Traitement de l'embolie pulmonaire. Recommandations ESC 2014

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Conflits d'intérêt G Meyer

- Investigateur: Bayer, Daichi-Sankyo, Sanofi Aventis, Leo Pharma
- Subvention de recherche: Leo Pharma, Boehringer-Ingelheim, Bayer
- Interventions, boards non rémunérés: Sanofi Aventis, Leo Pharma, Bayer, Boehringer-Ingelheim, Pfizer
- Invitations congrès: Leo Pharma, Boehringer-Ingelheim, Bayer, Daichi-Sankyo

EP: stratification du risque

Examen clinique	Pas de choc, PA > 90 mmHg PESI I-II or sPESI=0	Pas de choc, PA > 90 mmHg PESI > II or sPESI > 0	Hypotension ou choc

Age > 80 yrs	1
Cancer	1
Cardio-pulmonary disease	1
SBP< 100 mmHg	1
Heart rate > 110 bpmin	1
SpO2 < 90%	1

0: Low risk (30d death rate: 2.1% ; 1.7-2.6)

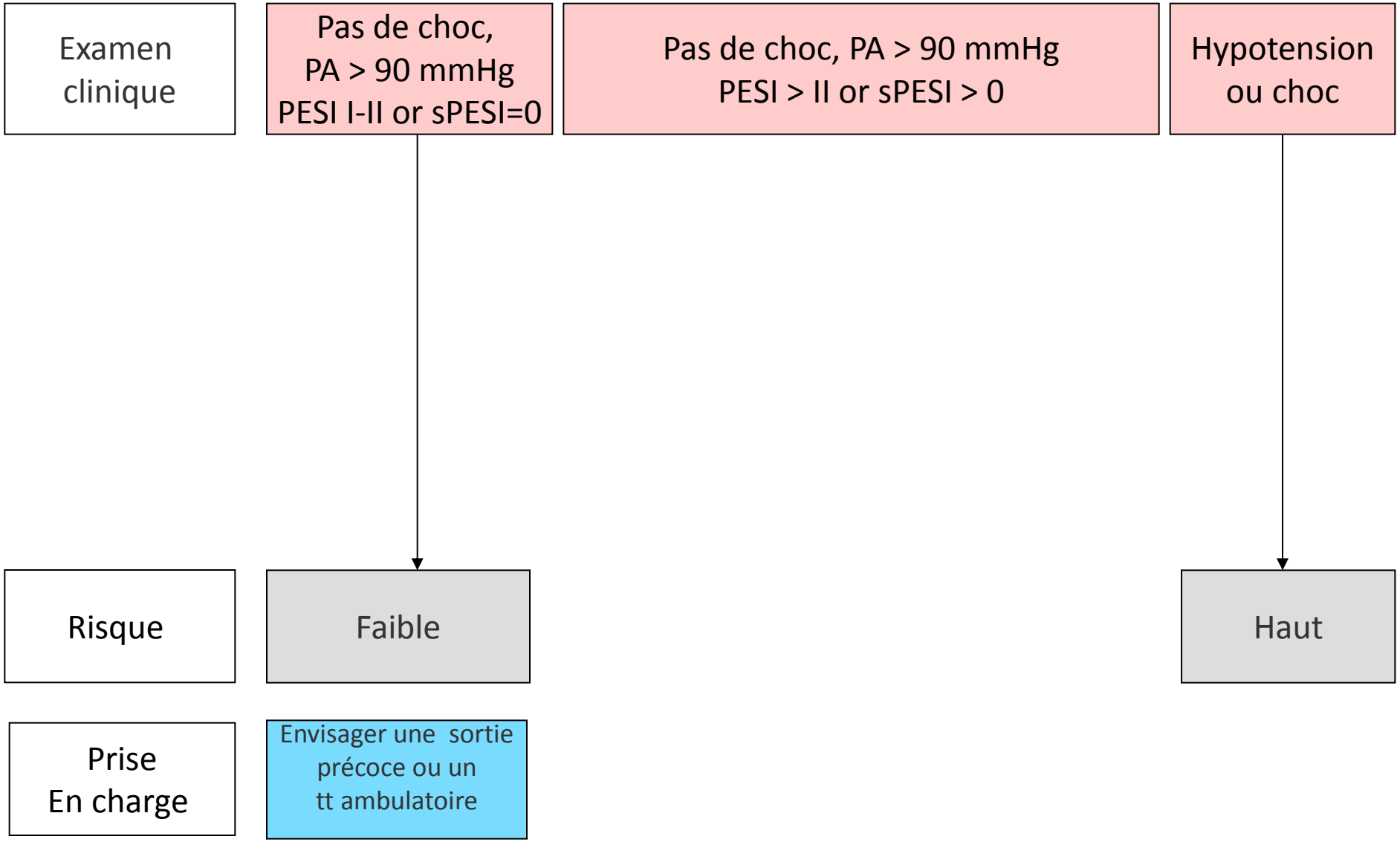
≥1: High risk (30d death rate 14.0%; 13.1-14.9)

Haut

Jimenez D. et al. *Arch Intern Med* 2010;170:1383-9

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

EP: stratification du risque



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

Traitement ambulatoire de l'EP

	Décès	Récidives	Saignements
Ambulatoire	1.9% (0.79-4.6)	1.7% (0.92-3.1)	0.97% (0.58-1.6)
Hospitalisation < 72h	2.3% (1.1-5.1)	1.1% (0.22-5.4)	0.78% (0.16-3.7)
Hospitalisation	0.74% (0.04-11)	1.2% (0.16-8.1)	1.0% (0.39-2.8)

