Trombofilia e Tromboembolismo Venoso Ricorrente

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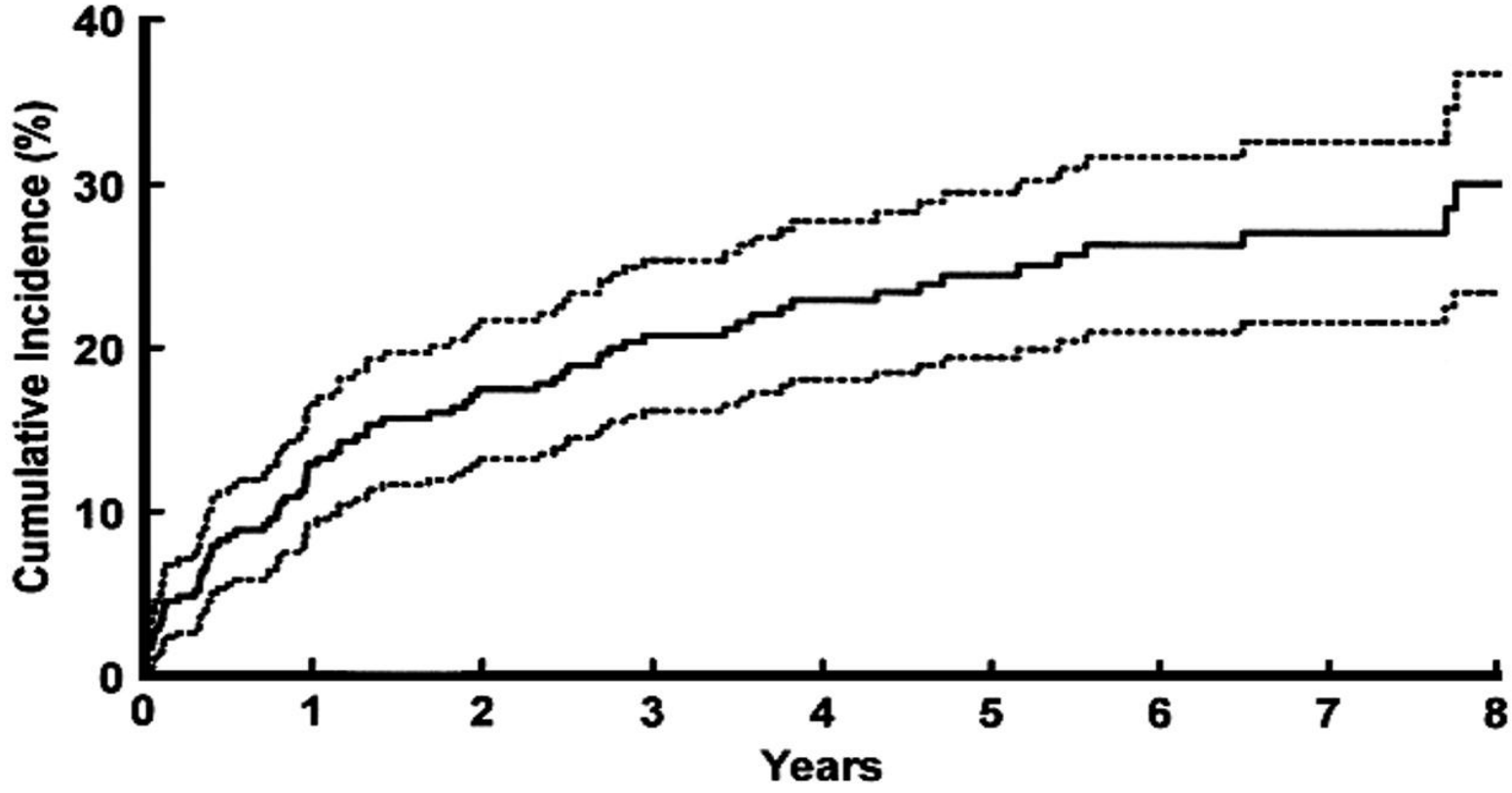
SECONDARY PROPHYLAXIS OF VENOUS THROMBOEMBOLISM

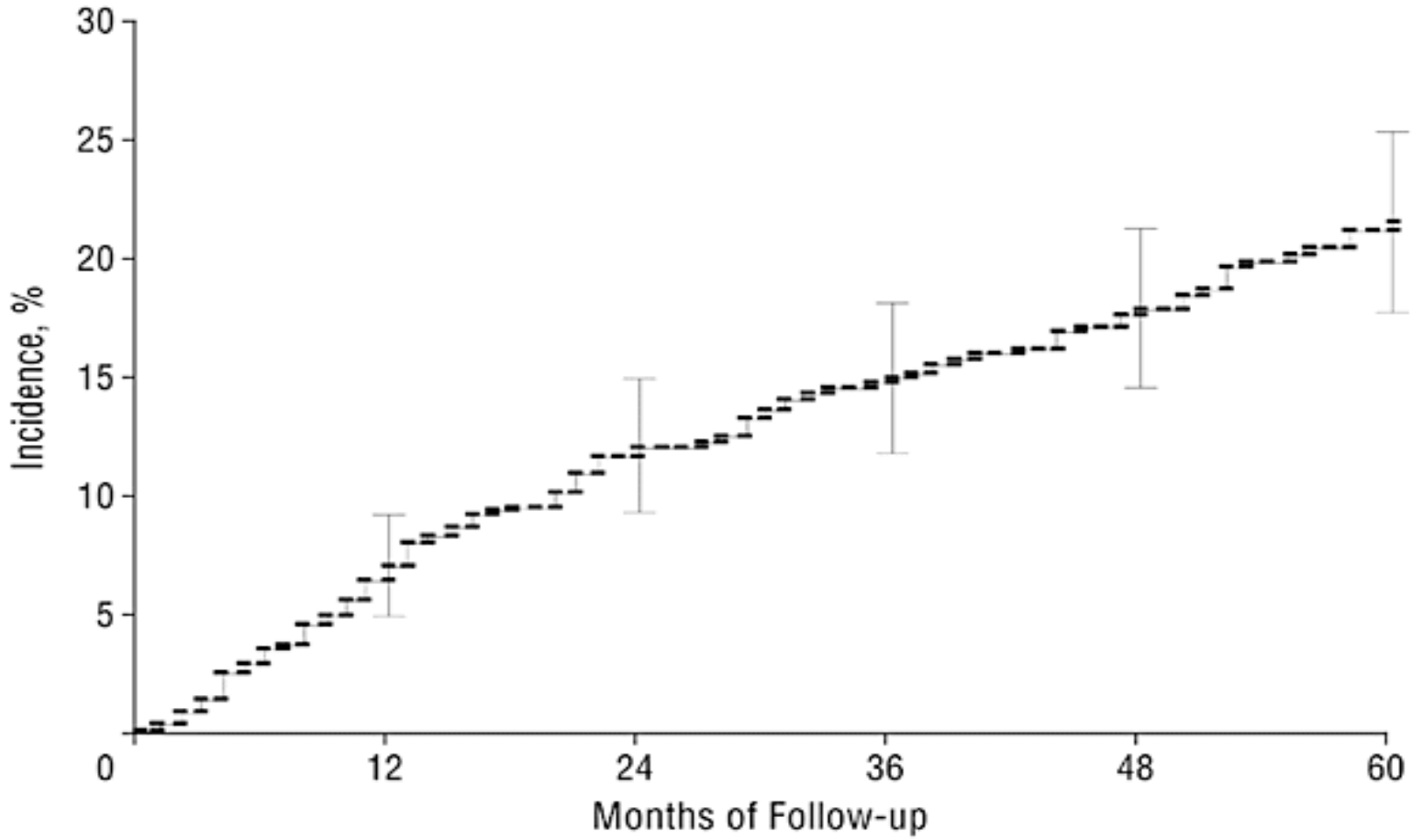
- Incidence of recurrent VTE
- Bleeding events related with OAT
- Duration of secondary prophylaxis
- Recommended intensity of OAT
- Risk factors for recurrent VTE and identification of candidate patients to life-long prophylaxis

The cumulative incidence of recurrent venous thromboembolism in patients with a first episode of symptomatic deep venous thrombosis



Prandoni, P. et. al. Ann Intern Med 1996;125:1-7

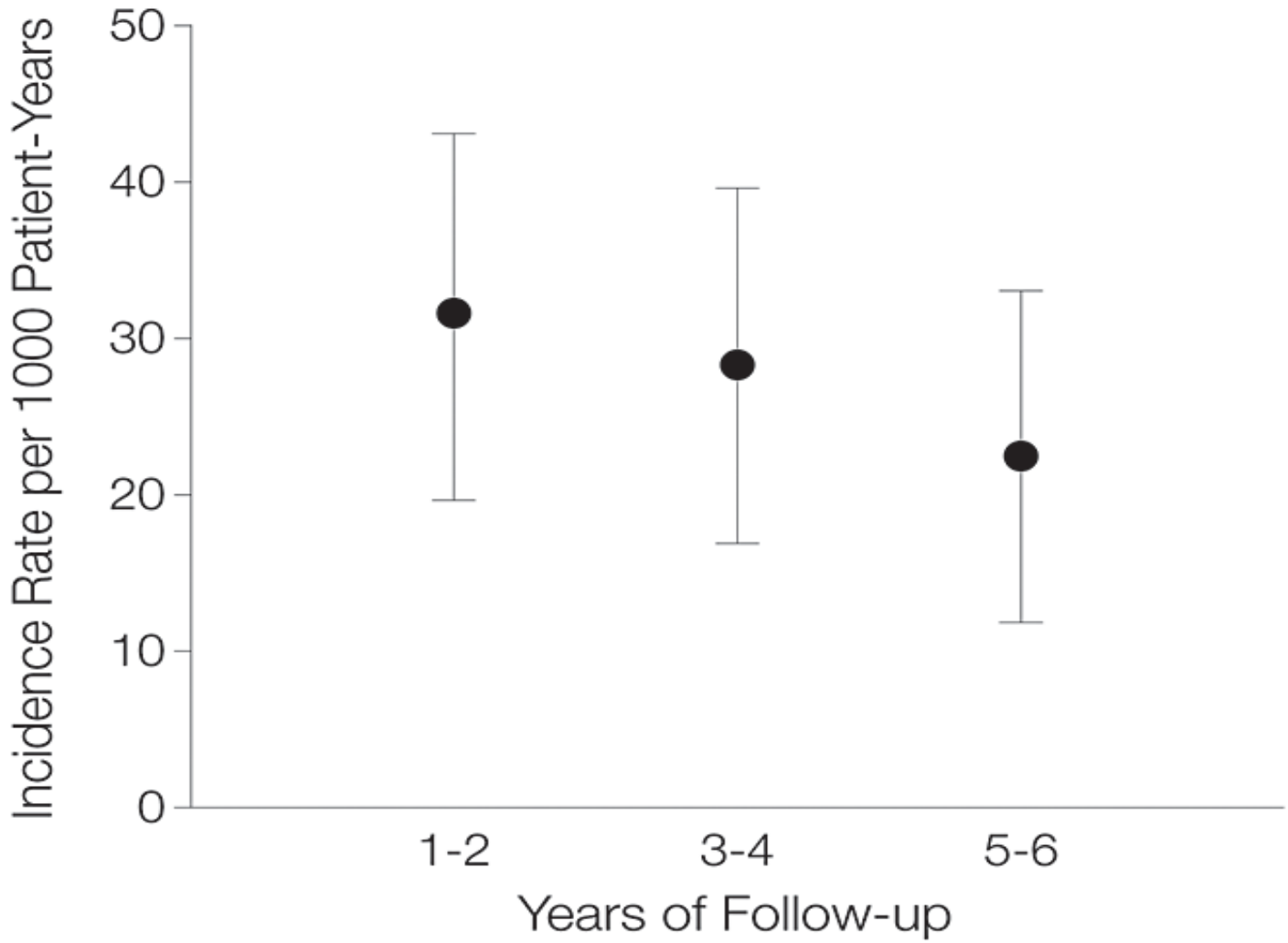
Annals of Internal Medicine



Hansson, P.-O. et al. Arch Intern Med 2000;160:769-774.

