Embolie pulmonaire :

ce que le cardiologue doit savoir en 2018

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Disclosures

Research Support

- Bayer HealthCare, Bristol-Myers Squibb, Pfizer, Daiichi-Sankyo, Boerhinger

Consultant

- Bayer HealthCare, Boerhinger, Bristol-Myers Squibb, Pfizer, St Jude medical, Edwards LIfesciences

Scientific Advisory Board

- Bristol-Myers Squibb

Le contenu et/ou les opinions exprimées lors de cette présentation, notamment celui ou celle(s) relatifs à la stratégie thérapeutique ont été réalisés en toute indépendance et sous ma responsabilité. La prescription des produits en France doit se faire dans le cadre de l'AMM et des RCP et être conforme à la stratégie thérapeutique émise par la Haute Autorité de Santé(Avis de la Commission de Transparence) .

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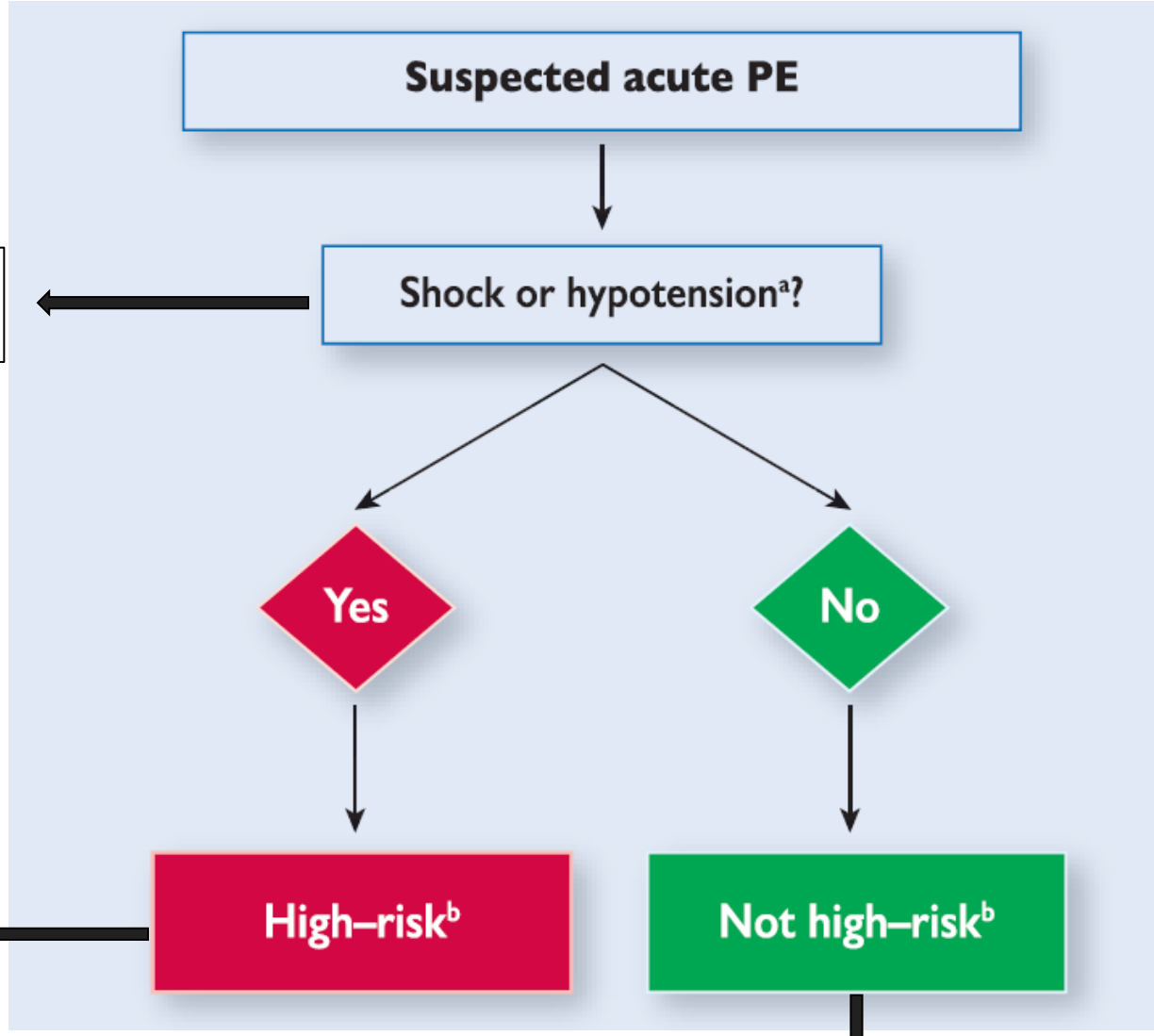
1. Sur le plan diagnostique

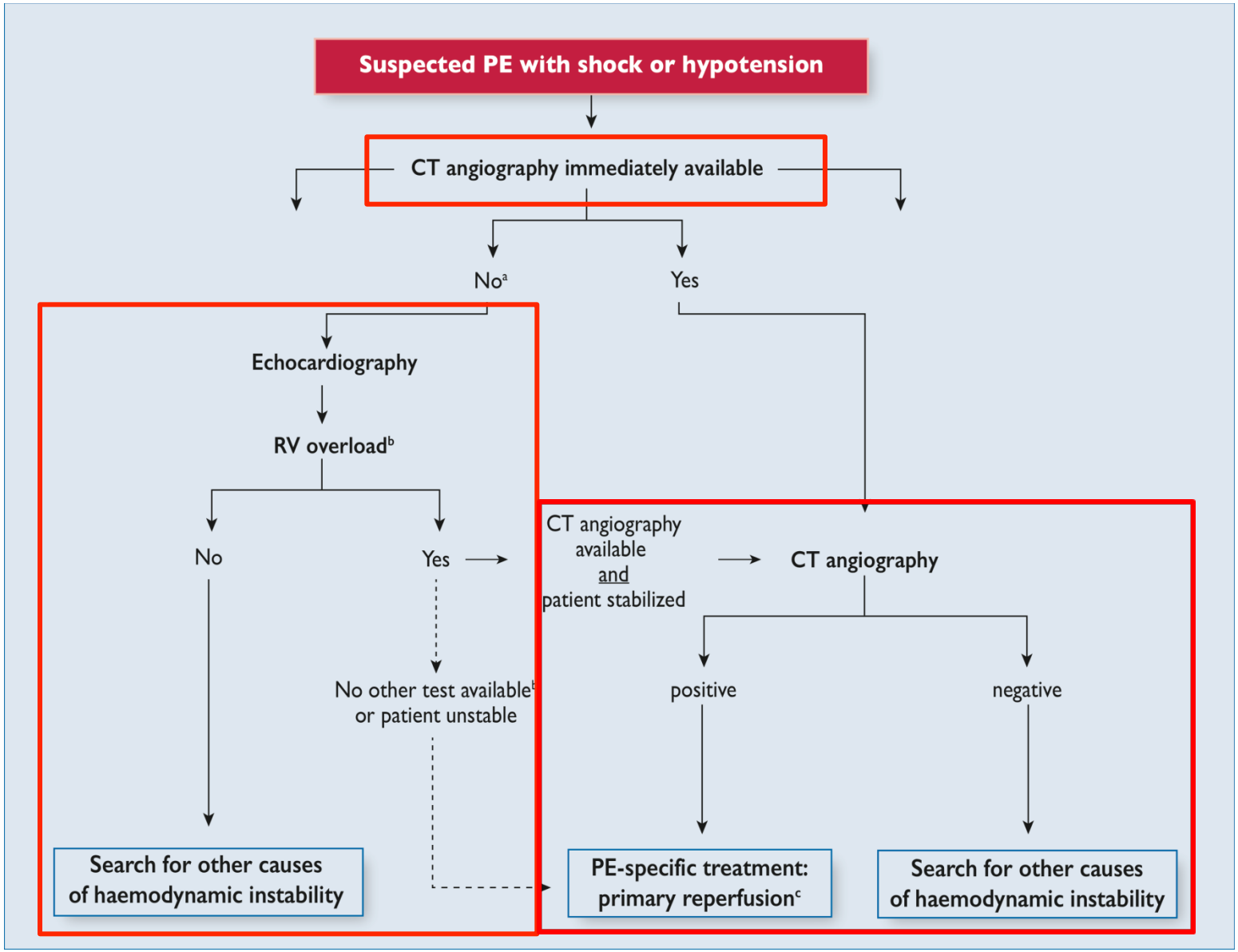
Initial risk stratification of acute PE



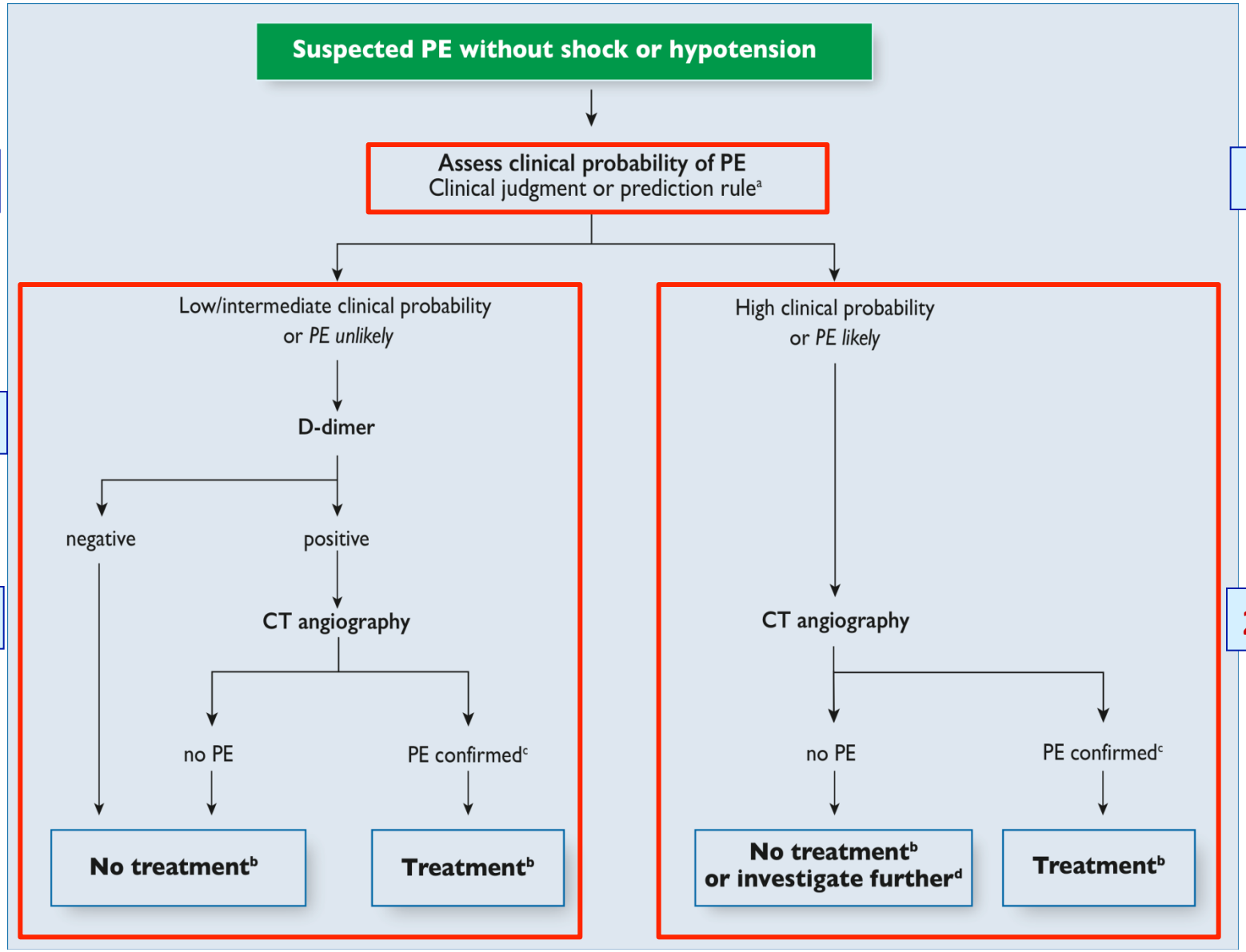
[a]Defined as systolic blood pressure <90 mmHg, or a systolic pressure drop by ≥40 mmHg, for >15 minutes, if not caused by new-onset arrhythmia, hypovolaemia, or sepsis.
[b]Based on the estimated PE-related in-hospital or 30-day mortality.

Diagnostic algorithm: high-risk PE

1st Step

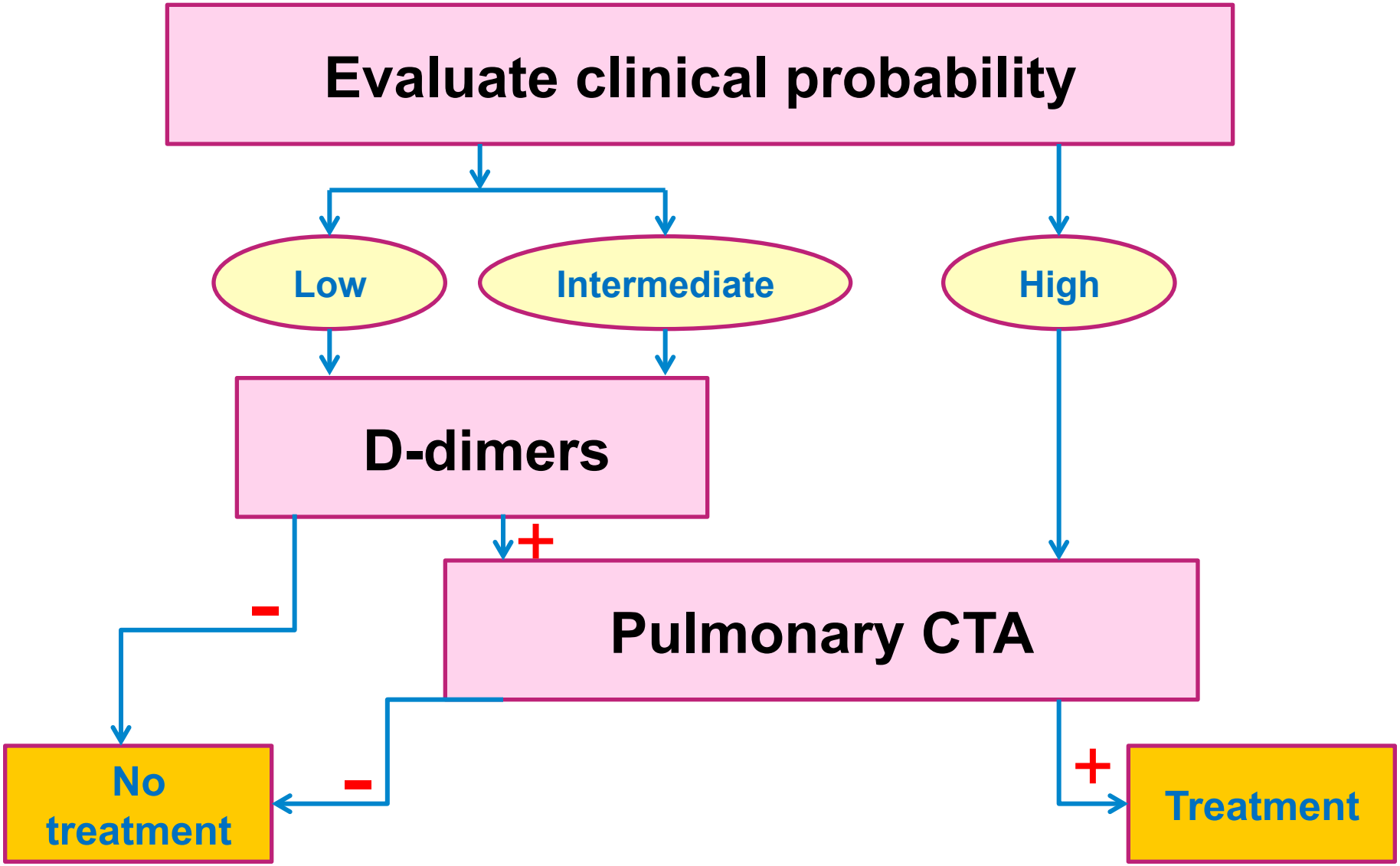


Diagnostic algorithm: not high-risk PE



Diagnostic algorithm: not high-risk PE

Diagnostic Work-Up in 2/3 Stages



Not high-risk PE
Revised Scores

Wells rule

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

Geneva score

Clinical prediction rules for pulmonary embolism (cont.)		
	Clinical decision rule points	
Revised Geneva score	Original version	Simplified version
Previous DVT or PE	3	1
Heart rate 75–94 b.p.m. ≥95 b.p.m.	 3 5	 1 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

Prospective validation of D-dimer age-adjusted cut-off : the ADJUST study

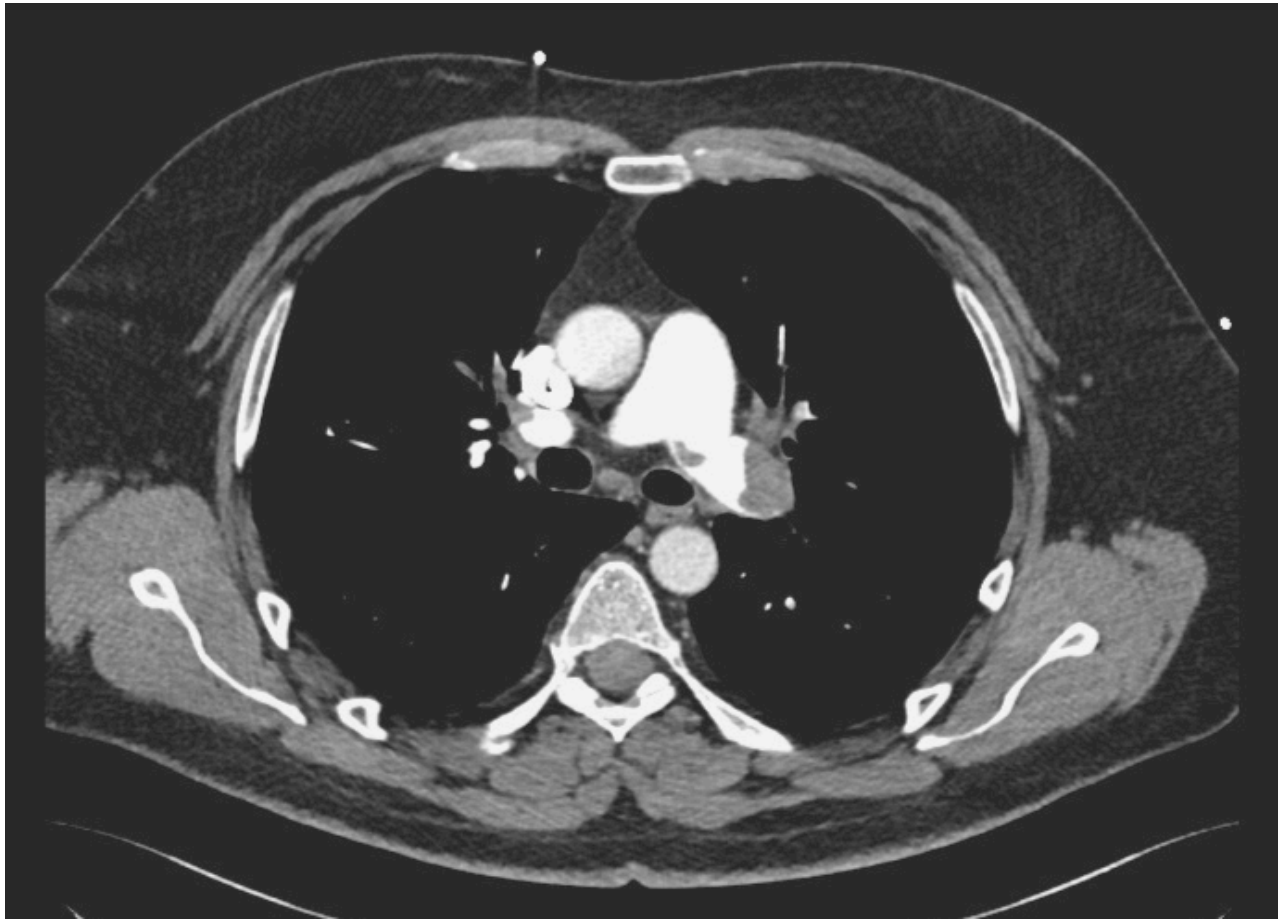
- Age adjusted cut-off :
  - Age ≤ 50 years : 500 ng/ml
  - Age > 50 years : age x 10 ng/mL

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)

- Increase the exclusion rate of D-dimer by 10% (34% vs 24%)
- Very low failure rate (0.3% [0.1-1.7])
- Results stable across D-dimer assays

Righini M et al. JAMA 2014;311:1117-24.