Meta-analyse, patients à faible risque, suivi à 3 mois

Ambulatoire: 13 études, 1657 patients

Hospitalisation < 72h: 3 études, 256 patients

Hospitalisation: 5 études, 383 patients

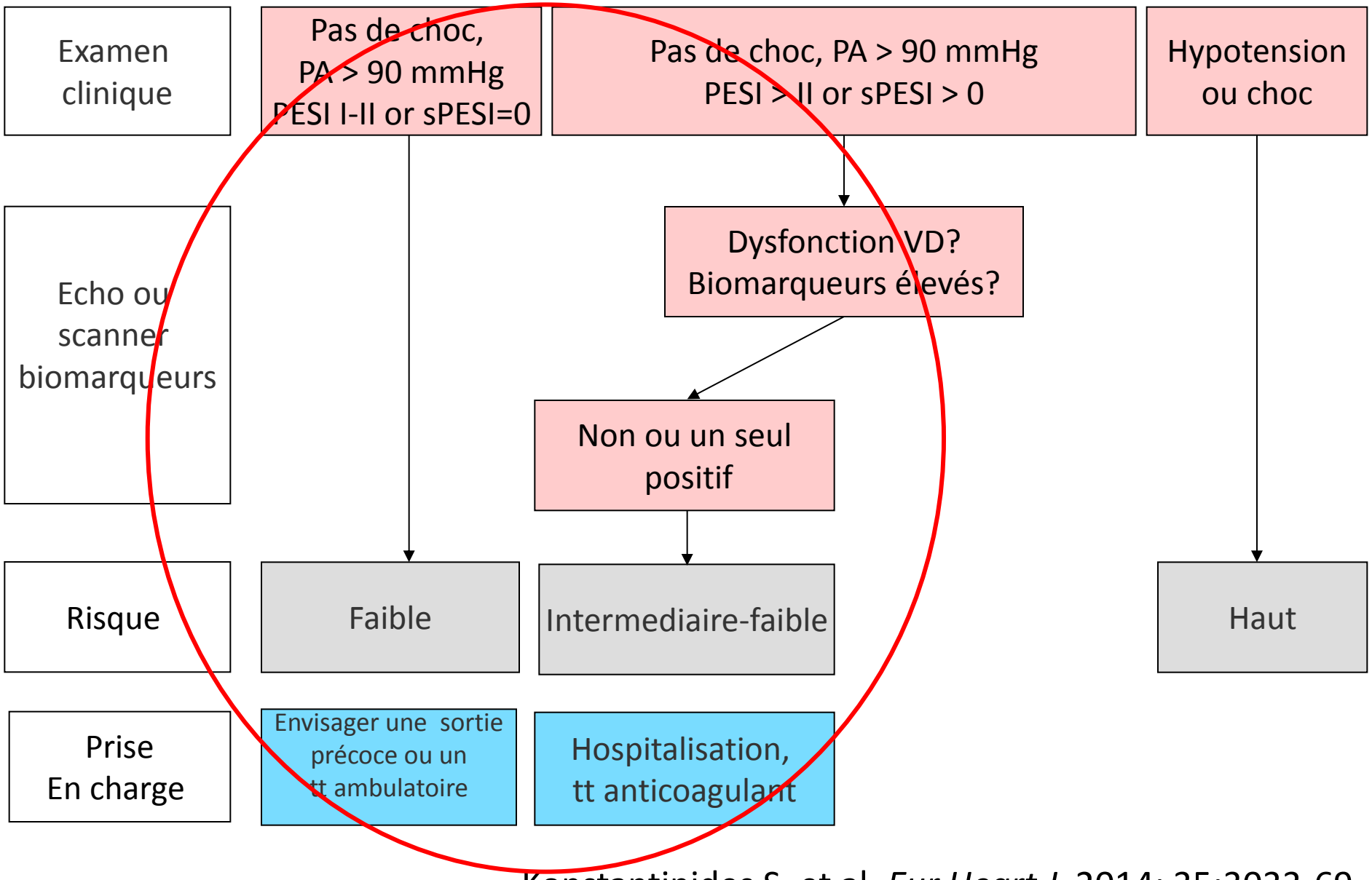
Zondag W. et al. *Eur Respir J* 2012; 42:134–44.

Traitement ambulatoire de l'EP

Outpatient treatment of low-risk patients with PE should be restricted to hospitals with an available dedicated thrombosis clinic including a 24 hours service to follow patients and to rapidly re-admit them in case of complications and to patients with well-maintained living conditions, strong support from family or friends, phone access, and ability to quickly return to the hospital if there is deterioration