ARCHIVES OF
INTERNAL MEDICINE

Incidence Rate of Recurrent Thrombotic Event Error bars indicate 95% confidence intervals



Christiansen, S. C. et al. JAMA 2005;293:2352-2361.

LETS: pts <70, without cancer

JAMA

Cumulative risk of recurrent VTE

Proximal DVT and/or PE	1 year after VKA	5 years after VKA
VTE provoked by surgery	**1%**	**3%**
VTE provoked by a nonsurgical reversible risk factor	**5%**	**15%**
unprovoked VTE	**10%**	**30%**

ACCP Guidelines, Chest 2008

Reference	Cumulative probability of recurrent VTE at 1 year of treatment	
	Intention-to-treat	On treatment
Kearon C et al, NEJM 2003 [1]	approx. 0.5%	not reported
EINSTEIN trial, NEJM 2010 [2]	3.0%	defined as similar
EINSTEIN-PE trial, NEJM 2010 [3]	1.8%.	defined as similar
Schulman S et al, NEJM 2013 [4]	approx. 0.5%	not reported
Agnelli G et al, NEJM 2013 [5]	2.7%	not reported
Hokusai trial, NEJM 2013 [6]	3.5%	1.9 %

Reference	Cumulative probabilityat 1 year of treatment	
	Major bleeding	Composite outcome (MB + recurrent vTE)
EINSTEIN trial, NEJM 2010 [2]	1.2%	4.2%
EINSTEIN-PE trial, NEJM 2010 [3]	2.2%.	4.0%
Agnelli G et al, NEJM 2013 [5]	1.8%	not reported
Hokusai trial, NEJM 2013 [6]	1.6%	not reported

Bleeding complications of OAT
Palareti et al, Lancet 1996

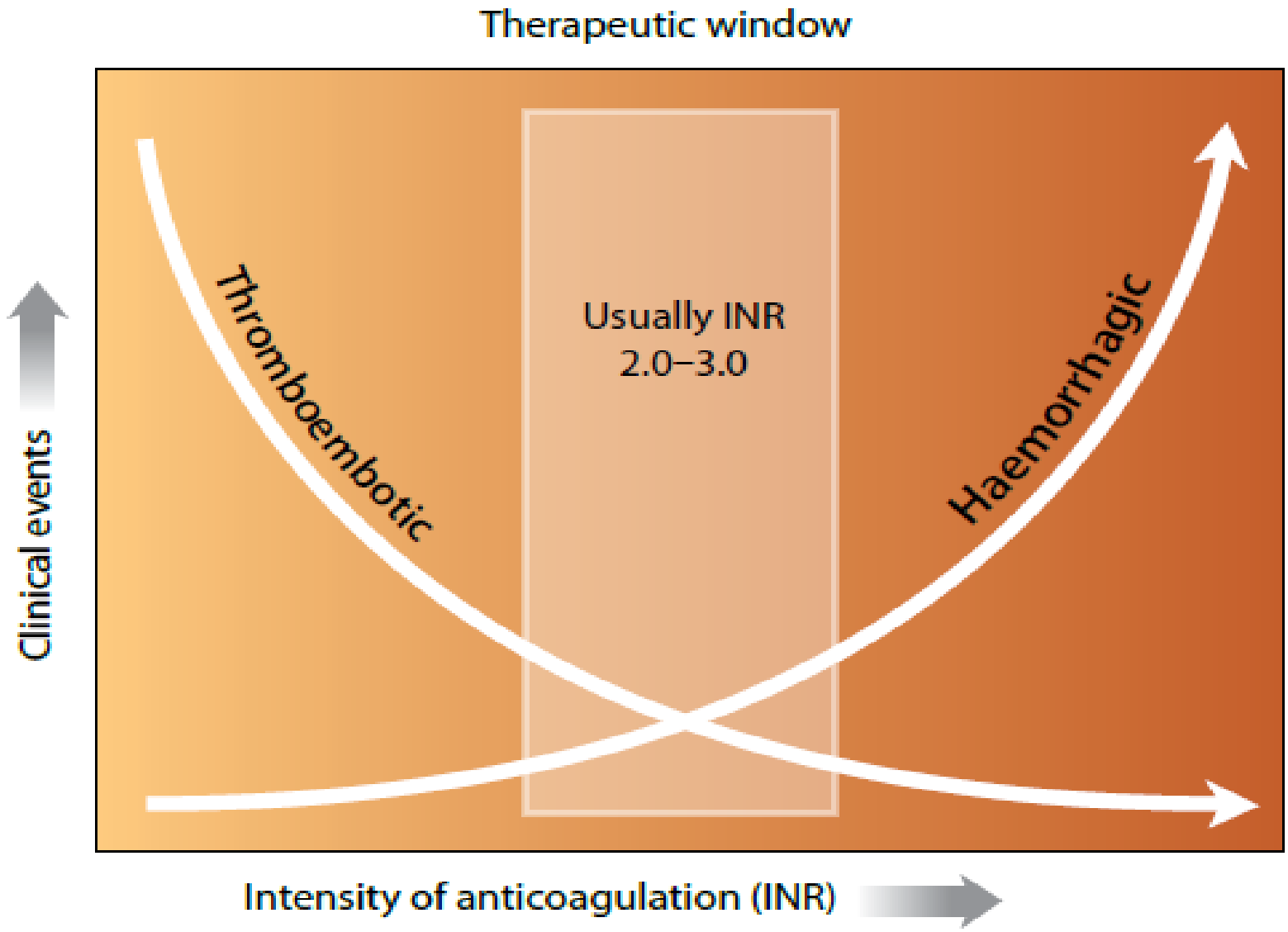
- 2745 pts on OAT, followed for total 2011 pt-years
- Bleeding complications 7.6% pt-years:

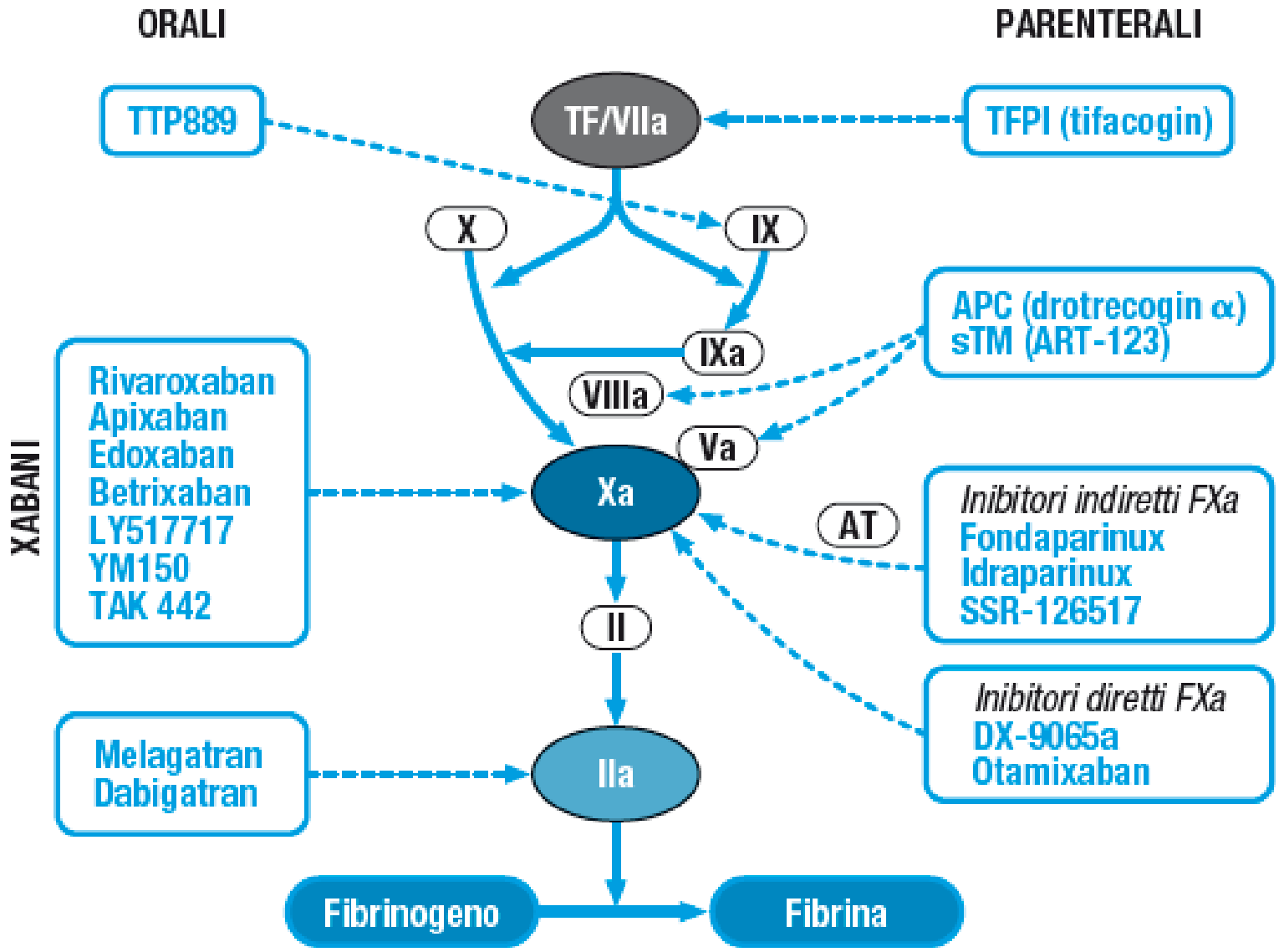
  0.25 fatal, 1.1 major, 6.2 minor
- Bleeding complications occurring at INR<2: 7.7% pt-years; INR 2.0-2.9: 4.8; INR 3.0-4.4: 9.5; INR 4.5-6.9: 40.5
- Higher rate of bleeding complications in patients aged 70 or over, during the first 90 days of treatments, when the indication was peripheral and/or cerebrovascular arterial

- *The incidence of major bleeding during OAT is 1.1% pt-years (0.25 fatal).*

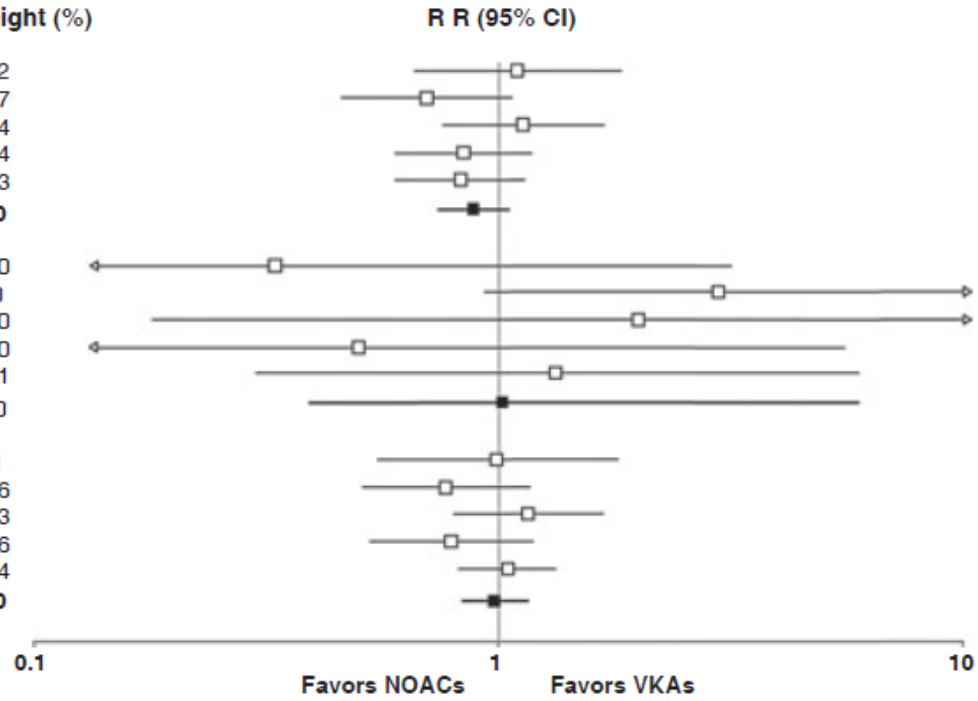
- *The annual incidence of pulmonary embolism in the general population is 42 /100.000 (Silverstein et al, 1998)*

