the diagnostic strategy on clinical probability assessed either by clinical judgement or a validated prediction rule.	I	A
D-dimer		
Plasma D-dimer measurement is recommended in outpatients / emergency department patients with low or intermediate clinical probability, or PE-unlikely, to reduce the need for unnecessary imaging and irradiation, preferably using a highly sensitive assay.	I	A
In low clinical probability or PE-unlikely patients, normal D-dimer level using either a highly or moderately sensitive assay excludes PE.	I	A
Further testing may be considered in intermediate probability patients with a negative moderately sensitive assay.	IIb	C
D-dimer measurement is not recommended in patients with high clinical probability, as a normal result does not safely exclude PE even when using a highly sensitive assay.	III	B

Validation prospective du seuil de D-dimères ajusté à l'âge: l'étude ADJUST

- **Objectif**: évaluer si un **seuil de D-dimères ajusté à l'âge** (age × 10 chez les patients > 50 ans) est associé à une augmentation du rendement diagnostique des D-dimères chez les patients âgés avec suspicion d'EP
- **Cadre**: étude prospective multicentrique de "management" dans 19 centres (Belgique, France, Pays-Bas, Suisse)
- **Stratégie Dx**:
  - Probabilité clinique évaluée par le score simplifié de Genève ou le score simplifié de Wells combiné à un dosage de D-dimères très sensible
  - AngioCT chez tous les patients avec un taux de D-dimères supérieur au seuil ajusté à l'âge
- **Critère de jugement**: taux d'échec de la stratégie diagnostique
  - Ev. Thromboemboliques durant le suivi de 3 mois chez les patients non traités sur la base d'un résultat de D-dimères négatif selon le seuil ajusté à l'âge

Righini et al. JAMA. 2014 (April 23-30);311:1117-1124

Validation prospective du seuil de D-dimères ajusté à l'âge: l'étude ADJUST

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)

28% **12%**

- Le seuil ajusté à l'âge a augmenté le taux d'exclusion par les D-dimères de 12% (40% vs. 28%)
- Taux d'échec très bas (0.3% [0.1 to 1.7])
- Résultats stables pour tous les essais testés (mais puissance limitée)

Righini et al. JAMA. 2014 (April 23-30);311:1117-1124

Probabilité clinique et D-dimères: recommandations

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Pas de recommandation formelle sur le seuil adapté à l'âge