Imagerie diagnostique de 1ère intention : Angioscanner pulmonaire



Alternative diagnostic tests and pathways: not high-risk PE

Diagnostic criterion	Clinical probability of PE				
	Low	Intermediate	High	PE unlikely	PE likely
Exclusion of PE					
D-dimer					
Negative result, highly sensitive assay	+	+	–	+	–
Negative result, moderately sensitive assay	+	±	–	+	–
Chest CT angiography					
Normal multidetector CT alone	+	+	±	+	±
V/Q scan					
Normal perfusion lung scan	+	+	+	+	+
Non-diagnostic lung scan[a] and negative proximal CUS	+	±	–	+	–
Confirmation of PE					
Chest CT angiogram showing at least segmental PE	+	+	+	+	+
High probability V/Q scan	+	+	+	+	+
CUS showing proximal DVT	+	+	+	+	+

Outpatients with low clinical probability and normal chest X-ray, in **young (particularly female) pts**, in **pregnancy**, in pts with **history of contrast-medium induced anaphylaxis**, in severe **renal failure**, in pts with **myeloma and paraproteinaemia**…

MRI for diagnosing PE

Study	Pts (N)	Inconclusive scans (%)	Sn (%)	SP (%)	Agreement
PIOPED III [1]	371	25%	78%	99%	24%
IRM-EP [2]	274	28-30%	79-85%	99-100%	Kappa 0.93

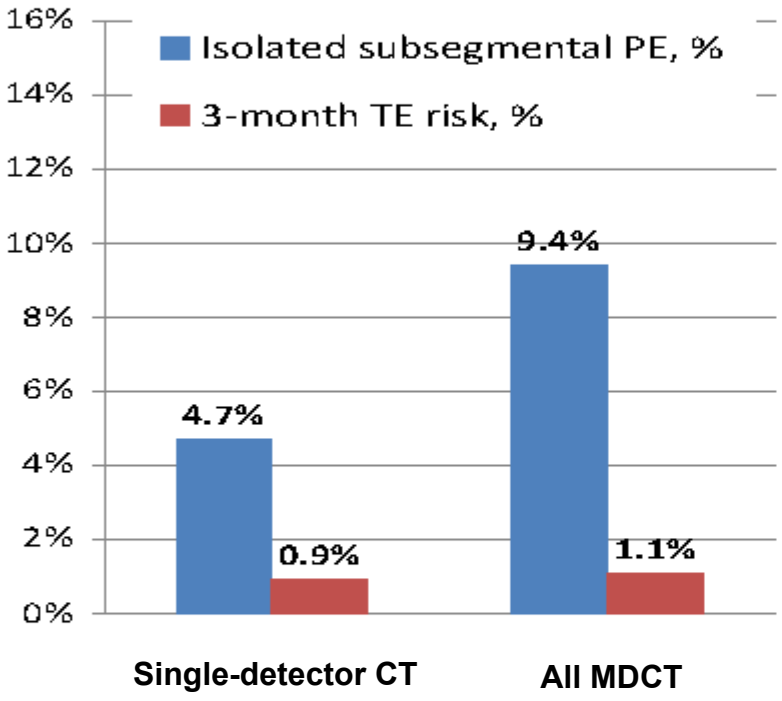
MRA		
MRA should not be used to rule out PE.	III	A

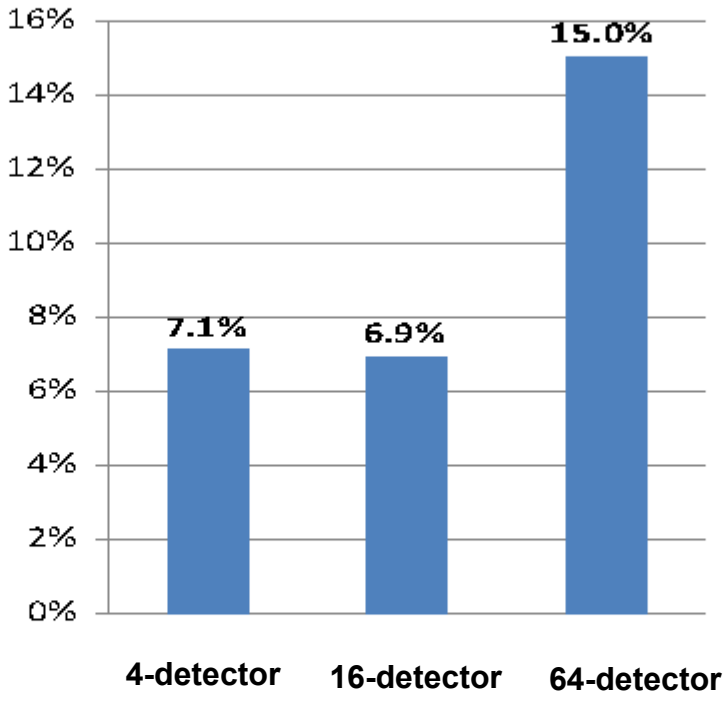
[1] Ann Intern Med 2010;152:434-43,
[2] J Thromb Haemost 2012;10: 743-50.

Areas of uncertainty regarding CT angiography

Isolated subsegmental PE : metaanalysis

NB : definition not uniform : single vs multiple subsegmental clots





Untreated pts :
- Fatal recurrence 0% [0-3.5]
- Non fatal recurrence 0% [0-6.2]
- Low interobserver agreement !!

Further testing ?

To treat or not to treat ?

Take into account :
- Single vs multiple subsegmental clots
- Clinical probability
- Bleeding risk

Stein et al. Clin Applied Thromb Haemostasis 2012;18:20-26. J Thromb Haemost 2010;8:1716-22.

Areas of uncertainty regarding CT angiography

Incidental PE : metaanalysis

Study	Incidental PE	Incidental PE	OR
Outpatients vs **inpatients**	1.2%	4%	4.3 [2.6-7]
Cancer vs non cancer	3.1%	2.5%	1.8 [1.2-2.8]
Overall	**2.6% [1.9-3.4]**		

Recommendations	Class[a]	Level[b]
Incidental PE in patients with cancer should be managed in the same manner as symptomatic PE.	IIa	C

- No recommendation in the absence of cancer
- Review of physician practices : most would treat, except maybe an incidental and isolated subsegmental PE

Dentali et al. Thromb Res 2010;125:518-22.

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2. Sur la stratification du risque

Prognostic assessment in « not high-risk » PE Pts : validated clinical pronostic score

Original & simplified PESI score

Parameter	Original version	Simplified version
Age	+ 1 per year	1 pt if age > 80
Male sex	+ 10	
Comorbid conditions		
Cancer	+ 30	1 pt
Chronic heart failure	+ 10	1 pt
Chronic respiratory disease	+ 10	
Physical examination findings		
HR > 110/mn	+ 20	1 pt
SBP < 100 mmHg	+ 30	1 pt
RR > 30/mn	+ 20	
Temperature < 36°C	+ 20	
Altered mental status	+ 60	
Arterial O_2 saturation < 90%	+ 20	1 pt

Aujesky et al. Am J Respir Crit Care Med 2005 ;172:1041-6.

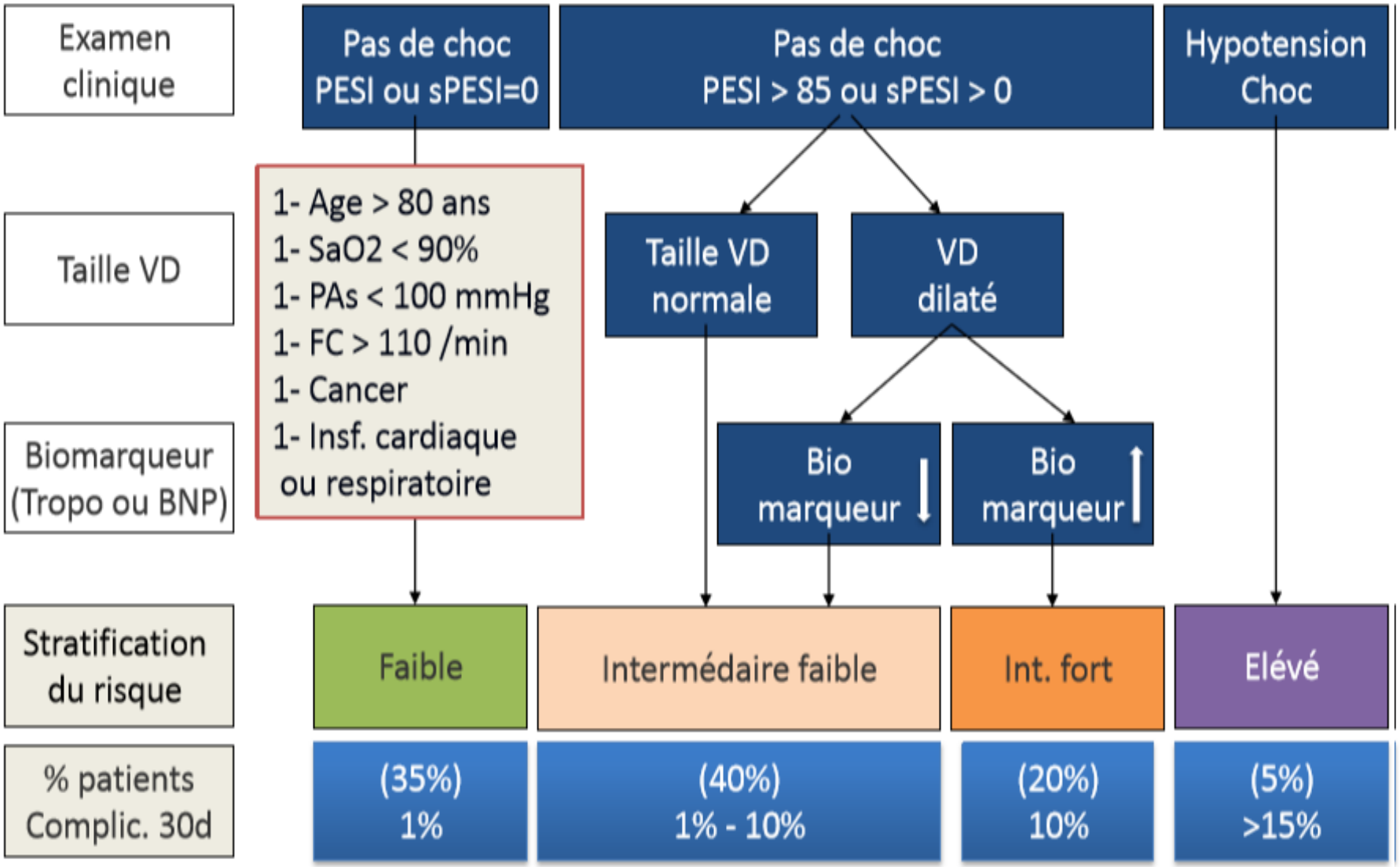
Prognostic assessment in « not high-risk » PE Pts : validated clinical pronostic score

Original & simplified PESI score

	Original version	Simplified version
	Risk strata[a]	
Low-risk PE (# 30-40% of pts)	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%)
Intermediate -risk PE (# 60% of pts)	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%)

Aujesky et al. Am J Respir Crit Care Med 2005 ;172:1041-6.

Pourquoi s'intéresser à l'ambulatoire ?



Konstantinides S et al. Eur Heart J 2014.

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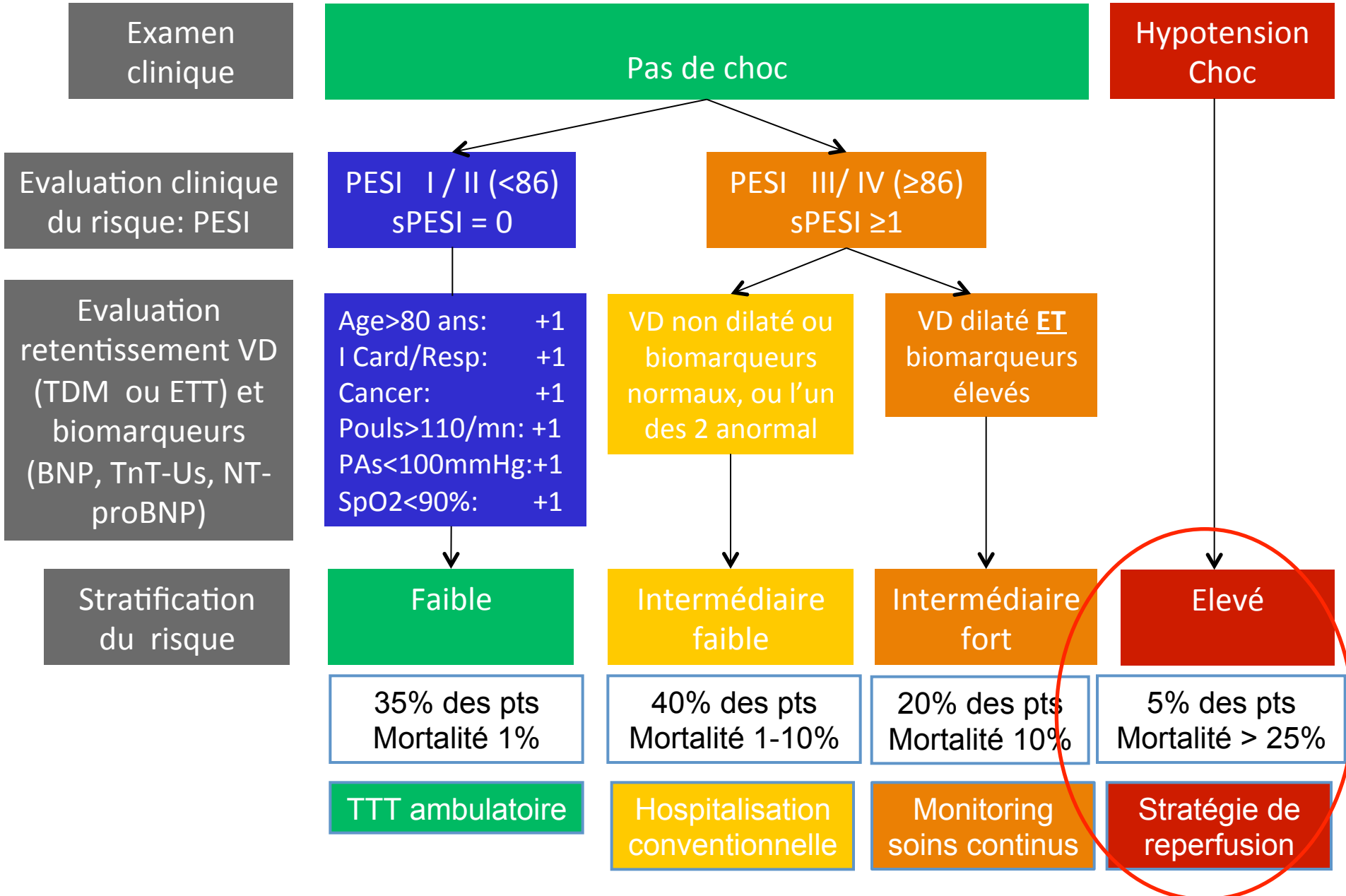
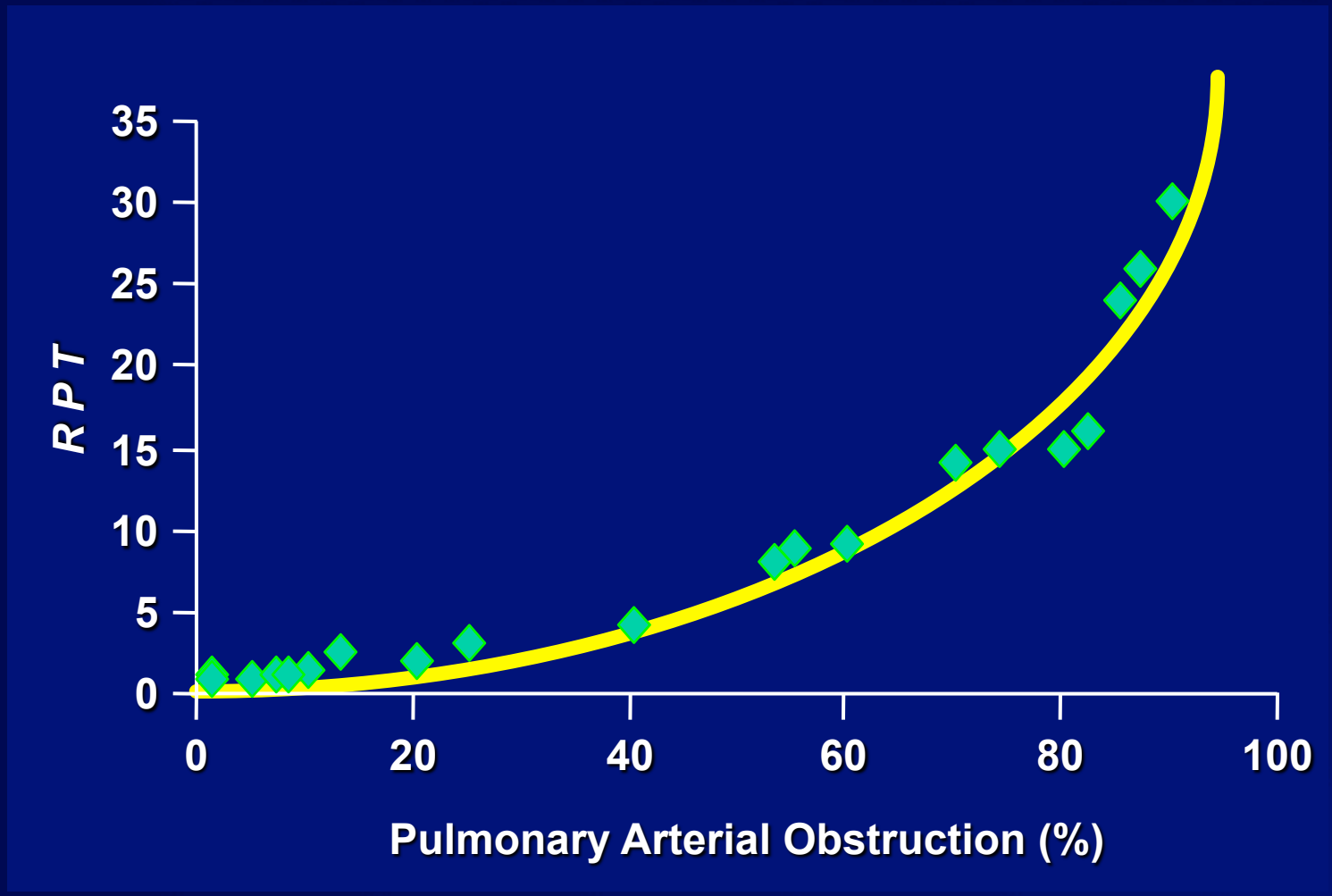
3. Sur la prise en charge thérapeutique

Stratification du Risque – ESC 2014



Relationship between Pulmonary Vascular Obstruction and Total Pulmonary Resistance



Petitprez Circulation 1984

Systemic thrombolytic therapy for acute PE

Efficacy outcomes, subgroup analyses

	All studies			Studies including[a] High-risk PE	Intermediate-risk PE	Low and intermediate-risk PE	Group difference
	OR (95% CI)	*P*-value	I^2 (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)	*P*-value
Mortality	0.59 (0.36 to 0.96)	0.034	0	0.48 (0.20 to 1.15)	0.42 (0.17 to 1.03)	0.96 (0.41 to 2.24)	0.36
PE mortality	0.29 (0.14 to 0.60)	<0.001	0	0.15 (0.03 to 0.78)	0.17 (0.05 to 0.67)	0.63 (0.20 to 1.97)	0.23
Death or treatment escalation	0.34 (0.22 to 0.52)	<0.001	0	0.18 (0.04 to 0.79)	0.37 (0.20 to 0.69)	0.35 (0.18 to 0.66)	0.67
PE recurrence	0.50 (0.27 to 0.94)	0.031	0	0.97 (0.31 to 2.98)	0.25 (0.06 to 1.03)	0.46 (0.17 to 1.21)	0.33

Safety outcomes, subgroup analyses

	All studies			Alteplase	Tenecteplase	Other thrombolytics	Group difference
	OR (95% CI)	*P*-value	I^2 (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)	*P*-value
Major bleeding	2.91 (1.95 to 4.36)	<0.001	25	1.07 (0.43 to 2.62)	5.02 (2.72 to 9.26)	2.16 (1.03 to 4.54)	0.02
Fatal/intracranial haemorrhage	3.18 (1.25 to 8.11)	0.008	0	1.09 (0.27 to 4.40)	7.32 (1.64 to 32.63)	NA	0.07

Marti C et al. Eur Heart J 2014.