- *The incidence of fatal pulmonary embolism after discontinuation of OAT is 0.17 (definite PE) to 0.43 events % pt-years in patients with VTE (Douketis et al, 2007).*

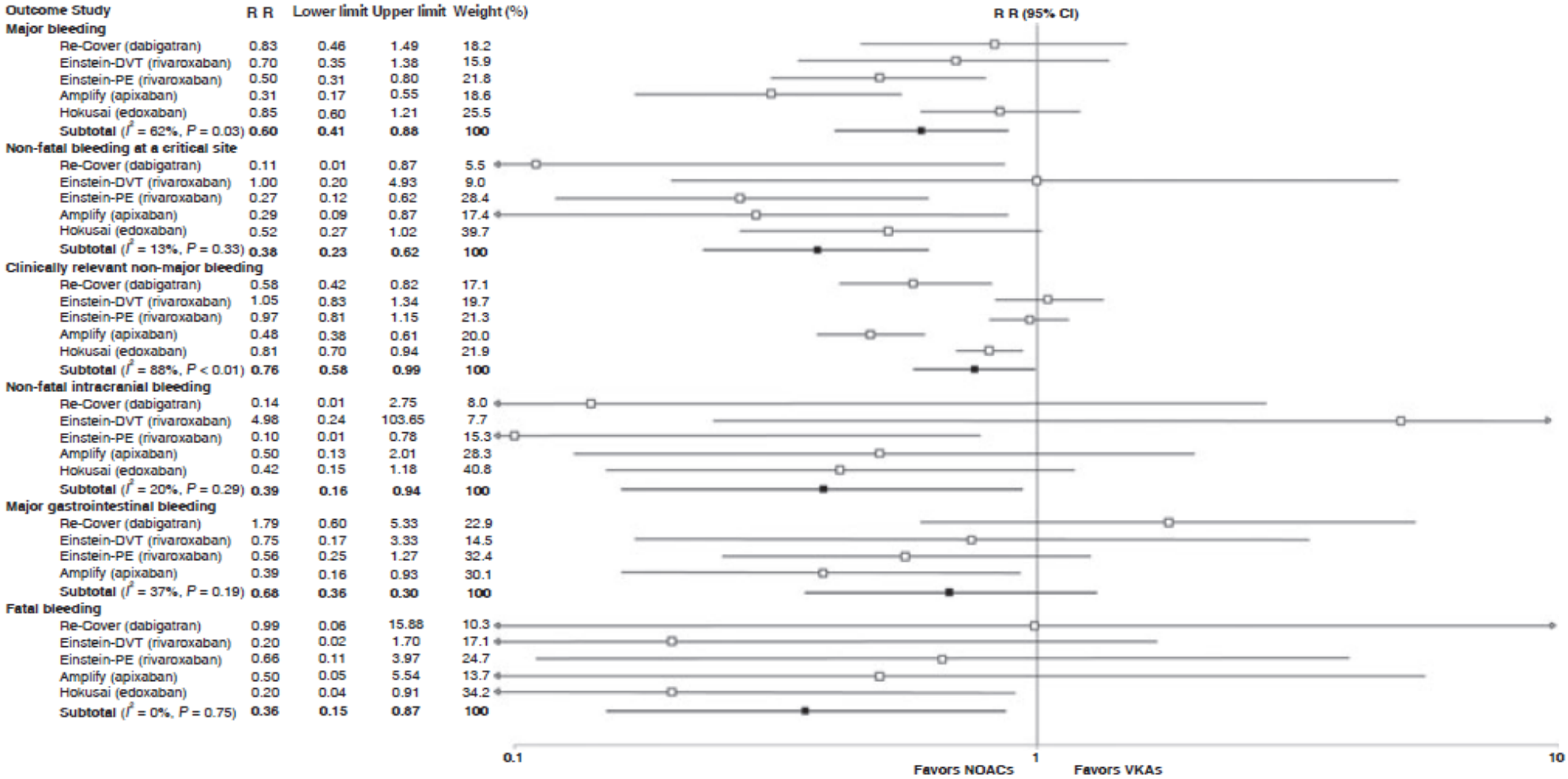

Therapeutic window
Thromboembotic
Usually INR
2.0–3.0
Haemorrhagic
Clinical events
Intensity of anticoagulation (INR)


ORALI
PARENTERALI
TTP889
TF/VIIa
TFPI (tifacogin)
X
IX
APC (drotrecogin α)
sTM (ART-123)
IXa
VIIIa
Va
XABANI
Rivaroxaban
Apixaban
Edoxaban
Betrixaban
LY517717
YM150
TAK 442
Xa
AT
Inibitori indiretti FXa
Fondaparinux
Idraparinux
SSR-126517
II
Inibitori diretti FXa
DX-9065a
Otamixaban
Melagatran
Dabigatran
IIa
Fibrinogeno
Fibrina

Outcome Study	R R	Lower limit	Upper limit	Weight (%)
Recurrent VTE				
Re-Cover (dabigatran)	1.10	0.66	1.84	11.2
Einstein-DVT (rivaroxaban)	0.70	0.46	1.07	16.7
Einstein-PE (rivaroxaban)	1.13	0.76	1.69	18.4
Amplify (apixaban)	0.84	0.60	1.18	25.4
Hokusai (edoxaban)	0.83	0.60	1.14	28.3
Subtotal (I^2 = 0%, P = 0.46)	**0.88**	**0.74**	**1.05**	**100**
Fatal PE				
Re-Cover (dabigatran)	0.33	0.03	3.18	18.0
Einstein-DVT (rivaroxaban)	2.98	0.12	73.04	9.0
Einstein-PE (rivaroxaban)	2.00	0.18	21.99	16.0
Amplify (apixaban)	0.50	0.05	5.57	16.0
Hokusai (edoxaban)	1.33	0.30	5.96	41.1
Subtotal (I^2 = 0%, P = 0.71)	1.02	0.39	5.96	100
Overall mortality				
Re-Cover (dabigatran)	0.99	0.55	1.81	7.1
Einstein-DVT (rivaroxaban)	0.77	0.51	1.17	14.6
Einstein-PE (rivaroxaban)	1.16	0.80	1.68	18.3
Amplify (apixaban)	0.79	0.53	1.19	15.6
Hokusai (edoxaban)	1.05	0.82	1.33	44.4
Subtotal (I^2 = 0%, P = 0.50)	**0.97**	**0.83**	**1.14**	**100**



van der Hulle et al. JTH 2014



van der Hulle et al. JTH 2014

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Regular Article

Case-fatality of recurrent venous thromboembolism and major bleeding associated with aspirin, warfarin, and direct oral anticoagulants for secondary prevention

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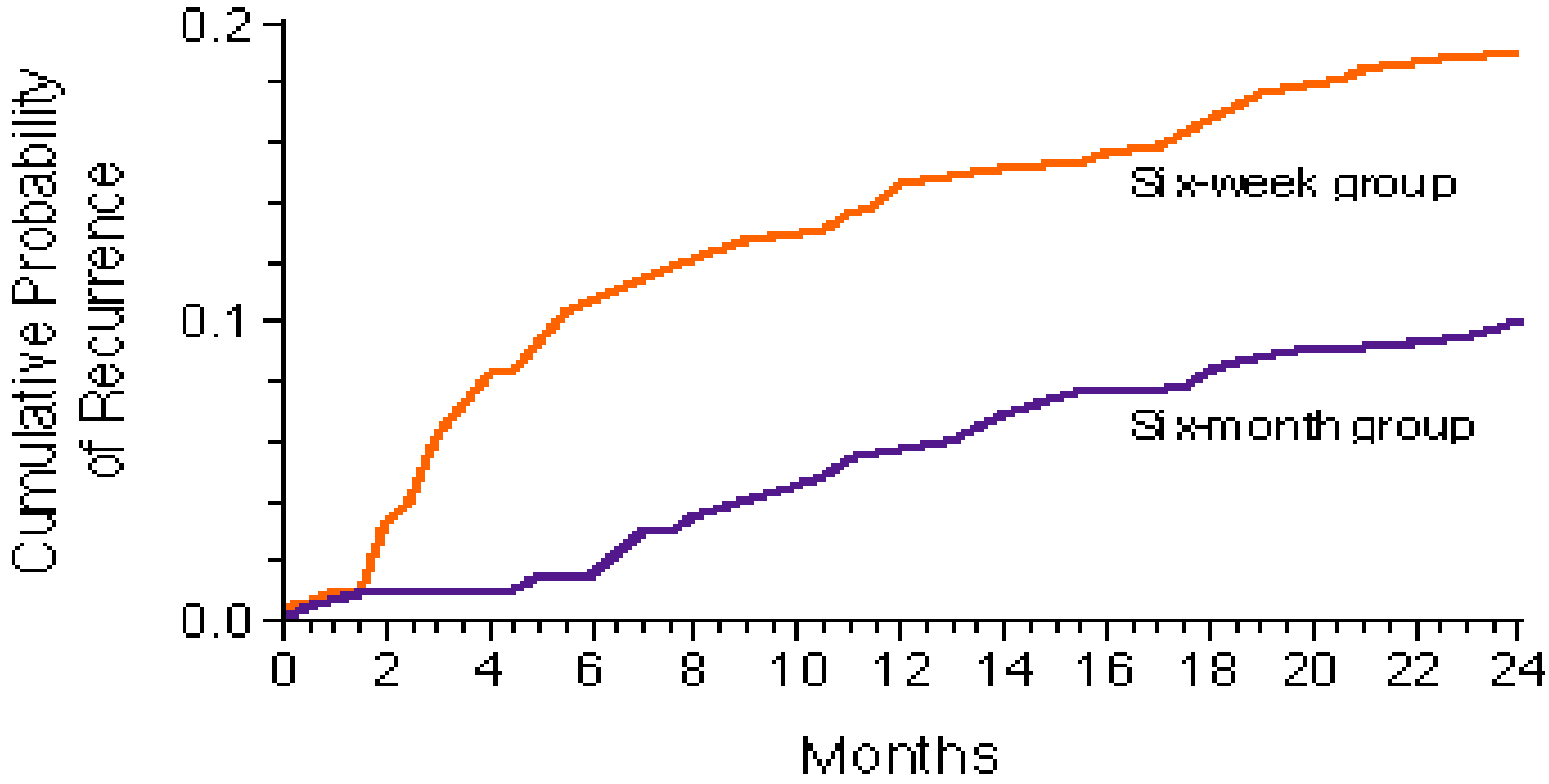
[c] Department of Medicine, McMaster University, Hamilton, Ontario, Canada

Table 3
Comparison between the rate of bleeding and Recurrent VTE in patients on DOACs vs VKA for extended VTE treatment.