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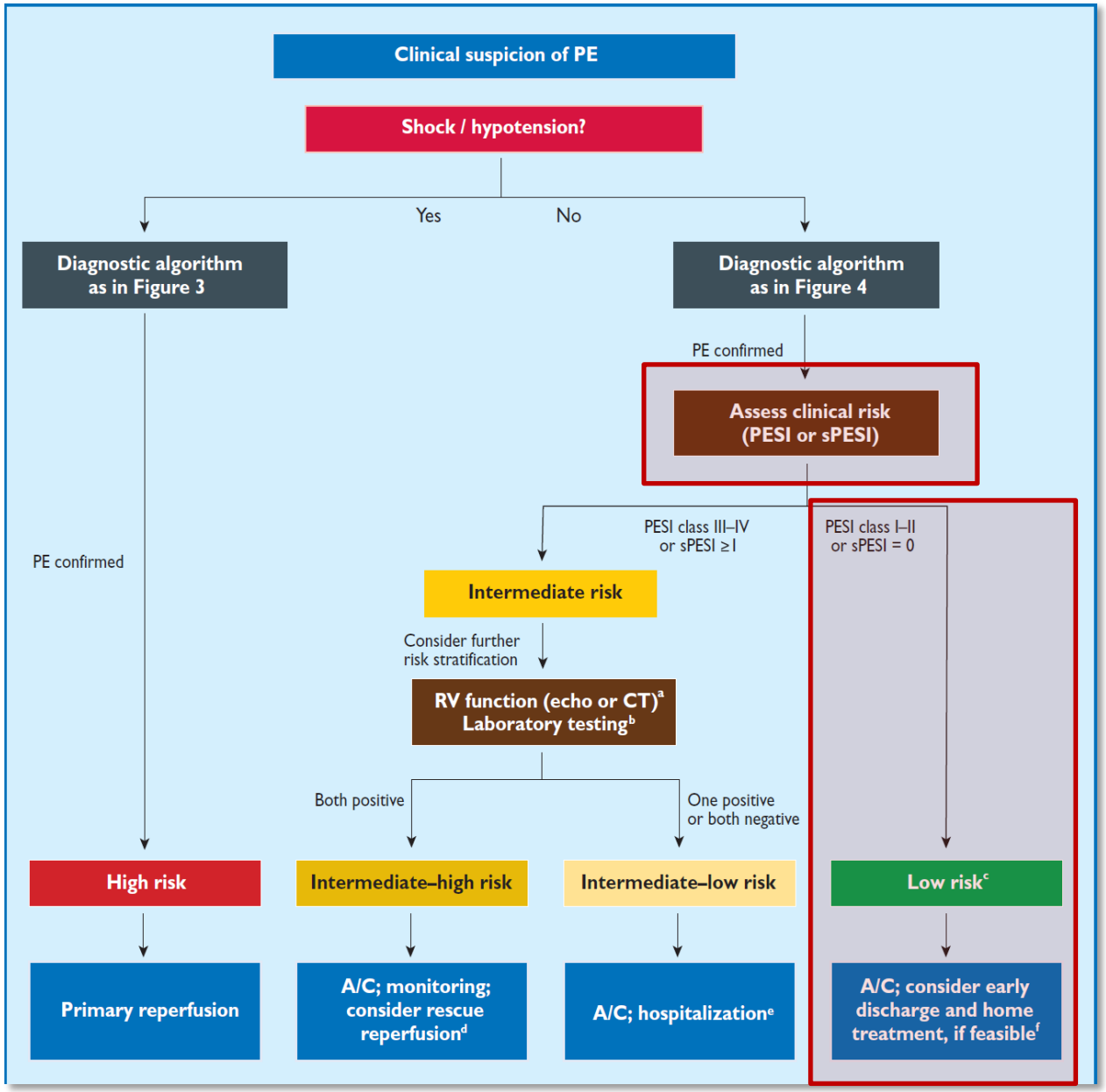
Algorithme de prise en charge globale de l'EP



Stratification du risque

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Le score PESI (original et simplifié)

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%)

Am J Respir Crit Care Med 2005;172(8):1041–1046 . Arch Intern Med 2010;170(15):1383–1389.

Traitement ambulatoire de l'EP: étude OTPE

Outcomes, n(%)	Outpatient (n=171)	Inpatient (n=168)
Recurrent VTE at 90 days	1 (0.6)	0
Major bleeding		
at 14 days	2 (1.2)	0
at 90 days	3 (1.8)	0
Overall mortality at 90 days	1 (0.6)	1 (0.6)
Non-inferiority margin= 4%		

- Traitement ambulatoire possible chez 30% des patients
- Age moyen 47/49 ans, cancer 1-2%, EP centrale 10-14%
- Durée de séjour 0.5 vs. 3.9 jours
- Pas d'augmentation des consultations en urgence

Lancet 2011;378:41-48

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Anticoagulants non-vit K dépendants (NOAC) et EP

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 **Hémor. majeures 1.1% vs. 2.2%**
	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

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NOAC et traitement aigu de la TVP/EP

	Efficacité	Sécurité	Hémorragies majeures	NNT
Dabigatran	Non-inférieur	Idem	NS	NS
Rivaroxaban*	Non-inférieur	Supérieur	1.1% vs. 2.2%	90
Apixaban	Non-inférieur	Supérieur	0.6% vs. 1.8%	83
Edoxaban	Non-inférieur	Idem	NS	NS

*seule étude à n'inclure que des EP

Rivaroxaban et apixaban: traitement initial dès Dx posé
Dabigatran et edoxaban: traitement initial HBPM et relais à 5-7 jours

Rivaroxaban: analyse combinée EINSTEIN DVT et PE

Efficacité

	Rivaroxaban		Enoxaparin/VKA		HR (95% CI)	
	n/N	%	n/N	%	Favors Rivaroxaban	Favors Enoxaparin/VKA
Nonfragile	65/3359	1.9	65/3349	1.9		

Hémorragies maj.

