Quelle est la durée optimale du traitement anticoagulant après une TVP ou une EP?

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Maladie thromboembolique veineuse Epidémiologie

- La maladie thromboembolique veineuse est une maladie potentiellement fatale.

- Incidence: 85 hospitalisation pour MTEV /100 000 persons /ans en France

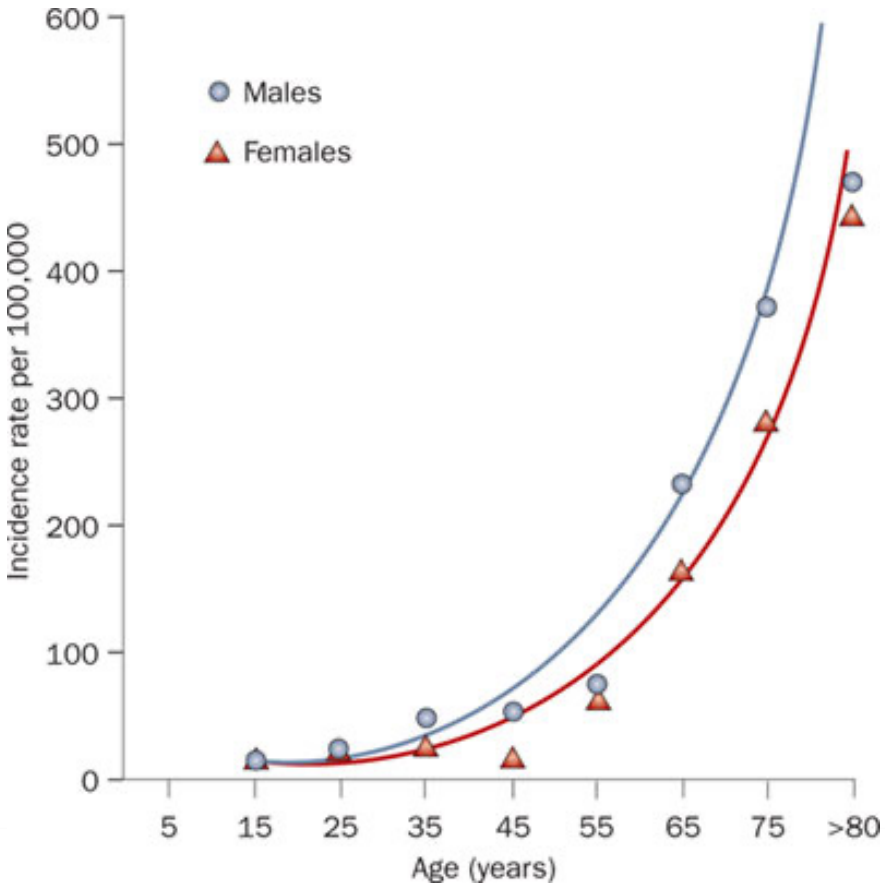
- 250 000 cas incident par an en Europe de l'Ouest.

Bull Epid Hospit 2013
Doume Nature Rev Cardiol 2010

Annual incidence of venous thromboembolism (pulmonary embolism and deep-vein thrombosis combined) among residents of Worcester, MA, USA in 1986 by age and sex

MTEV est frequemment une **pathologie des personnes agés**

Les taux d'incidence augmente exponentiellement avec l'âge, pour le TVP et pour l'EP



Reproduced Arch. Intern. Med. 1 May 1991, **151**, 933–938.

Douma, R. A. *et al.* (2010)