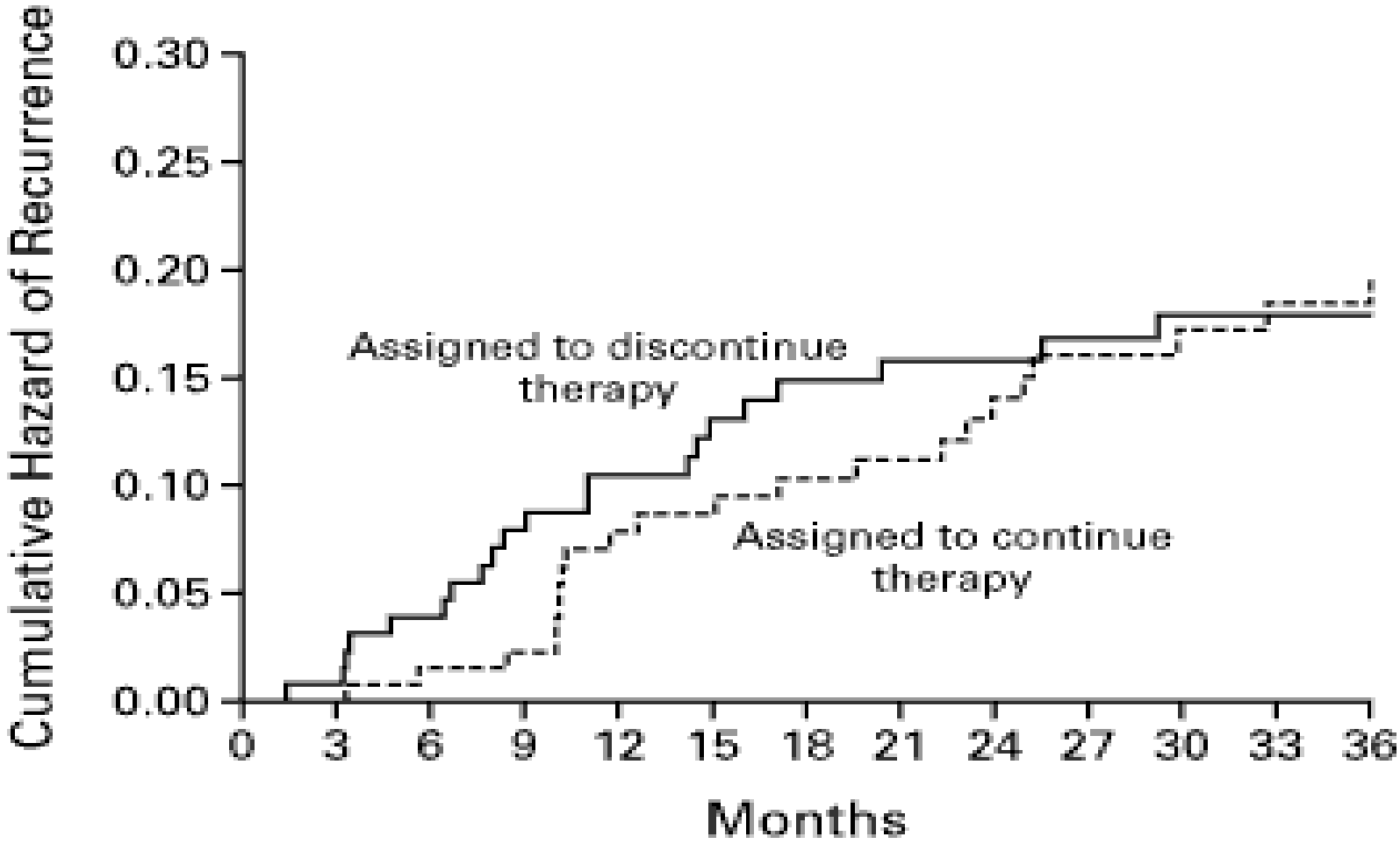
Incidence Rate Ratios	Major bleeding (95% CI)	Recurrent VTE (95% CI)	Fatal Bleeding (95% CI)	Fatal recurrent VTE (95% CI)	composite fatal bleeding and fatal recurrent VTE (95% CI)
DOACs versus VKA	0.35 (0.17-0.68, P = 0.0023)	0.88 (0.16-4.8, P = 0.88)	N/A*	1.1 (0.15-7.5, P = 0.95)	0.75 (0.22-2.7, P = 0.61)
DOACs versus placebo	1.7 (0.65-4.6, P = 0.28)	0.15 (0.08-0.25, P < 0.0001)	N/A*	0.48 (0.17-1.2, P = 0.1)	0.40 (0.14-1.0, P = 0.03)
VKA versus placebo	3.57 (1.7-7.7, P = 0.0012)	0.23 (0.08-0.67, P = 0.007)	0.29 (0.02-4.6, P = 0.38)	0.32 (0.06-1.1, P = 0.06)	0.54 (0.18-1.4, P = 0.18)
ASA versus placebo	1.66 (0.35-7.9, P = 0.52)	0.39 (0.17-0.88, P = 0.023)	N/A*	0.34 (0.04-1.5, P = 0.14)	0.29 (0.03-1.2, P = 0.08)

* : No case of fatal bleeding in the numerator; DOACs, direct oral anticoagulants; VKA: vitamin K antagonists; ASA: aspirin.

How long is the optimal duration of treatment ?



Schulman et al, N. Engl. J. Med. 1995



Agnelli et al, N. Engl. J. Med. 2001

3% major bleeding during the extended period of OAT

7th ACCP Conference
Chest 2004

- **For patients with a first VTE secondary to transient risk factors, OAT for 3 months over shorter periods is recommended.**

- **For patients with a first VTE idiopathic, OAT for at least 6 months to 12 months is recommended (indefinite OAT should be considered).**

8th ACCP Conference
Chest 2008

- **For patients with a first unprovoked proximal DVT or PE, and in whom risk factors for bleeding are absent and for whom good anticoagulant monitoring is achievable, long-term OAT is recommended (grade 1A).**
- **For patients with a first unprovoked distal DVT, 3 months of OAT are suggested to be sufficient (grade 2B).**

9th ACCP Conference
Chest 2012

- **In patients with a first VTE that is an unprovoked proximal DVT of the leg and who have a low or moderate bleeding risk, we suggest extended anticoagulant therapy over 3 months of therapy**
- **In patients who have a high bleeding risk, we recommend 3 months of anticoagulant therapy over extended therapy.**
- **For patients with a first unprovoked proximal DVT or PE, and in whom risk factors for bleeding are absent and for whom good anticoagulant monitoring is achievable, long-term OAT is recommended (grade 1A).**
- **For patients with a first unprovoked distal DVT, 3 months of OAT are suggested to be sufficient (grade 2B).**

8th – 9th ACCP Conference
Chest 2008 - 2012

- **In patients who receive long-term anticoagulant treatment, the risk-benefit ratio of continuing such treatment should be reassessed in the individual patient at periodic intervals**

“ For patients with idiopathic DVT, the benefit of extended treatment is partially offset during therapy by the risk of bleeding, particularly major bleeding, and the benefit is lost when treatment is withdrawn”
(Buller et al, Chest 2004; 126: 401S)

“ In 2016 duration of longterm treatment remains a challenge”
(Buller at the XXIV Congress of SISET, 2016)

Who is candidate for indefinite VKA treatment ?

Is inherited thrombophilia a risk factor for recurrent VTE ?

	Evidence	Clinical relevance
Absence of a temporary risk condition[7,14,15]	Strong	High
Pulmonary embolism or proximal deep vein thrombosis[6,16,17]	Strong	High
More than two thrombotic events[6,18]	Strong	Restricted (consider bleeding risk during prolonged anticoagulation)
Male sex[19,20]	Strong	High
Residual vein thrombosis[21,22]	Strong	Low
Vena cava filter[23]	Strong	High
Continued oestrogen use[24,25]	Strong	High
Cancer[26,27]	Strong (for early recurrence)	High
Post-thrombotic syndrome[24,28]	Moderate	Moderate
Overweight[29]	Weak	Low

Table 1: **Clinical features associated with high risk of recurrent venous thrombosis**

Kyrle et al, Lancet 2010

6th ACCP Conference - Chest 2001
Duration of therapy

3 to 6 mo	**First event with reversible risk**
> 6 mo	**Idiopathic VTE, first event**
12 mo to lifetime	**First event with cancer, APL, AT defect** **Recurrent event, idiopathic or with thrombophilia**

Unclear duration in first event with homozygous FVL, HyO, PC or PS defect, or multiple alterations; and in recurrent events with reversible risk factors

7th ACCP Conference
Chest 2004

- For patients with a first VTE who have two or more thrombophilic conditions OAT is recommended for 12 months and is suggested indefinitely.

- For patients with a first VTE who have documented deficiency of AT, PC, PS, or FVL or PT20210A, HyO, or high FVIII levels, OAT is recommended for 12 months and is suggested indefinitely.

SECONDARY PROPHYLAXIS OF INDEFINITE DURATION

(Consensus of the Italian Working Group on Inherited Thrombophilia, 2004)

➢ ***Absolute consensus:***

- **Patients with two or more idiopathic VTE events**
- **Patients with one idiopathic VTE event and presence of high-titre LAC/ACA, cancer, or multiple thrombophilic alterations**

➢ ***Partial consensus:***

- **Patients with one idiopathic VTE event and AT deficiency or homozygous thrombophilia**

- **Additional factors considered strong enough to modify duration of therapy after VTE are:**
- isolated calf DVT versus proximal DVT (relative risk, RR, approximately 0.5); one or more previous episodes of VTE (RR, approximately 1.5).

- **Other additional factors predicting the risk of recurrent VTE include:**
- negative d-dimer 1 month after withdrawal of VKA (RR, approximately 0.4);
- presence of antiphospholipid antibodies (APLA) (RR, approximately 2);
- inherited thrombophilia (RR, approximately 1.5);
- males vs females (RR, approximately 1.6);
- Asian ethnicity (RR, approximately 0.8);
- residual thrombosis in the proximal veins (RR, approximately 1.5).

ACCP Guidelines, Chest 2008 – Chest 2012

- The following factors may favor long-term anticoagulation in patients with a first unprovoked proximal DVT or PE:
- male gender;
- moderate-to-severe post-thrombotic syndrome;
- ongoing dyspnoea (possibly related to unresolved or recurrent PE);
- satisfactory initial anticoagulant control;
- elevated D-dimer result based on individual D-dimer assay performance characteristics using a study-validated assay

Guidance from the SSC of the ISTH, J Thromb Haemost 2012

Thrombophilia Testing for heritable thrombophilic defects does not usefully predict likelihood of thrombosis recurrence after a first episode of VTE and for this reason testing for heritable thrombophilia is not routinely required [21]. Testing for heritable thrombophilias in selected patients, such as those with a strong family history of unprovoked recurrent thrombosis, may influence decisions regarding duration of anticoagulation. However, it is not possible to give a validated guidance statement as to how such patients should be selected as a family history is a poor predictor of likelihood of identifying a heritable thrombophilic defect [22].