Recommandations : thrombolyse ds EP à risque élevé

- C'est le TTT de 1ère intention des EP à risque élevé +++
- Toute contre indication doit être considérée comme relative +++

Approved thrombolytic regimens for pulmonary embolism	
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)

www.escardio.org/guidelines

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

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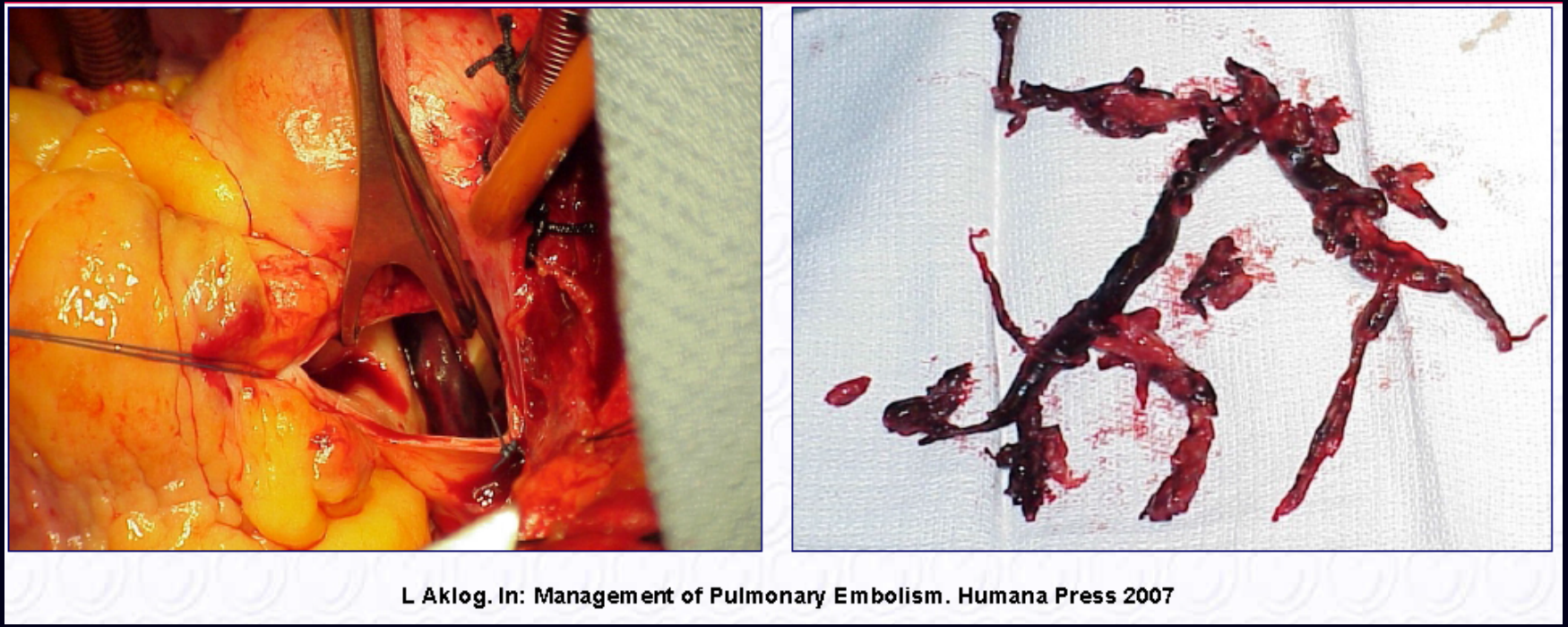
Embolectomie Chirurgicale

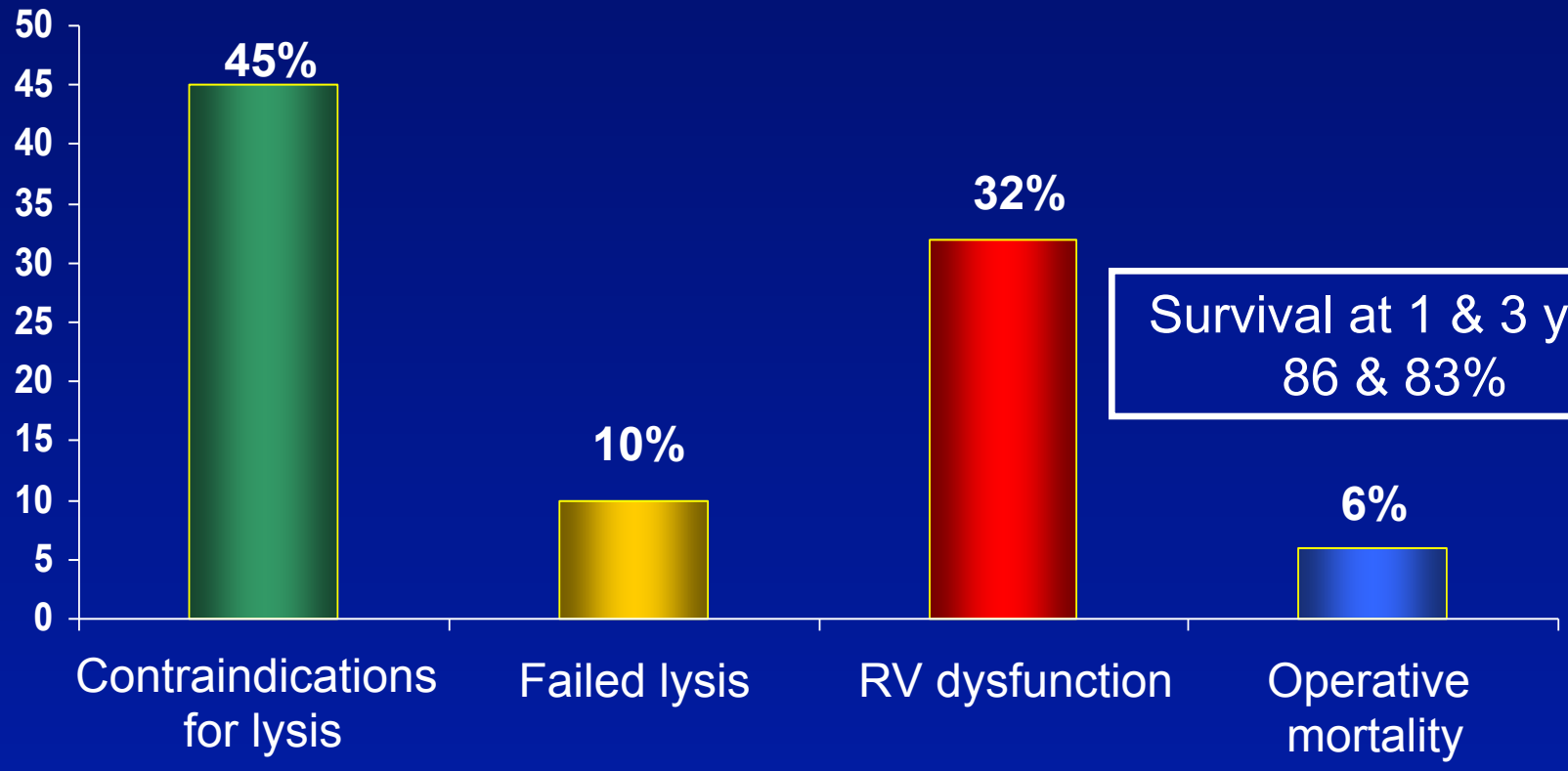


L Aklog. In: Management of Pulmonary Embolism. Humana Press 2007

- Approche multidisciplinaire rapide et individualisée, équipes expérimentées, mortalité périopératoire de 6%.
- Une thrombolyse pré-opératoire augmente le risque hgique mais ne constitue pas une contre indication.

Pulmonary Embolectomy : Contemporary Approach

- Expanded indications recently associated with a reduced operative risk
- Results in 47 consecutive pts with high & intermediate-risk PE

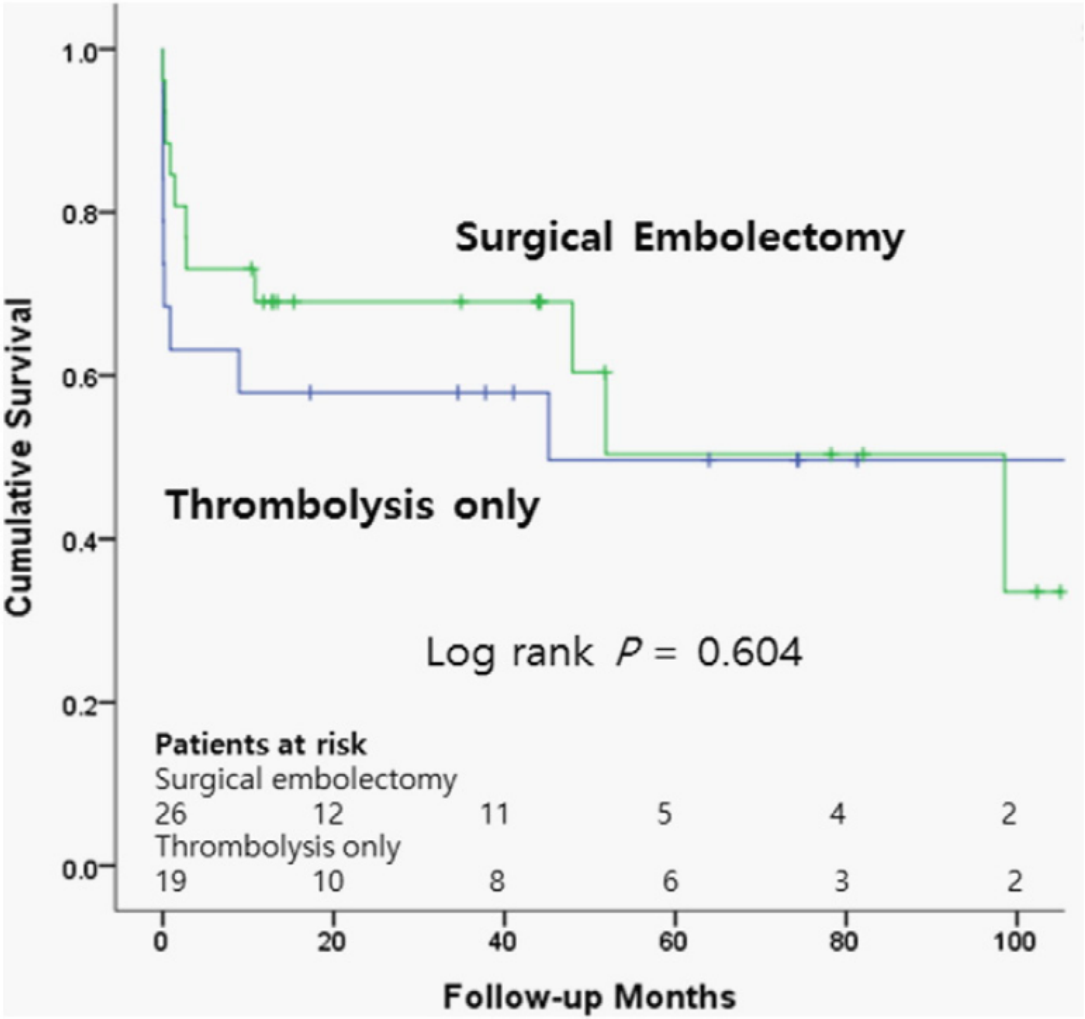


Survival at 1 & 3 yrs: 86 & 83%

Leacche M et al. J Thor Cardiovasc Surg 2005;129:101
Aklog L et al. Circulation 2002;105:1416-19.

Embolectomie vs Thrombolyse dans l'EP

Kaplan-Meier Survival Curves for All-Cause Mortality



Cho YH. Int J Cardiol 2016;203:579

Rescue embolectomy >> repeat thrombolysis

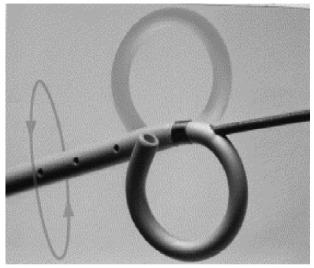
	Rescue Embolectomy (N=14)	Repeat Thrombolysis (N=26)	P value
Death	1 (7%)	10 (38%)	0.07
PE-related death	1 (7%)	6 (23%)	0.39
- recurrent PE	0	3 (11.5%)	0.15
- refractory shock	1 (7%)	3 (11.5%)	0.49
Bleeding complications	2 (14%)	6 (23%)	0.82
- major bleedings	2 (14%) (0 fatal)	4 (15%) (4 fatal)	0.55
- intracranial haemorrhage	0	1 (4%)	0.49
Recurrent PE (fatal & non fatal)	0	9 (35%)	0.015
Uneventful evolution	11 (79%)	8 (31%)	0.004

Meneveau N et al. Chest 2006;129:1043-50.

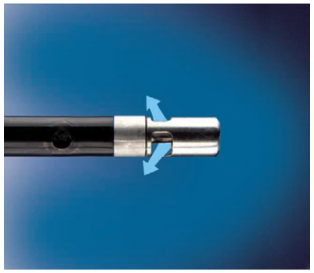
Endovascular techniques

Modern CDT for acute PE :

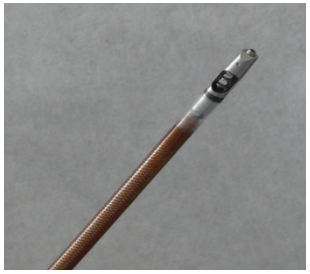
- Low-profile catheters (≤ 10 Fr)
- Catheter-directed mechanical fragmentation and/or aspiration of thrombus
- Pharmaco-mechanical systems combining local thrombolytic infusion with basic catheter fragmentation or ultrasound assistance
- Purpose : restore PA patency & relieve right heart strain



Rotating pigtail method



Helix thrombectomy device

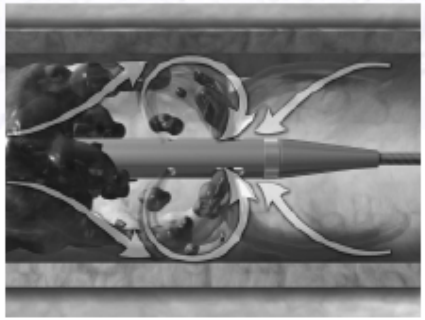
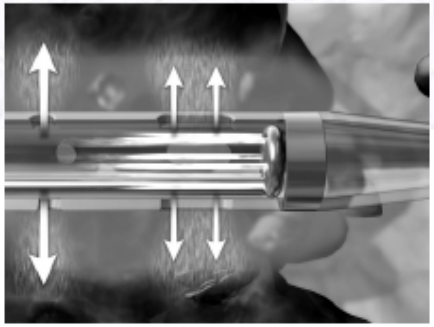
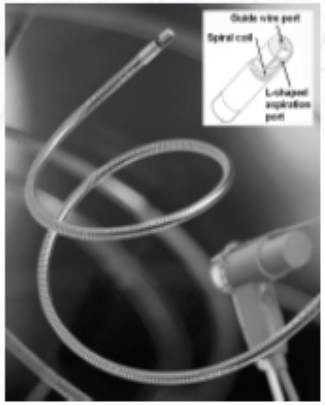


Aspirex device

*EKOS US-assisted catheter-directed thrombolysis

Kucher N et al. Radiology 2005; 236:852–858.
Kuo WT. J Vasc Interv Radiol 2012;23:167-79.

Thromboembolectomie percutanée

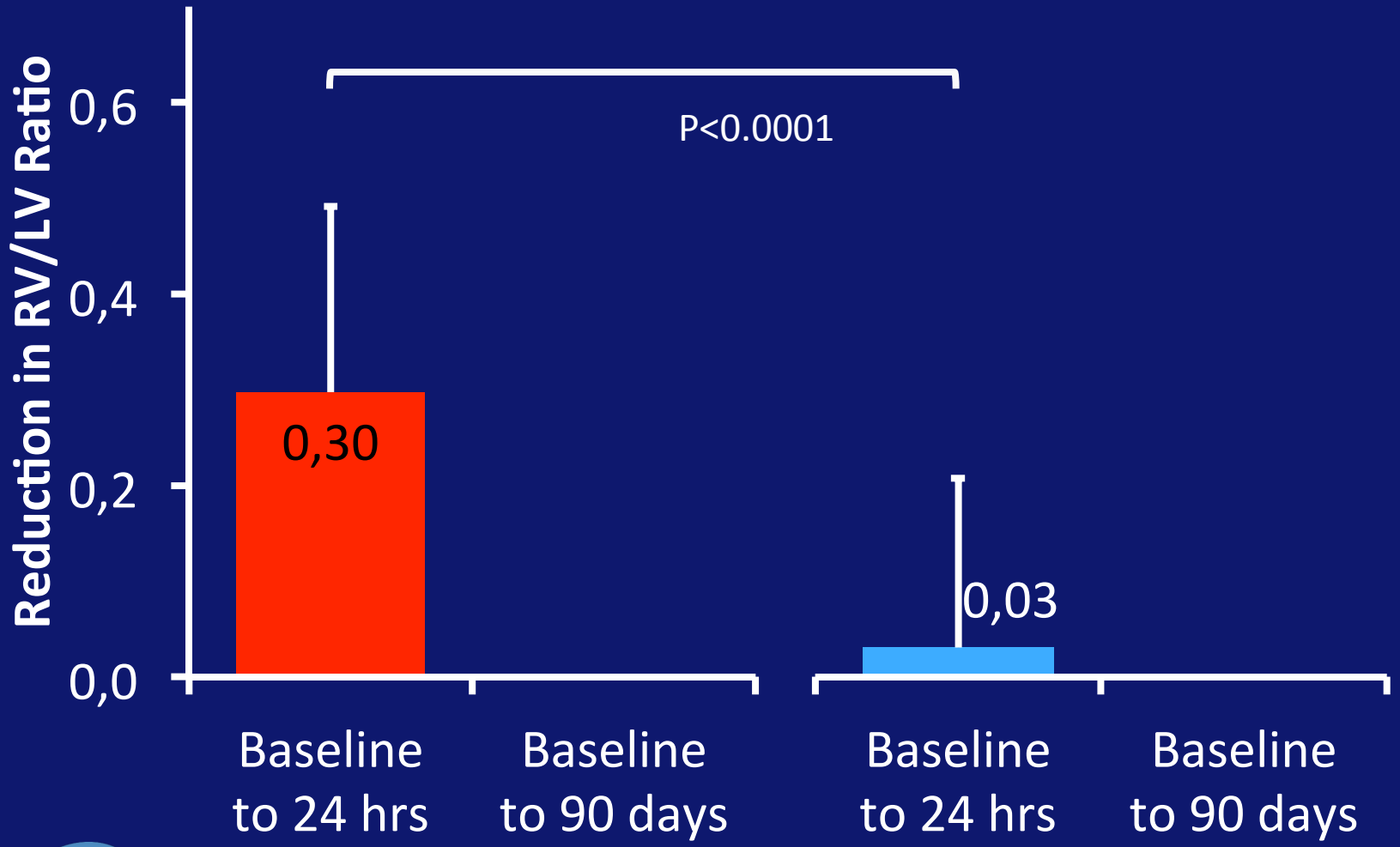
- 35 essais non randomisés (594 pts)
- **Succès clinique** = stabilisation hémodynamique, résolution de l'hypoxie, survie hospitalière : 87%.
- Contribution de l'intervention mécanique incertaine (67% de thrombolyse in situ).
- **Biais** : complications hgiques graves sous reportées (2%).

Pharmacomechanical Thrombolysis
= Local thrombolysis + mechanical intervention

AngioJet : Power Pulse thombolysis + thrombectomy
(Venturi effect)

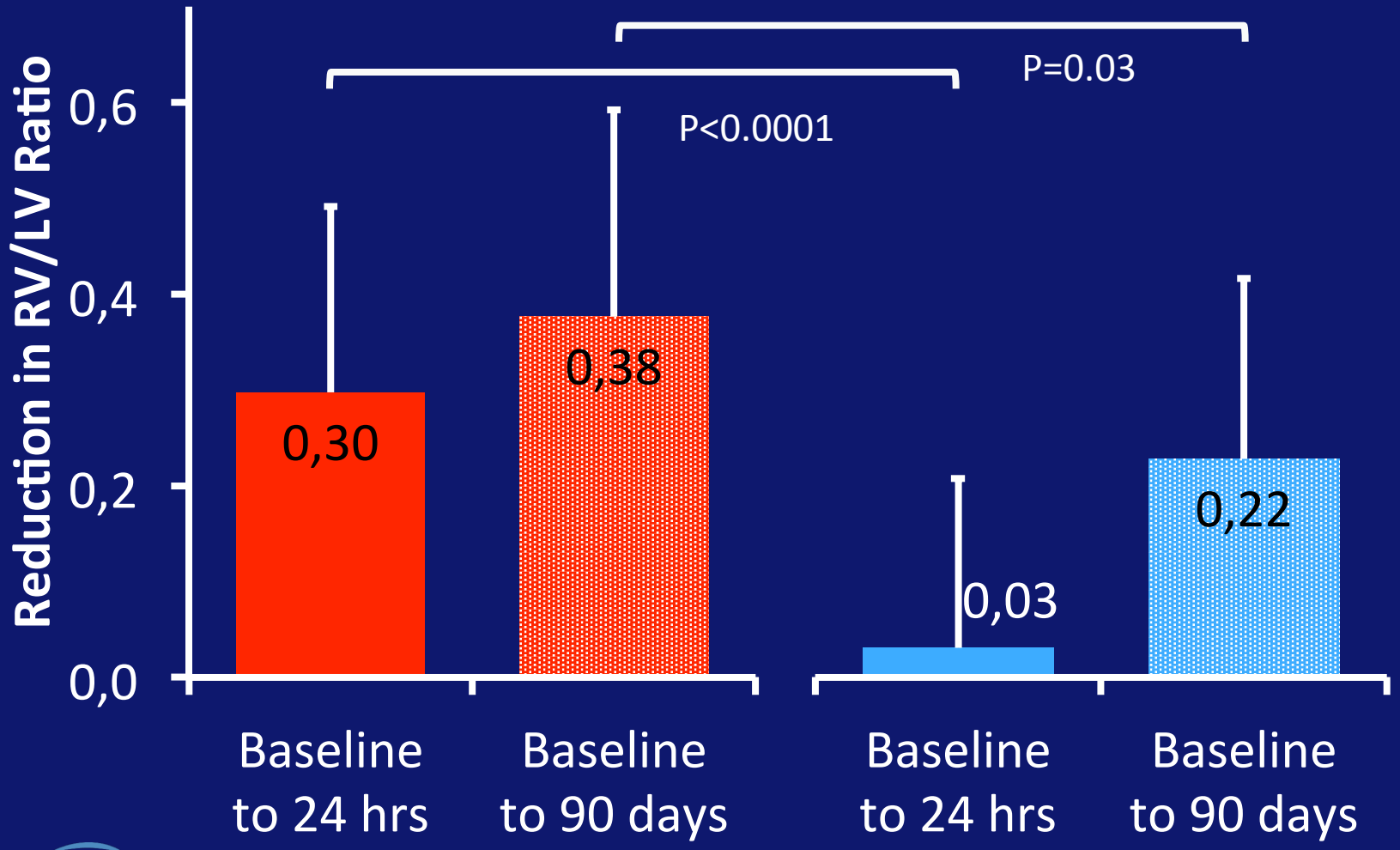
EKOS : Ultrasound-assisted thrombolysis

Primary endpoint: Reduction in RV/LV ratio



ULTIMA

Primary endpoint: Reduction in RV/LV ratio



Etude SEATTLE II : Cohorte prospective de 150 pts avec EP à haut et risque intermédiaire

- 150 pts with acute high-risk (n=31) or intermediate-risk (n=119) PE

CT-confirmed PE

- Symptoms ≤14 days AND
- High/intermediate-risk PE
- RV/LV diameter ≥ 0.9

USAT low-dose fibrinolysis

- tPA 1 mg/h for 24 h (1 device) OR
- tPA 1 mg/h for 12h (2 devices)
- TOTAL tPA dose = 24 mg

Outcomes

- 29 % decrease in CT-measured RV/ LV diameter over 48h
- 30% decrease in sPA pressure by the end of the procedure
- 30% decrease in PA obstruction over 48h
- Major bleeding rate = 10%
- No intracranial hemorrhage

Piazza G et al. J Am Coll Cardiol Intv 2015;8:1382-92.