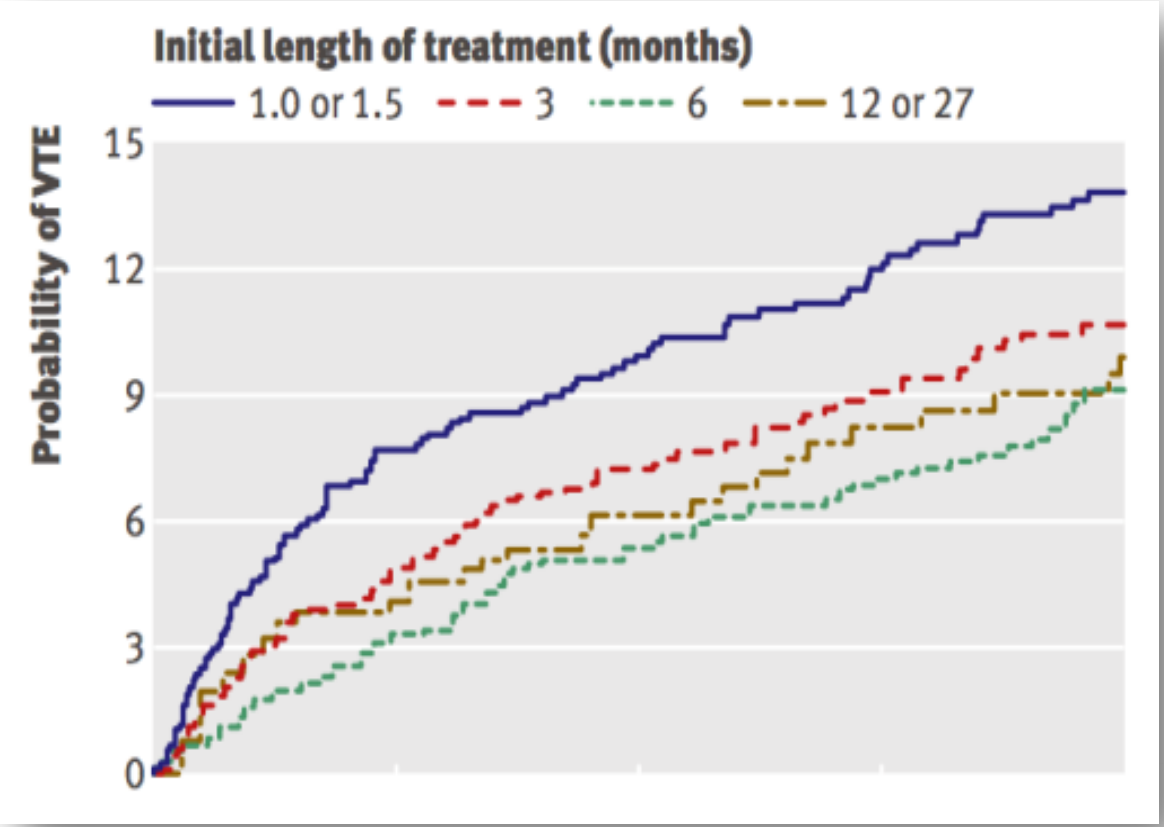
Anticoagulation et MTEV

- **Anticoagulation** : traitement de référence.

- **Un traitement initial de trois mois** après un épisode aigu :
  - **Réduit les décès**
  - **Réduit les récidives** (2-3% sous traitement)
  - **Réduit le syndrome post-thrombotique**

Cumulative probability of recurrent venous thromboembolism (VTE) after stopping treatment

Pooled data 2925 patients, no cancer first episode



1.5 mois vs une durée plus prolongée:
HR 1.52 (1.13-2.02)

3 mois vs une durée plus prolongée:
HR 1.19 (0.86-1.65)

Boutitie et al BMJ 2011

ACC/ACCP recommendations and ESC position paper

- **Les patients avec une TVP proximale ou une EP devraient être traités pour un minimum de 3 mois.**

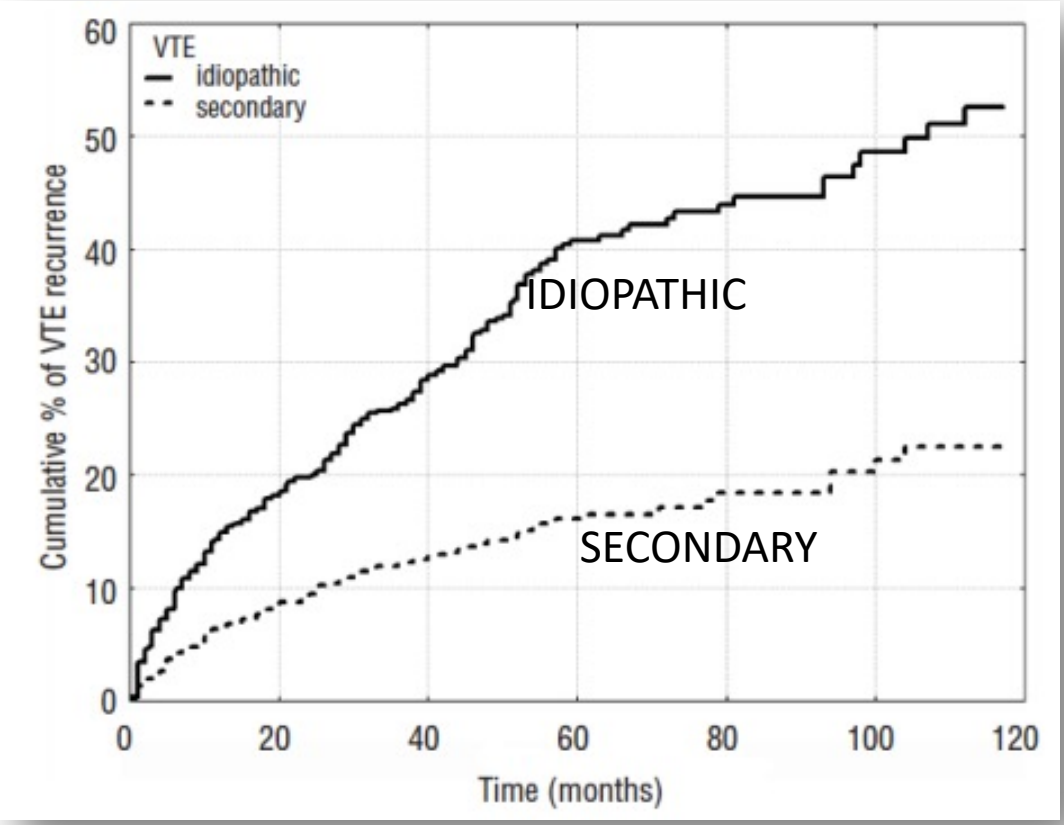
Kearon et al 2016
Mazzolai et al 2017

Risque de récidive : les circonstances de survenue sont déterminantes

15% **Fateurs de risque permanent** (cancer, antiphospholipid syndrome, déficit AT…)

9-10% **Idiopathique**

2-3% **Facteurs de risque transitoire** (chirurgie, immobilisation prolongée…)