Guidance from the SSC of the ISTH, J Thromb Haemost 2012

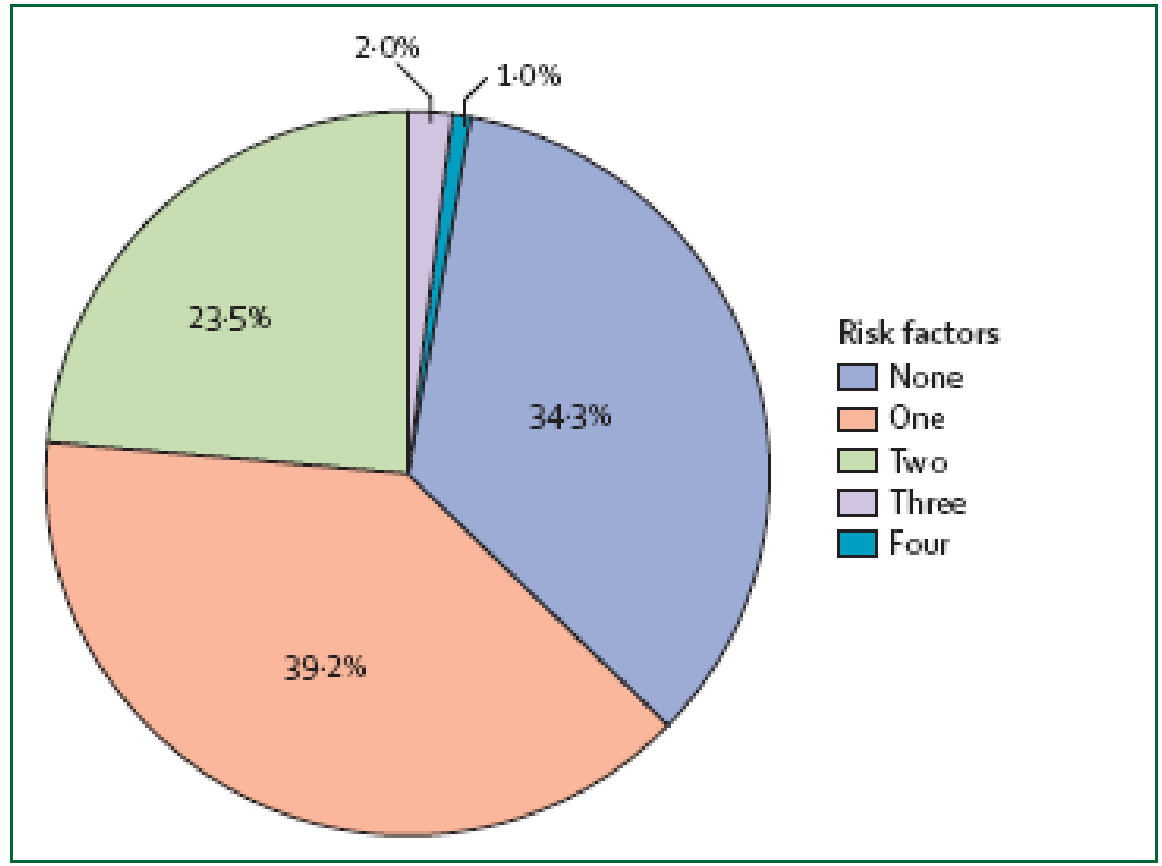


Figure 2: Number of risk factors identified by laboratory screening for thrombophilia in 158 patients without cancer with two episodes of unprovoked venous thrombosis

3 weeks after the incident event, patients were screened for deficiency of antithrombin, protein C, or protein S; presence of lupus anticoagulant, factor V Leiden, factor II G20210A; and high concentrations of homocysteine, factor VIII, or factor IX.

Kyrle et al, Lancet 2010

	Evidence	Clinical relevance
High concentrations of fibrinogen, factor VIII, or factor IX[24,51–55]	Strong	Uncertain
Hyperhomocysteinaemia[56,57]	Strong	Uncertain
Factor V Leiden[58–60]	Strong	None
Factor II G20210A (prothrombin mutation)[58–60]	Strong	None
High D-dimer[31,61–67]	Strong	To be confirmed
Increased generation of thrombin[68–71]	Strong	Uncertain
Partial deficiency of antithrombin, protein C, protein S, or tissue factor pathway inhibitor[24,72–76]	Weak	Uncertain
Phospholipid antibodies[46,47]	Weak	Uncertain
High concentrations of thrombin activatable fibrinolysis inhibitor[77]	To be confirmed	None
Single nucleotide polymorphisms (E-selectin gene polymorphism, heme oxygenase gene polymorphism)[78,79]	To be confirmed	None

Table 2: **Laboratory markers associated with increased risk of recurrent venous thrombosis**

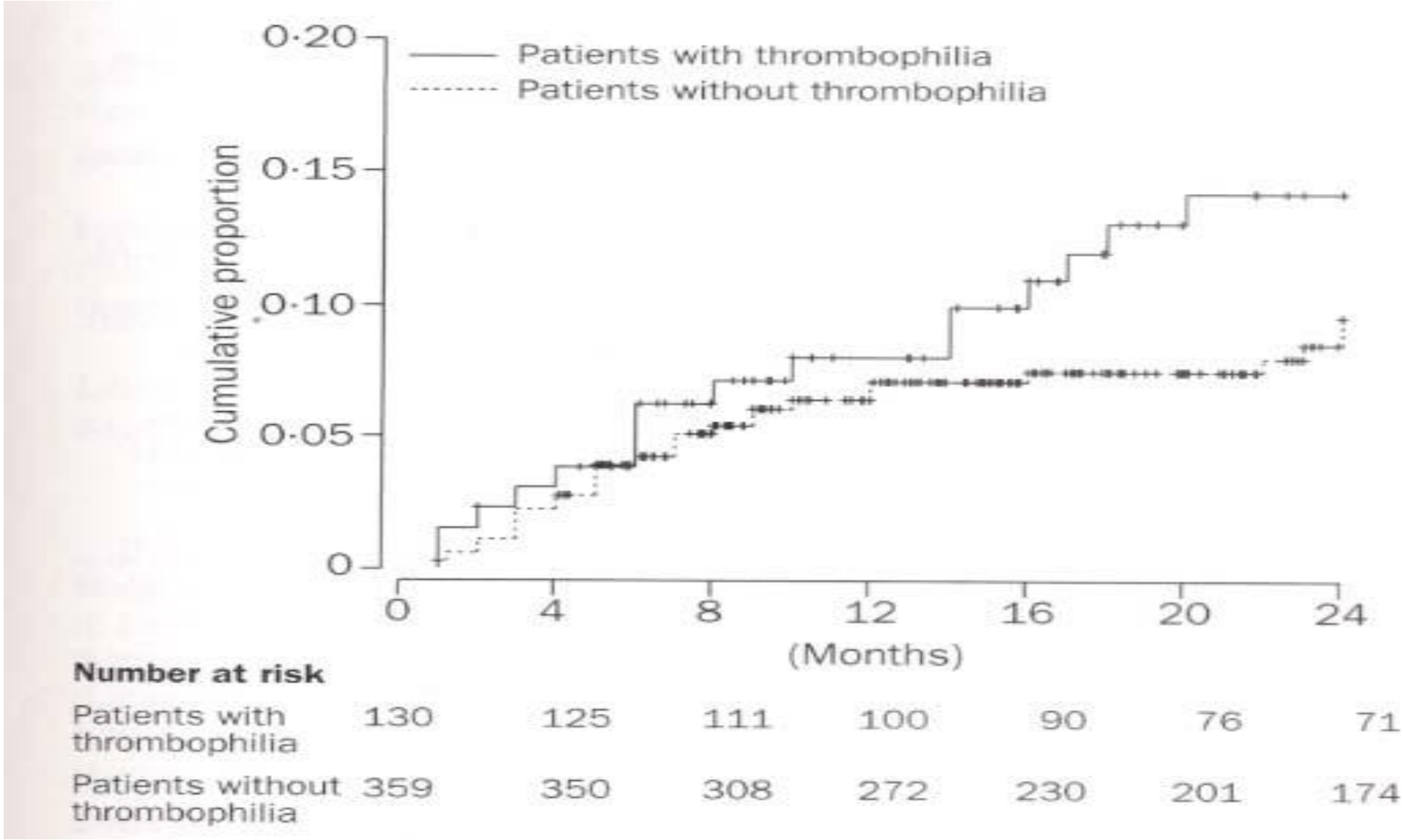
Kyrle et al, Lancet 2010

- There is no proof that thrombophilia screening helps patients, neither with regard to treatment of the acute event nor for prevention of recurrence.

- Routine screening for single laboratory markers should not be done in patients with a fi rst venous thrombosis for various reasons. Venous thrombosis has many causes and many patients have more than one abnormality, and the effect of combined defects on risk of recurrence is not known.

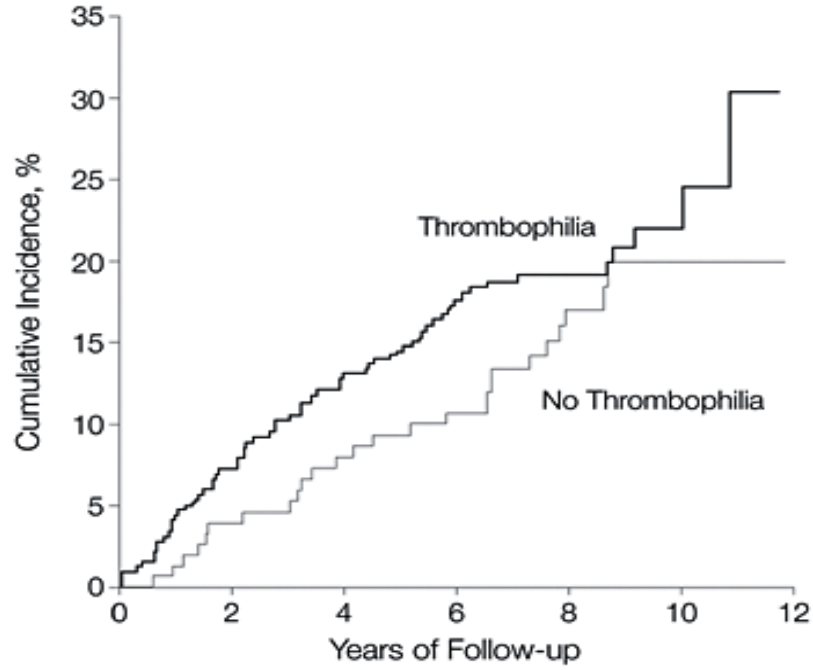
- A third of patients with recurrent unprovoked venous thrombosis have a normal test result. A negative finding from thrombophilia testing could therefore result in a false sense of safety for patients.

Kyrle et al, Lancet 2010



Baglin et al, Lancet 2003

Cumulative Incidence of Recurrent Thrombotic Events Patients with and without thrombophilia during the period from the end of the initial anticoagulation period (90 days) until January 1, 2000



No. at Risk

Thrombophilia	319	289	266	247	152	31
No Thrombophilia	155	146	137	131	81	20

Christiansen, S. C. et al. JAMA 2005;293:2352-2361.

Can inherited thrombophilia considered as a whole ?