	Rivaroxaban		Enoxaparin/VKA		HR (95% CI)	
	n/N	%	n/N	%	Favors Rivaroxaban	Favors Enoxaparin /VKA
Nonfragile	30/3342	0.9	37/3337	1.1		
Fragile	10/788	1.3	35/779	4.5		
Age >75 years	8/655	1.2	28/624	4.5		
Creatinine clearance <50 ml/min	3/329	0.9	13/320	4.1		
Body weight <50 kg	0/42	0.0	3/65	4.6	Nonestimable	

0.01 0.1 1 10

Thrombosis Journal 2013, 11:21

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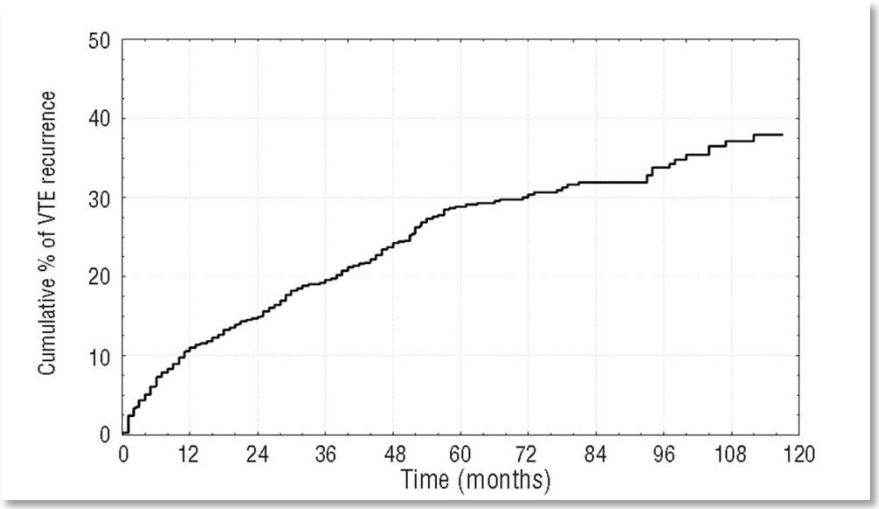
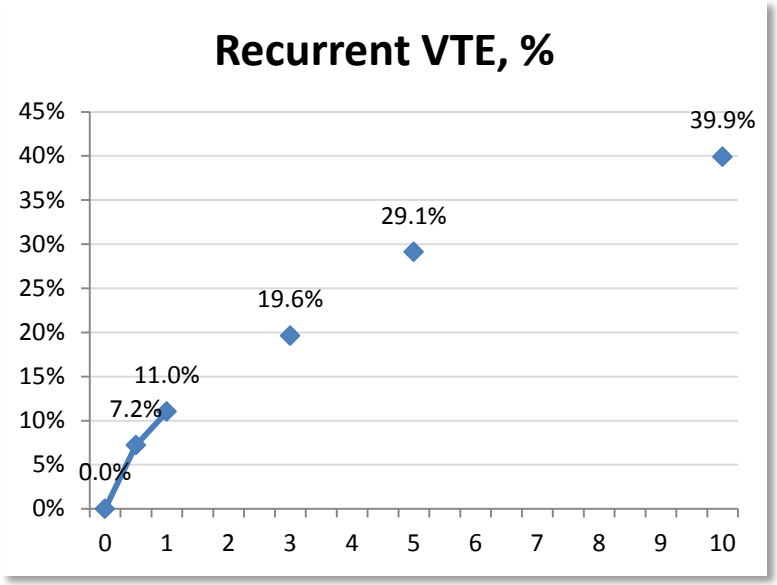
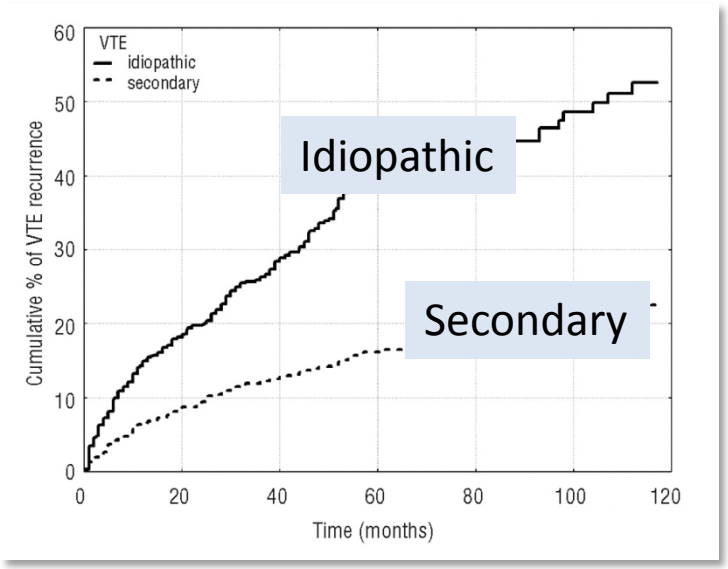
Risk of recurrent VTE after discontinung anticoagulation in a cohort of 1626 patients