Kearon C, et al. *Chest* 2012; 141: e419S-e494S

EP: stratification du risque



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

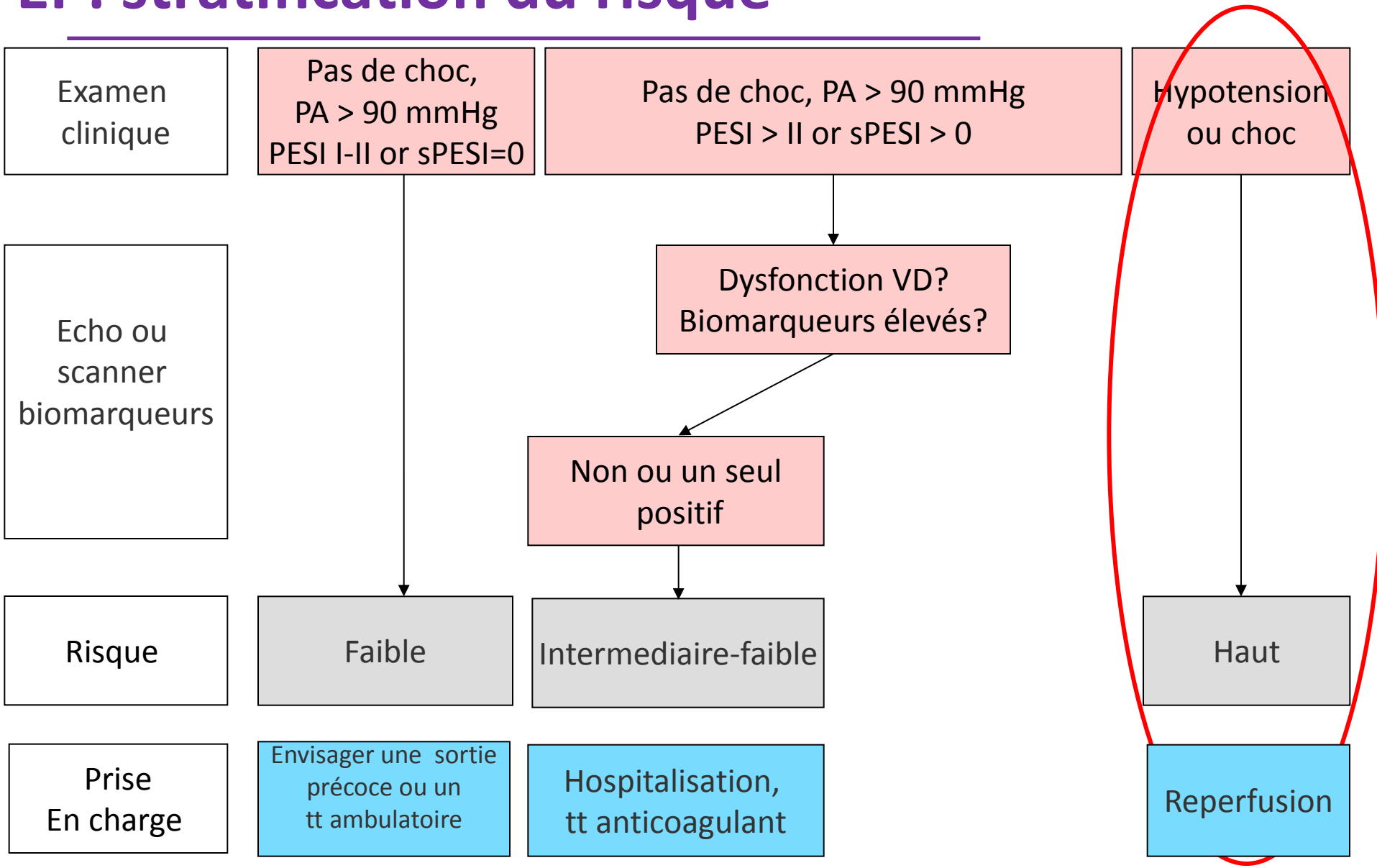
Traitement initial

- HBPM
- Fondaparinux
- Dose fixe, adaptée au poids, pas d'adaptation
- Relai précoce par AVK; INR 2-3
- AOD?

HNF ssi insuffisance rénale sévère

Mismetti P. et al. RBPC 2009 (http://www.afssaps.fr).

EP: stratification du risque



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

Thrombolyse dans l'EP grave

5 essais; n = 254, dont 37 patients à haut risque

	Thrombolyse (n = 128)	Héparine (n = 126)	Odds Ratio
Récidive	3.9%	7.1%	0.61 (0.23-1.62)
Décès	6.2%	12.7%	0.47 (0.20-1.10)
Récidive ou décès	9.4%	19.0%	0.45 (0.22-0.92)
Hémorragie grave	21.9%	11.9%	1.98 (1.00-3.92)

Wan S. et al. *Circulation* 2004; 110: 744-9

Autres options pour l'EP à haut risque

- Embolectomie chirurgicale
  - Cohortes rétrospectives
  - Mortalité: 19% dans les séries récentes (EP grave)
- Embolectomie par catheter
  - Cohortes rétrospectives,
  - Association fréquente avec fibrinolyse locale
  - Expertise locale
- ECMO
  - Evidence encore anecdotique

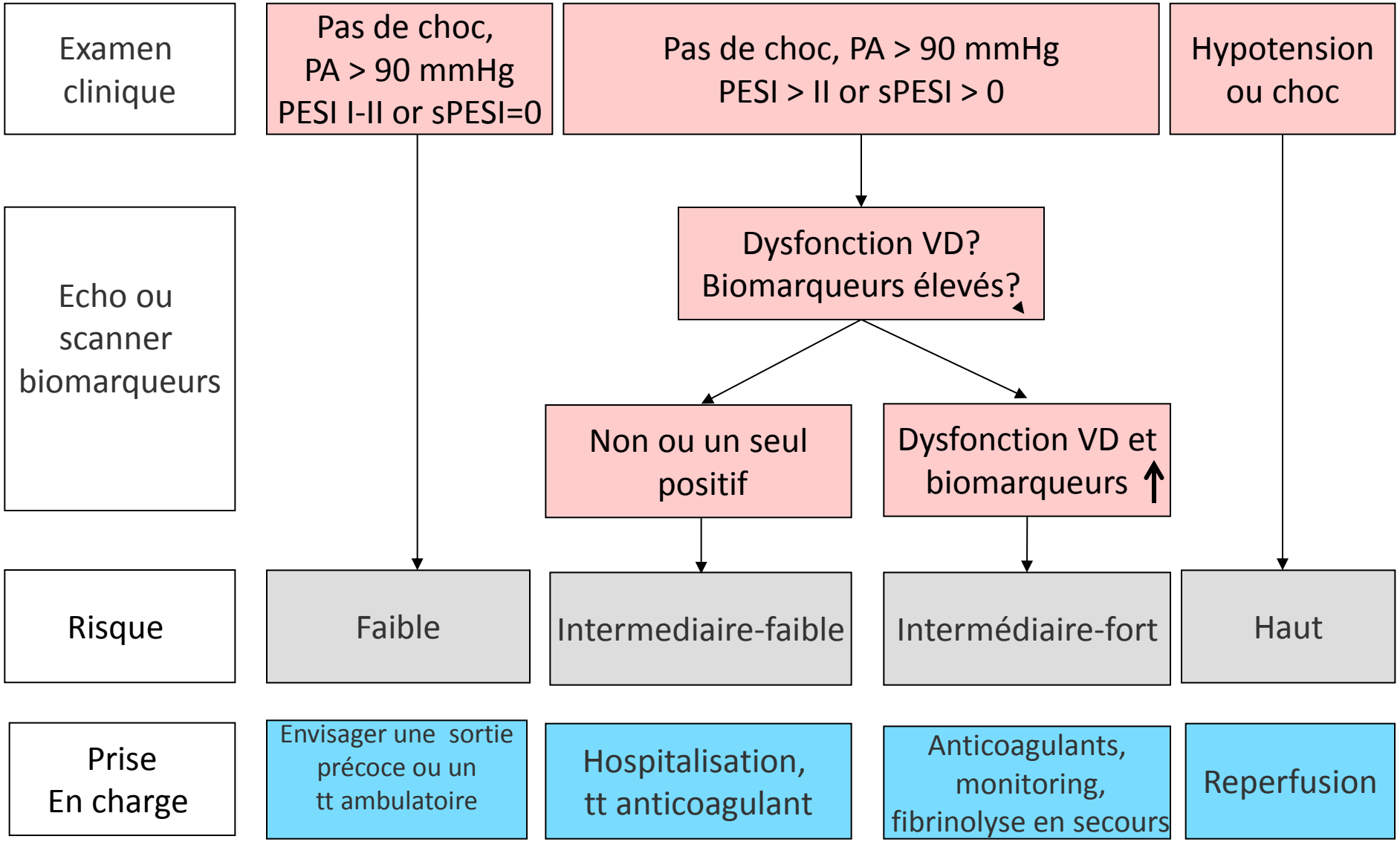
Samoukovic G. et al. *Interactive Cardiovasc Thorac Surg* 2010; 11: 265–270
Kuo WT. et al. *J Vasc Interv Radiol* 2009; 20: 1431–1440