Table 3 | Incidence of VTE in studies of families with thrombophilia

Reference (year)	Study information			Incidence of VTE per 100 person-years (where available, the relative risk vs noncarriers is in brackets)				
	Relatives/ carriers	Observation years	Antithrombin deficiency	Protein C deficiency	Protein S deficiency	FVL	PT20210A	Multiple defects
Prospective studies								
Pabinger (1994)[157]	93/44	211	NA	2.5	2.2	NA	NA	NA
Sanson (1999)[158]	735/208	611	4.0	1.0	0.7	NA	NA	NA
Middeldorp (2001)[159]	855/470	1,564	NA	NA	NA	0.58§	NA	NA
Simioni (2002)[160]	561/313	1,255	NA	NA	NA	0.67	NA	NA
Vossen (2005)[161]	575‡	3,283	1.7	0.7	0.8	0.1	NA	NA
Coppens (2006)[162]*	464/236	1,816	NA	NA	NA	NA	0.37§ (3.1)	NA
Mahmoodi (2010)[163]	382/149	3,472	2.29§ (10.2)	0.95§ (4.1)	1.55§ (9.6)	NA	NA	NA
Retrospective studies								
Lijfering (2009)[63]*	2,479/1,528	NA	1.77§ (28.2)	1.52§ (24.1)	1.90§ (30.6)	0.49§ (7.5)	0.34§ (5.2)	NA
Martinelli (1998)[164]*	723/396	NA	1.0 (8.1)	0.72 (7.4)	0.78 (10.4)	0.25 (4.6)	NA	NA
Middeldorp (1998)[165]	437/236	12,240	NA	NA	NA	0.45§ (4.2)	NA	NA
Bucciarelli (1999)[166]	513‡	19,542	1.07	0.54	0.50	0.30	NA	0.67
Simioni (1999)[167]	793/405	19,685	0.87 (10.6)‖	0.43 (10.6)‖	1.65 (10.6)‖	0.28 (2.8)	NA	NA
Lensen (2000)[168]	197/108	8,760	NA	NA	NA	0.34 (2.9)	NA	NA
Martinelli (2000)[169]*	1,093/640	43,208	NA	NA	NA	0.19 (2.9)	0.13 (2.0)	0.42 (6.4)
Tirado (2001)[170]	722/435	NA	2.94 (10.6)	0.36 (6.4)	1.04 (7.6)	0.31 (6.2)	0.23 (4.2)	NA
Bank (2004)[171]*	407/209	12,085	NA	NA	NA	NA	0.35 (1.9)	NA
Tormene (2004)[172]	294/152	8,347	NA	NA	NA	NA	0.11 (1.7)	NA
Brouwer (2006)[173]	468/224	4,174	1.94 (18.3)	1.58 (16.2)	1.50 (16.2)	NA	NA	NA
Couturaud (2006)[174]	553/322	17,532	NA	NA	NA	0.43 (2.5)	NA	NA
Rossi (2011)[175]	1,088/625	40,405	0.92 (12.8)	0.12 (5.1)‖	0.12 (5.1)‖	0.14 (2.3)¶	0.05 (0.6)¶	0.24/0.19/0.58#
Holzhauer (2012)[176]	533/146	18,278	2.82 (25.7)**	2.82 (25.7)**	2.82 (25.7)**	0.25 (1.7)	0.42 (2.6)	2.33 (19.6)

*Including probands with a history of VTE or arterial thrombosis. ‡Recruitment limited to carrier relatives of patients with VTE diagnosed with thrombophilia. §Observation period starting from 14–15 years of age. ‖Relative risk calculated on the total carriers of antithrombin, protein C, and protein S deficiencies. ¶Homozygotes excluded. #Incidence estimated in double heterozygotes for FVL and PT20210A, homozygotes for FVL or PT20210A, and in carriers of other multiple abnormalities. **Incidence for antithrombin, protein C, and protein S deficiencies combined.
Abbreviations: FVL, factor V Leiden; NA, data not available; PT, prothrombin; VTE, venous thromboembolism.

Martinelli, De Stefano & Mannucci, Nature Rev Cardiol 2014

Inherited thrombophilia and risk for venous thromboembolism (familial studies)

Thrombophilic abnormality	Risk (Odds Ratio)
AT deficiency	10.2 - 18.3 (28.2)
PC deficiency	4.1 - 16.2 (24.1)
PS deficiency	7.6 - 16.2 (30.6)
FV Leiden	2.5 - 7.5
PT G20210A	1.7 - 5.2
Combined alterations	6.4 (FVL + PT)

Reviewed in Rossi et al, Thromb Hemostas 2011

Are Factor V Leiden or Prothrombin G20210A risk factor for recurrent DVT ?

- Positive studies:

Miles et al, J Am Coll Cardiol 37,215,2001

Ridker et al, Circulation 92,2800,1995

Simioni et al, NEJM 336,399,1997

Simioni et al, Blood 96,3329,2000

Are Factor V Leiden or Prothrombin G20210A risk factors for recurrent DVT ?

- Negative studies:

De Stefano et al, NEJM 341,801,1999

De Stefano et al, BJH 113,630,2001

Eichinger et al, T & H 77,624,1997

Eichinger et al, T & H 81,14,1999

Lindmarker et al, T & H 81,684,1999

Margaglione et al, T & H 82, 1583, 1999

	Events/ patients	Factor V Leiden	Prothrombin mutation
Ho et al (2006)[58]	3104/2903	1·41 (1·14–1·75)	1·72 (1·27–2·31)
Marchiori et al (2007)[59]	3202/3208	1·39 (1·15–1·76)*	1·20 (0·89–1·61)*
Segal et al (2009)[60]	4730/3636	1·56 (1·14–2·12)	1·45 (0·96–2·21)

Data are number or odds ratio (95% CI), unless otherwise stated. *Risk ratio (95% CI).

Table 3: **Risk of recurrent venous thrombosis in patients with factor V Leiden or prothrombin mutation**

Kyrle et al, Lancet 2010

Thrombosis • Brief Report

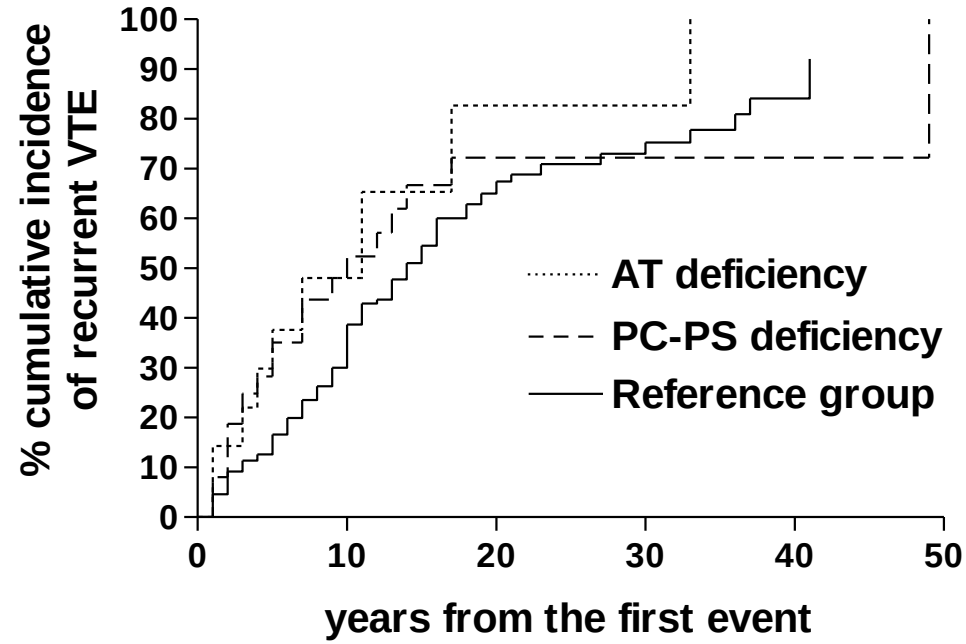
The risk of recurrent venous thromboembolism in patients with inherited deficiency of natural anticoagulants antithrombin, protein C and protein S

Valerio De Stefano
Paolo Simioni
Elena Rossi
Daniela Tormene
Tommaso Za
Antonio Pagnan
Giuseppe Leone

Few data are available on the risk of recurrent venous thromboembolism (VTE) associated with the rare inherited deficiencies of natural anticoagulants. We studied 602 patients with previous VTE: the incidence of first recurrence in the absence of anticoagulation was retrospectively estimated in 64 patients with deficiency of antithrombin (AT, n=14), protein C (PC, n=28), or protein S (PS, n=22) and 538 with no known defect, who acted as the reference group. After adjustment for sex, age, and circumstances of the first event, AT deficiency resulted an independent risk factor for recurrence (hazard ratio 1.9, 95% CI 1.0-3.9); the carriers of PC or PS deficiency had a marginal increase in risk (hazard ratio 1.4, 95% CI 0.9-2.2). In conclusion, patients with AT deficiency are potential candidates for long-term oral anticoagulation.

Key words: inherited thrombophilia, antithrombin deficiency, protein C deficiency, protein S deficiency, recurrent venous thromboembolism.

Haematologica 2006; 91:695-698



High long-term absolute risk of recurrent venous thromboembolism in patients with hereditary deficiencies of protein S, protein C or antithrombin

Jan-Leendert P. Brouwer[1]; Willem M. Lijfering[1]; Min Ki ten Kate[1]; Hanneke C. Kluin-Nelemans[1]; Nic J. G. M. Veeger[2]; Jan van der Meer[1]

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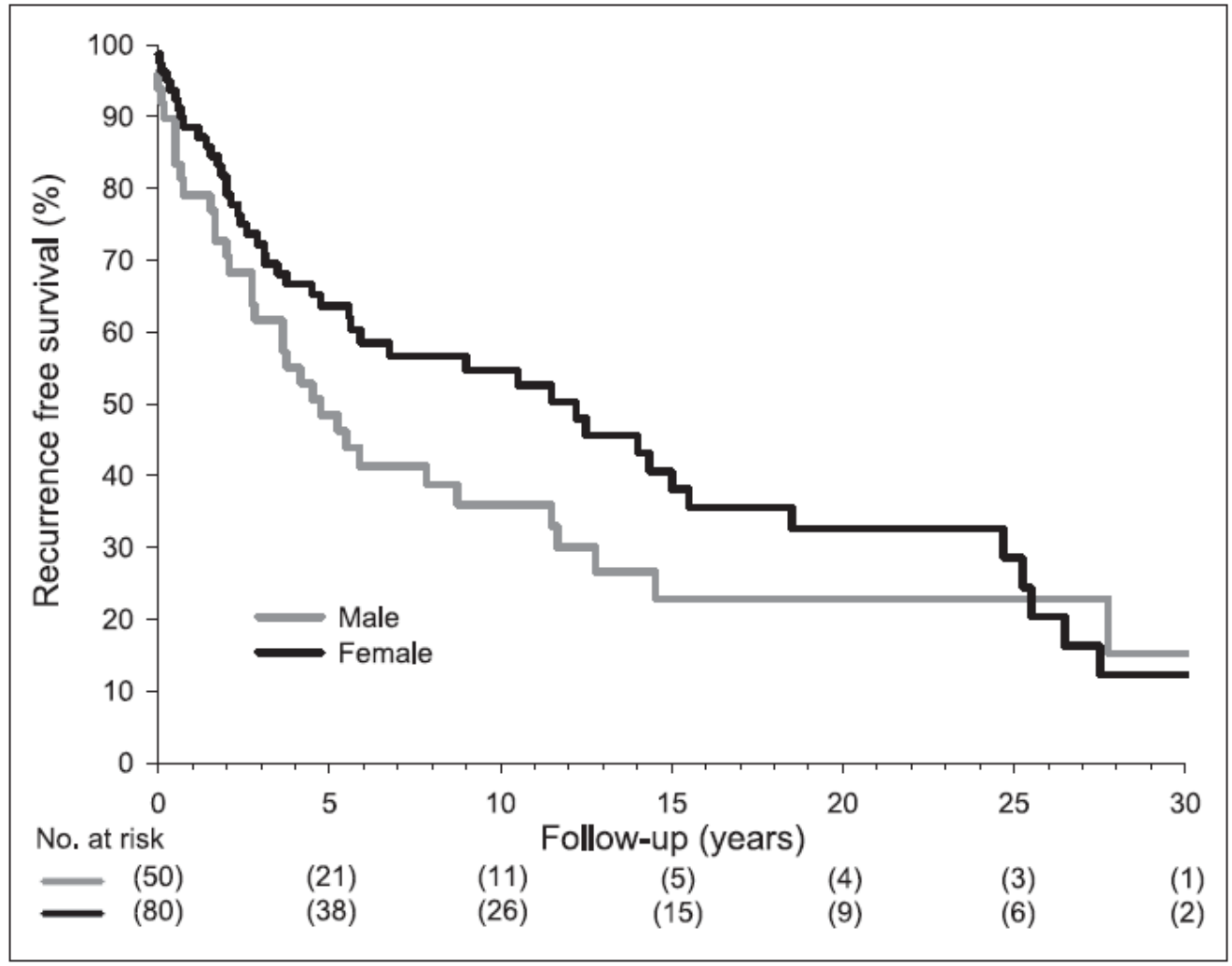
Summary