Advantages & potential limitations of catheter-based PE interventions

Advantages

- Rapid initiation of therapy
- Low doses of adjunctive thrombolytic therapy
- Efficacy on surrogate hemodynamic outcomes
- Shorter length of hospital stay
- Safety profile :
  - Low complications rates
  - Major bleeding rates # 6% (very few fatal & intracranial bleeding)

Potential Limitations

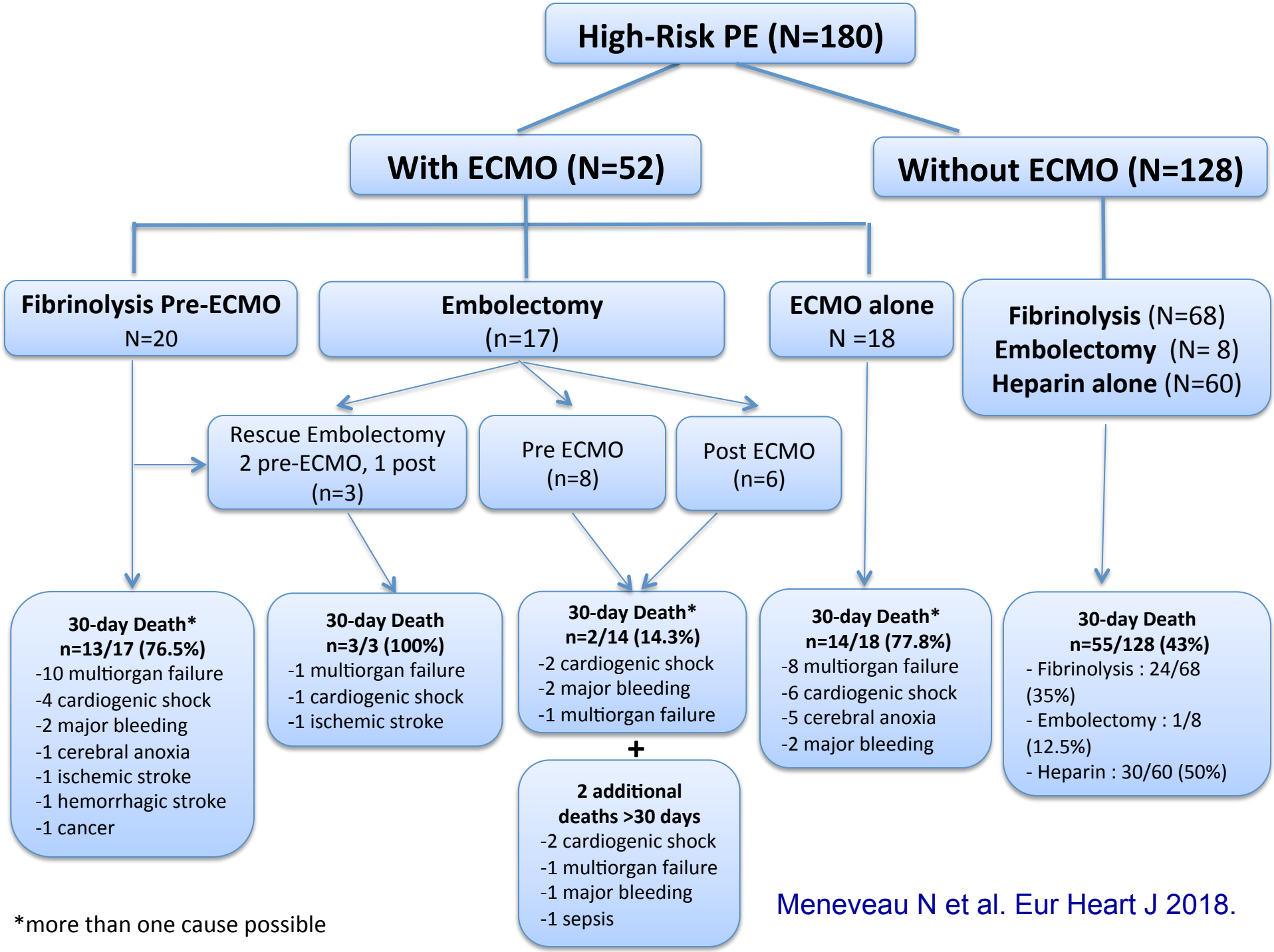
- Optimal duration of the procedure (?)
- Appropriate expertise & resources
- Expensive procedures
- Learning curve
- No long-term data with regard to recurrent PE, mortality, & CTEPH

Sobieszczyk P. Circulation 2012;126:1917-22. Engelberger RP et al. Eur Heart J 2014;35:758-64.

Recommendations for acute phase treatment

PE with shock or hypotension (high-risk)		
It is recommended to initiate intravenous anticoagulation with UFH without delay in patients with high-risk PE.	I	C
Thrombolytic therapy is recommended.	I	B
Surgical pulmonary embolectomy is recommended for patients in whom thrombolysis is contraindicated or has failed.[c]	I	C
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.[c]	IIa	C

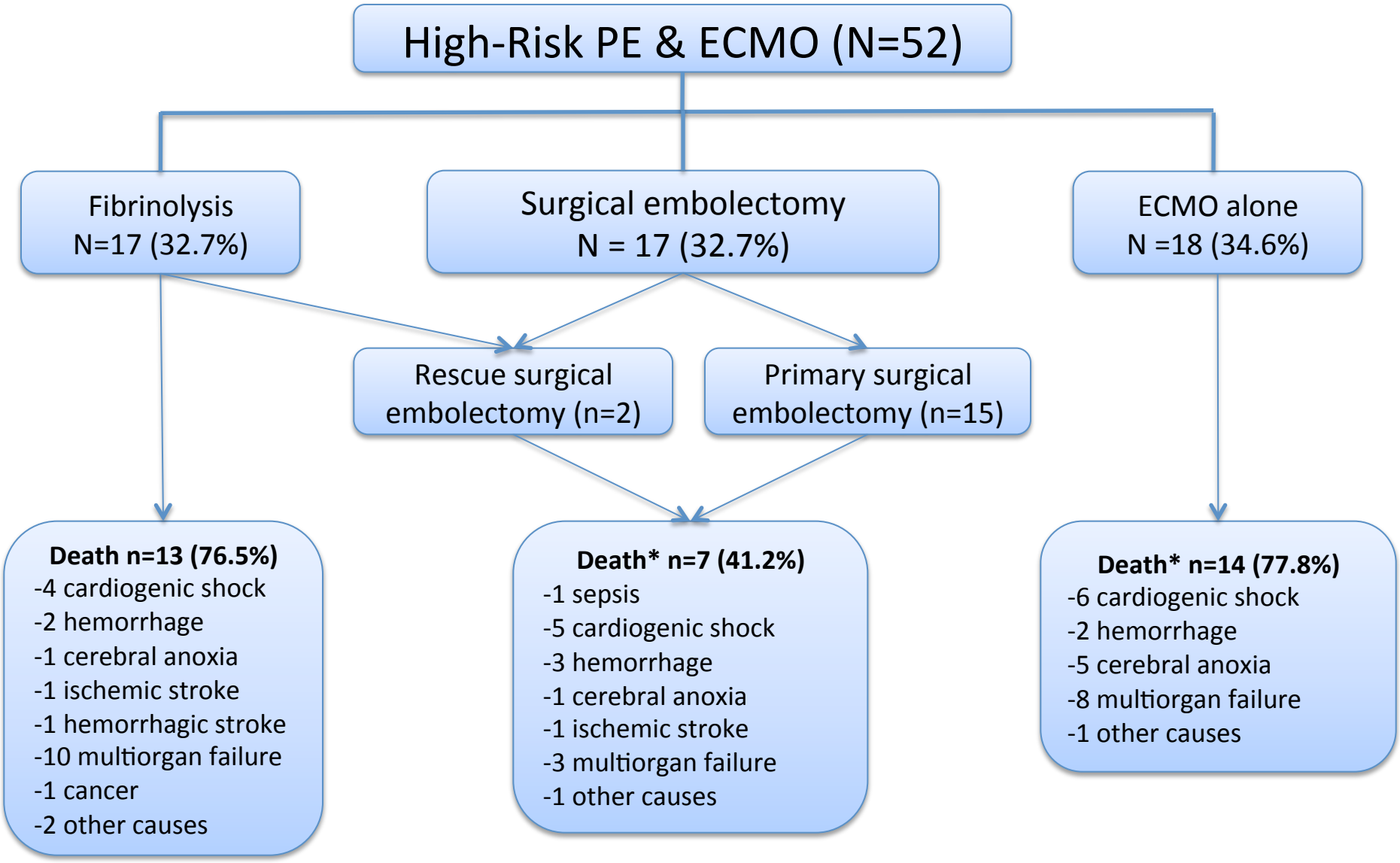
European Heart Journal (2014):doi:10.1093/eurheartj/ehu283



*more than one cause possible

Meneveau N et al. Eur Heart J 2018.

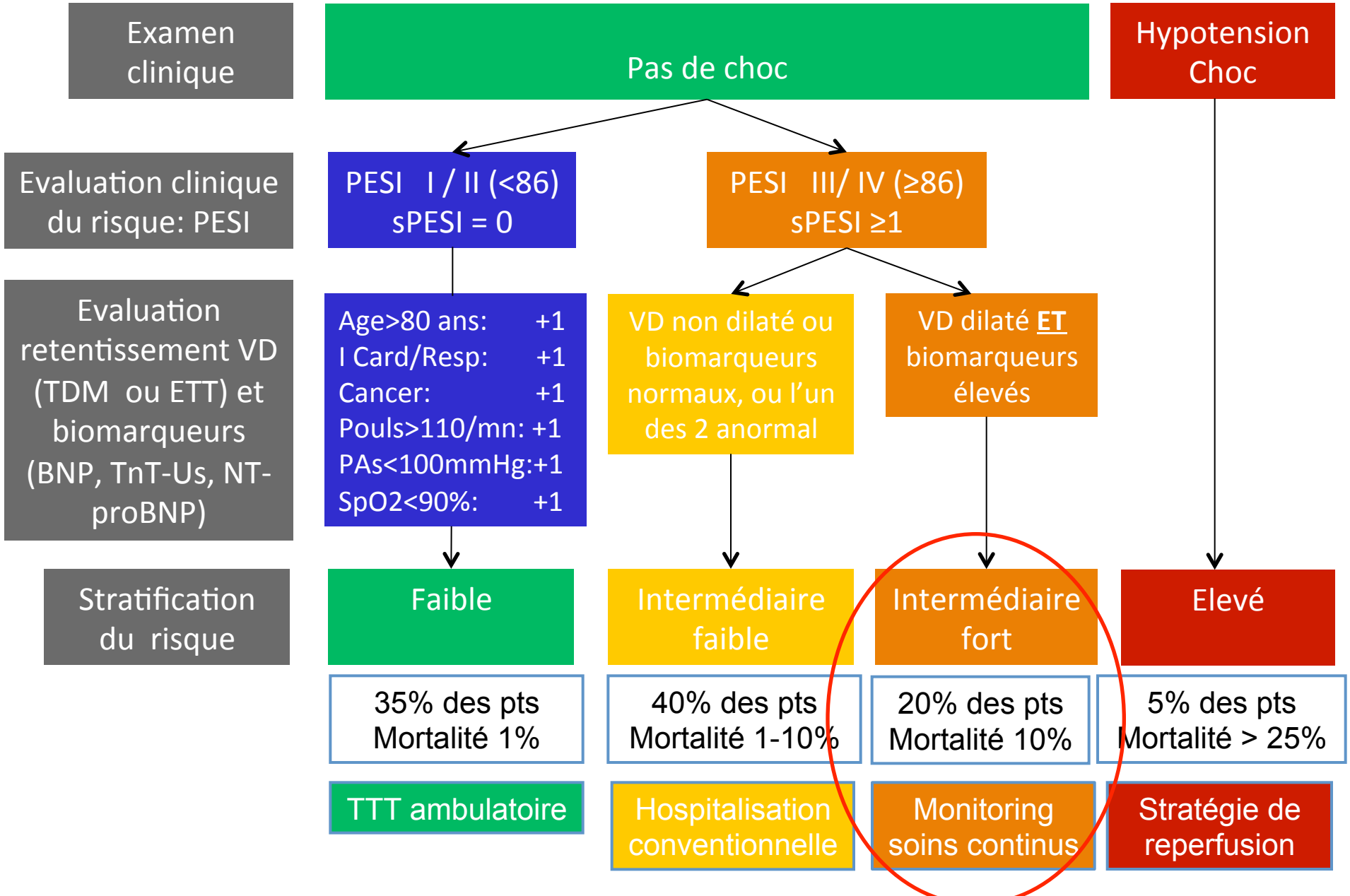
EP à haut risque et ECMO : Expérience nationale : l'ECMO n'est pas un TTT de l'EP



*more than one cause possible

Meneveau N et al. Eur Heart J 2018.

Stratification du Risque – ESC 2014



PEITHO: Secondary efficacy outcomes

	Tenecteplase (n=506)		Placebo (n=499)		*P* value
	n	(%)	n	(%)	
All-cause mortality within 7 days	6	(1.2)	9	(1.8)	0.43
Hemodynamic collapse within 7 days	8	(1.6)	25	(5.0)	0.002

ITT population

The PEITHO Investigators

Recommendations for acute phase treatment in intermediate-risk PE

PEITHO: Efficacy and safety outcomes

	Tenecteplase (n=506)		Placebo (n=499)		*P* value
	n	(%)	n	(%)	
All-cause mortality within 7 days	**6**	**(1.2)**	**9**	**(1.8)**	**0.43**
Non-intracranial bleeding					
Major	32	(6.3)	6	(1.5)	<0.001
Minor	165	(33)	43	(8.6)	<0.001
Strokes by day 7	**12**	**(2.4)**	**1**	**(0.2)**	**0.003**
Hemorrhagic	10		1		
Ischemic	2		0		

Meyer G et al. N Engl J Med 2014;370:1402-11.

Recommendations for acute phase treatment (2)

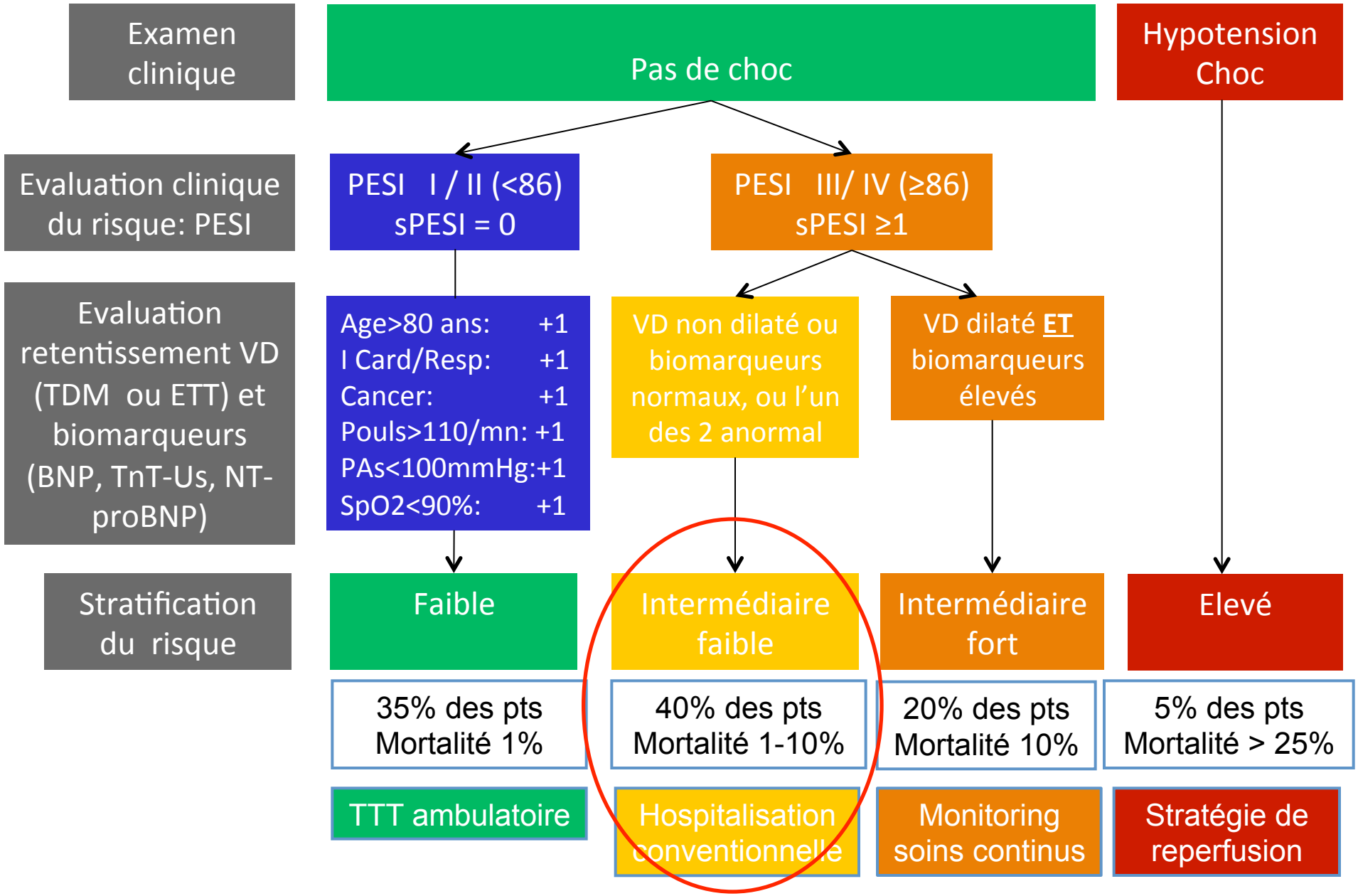
PE without shock or hypotension (intermediate or low risk)[c]		
Reperfusion treatment		
Routine use of primary systemic thrombolysis is not recommended in patients without shock or hypotension.	III	B
Close monitoring is recommended in patients with intermediate-high-risk PE to permit early detection of haemodynamic decompensation and timely initiation of rescue reperfusion therapy.	I	B
Thrombolytic therapy should be considered for patients with intermediate-high-risk PE and clinical signs of haemodynamic decompensation.	IIa	B
Surgical pulmonary embolectomy may be considered in intermediate-high-risk patients, if the anticipated risk of bleeding under thrombolytic treatment is high.[f]	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.[f]	IIb	B

www.escardio.org/guidelines

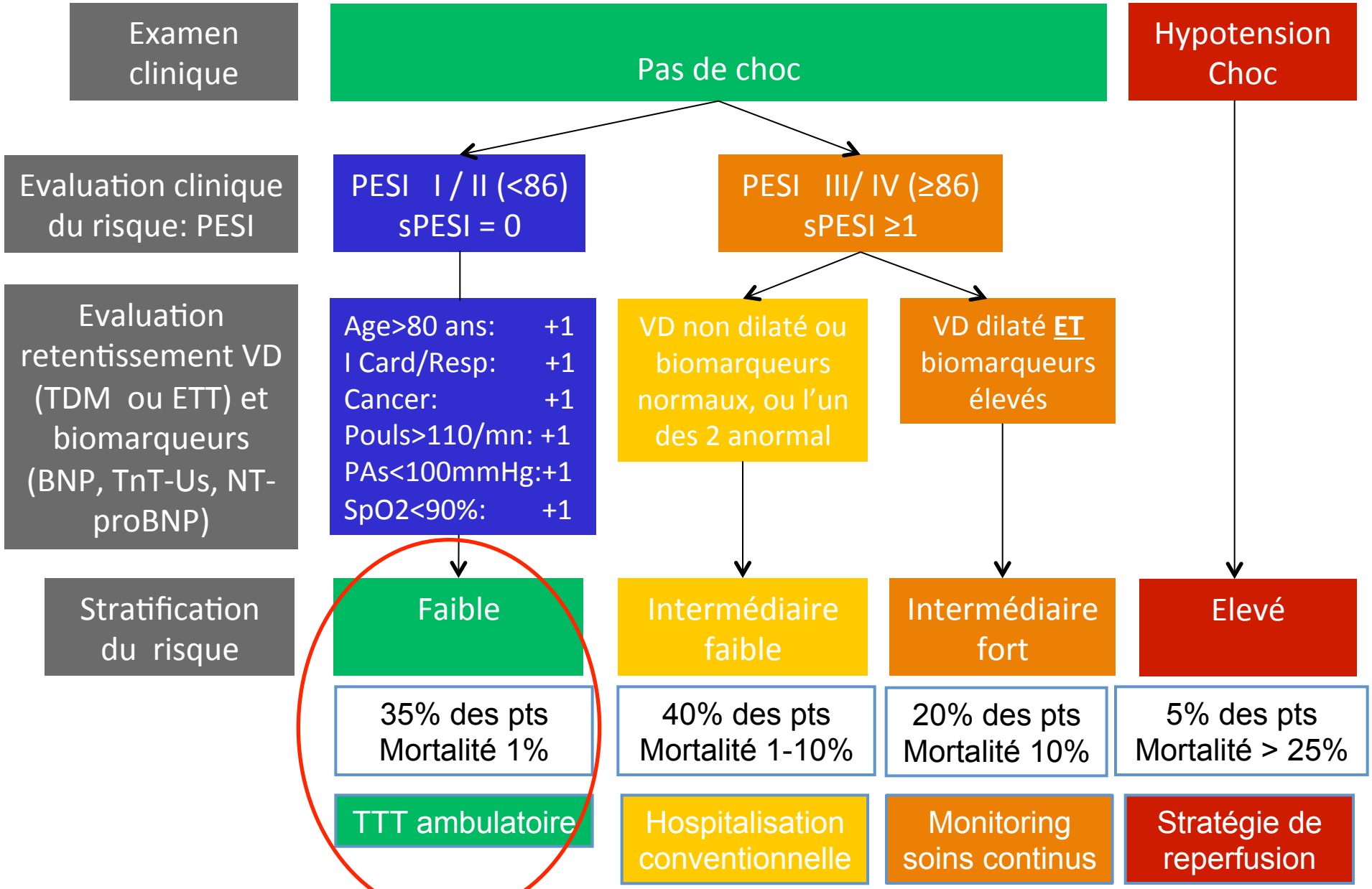
European Heart Journal (2014):doi:10.1093/eurheartj/ehu283