Recommandations EP à haut risque

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	

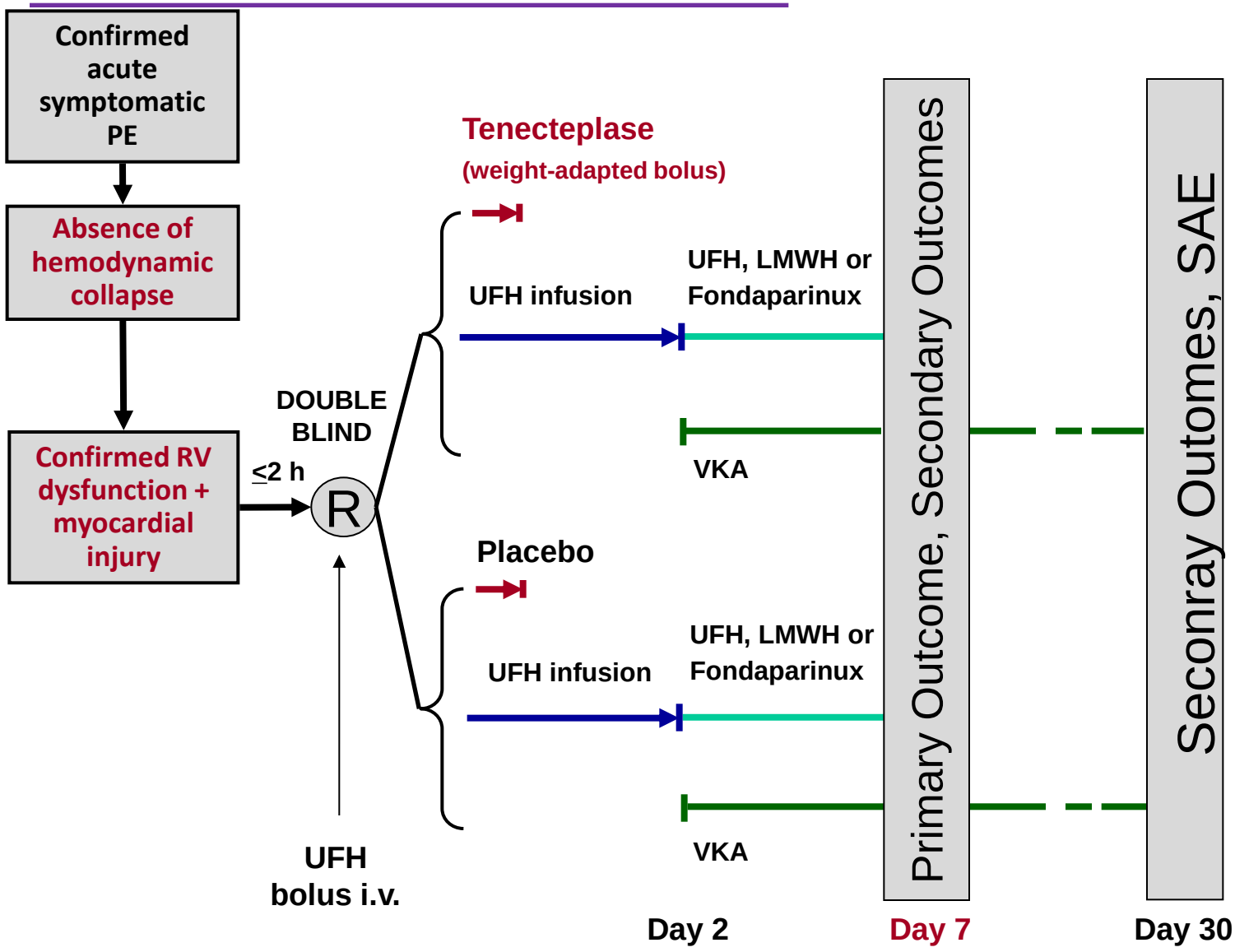
Konstantinides S. et al. *Eur Heart J* 2014; 35:3033-69

EP: stratification du risque



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

Pulmonary embolism Thrombolytic Trial (PEITHO)



PEITHO Steering Committee. *Am Heart J* 2012;163:33-38.