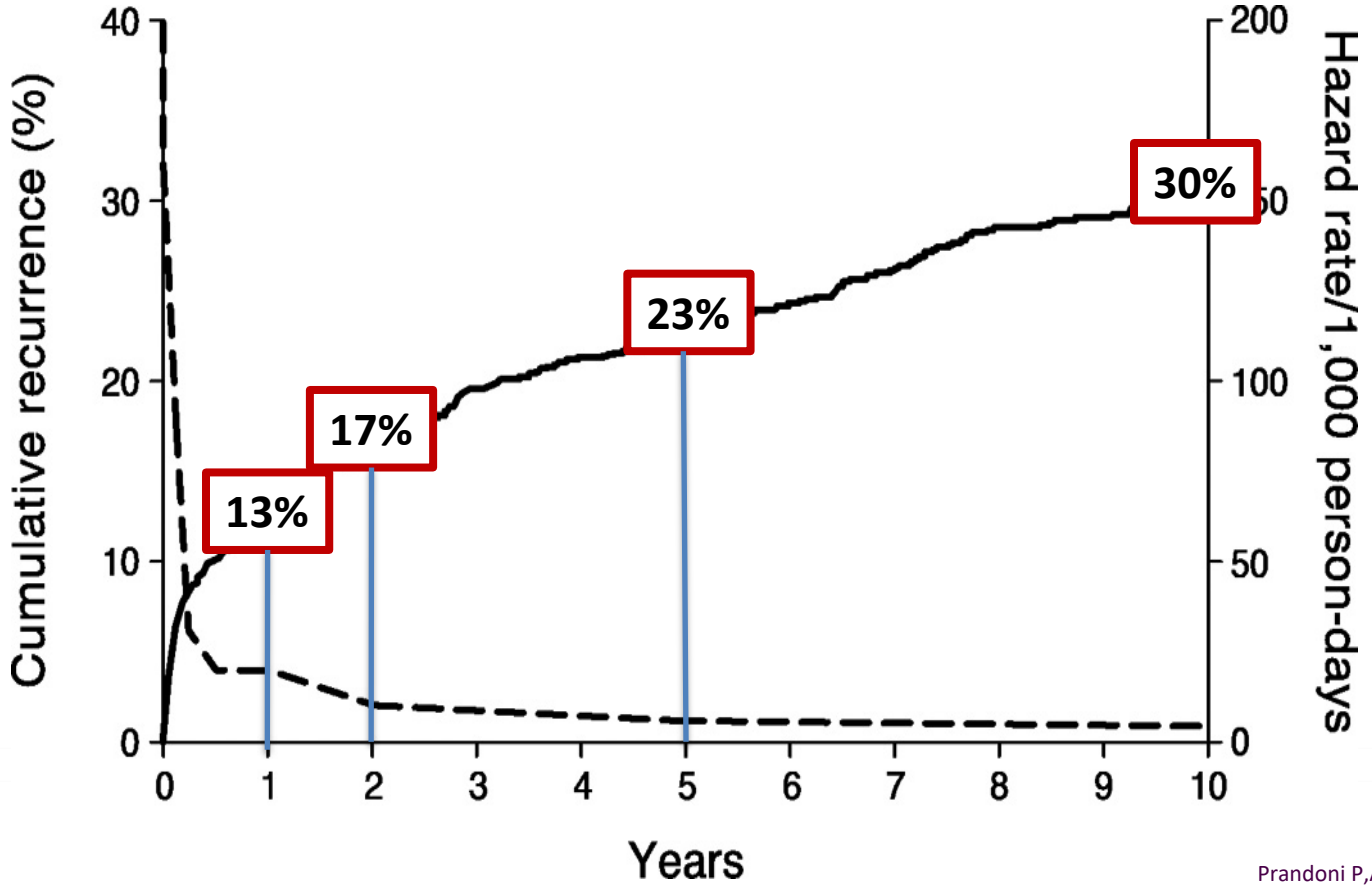


Prandoni, Haematologica 2007

Iorio et al, Arch Intern Med, 2010 : 1710-1716, Baglin et al. Lancet, 2003 : 523-526, Prandoni et al, Haematologica, 2007 : 199-205
Palareti et al, J Thromb Haemost 2000 : 805-810, Prandoni et al, Blood 2002 : 3484-3488, Palareti et al, Thromb Haemost 2002 : 7-12, Rosove et al Annals of Internal Medicine. 1992;117:303-308.