EUROPEAN SOCIETY OF CARDIOLOGY®

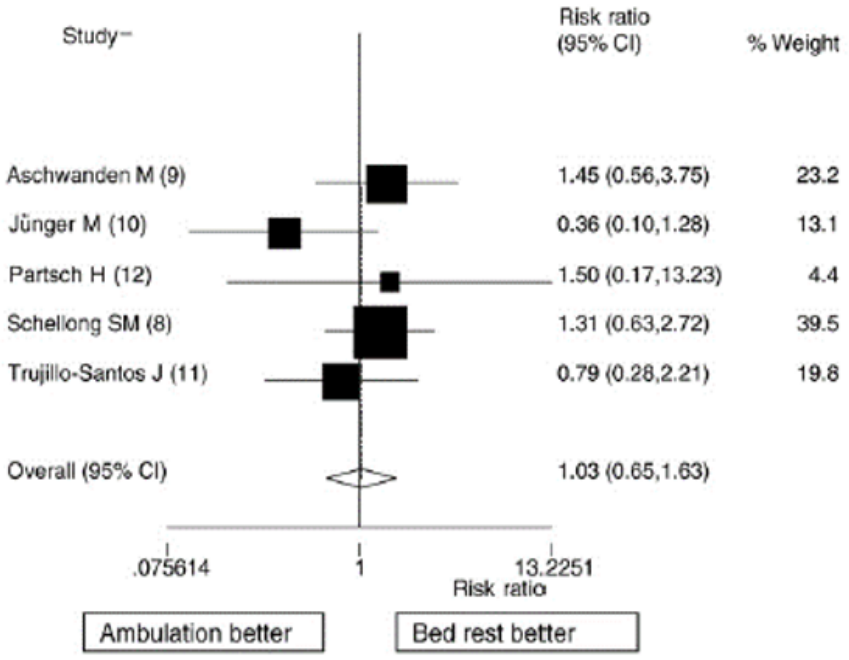
Stratification du Risque – ESC 2014



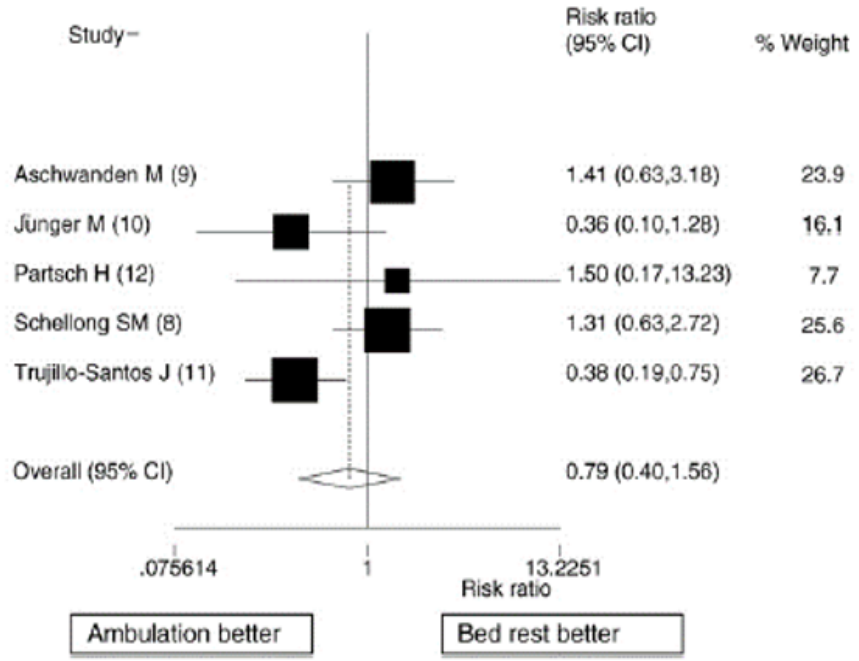
Stratification du Risque – ESC 2014



L'alitement n'est pas nécessaire … et pas recommandé



Incidence nouvelle EP



Incidence nouvelle EP et mortalité globale

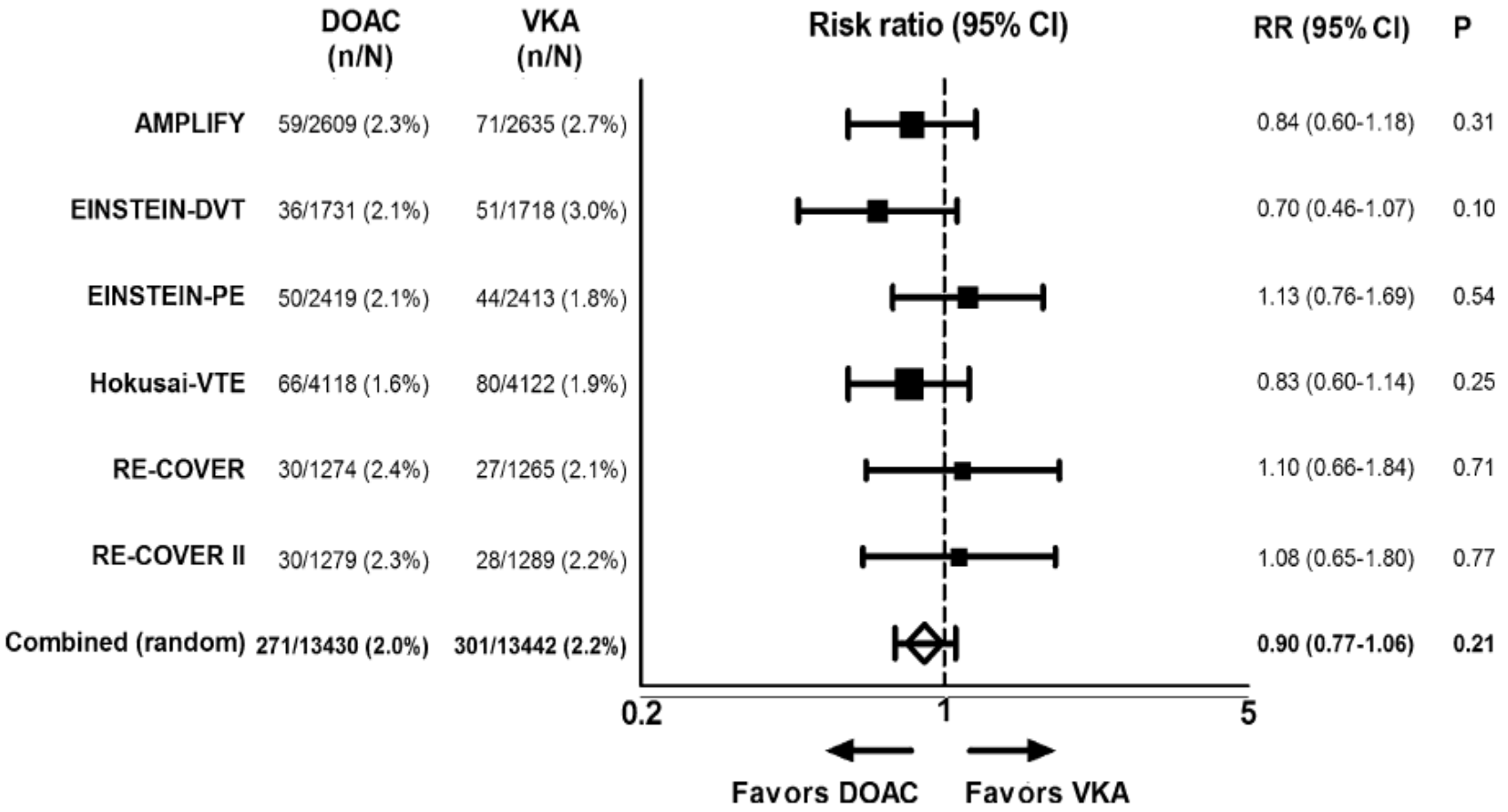
Meune et al. Int J Cardio 2009

Conclusions: Our findings confirm those from previous reports suggesting that bed rest has no influence on the risk of developing PE among patients with acute DVT of the lower limbs. In addition, our findings show for the first time the lack of influence of bed rest even in patients presenting with acute submassive PE.

Trujillo-Santos et al. Chest 2005

DOACs vs VKA for acute VTE : evidence from phase 3 trials

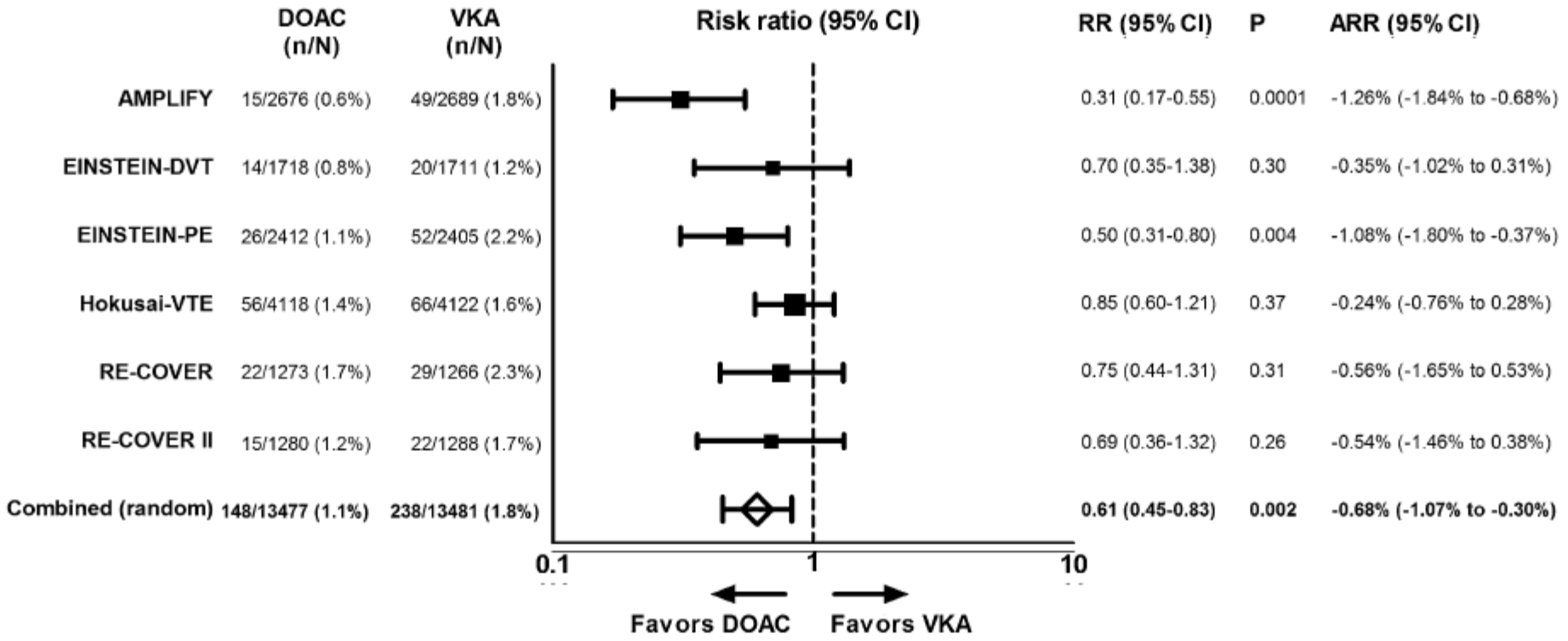
First recurrent VTE or VTE-related death



Van ES N et al. Blood. 2014;124(12):1968-1975.

DOACs vs VKA for acute VTE : evidence from phase 3 trials

Major bleeding



Van ES N et al. Blood. 2014;124(12):1968-1975.

Recommendations for acute phase treatment

PE without shock or hypotension (intermediate or low risk)[c]		
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
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
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[d]
As an alternative to VKA treatment, administration of edoxaban* is recommended following acute-phase parenteral anticoagulation.	I	B
New oral anticoagulants (rivaroxaban, apixaban, dabigatran, edoxaban) are not recommended in patients with severe renal impairment.[e]	III	A

Recommendations for acute phase treatment

[Evidence-Based Medicine]

CHEST

Antithrombotic Therapy for VTE Disease

CHEST Guideline and Expert Panel Report

Clive Kearon, MD, PhD; Elie A. Akl, MD, MPH, PhD; Joseph Ornelas, PhD; Allen Blaivas, DO, FCCP; David Jimenez, MD, PhD, FCCP; Henri Bounameaux, MD; Menno Huisman, MD, PhD; Christopher S. King, MD, FCCP; Timothy Morris, MD, FCCP; Namita Sood, MD, FCCP; Scott M. Stevens, MD; Janine R. E. Vintch, MD, FCCP; Philip Wells, MD; Scott C. Woller, MD; and COL Lisa Moores, MD, FCCP

Choice of Long-Term (First 3 Months) and Extended (No Scheduled Stop Date) Anticoagulant

1. In patients with proximal DVT or PE, we recommend long-term (3 months) anticoagulant therapy over no such therapy (Grade 1B).

***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 VKA therapy** (all Grade 2B).

Kearon C et al. Chest 2016.

Quels patients éligibles au traitement ambulatoire?

Deux approches différentes

- Analyse du risque de décès à moyen terme (+ critères pragmatiques)

Score PESI ou PESI simplifié

- Analyse pragmatique des soins nécessaires et des possibilités de suivi

Score HESTIA

Outpatient treatment in patients with acute pulmonary embolism: the Hestia Study

W. ZONDAG,* I. C. M. MOS,* D. CREEMERS-SCHILD,† A. D. M. HOOGERBRUGGE,‡ O. M. DEKKERS,§ J. DOLSMA,¶ M. EIJSVOGEL,** L. M. FABER,†† H. M. A. HOFSTEE,‡‡ M. M. C. HOVENS,§§ G. J. P. M. JONKERS,¶¶ K. W. VAN KRALINGEN,*** M. J. H. A. KRUIP,††† T. VLASVELD,‡‡‡ M. J. M. DE VREEDE§§§ and M. V. HUISMAN* ON BEHALF OF THE HESTIA STUDY INVESTIGATORS[1]

Is the patient hemodynamically unstable?*	Yes	No
Is thrombolysis or embolectomy necessary?	Yes	No
Active bleeding or high risk of bleeding?†	Yes	No
More than 24 h of oxygen supply to maintain oxygen saturation > 90%?	Yes	No
Is pulmonary embolism diagnosed during anticoagulant treatment?	Yes	No
Severe pain needing intravenous pain medication for more than 24 h?	Yes	No
Medical or social reason for treatment in the hospital for more than 24 h (infection, malignancy, no support system)?	Yes	No
Does the patient have a creatinine clearance of < 30 mL min^{-1}?‡	Yes	No
Does the patient have severe liver impairment?§	Yes	No
Is the patient pregnant?	Yes	No
Does the patient have a documented history of heparin-induced thrombocytopenia?	Yes	No

If ≥1 item is answered with YES, the patient CANNOT be treated at home

J Thromb Haemost 2011; 9: 1500-7

PESI ou HESTIA?

Critères d'exclusion	Aujesky 2011	Zondag 2011	Den Exter 2016
N	171	297	550
Nécessité d'un traitement à l'hôpital	X	X	X
-Monitoring cardiaque (PR, BP)	X	X	X
-Oxygénothérapie (Sp02)	X	X	X
-Gestion de la douleur	X	X	X
-Co-morbidité	X	X	X
Contreindication HBPM – AOD	X	X	X
- Insuffisance rénale sévère	X	X	X
Risque hémorragique majeur	X	X	X
Choix du patient	X	X	X
Critère spécifique de gravité	**PESI I-II**	**HESTIA ≤ 1**	
Mortalité à 3 mois	**0,6%**	**1%**	**1,4%**
Récidive thrombo-embolique	**0,6%**	**2%**	**1%**
Hémorragie majeure	**1,8%**	**0,7%**	**0,8%**

PESI ou HESTIA?

Critères d'exclusion	Aujesky 2011	Zondag 2011	Den Exter 2016
N	171	297	550
Nécessité d'un traitement à l'hôpital	X	X	X
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-Oxygénothérapie (Sp02)	X	X	X
-Gestion de la douleur	X	X	X
-Co-morbidité	X	X	X
Contreindication HBPM – AOD	X	X	X
- Insuffisance rénale sévère	X	X	X
Risque hémorragique majeur	X	X	X
Choix du patient	X	X	X
Critère spécifique de gravité	**PESI I-II**	**HESTIA ≥ 1**	

Une sécurité semblant similaire

PESI ou HESTIA?

Critères d'exclusion	Aujesky 2011	Zondag 2011	Den Exter 2016
N	171	297	550
Nécessité d'un traitement à l'hôpital	X	X	X
-Monitoring cardiaque (PR, BP)	X	X	X
-Oxygénothérapie (Sp02)	X	X	X
-Gestion de la douleur	X	X	X
-Co-morbidité	X	X	X
Contreindication HBPM – AOD	X	X	X
- Insuffisance rénale sévère	X	X	X
Risque hémorragique majeur	X	X	X
Choix du patient	X	X	X
Critère spécifique de gravité	**PESI I-II**	**HESTIA ≥ 1**	
Mortalité à 3 mois	0,6%	1%	1,4%
Récidive thrombo-embolique	0,6%	2%	1%
Hémorragie majeure	1,8%	0,7%	0,8%
Taux de traitement ambulatoire	**22%**	**51%**	**55%**

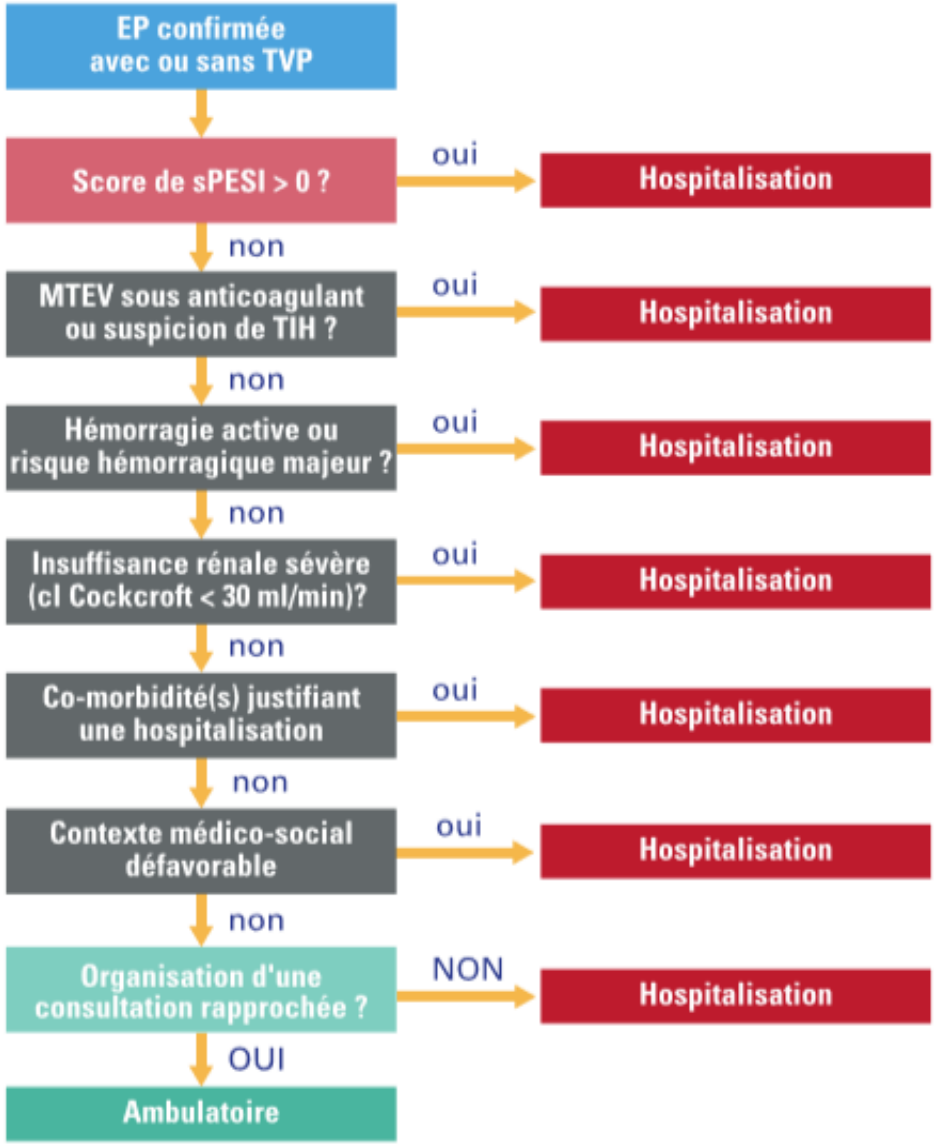
PESI ou HESTIA?