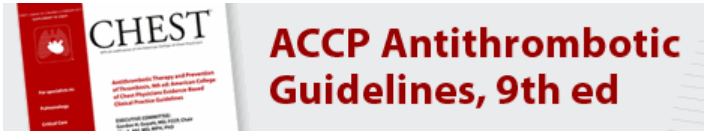






Prandoni P et al., Haematologica 2007; 92:199-205

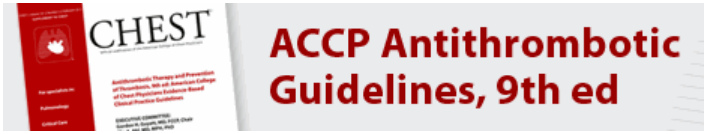
Duration of anticoagulation for acute PE



Situation	Recommended duration	Preferred over
PE provoked by surgery	3 months	• treatment of a shorter period (Grade 1B) • treatment of a longer time limited period (eg, 6 or 12 months) (Grade 1B), • extended therapy (Grade 1B regardless of bleeding risk) .
Unprovoked PE	At least 3 months Then evaluate for risk-benefit of extended therapy.	• Treatment of shorter duration

Chest 2012; 141(Suppl):e419S–e494S

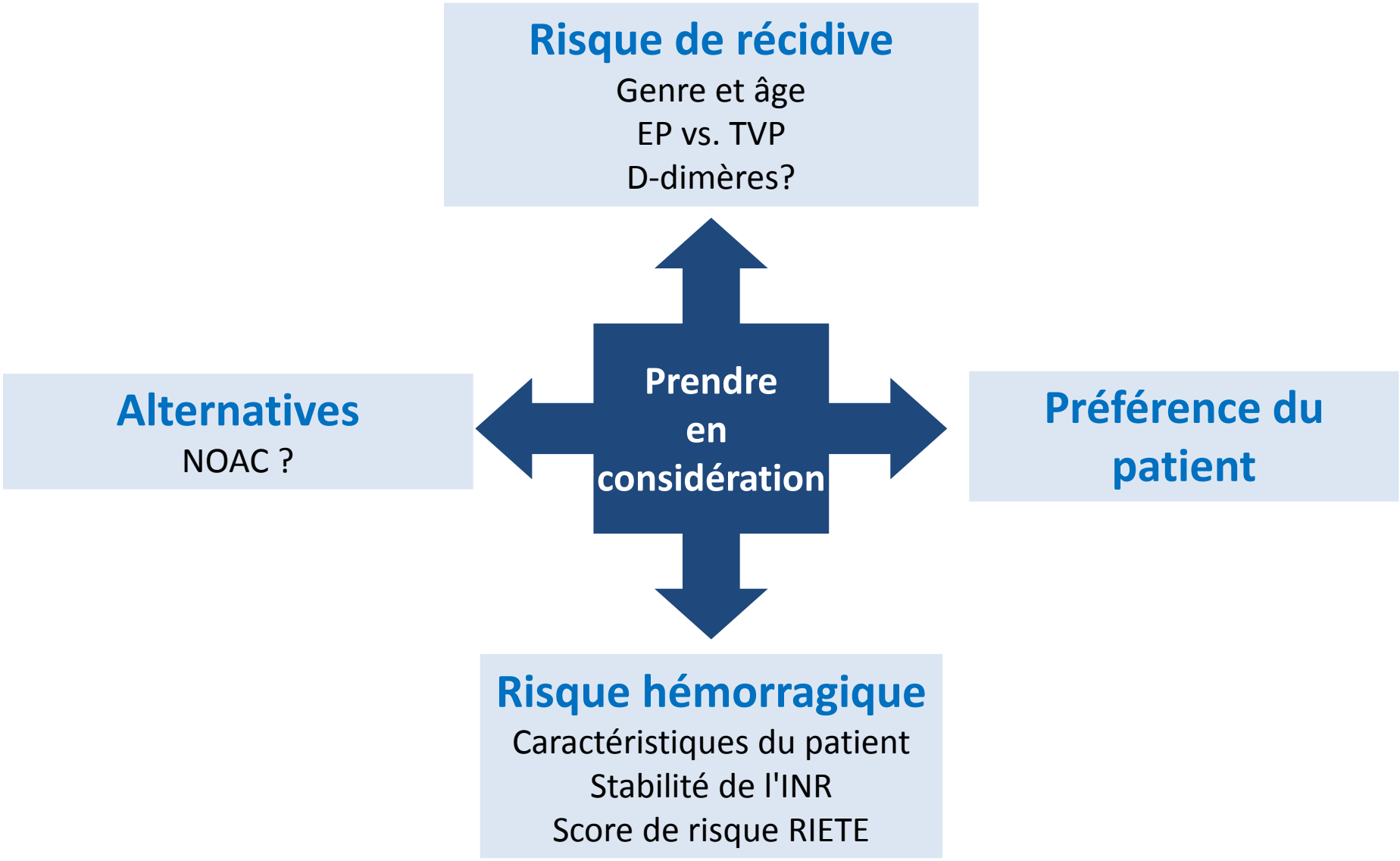
Duration of anticoagulation for acute PE