Late recurrence in idiopathic VTE

The risk of VTE **never returns to baseline**



Risk 10% the 1st year then 5%/y

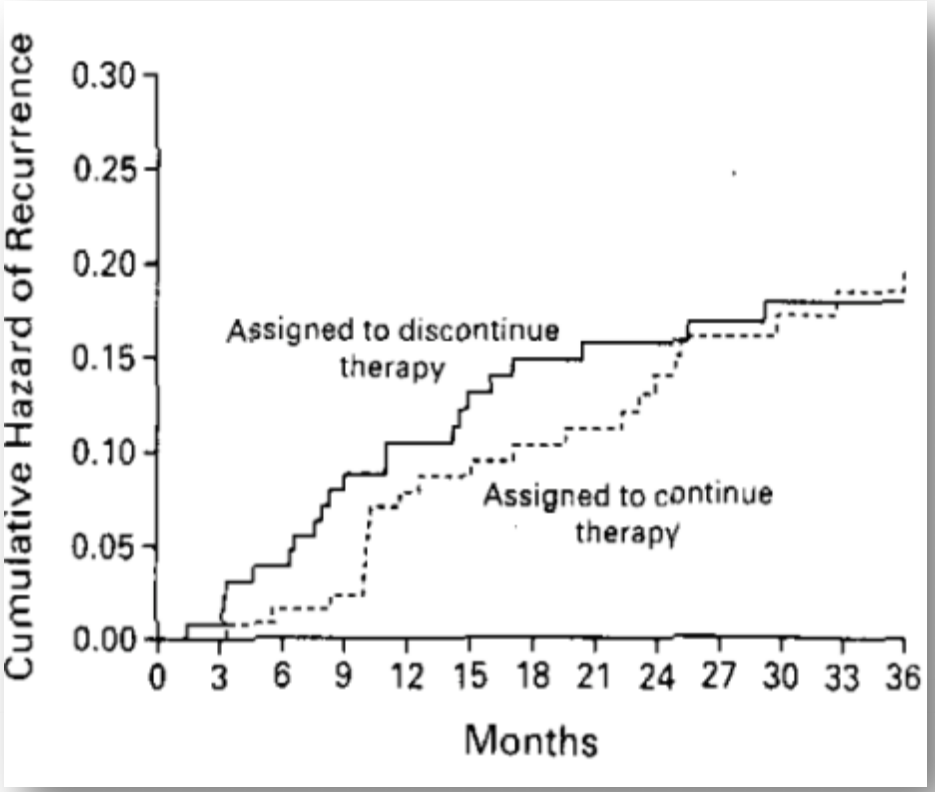
Recurrent VTE is fatal in 3.6% of cases.

Prandoni P,Ann Intern Med. 1996;125:1–7.
Hansson PO, Arch Intern Med.2000;160:769–774.
Schulman S, J Thromb Haemost. 2006;4:734–742.
Spencer F, Arch Intern Med. 2008;168:425–430.
Spencer F, J Thromb Thrombolysis. 2009;28:401–409.

WODIT DVT study

Proximal idiopathic DVT randomised after 3 months: placebo vs 1 year OAT

	Placebo N=133	Warfarin N=134
Recurrence (FU 1Y)	**8.3%**	**0.7%**
Recurrence (FU 3 y)	**15.8**	**15.7**
Major haemorrhage	1.5	3.0



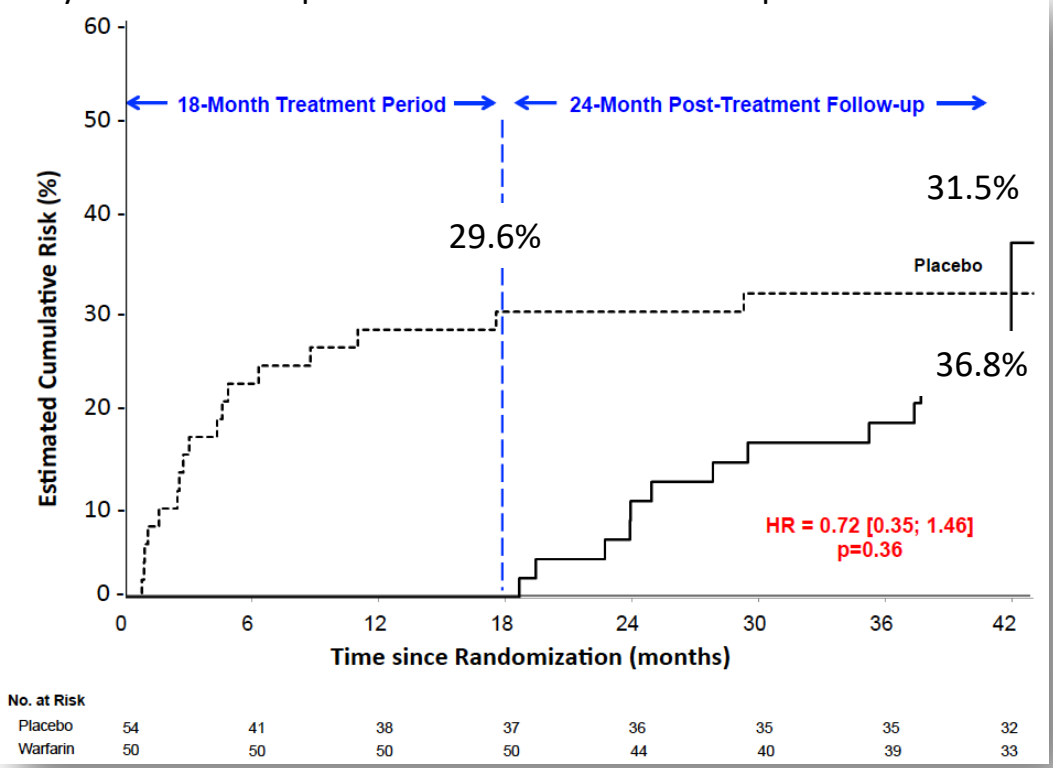
Agnelli NEJM 2001

PADIS DVT Study

Double-blind randomized trial

104 patients with a first unprovoked proximal DVT initially treated for 6 months. 18 months treatment vs placebo. FU 24 months.