Critères d'exclusion	Aujesky 2011	Zondag 2011	Den Exter 2016
N	171	297	550
Nécessité d'un traitement à l'hôpital	X	X	X
-Monitoring cardiaque (PR, BP)	X	X	X
-Oxygénothérapie (Sp02)	X	X	X
-Gestion de la douleur	X	X	X
-Co-morbidité	X	X	X
Contreindication HBPM – AOD	X	X	X
- Insuffisance rénale sévère	X	X	X
Risque hémorragique majeur	X	X	X
Choix du patient	X	X	X
Critère spécifique de gravité	**PESI I-II**	**HESTIA ≥ 1**	

Un taux de traitement ambulatoire du simple au double

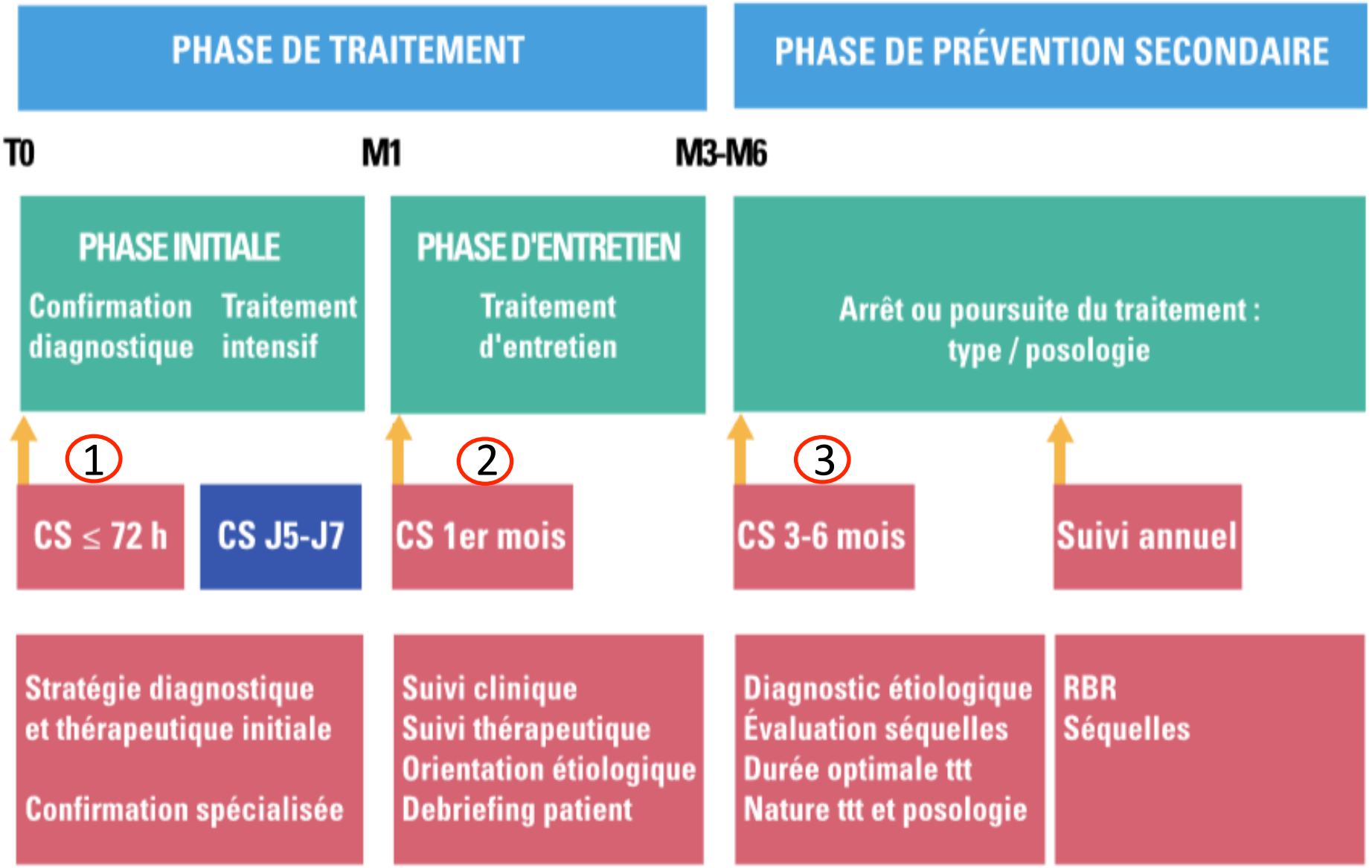
Taux de traitement ambulatoire	**22%**	**51%**	**55%**

Proposition d'algorithme pour une hospitalisation ou prise en charge ambulatoire d'une EP



- Analyse de gravité / contexte
- Traitement initié dès les urgences / le diagnostic
- Consultation précoce
  - Confirmation du diagnostic étiologique et de gravité
  - Information / compréhension du patient, médecin traitant ...
  - Confirmation – adaptation traitement
  - Coordination et organisation du suivi
- Organisation spécifique
  - Documents adaptés
  - Équipe spécialisée

Parcours de soins EP



Embolie pulmonaire :

ce que le cardiologue doit savoir en 2018

5. Sur l'évaluation du risque de récidives et la durée du traitement AC

Recommendations for duration of treatment (1)

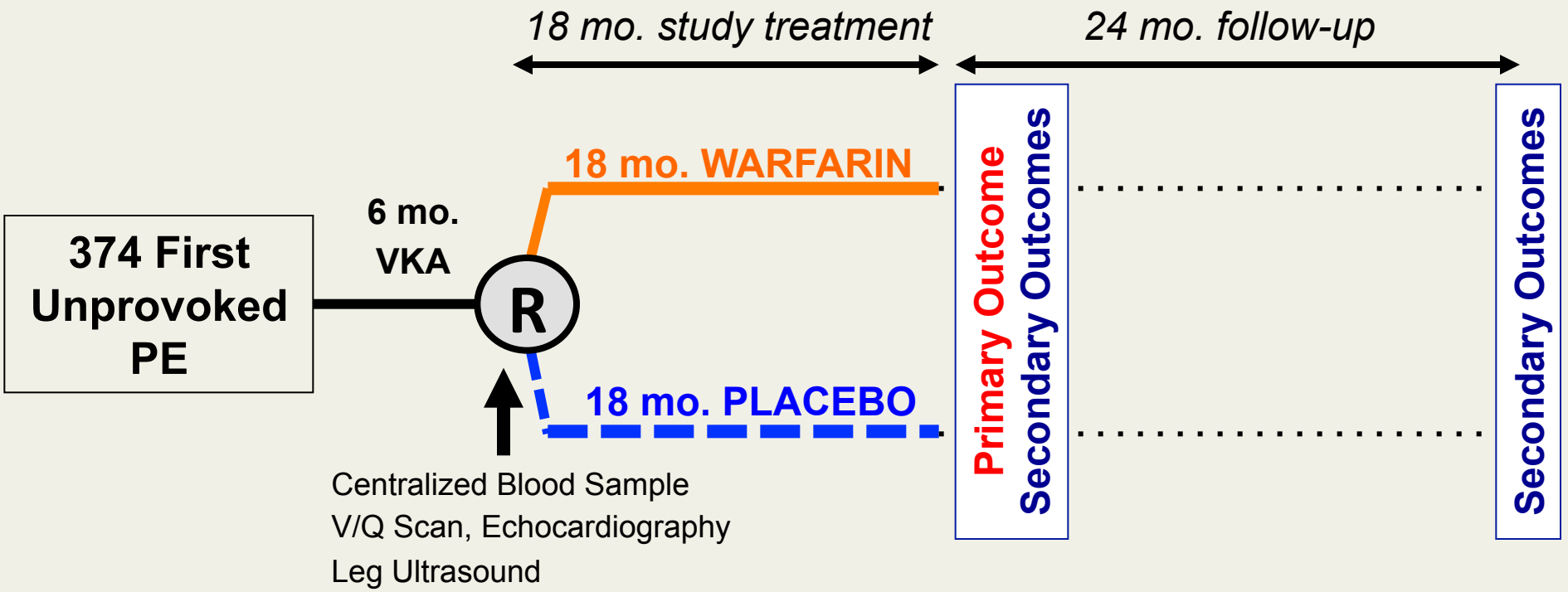
Recommendations for duration of anticoagulation after pulmonary embolism	Class[a]	Level[b]
For patients with PE secondary to a transient (reversible) risk factor, oral anticoagulation is recommended for 3 months.	I	B
For patients with unprovoked PE, oral anticoagulation is recommended for at least 3 months.	I	A
Extended oral anticoagulation should be considered for patients with a first episode of unprovoked PE and low bleeding risk.	IIa	B
Anticoagulation treatment of indefinite duration is recommended for patients with a second episode of unprovoked PE.	I	B
In patients who receive extended anticoagulation, the risk–benefit ratio of continuing such treatment should be reassessed at regular intervals.	I	C

Original Investigation

Six Months vs Extended Oral Anticoagulation After a First Episode of Pulmonary Embolism

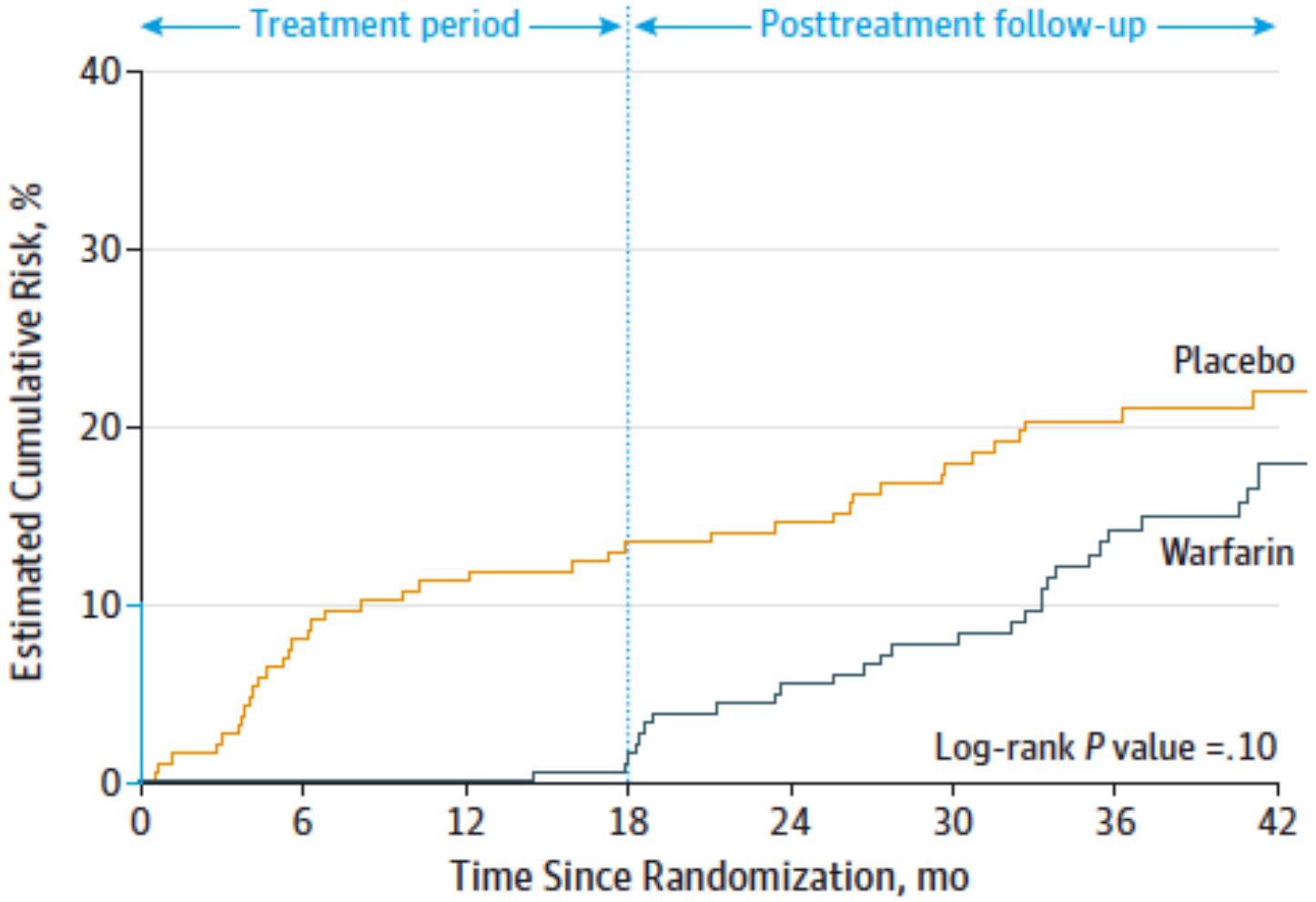
The PADIS-PE Randomized Clinical Trial

Francis Couturaud, MD, PhD; Olivier Sanchez, MD, PhD; Gilles Pernod, MD, PhD; Patrick Mismetti, MD, PhD; Patrick Jego, MD, PhD; Elisabeth Duhamel, MD; Karine Provost, MD; Claire Bal dit Sollier, MB; Emilie Presles, MS; Philippe Castellant, MD; Florence Parent, MD; Pierre-Yves Salaun, MD, PhD; Luc Bressollette, MD, PhD; Michel Nonent, MD, PhD; Philippe Lorillon, PharmD; Philippe Girard, MD; Karine Lacut, MD, PhD; Marie Guégan, MS; Jean-Luc Bosson, MD, PhD; Silvy Laporte, MS, PhD; Christophe Leroyer, MD, PhD; Hervé Décousus, MD; Guy Meyer, MD; Dominique Mottier, MD; for the PADIS-PE Investigators



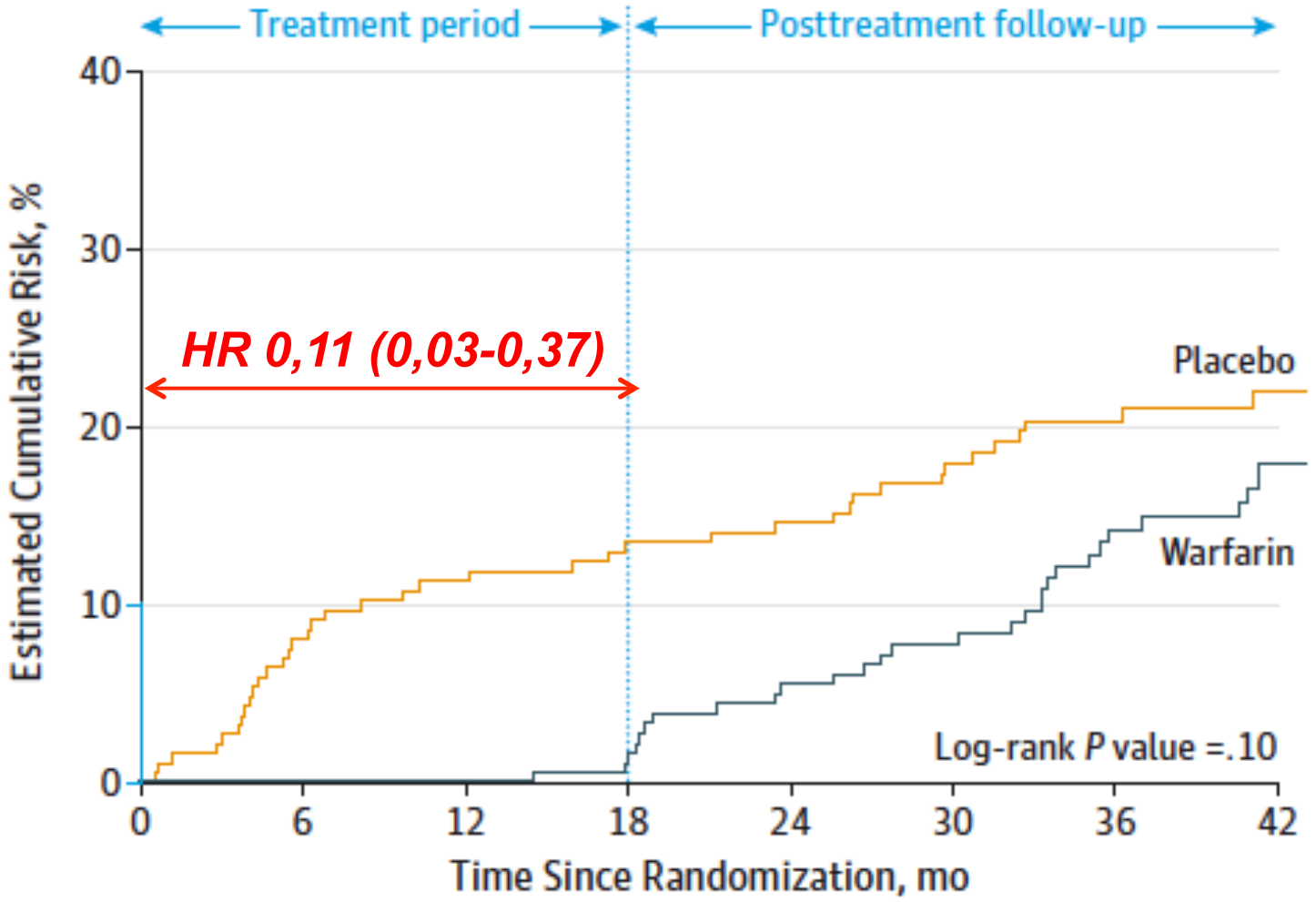
JAMA. 2015;314(1):31-40. doi:10.1001/jama.2015.7046

Risque de récidive thrombo-embolique



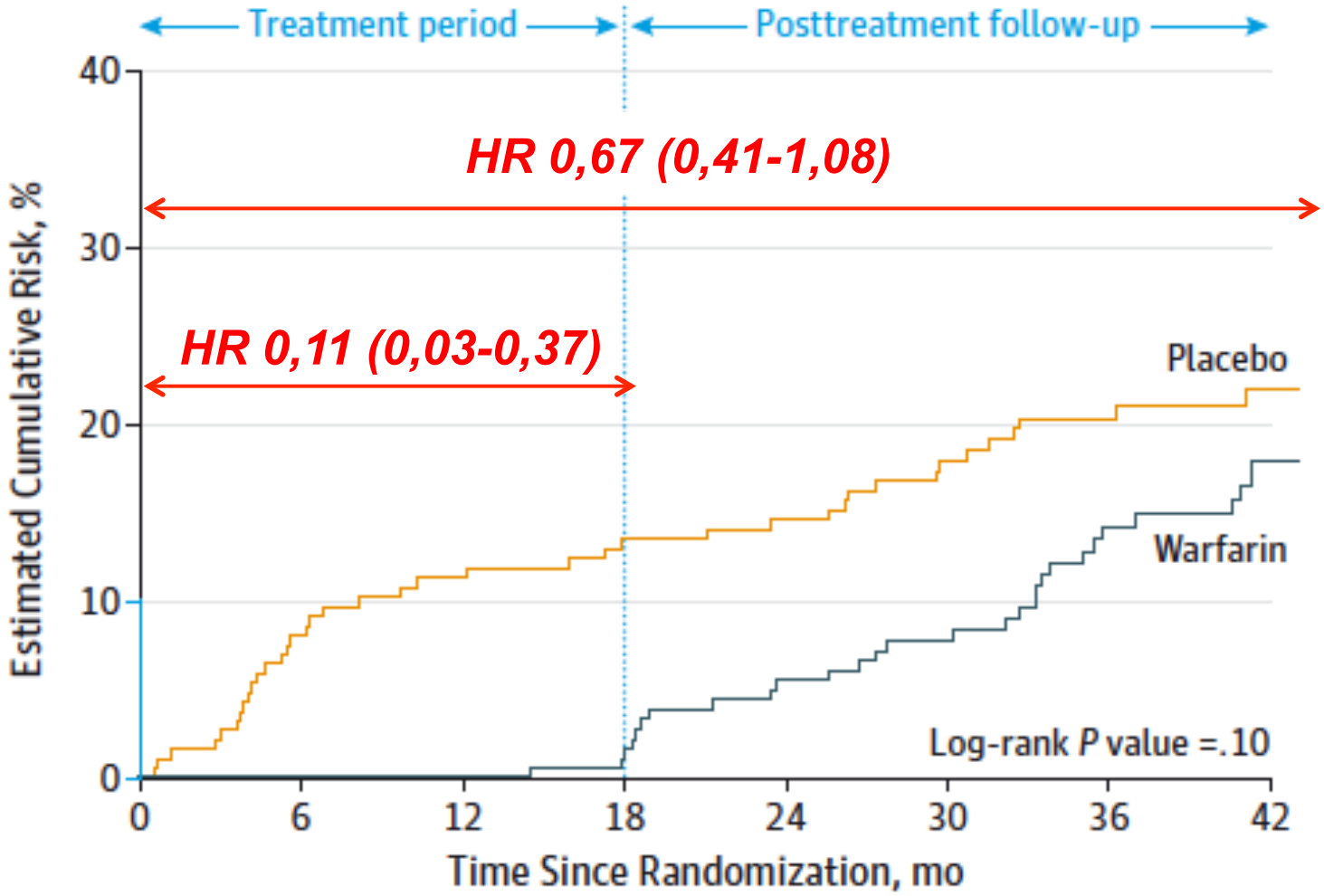
No. at risk								
Placebo	187	170	162	158	155	141	117	105
Warfarin	184	182	180	174	168	150	120	110