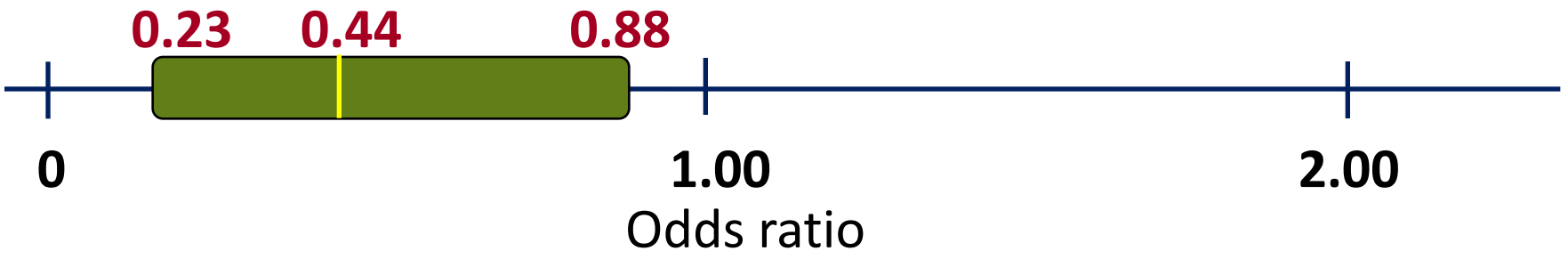
Patients

	Tenecteplase (n=506)	Placebo (n=499)
Age (y), mean±SD	66.5±14.7	65.8±15.9
Age (y), median (Q1-Q3)	70.0 (57.0-78.0)	70.0 (58.0-78.0)
Sex (female/male)	264/242	268/231
Weight (kg), mean±SD	82.5±17.9	82.6±18.2
Systolic blood pressure (mm Hg), mean±SD	130.8±18.3	131.3±18.5
Diastolic blood pressure (mm Hg), mean±SD	78.6±12.6	79.2±12.1
Heart rate (beats per min), mean±SD	94.5±17.1	92.3±16.7
Respiratory rate (breaths per min), mean±SD	21.8±5.8	21.6±5.7
Chronic obstructive pulmonary disease (%)	26 (5.1)	34 (6.8)
Chronic heart failure (%)	21 (4.2)	26 (5.2)
Previous VTE (%)	126 (24.9)	147 (29.5)
Known malignant tumor (%)	41 (8.1)	32 (6.4)
Surgery or trauma in previous 30 days (%)	31 (6.1)	27 (5.4)

The PEITHO investigators. *N Engl J Med* 2014; 370:1402-11.

PEITHO: critère de jugement principal

	Tenecteplase (n=506)		Placebo (n=499)		*P* value
	n	(%)	n	(%)	
All-cause mortality or hemodynamic collapse within 7 days of randomization	**13**	**(2.6)**	**28**	**(5.6)**	**0.015**



The PEITHO investigators. *N Engl J Med* 2014; 370:1402-11.

Critères secondaires d'efficacité

	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**
Need for CPR	1		5		
Hypotension / blood pressure drop	8		18		
Catecholamines	3		14		
Resulted in death	1		6		

The PEITHO investigators. *N Engl J Med* 2014; 370:1402-11.

Tolérance

	Tenecteplase (n=506)		Placebo (n=499)		*P* value
	n	(%)	n	(%)	
Non-intracranial bleeding					
Major	32	(6.3)	6	(1.5)	<0.001
Minor	165	(32.6)	43	(8.6)	<0.001
Strokes by day 7	**12**	**(2.4)**	**1**	**(0.2)**	**0.003**
Hemorrhagic	10		1		
Ischemic	2		0		

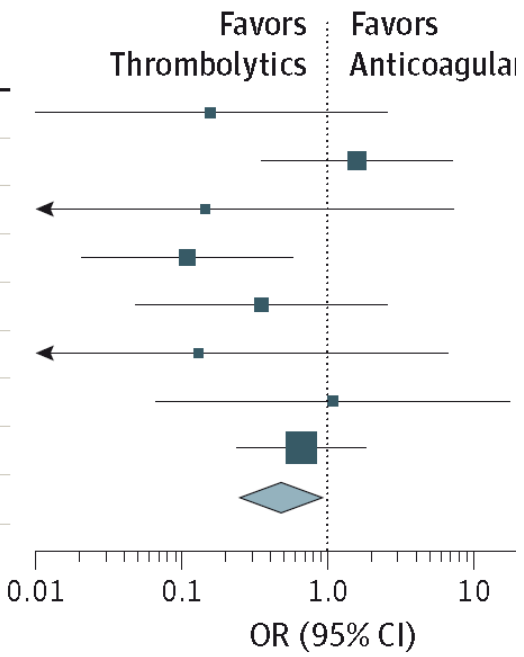
The PEITHO investigators. *N Engl J Med* 2014; 370:1402-11.

Meta-analyse, mortalité EP de risque intermédiaire

Source	Thrombolytics No. of Events	Thrombolytics No. of Patients	Anticoagulants No. of Events	Anticoagulants No. of Patients	OR (95% CI)
Goldhaber et al,[2] 1993	0	46	2	55	0.16 (0.01-2.57)
Konstantinides et al,[3] 2002	4	118	3	138	1.58 (0.35-7.09)
TIPES,[29] 2010	0	28	1	30	0.14 (0.00-7.31)
Fasullo et al,[11] 2011	0	37	6	35	0.11 (0.02-0.58)
MOPETT,[10] 2012	1	61	3	60	0.35 (0.05-2.57)
ULTIMA,[30] 2013	0	30	1	29	0.13 (0.00-6.59)
TOPCOAT,[9] 2014	1	40	1	43	1.08 (0.07-17.53)
PEITHO,[8] 2014	6	506	9	499	0.66 (0.24-1.82)
Total	12	866	26	889	0.48 (0.25-0.92)

Heterogeneity: $\chi^2_7 = 7.63$; $P = .37$; $I^2 = 8\%$

Overall effect: $z = 2.22$; $P = .03$



Chatterjee S. et al. *JAMA* 2014; 311:2414-421

Hémorragies majeures

Saignements graves	Fibrinolyse	Controle
Toutes les études	98/1061 (9.24)	36/1054 (3.42)
EP de gravité intermédiaire	67/866 (7.74)	20/889 (2.25)