Primary objective: superiority of warfarin vs placebo on the risk of the composite of recurrent VTE or major bleeding



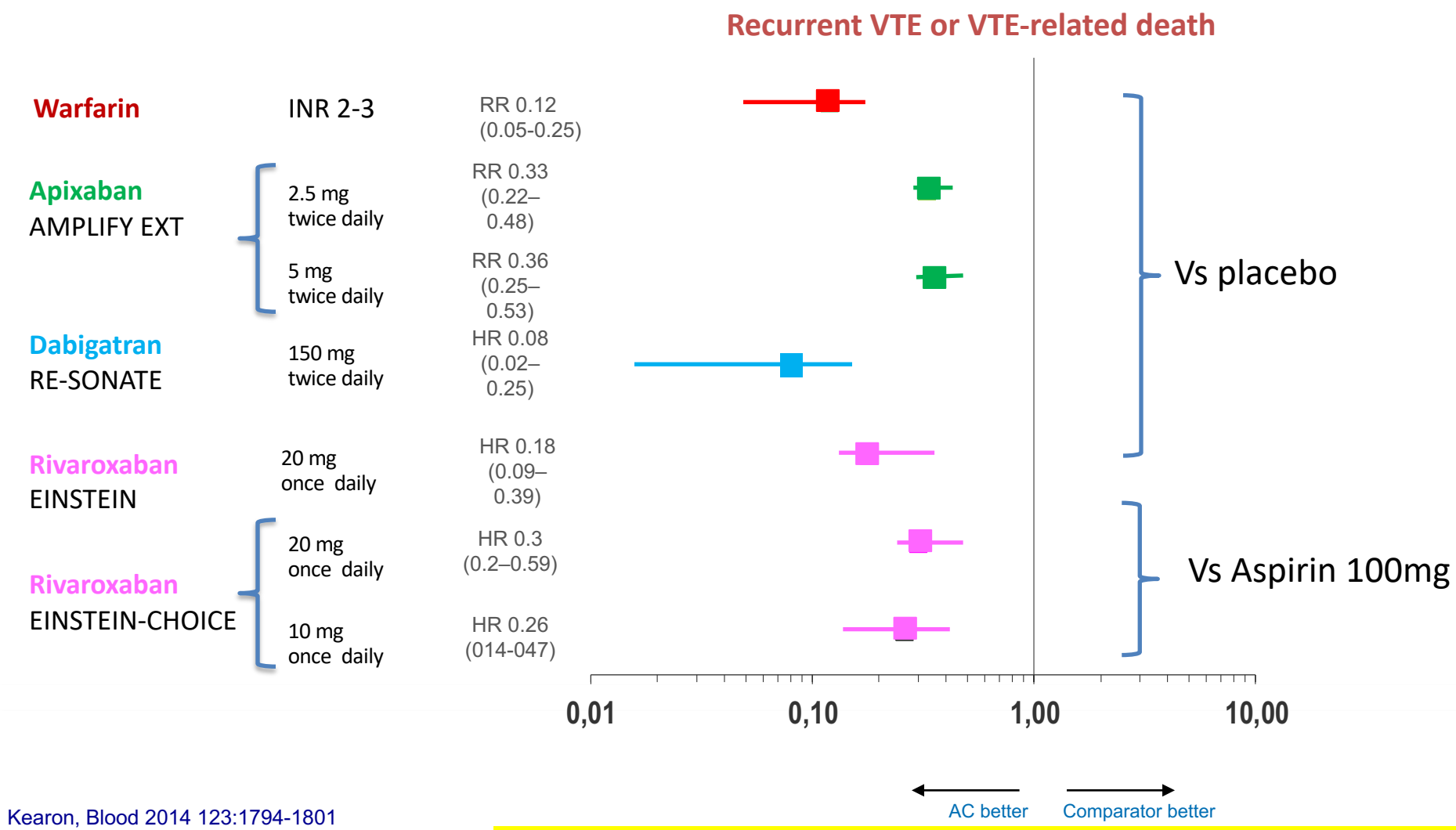
To prolong of some months the treatment is not worthed

F Couturaud, ISTH 2017

How long is long enough?

Bénéfices et risques d'une anticoagulation prolongée

Anticoagulants for extended prevention (>3-6 months) proximal DVT OR PE



Kearon, Blood 2014 123:1794-1801
Agnelli *et al. N Engl J Med* 2013;368:699-708
Bauersachs *et al. N Engl J Med* 2010;363:2499-2510
Schulman *et al. N Engl J Med* 2013;368:709-18
Weitz et al. N Engl J Med. 2017 Mar 30;376(13):1211-1222.