Risque de récidive thrombo-embolique



No. at risk								
Placebo	187	170	162	158	155	141	117	105
Warfarin	184	182	180	174	168	150	120	110

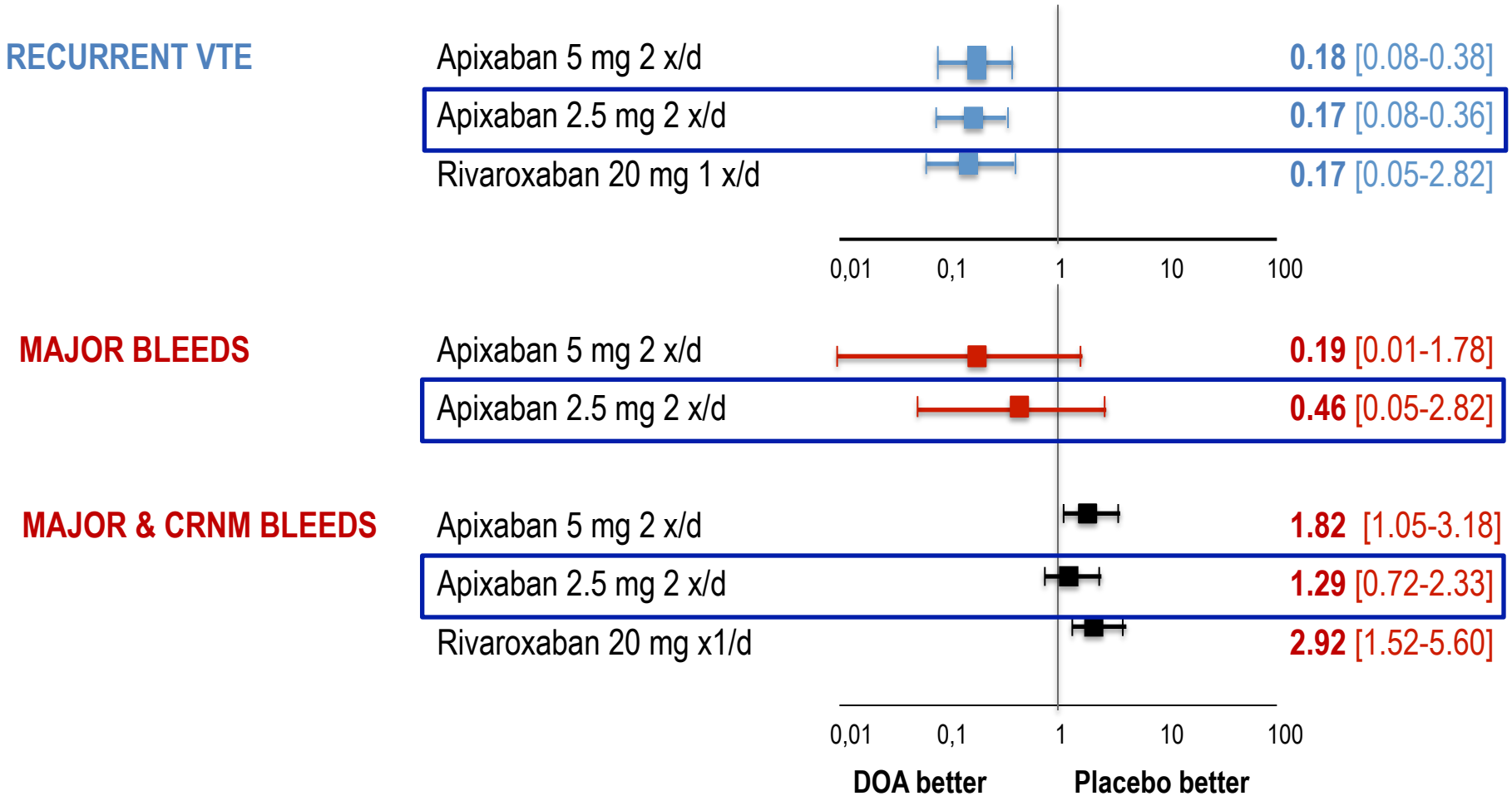
Risque de récidive thrombo-embolique



No. at risk

Placebo	187	170	162	158	155	141	117	105
Warfarin	184	182	180	174	168	150	120	110

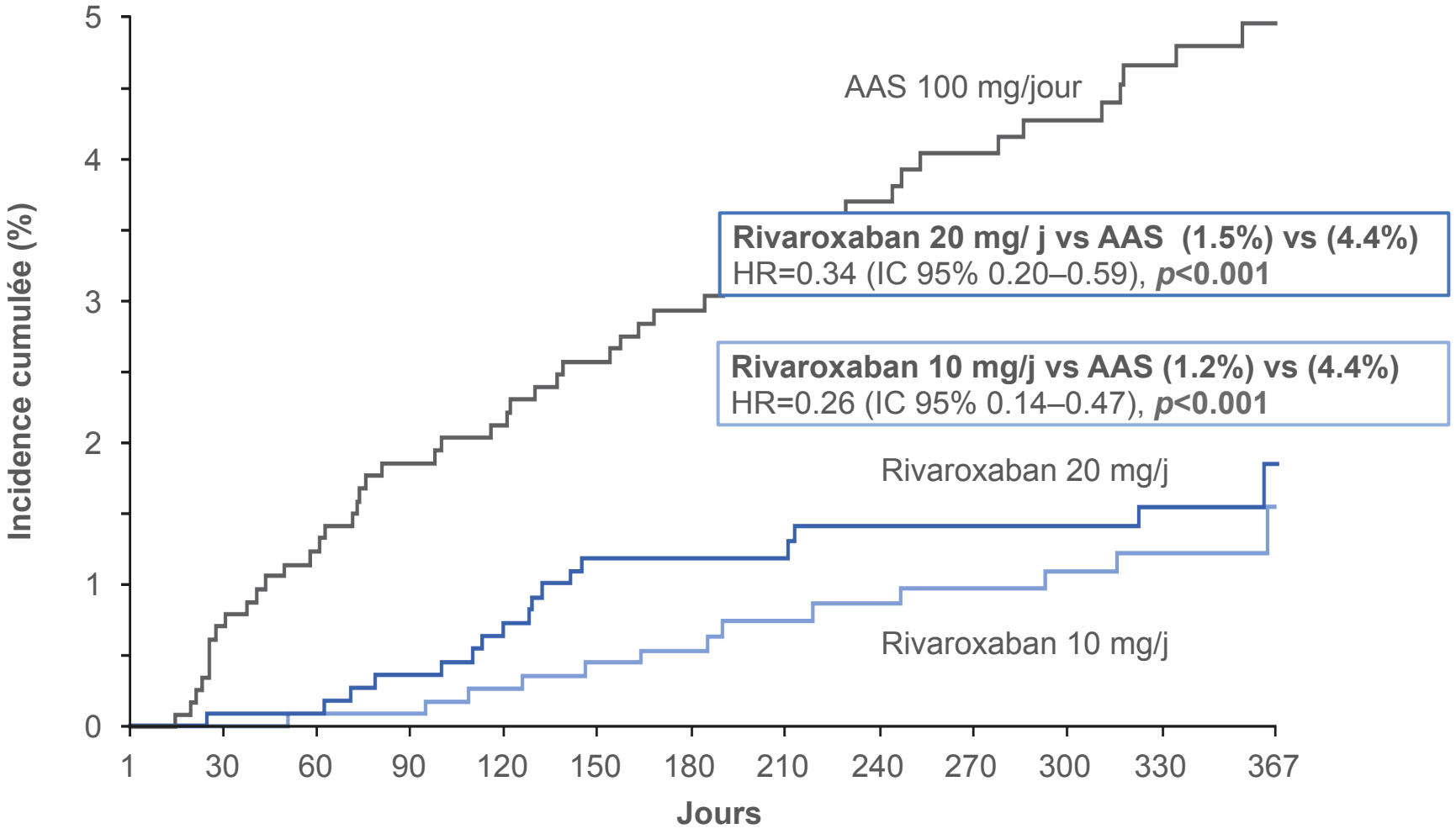
Trials of Long-Term Treatment with Xa Inhibitors



1. Büller HR, et al. N Engl J Med 2010;363:2499-510.
2. Agnelli *et al. N Engl J Med* 2013;368:699-708
3. Schulman *et al. N Engl J Med* 2013;368:709-18

EINSTEIN-CHOICE

Récidives d'évènements thromboemboliques veineux



*Récidive de TVP ou EP, fatale ou non, incluant décès inexpliqué pour lequel une EP ne peut être exclue

Weitz JI et al, N Engl J Med 2017;376:1211-22.

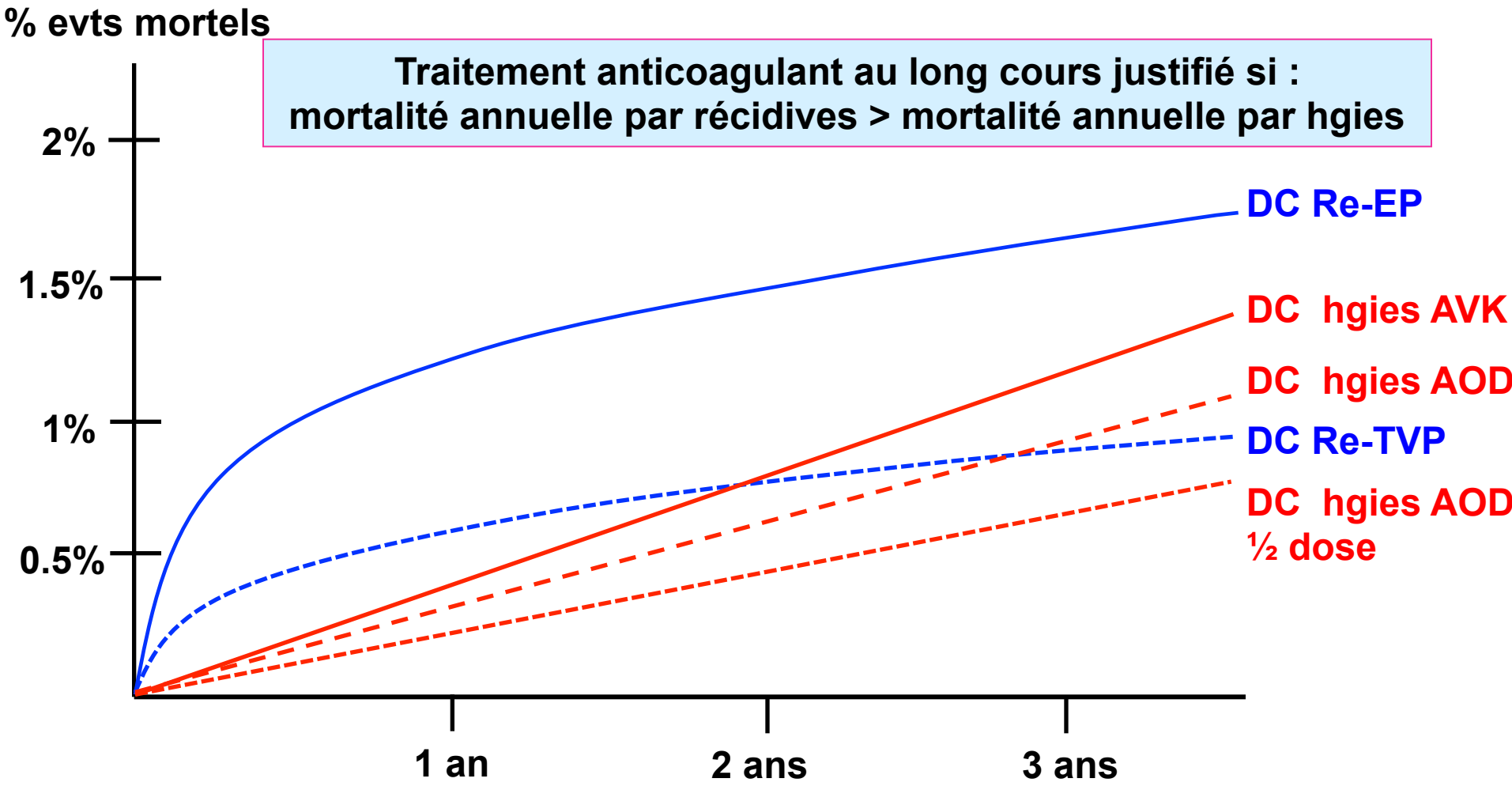
Recommendations for duration of treatment (2)

Recommendations for duration of anticoagulation after pulmonary embolism	Class[a]	Level[b]
Rivaroxaban (20 mg once daily), dabigatran (150 mg twice daily, or 110 mg twice daily for patients >80 years of age or those under concomitant verapamil treatment) or apixaban (2.5 mg twice daily) should be considered as an alternative to VKA (except for patients with severe renal impairment) if extended anticoagulation treatment is necessary.[c]	IIa	B[d]
In patients who refuse to take or are unable to tolerate any form of oral anticoagulants, aspirin may be considered for extended secondary VTE prophylaxis.	IIb	B

S Konstantinides et al Eur Heart J 2014;35:3033-69.

Personnaliser la durée du traitement anticoagulant

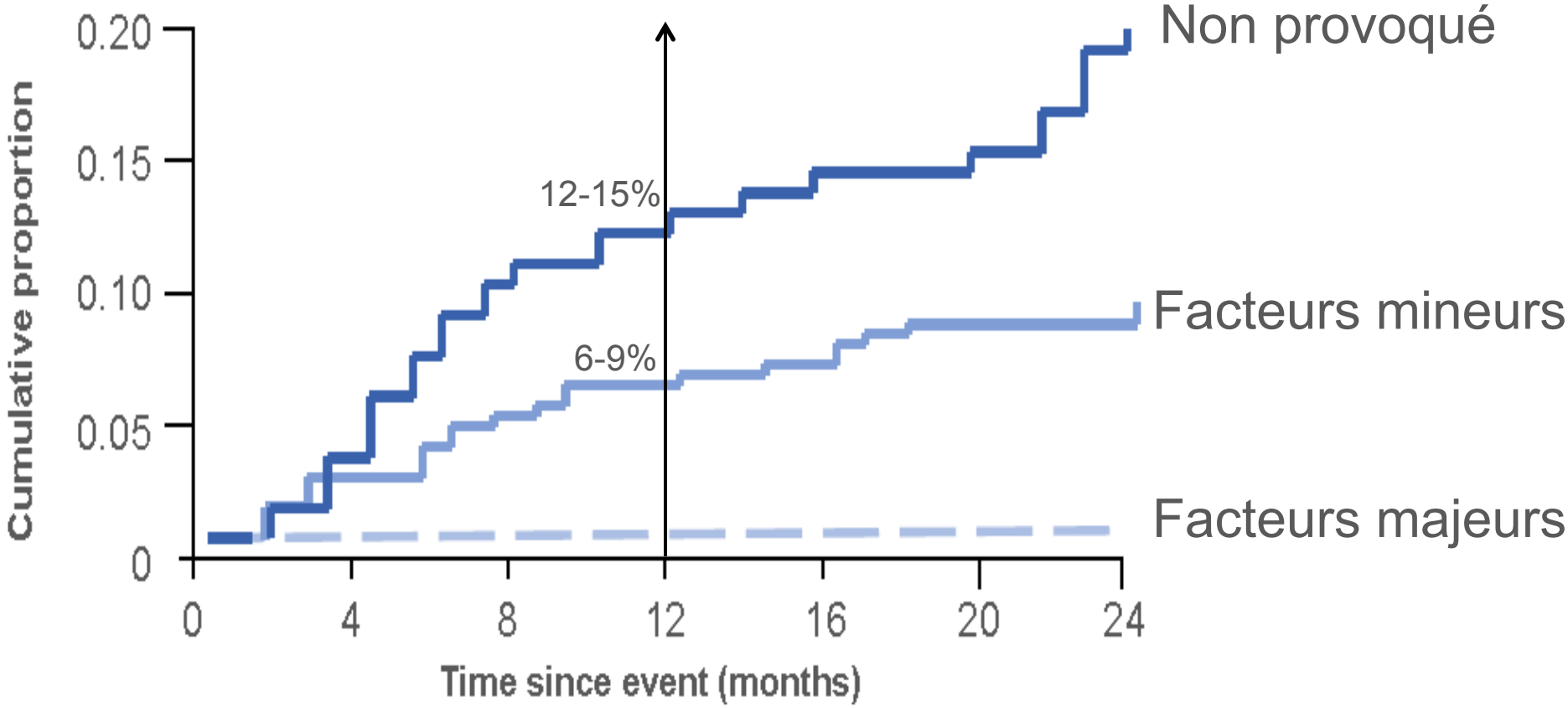
Mortalité par récidives EP/TVP après arrêt du TTT AC et mortalité par complications hgiques



Le Mao R et al. Press Med 2017:46;728-38.

Evaluation du risque de récidive

- Risque de récidive thromboembolique après arrêt du TTT AC (N= 570)
- 29% d'EP, 71% de TVP
- Exclusion des pts avec Kc et SAPL



1. Baglin T *et al*, *Lancet* 2003;362:523–526; 2. Kearon C *et al, Chest* 2016;149:315–352.

Classification des facteurs de risque de récidives thromboemboliques

Facteurs de risque de récidive majeurs

Transitoires	Persistants
Chirurgie sous AG ≤ 3 mois	Cancer
Fracture Mbs Inf ≤ 3 mois	SAPL
Alitement prolongé plus de 72 h datant de ≤ 3 mois	Maladies inflammatoires chroniques (Crohn, rectocolite hgique,…)
Contraception OP, grossesse, post partum, TTT hormonal ménopause	CPC post embolique

MTEV non provoquée : absence de facteurs de risque de récidive majeurs transitoires et persistants

Kearon C *et al, J Thromb Haemost 2016*;14(7):1480-83.

Classification des facteurs de risque de récidive thromboemboliques

Facteurs de risque de récidive mineurs : facteurs de modulation

Facteurs d'allongement du TTT AC	Facteurs de réduction du TTT AC
Thrombophilie majeure (déficit en AT, en prot C ou S < 30%)	Score HERDOO 2 ≤ 1
Filtre cave permanent	Femme ≤ 50 ans
Homme	TVP proximale
EP plutôt que TVP	Risque hgique élevé

Facteurs de risque de récidive incertains

Séquelles morphologiques, thrombophilies mineures, D-dimères, âge

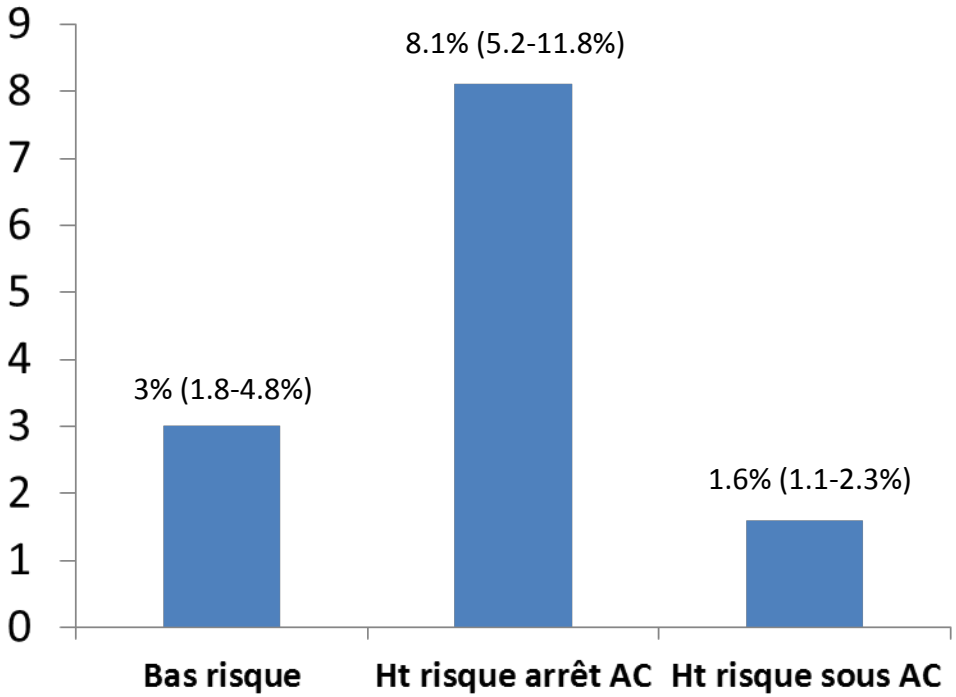
Kearon C *et al, J Thromb Haemost 2016*;14(7):1480-83. Rodger MA et al, *BMJ 2017*:356;j1065.
Weitz J et al. N engl J Med 2017: DOI:10.1056/NEJMc1705484. Le Mao R et al. Press Med 2017;46:728-38.