Chatterjee S. et al. *JAMA* 2014; 311:2414-421

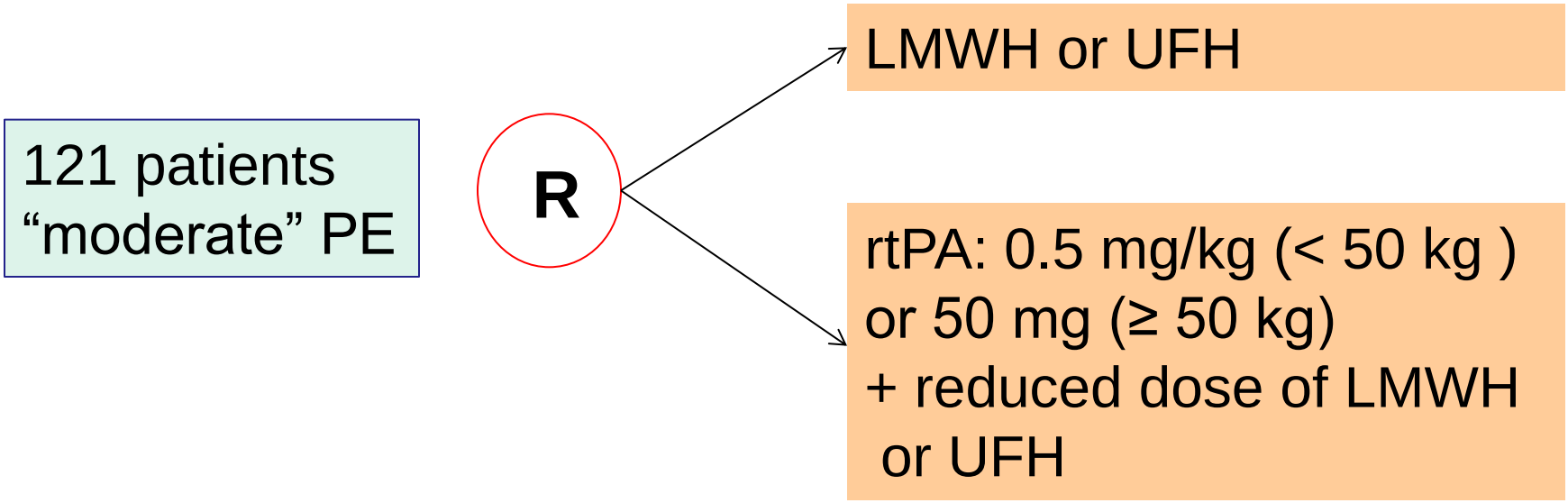
Fibrinolyse dans l'EP de risque intermédiaire

Reperfusion treatment		
Routine use of primary systemic thrombolysis is not recommended in patients not suffering from 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

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

Efficacité et sécurité de faibles doses de rtPA

MOPETT study: single center open-label randomized trial



Sharifi M. et al. *Am J cardiol* 2013; 111: 273-77

Efficacité et sécurité de faibles doses de rtPA

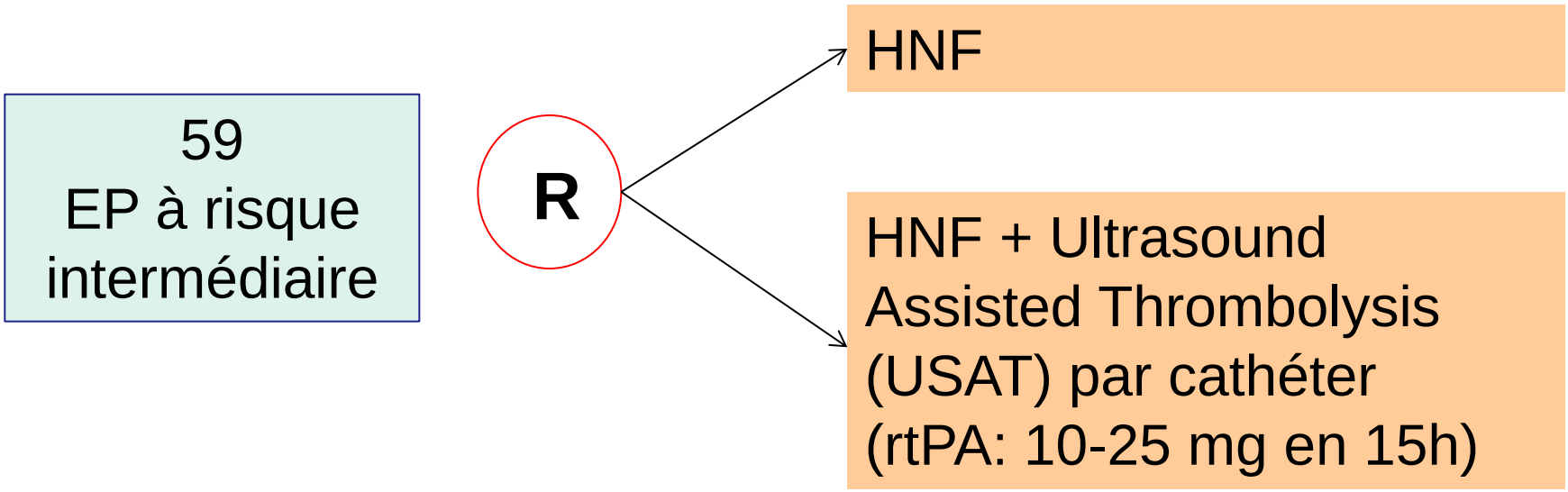
	rtPA n = 58*	Control n = 56*	p
PH/recurrent PE (28 months)	9 (16)	35 (63)	< 0.001
Death/recurrent PE (28 months)	1 (1.6)	6 (10)	0.049
Major bleeding (hospitalisation)	0	0	

*7 patients lost to follow-up

Sharifi M. et al. *Am J cardiol* 2013; 111: 273-77

Combiner fibrinolyse et traitement mécanique ?

ULTIMA : essai multicentrique ouvert avec jugement indépendant du critère d'efficacité



Kucher N. et al. *Circulation* 2014; 129:479-86

Combiner fibrinolyse et traitement mécanique ?

	USAT n = 30	Control n = 29
RV/LV before	1.28 ± 0.19	1.20 ± 0.14
RV/LV after (24h)	0.99 ± 0.17	1.17 ± 0.20
Major bleeding	0	0