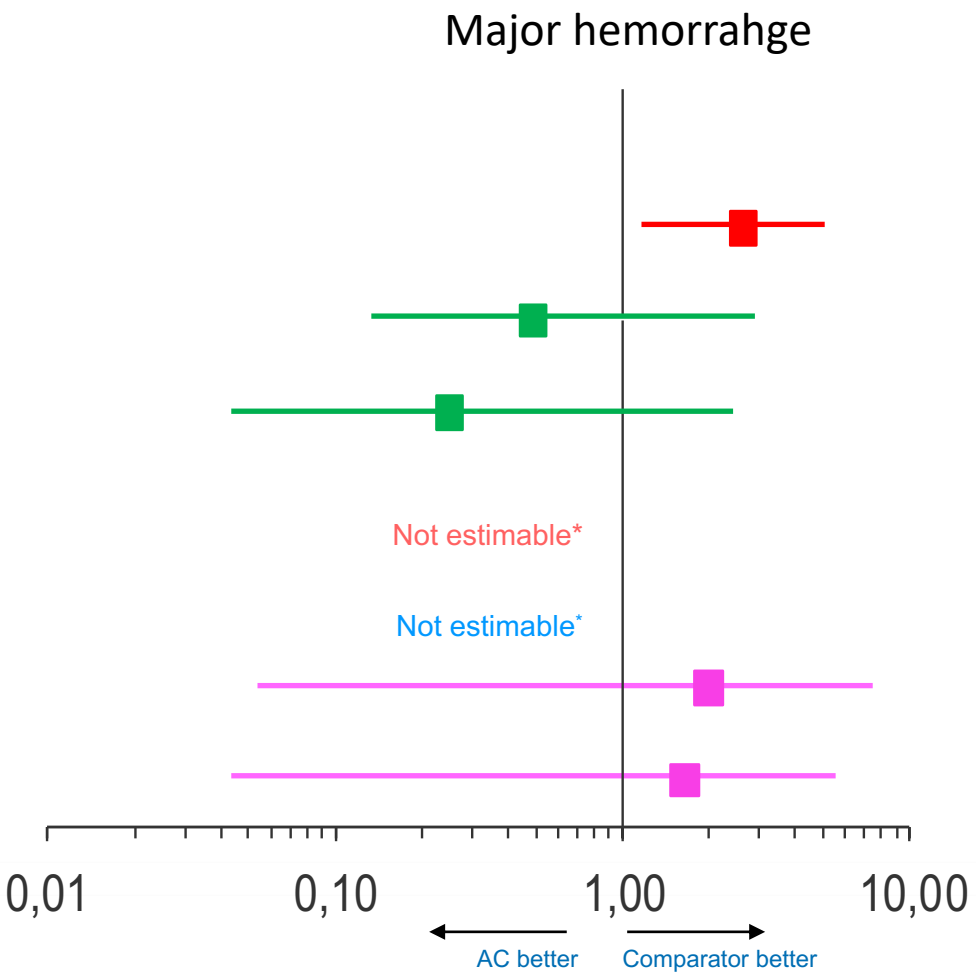
Head-to-head studies do not exist, therefore comparisons between agents cannot be made

No comparison with warfarin

Anticoagulants for extended prevention (>3-6 months)

proximal DVT OR PE

Warfarin	INR 2-3	RR 2.63 (1.02-6.68)
Apixaban AMPLIFY EXT	2.5 mg twice daily	RR 0.49 (0.09–2.64)
	5 mg twice daily	RR 0.25 (0.03–2.24)
Dabigatran RE-SONATE	150 mg twice daily	Not estimable*
Rivaroxaban EINSTEIN	20 mg once daily	Not estimable*
Rivaroxaban EINSTEIN-CHOICE	20 mg once daily	HR 2.01 (0.50-8.04)
	10 mg once daily	HR 1.64 (0.39-6.84)



Kearon, Blood 2014 123:1794-1801
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Schulman *et al. N Engl J Med* 2013;368:709-18
Weitz et al. N Engl J Med. 2017 Mar 30;376(13):1211-1222.

All the studies were underpowered to show a significant difference in safety

Problèmes avec l'anticoagulation prolongée

- **Le suivi** n'a pas dépassé les 5 ans
- **70% des patients** n'auront jamais une récidive.
- **Le risque depasse-t-il le bénéfice,** après une certaine durée?

Kearon C et al . J Thromb Haemost 2010;8:2313-5.

Longue maladie, long traitement?

- High efficacy of anticoagulation in preventing VTE recurrences, but risk of hemorrhage after 3 months anticoagulation:

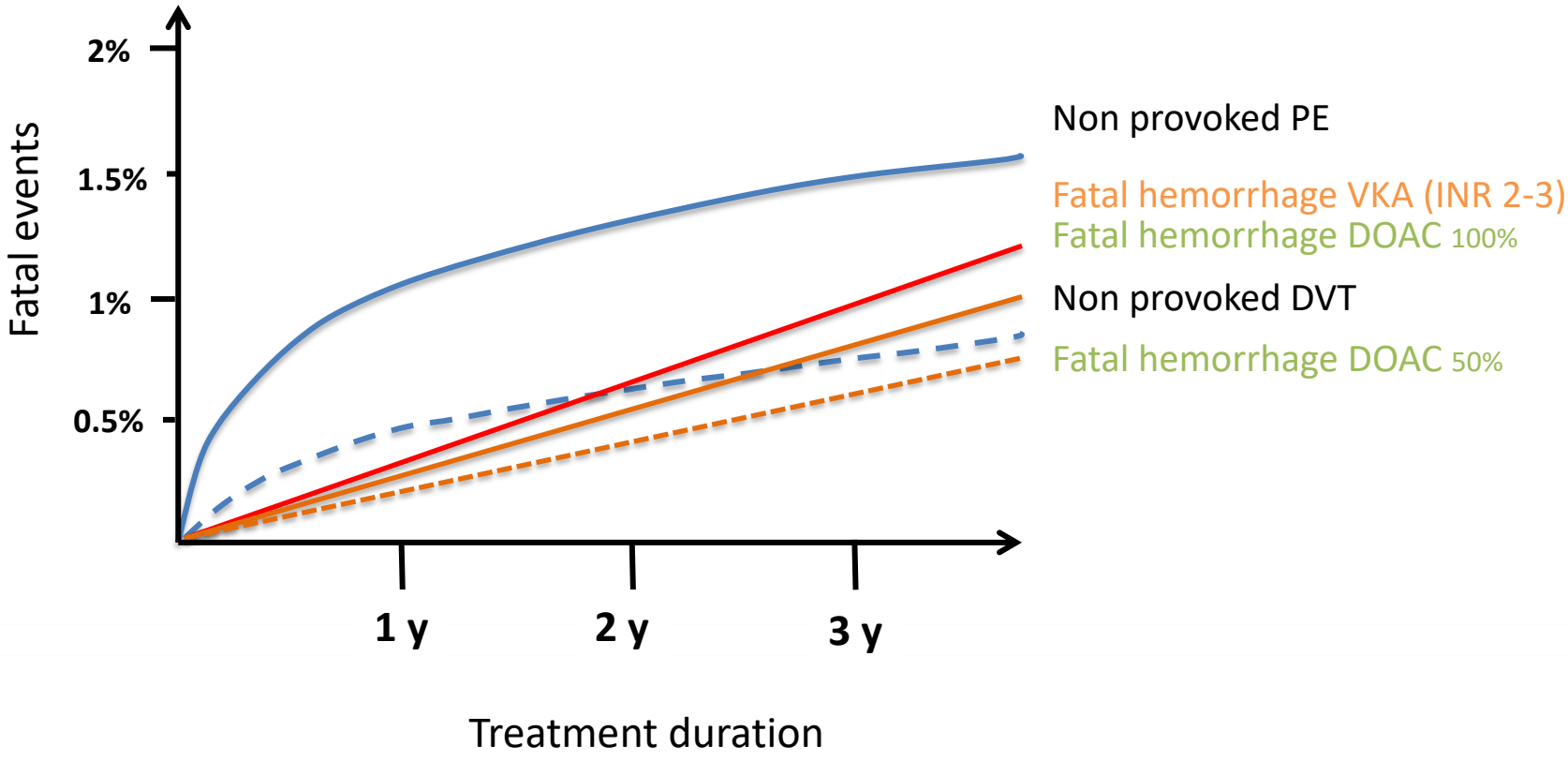
VTE case-fatality rate (Duketis, 1998)	8.8% (5.0-14.1%)
Bleeding case-fatality rate (Linkins, 2003)	9.1% (CI, 2.5% to 21.7%),
VTE case-fatality rate (RIETE, Lecumberri, 2013)	**2.0% (95% CI, 0–4.2)**
Bleeding case-fatality rate	**18.2% (95% CI, 14.0–23.2)**