Hereditary deficiencies of protein S, protein C and antithrombin are known risk factors for first venous thromboembolism. We assessed the absolute risk of recurrence, and the contribution of concomitant thrombophilic defects in a large cohort of families with these deficiencies. Annual incidence of recurrence was estimated in 130 deficient patients, with separate estimates for those with each of protein S, protein C, and antithrombin deficiency, and in eight non-deficient patients with prior venous thromboembolism. All patients were also tested for factor V Leiden, prothrombin G20210A, high levels of factors VIII, IX and XI, and hyperhomocysteinemia. There were 81 recurrent events among 130 deficient patients. Median follow-up was 4.6 years. Annual incidences (95% confidence interval) of recurrent venous thromboembolism were 8.4% (5.8–11.7) for protein S deficiency, 6.0% (3.9–8.7) for protein C deficiency, 10.0% (6.1–15.4) for antithrombin deficiency, and overall 7.7% (6.1–9.5). Relative risk of recurrence in patients with a spontaneous versus provoked first event was 1.5 (0.95–2.3). Cumulative recurrence rates at 1, 5 and 10 years were 15%, 38% and 53%. Relative risk of recurrence with concomitant defects was 1.4 (0.7–2.6) (1 defect) and 1.4 (0.8–2.7) (≥2 defects). Annual incidence was 1.0% (0.03–5.5) in eight non-deficient patients. Annual incidence of major bleeding in deficient patients on oral anticoagulant treatment was 0.5% (0.2–1.0). We conclude that patients with a hereditary protein S, protein C or antithrombin deficiency appear to have a high absolute risk of recurrence. This risk is increased after a first spontaneous event, and by concomitance of other thrombophilic defects.

Keywords

Epidemiology, recurrent venous thromboembolism, thrombophilia

Thromb Haemost 2009; 101: 93–99



Brouwer et al, Thromb Haemost 2009

Incidence of recurrent VTE in the EPCOT study
Vossen et al, ATVB 2005

	n	Incidence rate % year (95% CI)
AT deficiency	**11**	**10.5 (3.8 – 22.8)**
PC deficiency	**37**	**5.1 (2.5 – 9.4)**
PS deficiency	**25**	**6.5 (2.8 – 11.8)**
FV Leiden	**79**	**3.5 (1.9 – 6.1)**
Multiple defects	**28**	**5.0 (2.0 – 10.3)**

Thrombosis Research 135 (2015) 923–932

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Regular Article

Natural anticoagulants deficiency and the risk of venous thromboembolism: a meta-analysis of observational studies

Matteo Nicola Dario Di Minno [a,b,*], Pasquale Ambrosino [a], Walter Ageno [c], Frits Rosendaal [d], Giovanni Di Minno [a], Francesco Dentali [c]

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Risk for recurrent VTE

Regular Article

Natural anticoagulants deficiency and the risk of venous thromboembolism: a meta-analysis of observational studies

Matteo Nicola Dario Di Minno [a,b,*], Pasquale Ambrosino [a], Walter Ageno [c], Frits Rosendaal [d], Giovanni Di Minno [a], Francesco Dentali [c]

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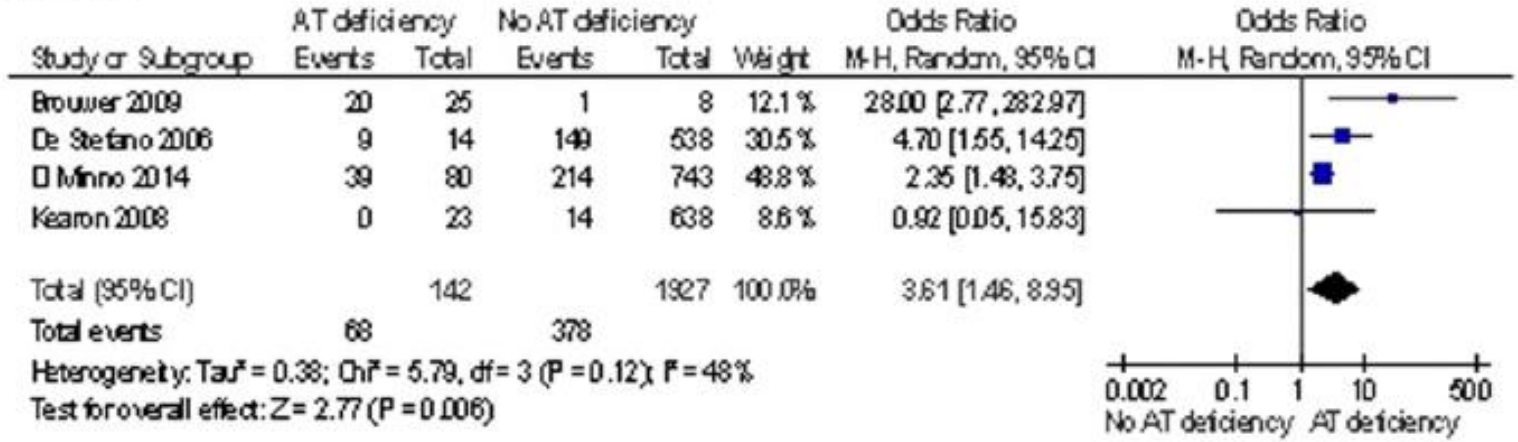
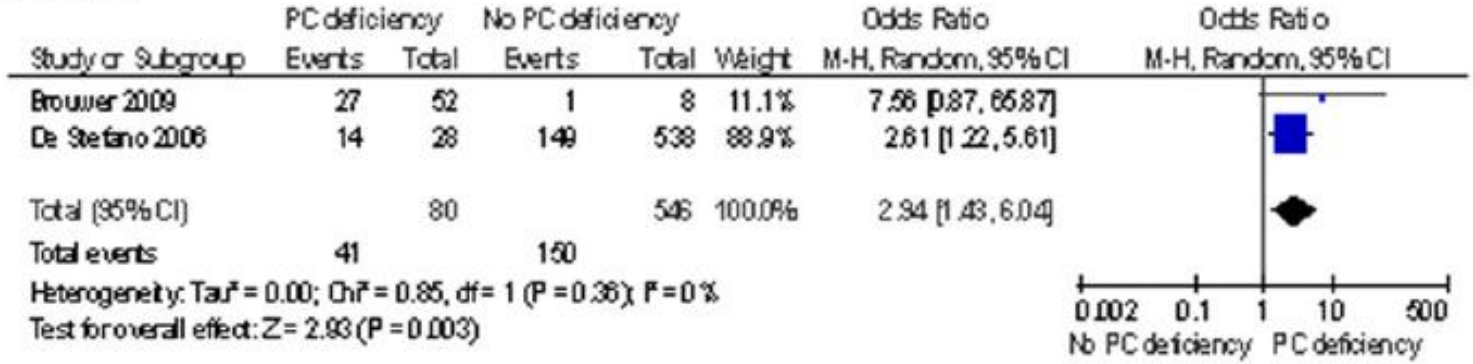
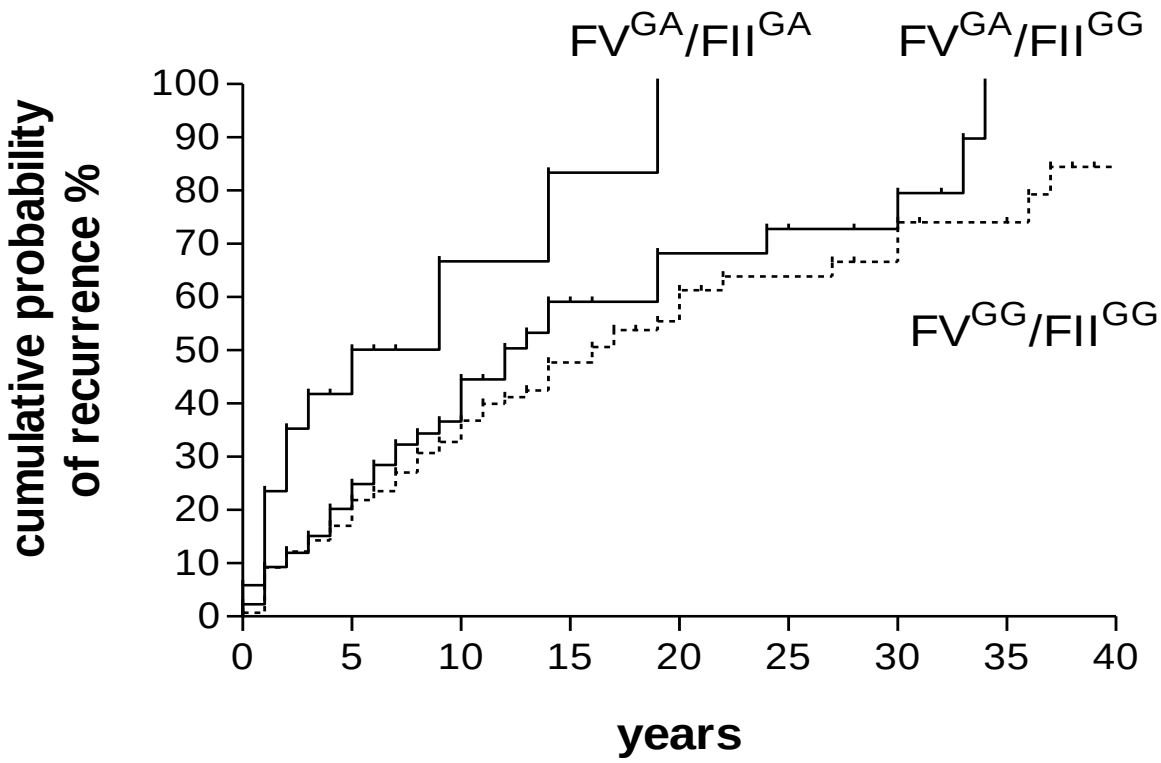
Panel B



Panel B





De Stefano et al, N. Engl. J. Med. 1999

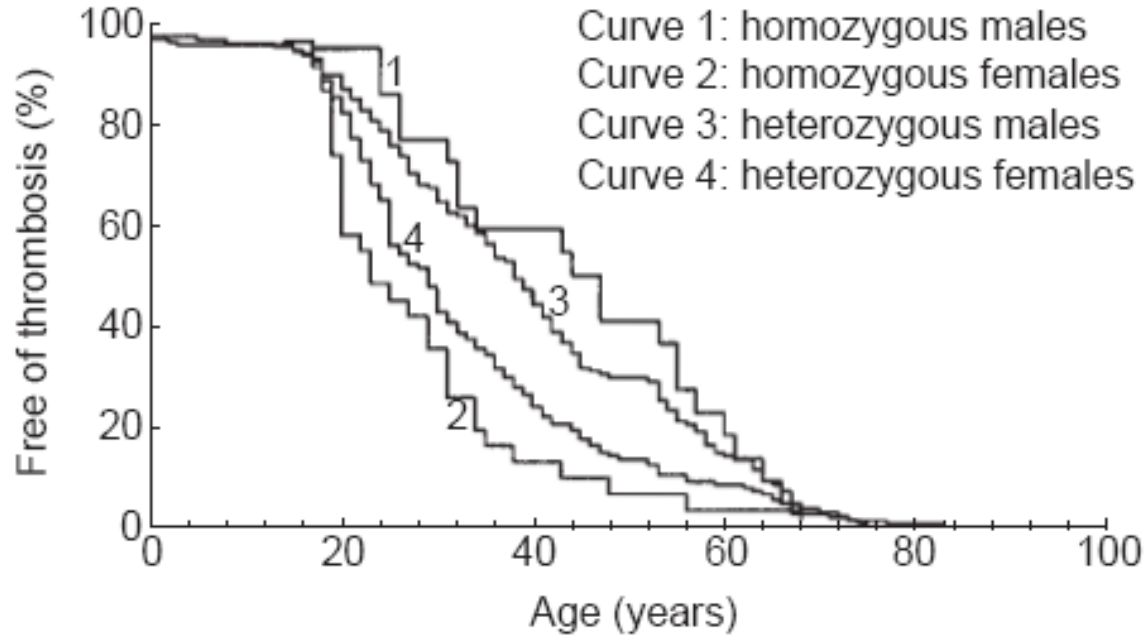


Figure 1. The probability of being free from thrombosis at a certain age (Kaplan–Meier analysis) for 59 homozygotes (25 males, 34 females) and 296 heterozygotes (142 males, 154 females) for the R506Q mutation. The Kaplan–Meier analysis has been carried out on symptomatic individuals. Difference between homozygous males and females was highly significant ($P < 0.001$).