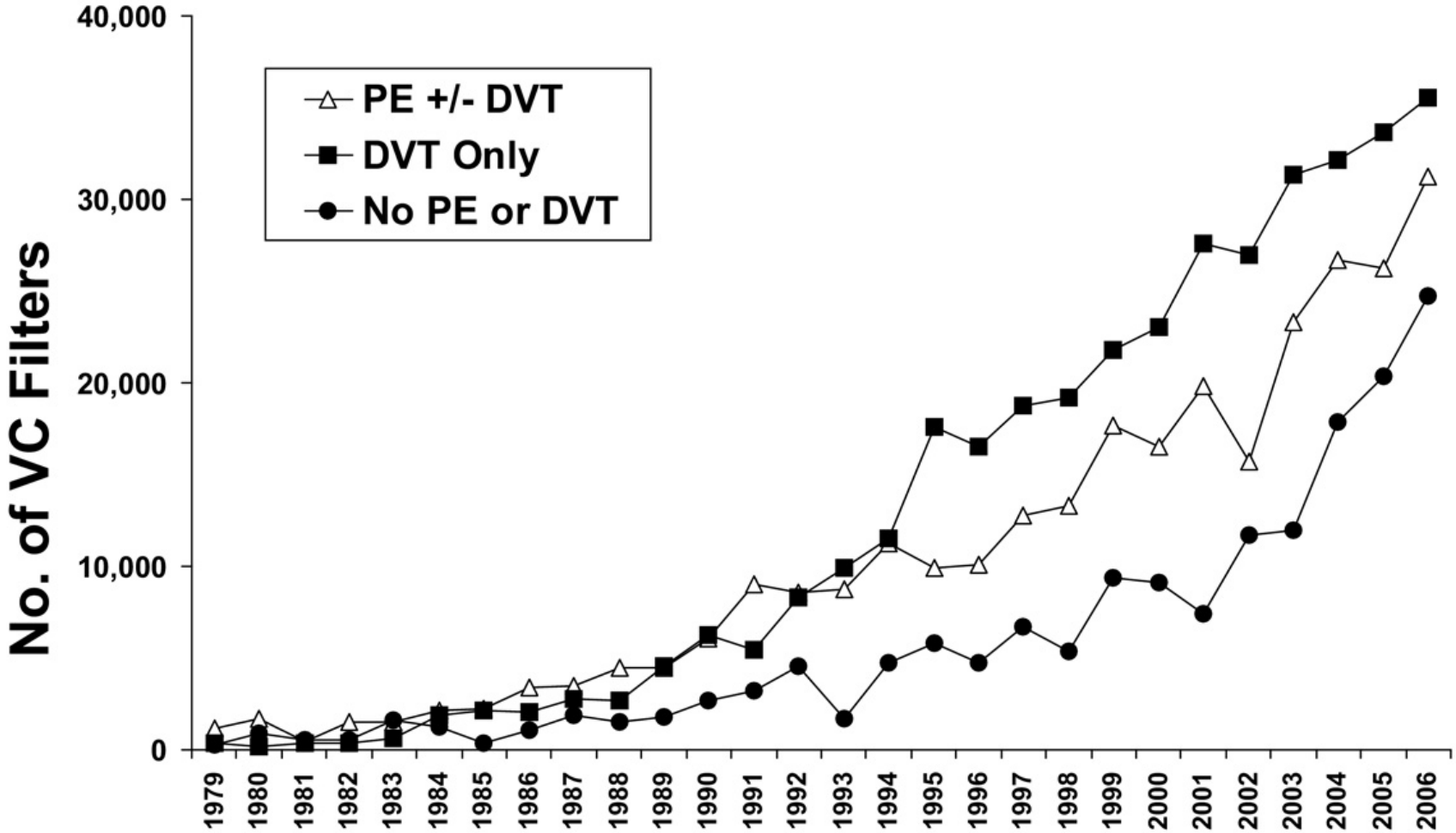
Kucher N. et al. *Circulation* 2014; 129:479-86

Interruption de veine cave, une vieille idée..

« Peut-être le médecin pourrait-il placer une barrière entre le caillot et le cœur? »

Trousseau A, Phlegmatia alba dolens, Clinique médicale de l'Hôtel-Dieu de Paris, 1868, vol 3, p 670.

Filtres cave aux USA

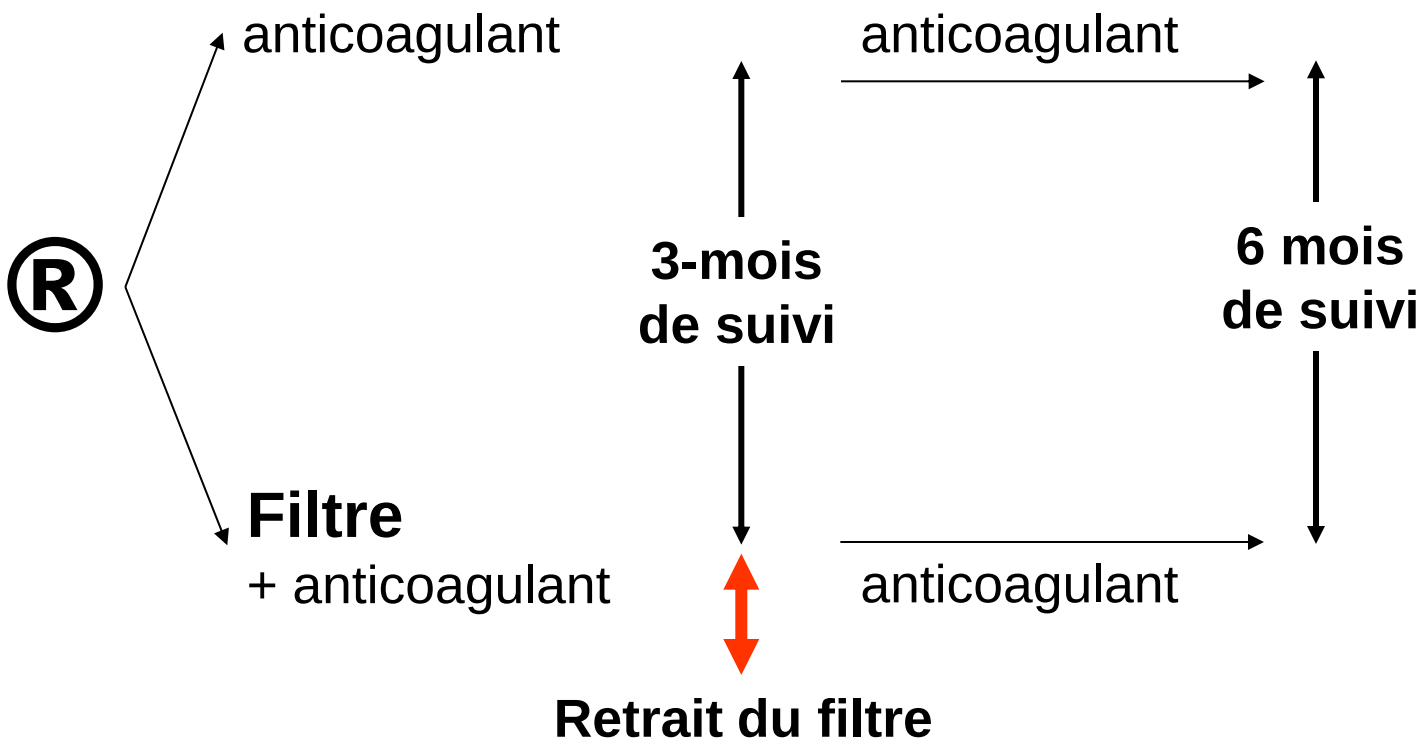


Stein PD. et al. *Am J Med* 2011;124:655-61.