Situation	Recommended duration	Preferred over
First unprovoked PE and low or moderate bleeding risk	Extended anticoagulant therapy	• 3 months of therapy (Grade 2B) .
First unprovoked PE and high bleeding risk	3 months	• Extended therapy (Grade 1B)

Chest 2012; 141(Suppl):e419S–e494S

Prolongation du ttt. anticoagulant au-delà de 3 à 6 mois en prévention secondaire de la TVP/EP idiopathique



NOAC en prévention secondaire

Study	Active[a]	Comparator	Design	Expected reduction	Treatment duration	No. Patients enrolled	VTE rate in control group	Risk reduction for recurrent VTE	Major or CRNM bleeding in active[a] group
RE-SONATE[370]	Dabigatran 150 mg b.i.d.[c]	Placebo	Superiority	70%	6 months	1343	5.6%	92%	5.3%
RE-MEDY[370]	Dabigatran 150 mg b.i.d.[c]	Warfarin (INR 2–3)	Non-inferiority	Absolute increase, <2.8	18–36 months	2856	1.3%	Risk difference, 0.38% vs. VKA	5.6% (vs. 10.2% in warfarin arm)
EINSTEIN Ext[295]	Rivaroxaban 20 mg daily	Placebo	Superiority	70%	6–12 months	1196	7.1%	82%	6.0%
AMPLIFY Ext[371]	Apixaban 5.0 mg b.i.d.	Placebo	Superiority	41%	12 months	2486	8.8%	80%	4.2%
	Apixaban 2.5 mg b.i.d.[d]							81%	3.0%