But overall case fatality-rate decreased in the last years (Carrier et al, 2010)

Duketis, JAMA 1998
Linkins, Ann Intern Med 2003

Lecumberri, et al, TH 2013

Benefit risk balance



Couturaud, Press Med 2017

Prolonged anticoagulation

- Few bleeding scores available and no clinical decision rule has been validated on the basis of the bleeding risk.

- Are we able to find patients at high or **low risk of recurrence**?

Risk factors for recurrence and clinical relevance

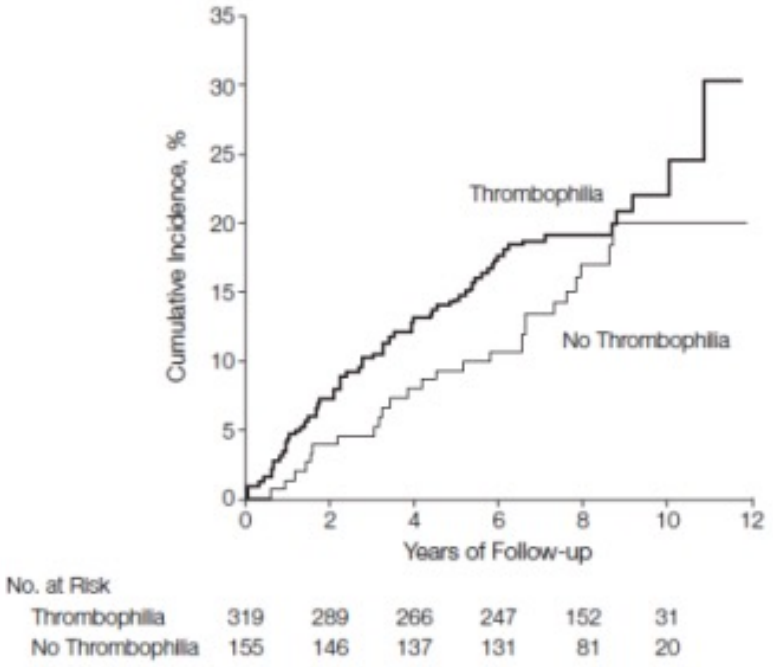
		Relevance
Patient characteristics	Age	Incidence stable during time, >65years
	Sex	**RR 1.5-2.0**
	BMI	**Moderate, Linear**
	Chronic inflammatory disease	**RR 2**
VTE characteristics		
	Vena cava filter	**RR 1.8 after 8 years**
	Post-thrombotic syndrome	**RR X2**
	More than 2 events	**RR 2**

Kyrle PA, N Engl J Med 2004; 350: 2558–63.
McRae S, Lancet 2006; 368: 371–78.
Duketis BMJ 2011
Eichinger Arch Intern Med 2008

Hansson PO, et al. Arch Intern Med 2000; 160: 769–74.
Ridker PM, et al. . N Engl J Med 2003; 348: 1425–34.
Schulman S, et al. N Engl J Med 1997; 336: 393–98.
Schulman S et al. N Engl J Med 2003; 349: 1713–21

Biological/imaging markers of recurrences and clinical relevance

	Relevance
Inherited thrombophilia	Uncertain RR 1.4
Antiphospholipid syndrome	Probably high RR 2
D-Dimers >250 UI/L	RR 2.5
Ultrasound evidence of residual thrombosis	RR 1.5



Baglin, Lancet 2003
Christiansen, JAMA 2005
Lefebvre P, Thromb Haemost 2013

Palareti NEJM 2006
Cosmi PROLONG II Blood 2010,
Eichinger Circulation 2007

Modèles predictifs

- Des modèles prédictifs ont été construits pour aider dans le choix

- Men continue and HERDOO 2 est le plus validé

Eichinger Circulation 2010, Tosetto JTH 2012

M Rodger CMAJ, 2008
M Rodger, BMJ 2017;356:j106

Men continue and HERDOO2

646 first, unprovoked major venous thromboembolism
Data for **69 potential predictors of recurrent venous thromboembolism** to derive a clinical decision rule.