Filtre retirable et anticoagulants. PREPIC2

Essai randomisé multicentrique avec adjudication indépendante des évènements critiques

EP + TVP
Age > 75
Cancer
RVD
IRC ou ICC
TVP
bilatérale



Mismetti P. et al. *JAMA* 2015;313:1627-635

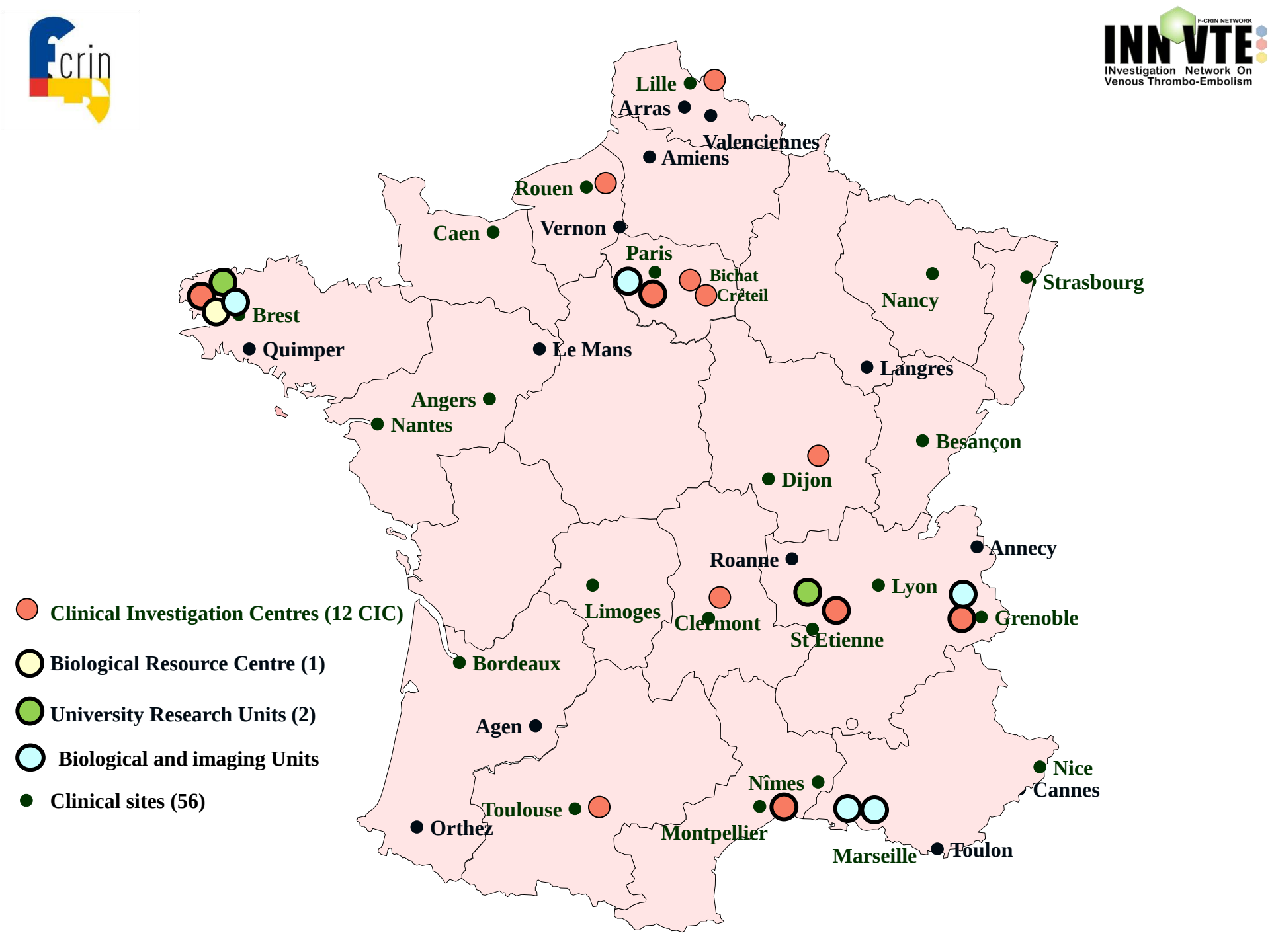
Filtre retirable et anticoagulants. PREPIC2

	Filtre N = 200	Controle N = 199	RR
Récidive 3 mo	6 (3%)	3 (1.5%)	2.00 (0.51-7.89)
Récidive 6 mo	7 (3.5%)	4 (2%)	1.75 (0.52-5.88)

Mismetti P. et al. *JAMA* 2015;313:1627-163

Conclusions

- Traitement ambulatoire possible, mais il faut s'organiser.
- AOD aussi efficaces et mieux tolérés.
- Fibrinolyse à forte dose: amélioration hémodynamique mais saignements. Doses réduites?
- Embolectomie par cathéter, résultats très préliminaires, coût.
- Filtres à option de retrait: pas d'indication sauf contre-indication aux anticoagulants.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Valenciennes
Amiens
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St Etienne
Bordeaux
Agen
Nice
Cannes
Nîmes
Toulouse
Orthez
Montpellier
Marseille
Toulon
Clinical Investigation Centres (12 CIC)
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University Research Units (2)
Biological and imaging Units
Clinical sites (56)