Identification des phénotypes à faible risque de récidives thromboemboliques

HERDOO2[1]	
HOMME ou FEMME + ≥ 2 items: **- Âge ≥ 65** **- DD ≥ 250 avec AC** **- PTS** **- BMI≥30**	
FEMME HERDOO2 ≤ 1	3%
FEMME HERDOO2 ≥ 2 ou HOMME	7% à 8%

Etude REVERSE II

2785 pts 1er épisode TEV non provoqué



Faible risque : stop traitement

Rodger MA et al, *BMJ 2017*:356;j1065.

Risk of Recurrence after a 1st Episode of Unprovoked VTE

Risk Factors for DVT Recurrence (modulating factors)		
Proximal DVT	Male sex	Persistent residual vein thrombosis
Obesity	Non-O blood group	High D-dimer values
Old age	Early PTS development	Thrombophilia (controversial)

Vienna	DASH	HERDOO-2
D-dimers at 3 weeks & 3, 9, 15, 24 months after stopping anticoagulation	D-dimers 3-5 weeks after stopping anticoagulation	D-dimers before stopping anticoagulation
Male sex	Male sex	Post thrombotic symptoms
VTE location (distal DVT, proximal DVT, PE)	Age < 50 years	Age ≥ 65 years
	VTE not associated with OP therapy	BMI ≥ 30
Validation +	Validation +	Validation +

Mazzolai L et al. Eur Heart J 2017;00,1-14.

Durée du traitement AC

- AOD en 1ère intention chez la plupart des pts avec MTEV
- Durée de TTT anticoagulant pleine dose (AOD, AVK) :
  - 3 mois en présence d'un facteur de risque de récidive majeur et transitoire
  - "illimitée" en présence d'une MTEV non provoquée récidivante
- Evaluation systématique du rapport bénéfice risque :
  - si 1er épisode TE veineux non provoqué
  - en présence de facteurs de risques de récidives permanents
  - efficacité et sécurité d'emploi de doses réduites d'AOD dans le cadre d'un TTT "illimité" bien établies
- Duréé de TTT anticoagulant limitée à 3-6 mois si risque hgique élevé
- Question non résolue :
  - Efficacité des AOD à ½ dose vs AOD ou AVK à pleine dose chez les pts à haut risque de récidive (thrombophilie majeure, MTEV récidivante, …)

Weitz JI et al, N Engl J Med 2017;376:1211-22.

Durée du traitement AC : recos SPLF 2018

Risque de récidive	Définition	Durée	Dose
Faible	MVTE provoquée par un **facteur transitoire majeur**	3 – 6 mois maximum [1] (Grade 1+)	AVK (INR 2-3) AOD pleine dose (Grade 1+)
	Femmes avec un 1er épisode de **MVTE non provoqué et un score HERDOO2 ≤ 1** **Femmes ≤ 50 ans avec un 1er épisode de MVTE**	6 mois maximum [1] (Grade 2+)	AVK (INR 2-3) AOD pleine dose (Grade 1+)
Modéré	**Hommes avec un 1er épisode de MVTE non provoqué** et en l'absence de facteur persistant majeur[3] **Femmes avec un 1er épisode de MVTE non provoqué en l'absence de facteur persistant majeur et un score HERDOO2 ≥ 2[3]**	6 mois ou Non limitée[2] (Grade 1+)	*6 premiers mois* AVK (INR 2-3) AOD pleine dose (Grade 1+) *Après le 6ème mois* AVK (INR 2-3) AOD pleine dose AOD ½ dose (Grade 1+)

Durée du traitement AC : recos SPLF 2018

Risque de récidive	Définition	Durée	Dose
Elevé	**Cancer actif**	Non limitée[2] (Grade 1+)	*6 premiers mois* HBPM (Grade 1+) *Après le 6ème mois* HBPM (Grade 2+) ou AVK (Grade 2+) ou AOD pleine dose (Grade 2+)
	SAPL		AVK (INR (2-3) (Grade 1+)
	MVTE récidivante non provoquée 1er épisode de MVTE non provoquée avec une thrombophilie majeure (déficit en AT)		AVK (INR 2-3) (Grade 1+) AOD pleine dose (Grade 1+)
	1er épisode d'EP à haut risque non provoquée	Non limitée[2] (Grade 2+)	
	HTP-TEC	Non limitée[2] (Grade 1+)	AVK (INR 2-3) (Grade 1+)

Embolie pulmonaire :

ce que le cardiologue doit savoir en 2018

6. Sur quelques situations particulières

Recommendations for PE in pregnancy

Suspicion of PE in pregnancy warrants formal diagnostic assessment with validated methods.	I	C
D-dimer measurement may be performed in order to avoid unnecessary irradiation, as a negative result has a similar clinical significance as in non-pregnant patients.	IIb	C
Venous compression ultrasonography may be considered in order to avoid unnecessary irradiation, as a diagnosis of proximal DVT confirms PE.	IIb	C
Perfusion scintigraphy may be considered to rule out suspected PE in pregnant women with normal chest X-ray.	IIb	C
CT angiography should be considered if the chest X-ray is abnormal or if lung scintigraphy is not readily available.	IIa	C
A weight-adjusted dose of LMWH is the recommended therapy during pregnancy in patients without shock or hypotension.	I	B

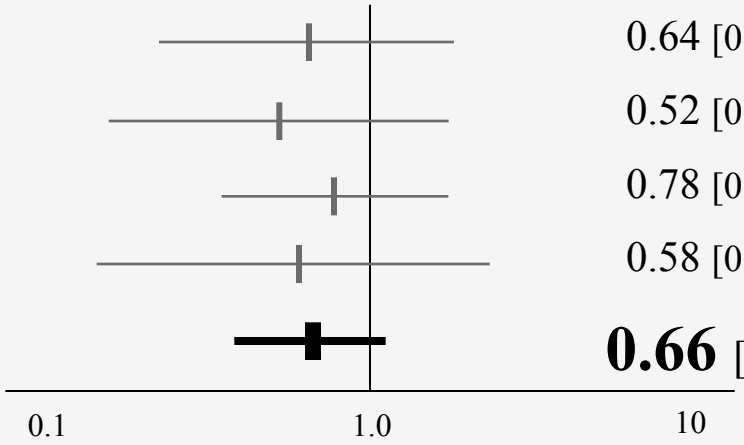
Recommendations for PE in cancer

Incidental PE in patients with cancer should be managed in the same manner as symptomatic PE.	IIa	C
Negative D-dimer levels have the same negative diagnostic value as in non-cancer patients.	IIa	B
For patients with PE and cancer, weight-adjusted subcutaneous LMWH should be considered for the first 3 to 6 months.	IIa	B
For patients with PE and cancer, extended anticoagulation (beyond the first 3 to 6 months) should be considered for an indefinite period or until the cancer is cured.	IIa	C

AOD MTEV et cancer : méta-analyse

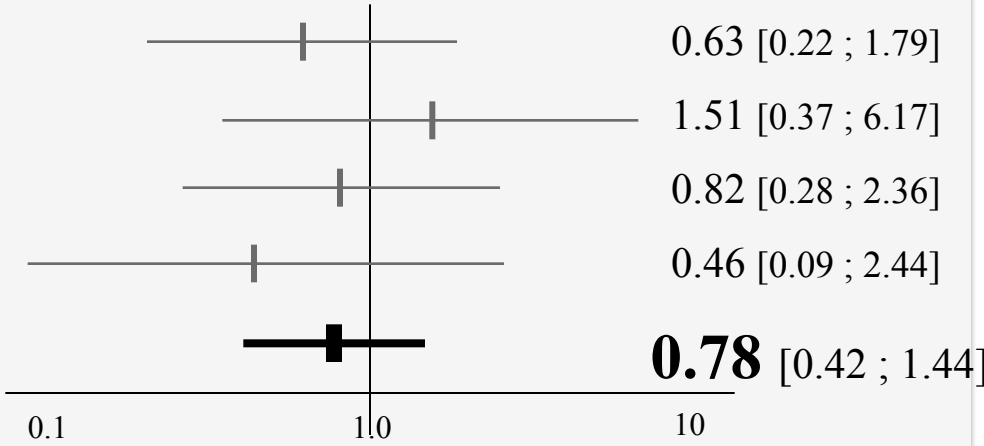
Rec ETE

	AOD	enox/AVK	RR [CI95%]
EINSTEIN	6/232	8/198	0.64 [0.23 ; 1.81]
HOKUSAI	4/109	7/99	0.52 [0.16 ; 1.72]
RECOVER	10/173	12/102	0.78 [0.35 ; 1.76]
AMPLIFY	3/81	5/78	0.58 [0.14 ; 2.34]
total	25/595	32/537	**0.66** [0.39 ; 1.11]



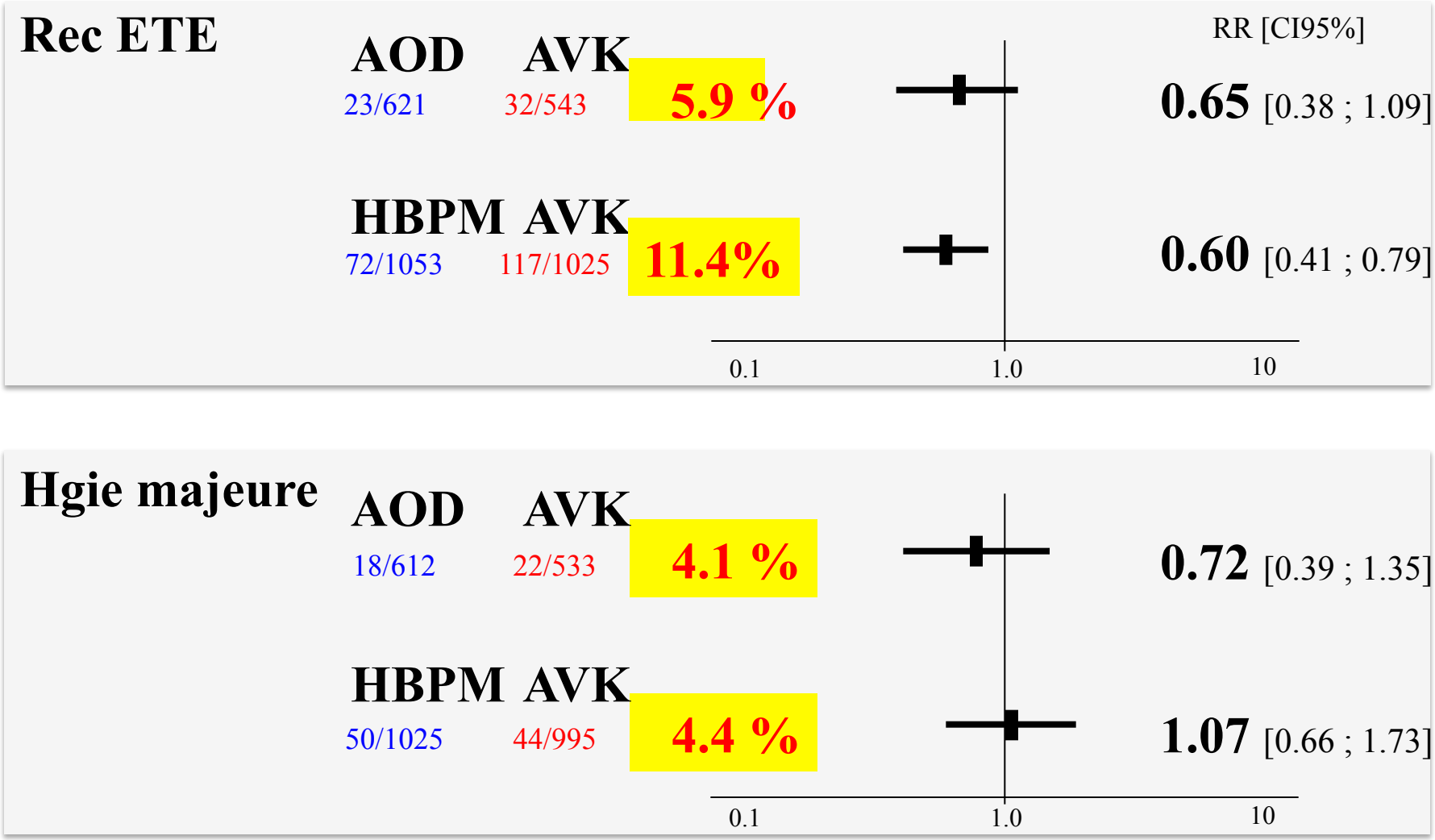
Hgie majeure

	AOD	enox/VKA	
EINSTEIN	6/232	8/196	0.63 [0.22 ; 1.79]
HOKUSAI	5/109	3/99	1.51 [0.37 ; 6.17]
RECOVER	6/159	7/152	0.82 [0.28 ; 2.36]
AMPLIFY	2/87	4/80	0.46 [0.09 ; 2.44]
total	19/587	22/527	**0.78** [0.42 ; 1.44]



Carrier M. et al. *Thromb Res* 2014;134:1214-9.

AOD MTEV et cancer : méta-analyse

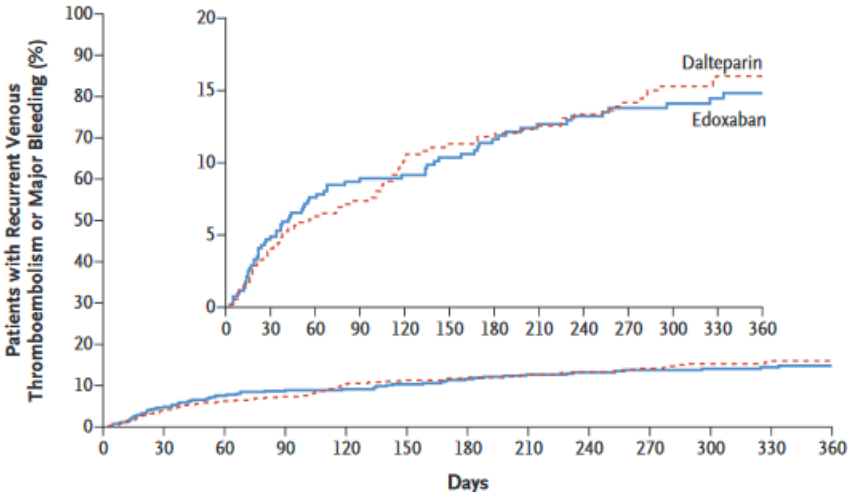


Posh F. et al. *Thromb Res* 2015;136: 582-89.

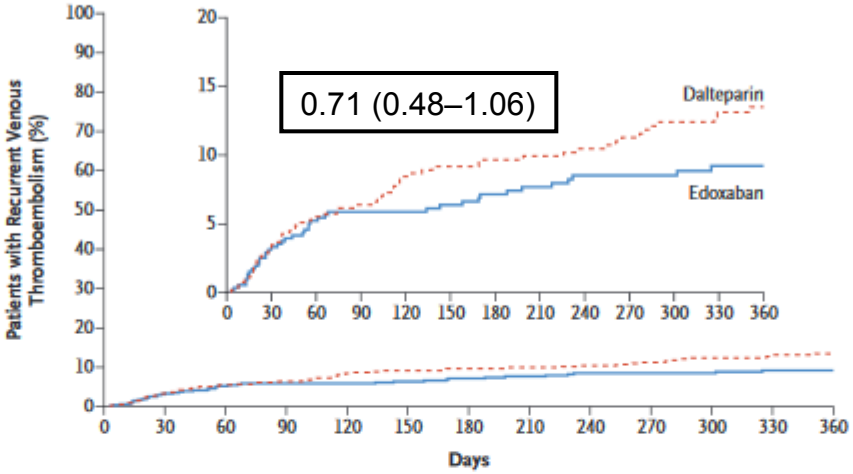
Quelle place pour les AODs ?

HOKUSAÏ VTE Cancer

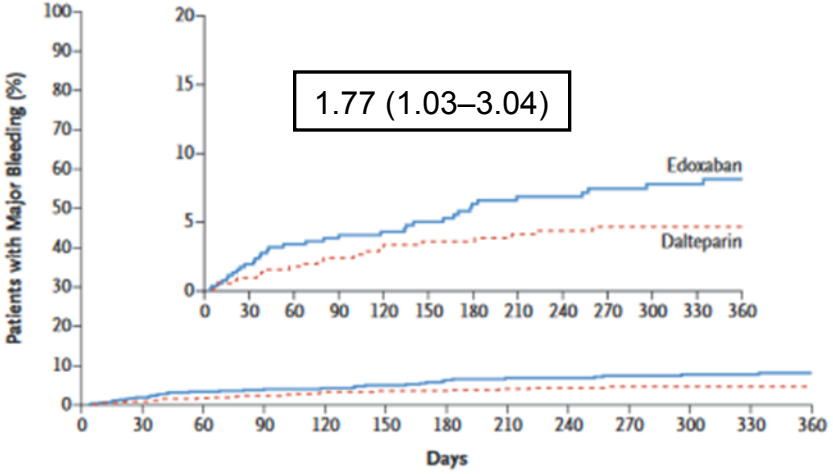
Endpoint I : recurrent venous thromboembolism or major bleeding



Recurrent venous thromboembolism



Major bleeding



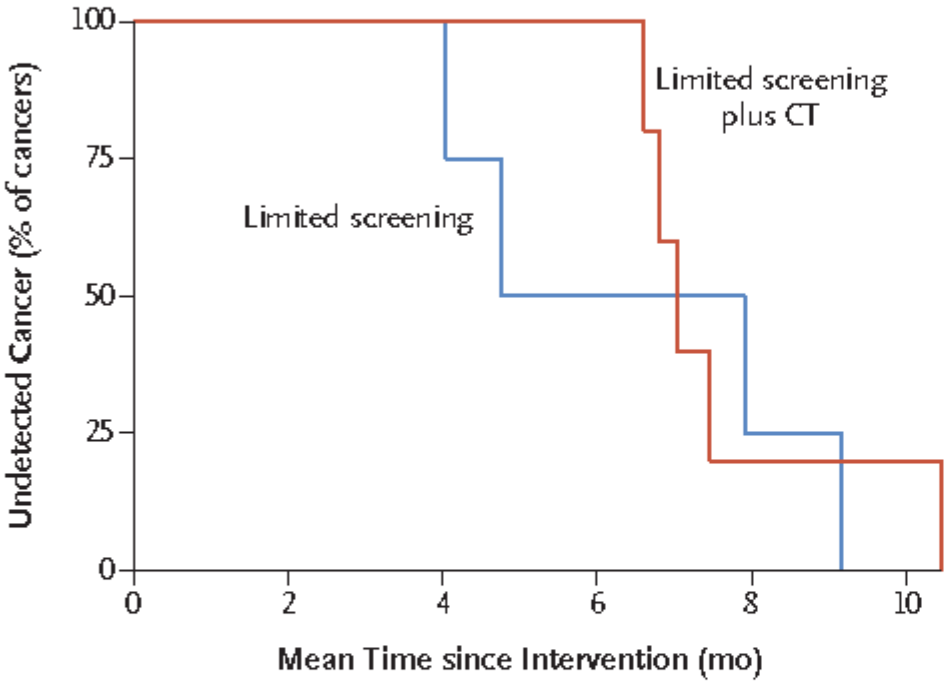
Raskob JE et al. N Engl J Med 2018;378:615-24.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Screening for Occult Cancer in Unprovoked Venous Thromboembolism

Marc Carrier, M.D., Alejandro Lazo-Langner, 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. (Funded by the Heart and Stroke Foundation of Canada; SOME ClinicalTrials.gov number, NCT00773448.)

Recommandations sur les filtres caves

Recommendations for venous filters	Class[a]	Level[b]
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 PE recurrence despite therapeutic levels of anticoagulation.	IIa	C
Routine use of IVC filters in patients with PE is not recommended.	III	A

www.escardio.org/guidelines

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

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Quelle place pour les filtre temporaires ? Etude PREPIC II

Clinical Outcomes	Group, No. With Events (%)		Relative Risk, % (95% CI)	*P* Value[b]
	Filter (n = 200)[a]	Control (n = 199)		
At 6 Months				
Recurrent pulmonary embolism[c]	7 (3.5)	4 (2.0)	1.75 (0.52-5.88)	.54
Fatal	6 (3.0)	3 (1.5)		
Nonfatal	1 (0.5)	1 (0.5)		
Recurrent deep vein thrombosis	1 (0.5)	2 (1.0)	0.50 (0.05-5.47)	>.99
Recurrent venous thromboembolism	8 (4.0)	6 (3.0)	1.33 (0.47-3.77)	.59
Major bleeding	13 (6.5)	15 (7.5)	0.87 (0.42-1.77)	.69
Death	21 (10.6)	15 (7.5)	1.40 (0.74-2.64)	.29

Mismetti P et al. *JAMA*. 2015;313(16):1627-1635.

Conclusion

- **Embolie pulmonaire**

  Pathologie :

  - fréquente
  - grave
  - sous estimée
- **Progrès dans la prise en charge :**
  - stratification du risque
  - thérapeutique « à la carte » ajustée sur le profil de risque
  - avènement des AODs
- **Pbs non résolus :**
  - amélioration du dépistage : trop d'EP non diagnostiquées
  - optimisation de la prise en charge des EP à risque intermédiaire élevé
  - pts candidats à un TTT AC au long cours, avec quel TTT AC ?