HERDOO Predictors

- Hyperpigmentation or Edema or redness (HER) on exam either leg =1 point
- Vidas D-Dimer ≥250= 1 point
- Obesity, BMI ≥30= 1 point
- Older age ≥ 65 years= 1 point

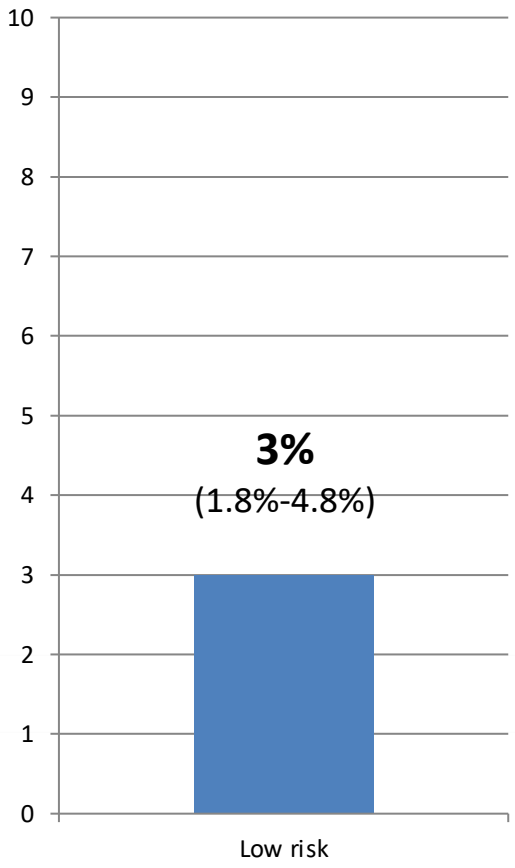
- **Men continue** anticoagulants
  - 13.9 annual risk of recurrent DVT
- **Women with < 2 points discontinue anticoagulants**
  - 1.6% (95%CI 0.3-4.6%) annual risk of recurrent DVT

Rodger CMAJ, 2008

REVERSE II propective validation « Men continue and HERDOO2 »

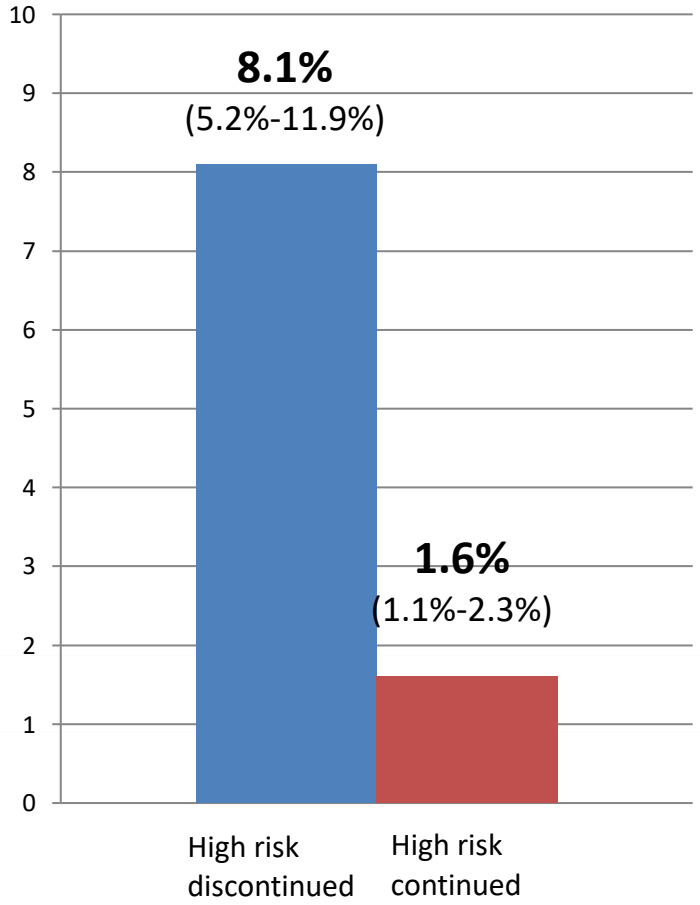
2785 first unprovoked (VTE, proximal leg deep vein thrombosis or pulmonary embolism) who completed 5-12 months of short term anticoagulant treatment,

Primary analysis



ISTH > 5% at 1 year
Continue OAC

Secondary analysis



M Rodger, BMJ 2017;356:j1065

Conclusions

- Les patients avec une TVP proximale ou une EP devraient recevoir **au moins trois mois d'anticoagulation..**

- Une **discussion sur une anticoagulation prolongée** devrait être effectuée pour tous les patients avec une EP (ou une thrombose proximale?)

- Des modèles re stratification du risque **pour identifier des patients à faible risque** peuvent aider pour décider qui peut arrêter sans risque après 3-6 mois.

Merci de votre attention!