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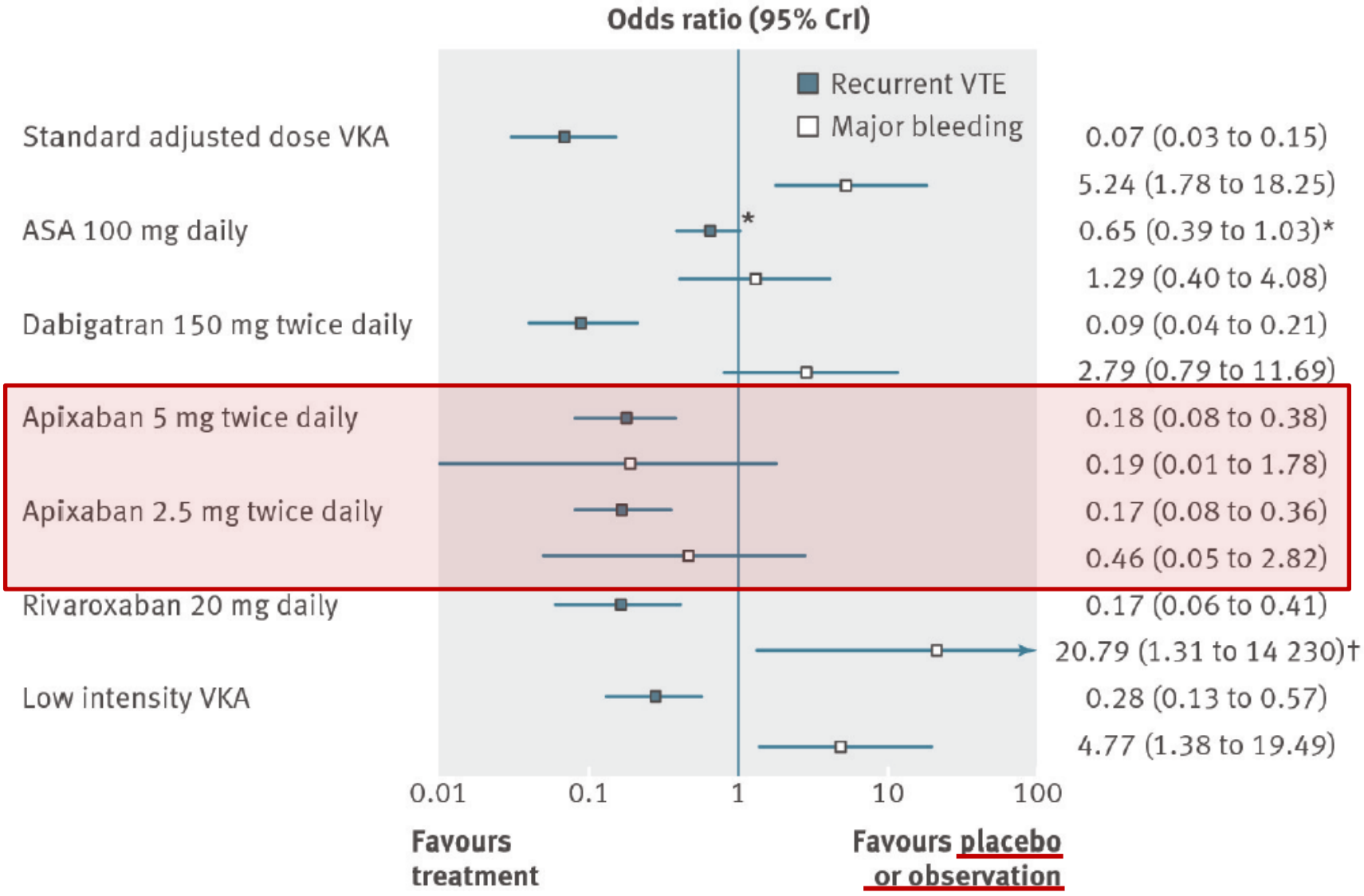
NOAC en prévention secondaire: méta-analyse en réseau



BMJ 2013;347:f5133 doi: 10.1136/bmj.f5133

Embolie pulmonaire: nouveautés

- Données robustes pour justifier l'emploi des scores de probabilité clinique et les D-dimères
- Seuil de D-dimères ajusté à l'âge prometteur
- Stratification du risque basée sur la clinique (score PESI/sPESI) et traitement ambulatoire possible chez les patients à faible risque
- NOAC aussi efficaces que les AVK dans le traitement aigu avec risque hémorragique plus faible (rivaroxaban et apixaban seulement)
- NOAC aussi efficaces que les AVK en prévention secondaire avec risque hémorragique plus faible (apixaban seulement)
- Prolongation du ttt. anticoagulant au-delà de 3 à 6 mois (prévention secondaire) à discuter de cas en cas chez les patients qui ont une EP non-provoquée