Procare Group, Blood Coag Fibrinol 2000

Results We reviewed 7777 titles and included 46 articles. Heterozygosity (odds ratio [OR], 1.56; 95% confidence interval [CI], 1.14-2.12) and homozygosity (OR, 2.65; 95% CI, 1.2-6.0) for FVL in probands are predictive of recurrent VTE compared with individuals without FVL. Heterozygosity for FVL predicts VTE in family members (OR, 3.5; 95% CI, 2.5-5.0), as does homozygosity for FVL (OR, 18; 95% CI, 7.8-40) compared with family members of adults without FVL. Heterozygosity for prothrombin G20210A is not predictive of recurrent VTE in probands compared with individuals without prothrombin G20210A (OR, 1.45; 95% CI, 0.96-2.2). Evidence is insufficient regarding the predictive value of prothrombin G20210A homozygosity for recurrent VTE and the risk of VTE in family members of individuals with prothrombin G20210A. High-grade evidence supports that anticoagulation reduces recurrent VTE events in probands with either mutation. Low-grade evidence supports that this risk reduction is similar to that in individuals with a history of VTE and without mutations.

Segal et al, JAMA 2009

INHERITED THROMBOPHILIA AND RECURRENT VENOUS THROMBOSIS

Patients with severe thrombophilia (deficiency of natural anticoagulants, homozygous or multiple defects) are a minority and the associated risk is likely diluted in the overall cohort labeled as “thrombophilia”

Moreover, the number is too small to reach the statistical significance

Recurrence Rates for Prothrombotic Laboratory Abnormalities in 474 Patients

Table 4. Recurrence Rates for Prothrombotic Laboratory Abnormalities in 474 Patients

Abnormality	No. of Recurrences	Incidence Rate (95% CI)*	Hazard Ratio (95% CI)†	Hazard Ratio (95% CI)‡
Factor V Leiden	20	30 (18-46)	1.2 (0.7-1.9)	1.3 (0.8-2.1)
Prothrombin G20210A	4	19 (5-48)	0.7 (0.3-2.0)	0.7 (0.3-2.0)
Anticoagulant deficiency§‖	8	45 (19-88)	1.8 (0.9-3.7)	1.8 (0.9-3.8)
High factor ¶				
VIII (>166 IU/dL)	23	29 (18-43)	1.1 (0.7-1.8)	1.3 (0.8-2.1)
IX (>129 U/dL)	13	21 (11-36)	0.9 (0.5-1.7)	1.2 (0.6-2.1)
XI (>121 U/dL)	11	16 (8-29)	0.6 (0.3-1.1)	0.6 (0.3-1.1)
Hyperfibrinogenemia‖	22	38 (24-58)	1.6 (1.0-2.6)	1.7 (1.1-2.8)
Hyperhomocysteinemia#	14	23 (13-39)	0.9 (0.5-1.6)	0.9 (0.5-1.6)

Abbreviation: CI, confidence interval.
*Per 1000 patient-years.
†Relative to those without the abnormality (crude ratio).
‡Relative to those without the abnormality and adjusted for age, sex, and anticoagulation as a time-dependent covariate.
§Deficiency of protein C, protein S, or antithrombin.
‖Cut-off points: protein C: <0.67 (0.33) IU/mL; protein S: <0.67 (0.33) IU/mL; antithrombin: <0.80 U/mL; fibrinogen: >4.1 g/L.
¶Cut-off points are in parentheses.
#Cut-off points: homocysteine: >16.7 µmol/L (Leiden); 19.8 µmol/L (Amsterdam); 20.3 µmol/L (Rotterdam).

Christiansen, S. C. et al. JAMA 2005;293:2352-2361

JAMA

Recurrence Rate for Number of Prothrombotic Laboratory Abnormalities in 474 Patients

Table 3. Recurrence Rate for Number of Prothrombotic Laboratory Abnormalities in 474 Patients

	Abnormality			
	None	1	>1	Any
Incidence rate (95% CI)*	22 (14-32)	25 (17-37)	30 (21-42)	28 (22-36)
Hazard ratio (95% CI)†	Referrent	1.2 (0.7-2.0)	1.4 (0.8-2.3)	1.3 (0.8-2.0)
Hazard ratio (95% CI)‡	Referrent	1.2 (0.7-2.1)	1.6 (1.0-2.7)	1.4 (0.9-2.2)

Abbreviation: CI, confidence interval.
*Per 1000 patient-years.
†Relative to those without an abnormality (crude ratio).
‡Relative to those without an abnormality and adjusted for age, sex, and anticoagulation as a time-dependent covariate.

Christiansen, S. C. et al. JAMA 2005;293:2352-2361.

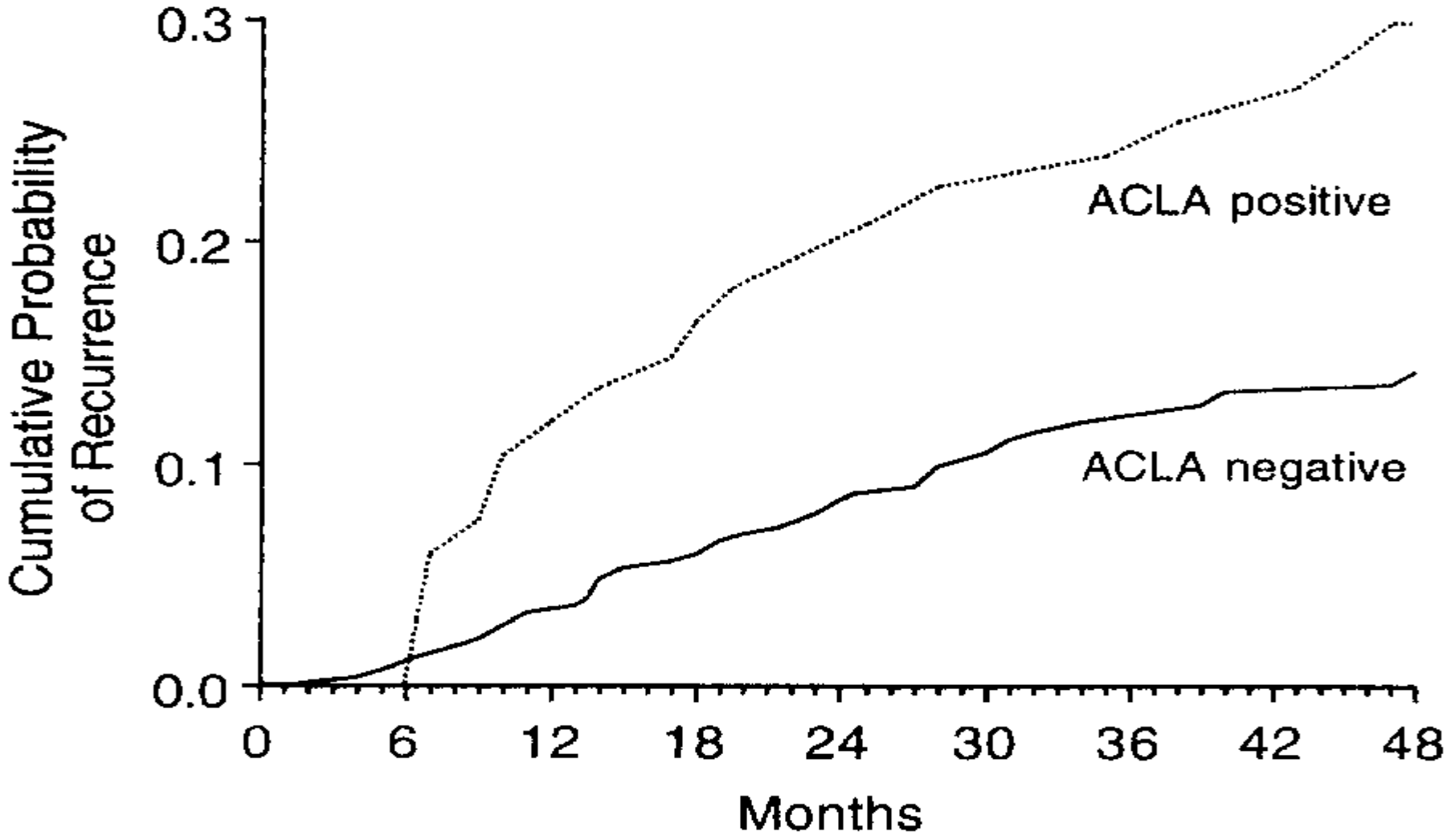
Christiansen, S. C. et al. JAMA 2005;293:2352-2361.

- Rarity of severe thrombophilia does not allow to obtain any firm conclusion about laboratory screening and clinical management

- This prompted many experts to adopt a negative position about this issue

- Indeed, at least 10% of patients with venous thromboembolism are carriers of severe thrombophilia and have a risk for recurrence at least doubled.

Antiphospholipid Antibodies



Schulman et al, Am. J. Med. 1998

Study or Subgroup	APLA Events	APLA Total	No APLA Events	No APLA Total	Weight	Risk Ratio M-H, Random, 95% CI
Ginsberg 1995	2	11	6	34	5.1%	1.03 [0.24, 4.39]
Kearon 1999	4	6	12	71	13.5%	3.94 [1.83, 8.48]
Kearon 2004	1	17	6	124	2.7%	1.22 [0.16, 9.49]
Rodger 2008	56	384	31	235	25.0%	1.11 [0.74, 1.66]
Schulman 2006	38	116	194	694	30.1%	1.17 [0.88, 1.56]
Taliani 2009	3	6	76	291	12.3%	1.91 [0.84, 4.36]
Wahlander 2005	5	48	49	465	11.3%	0.99 [0.41, 2.36]
Total (95% CI)		**588**		**1914**	**100.0%**	**1.41 [0.99, 2.00]**
Total events	109		374			

Heterogeneity: Tau² = 0.08; Chi² = 10.96, df = 6 (P = 0.09); I² = 45%

Test for overall effect: Z = 1.92 (P = 0.06)

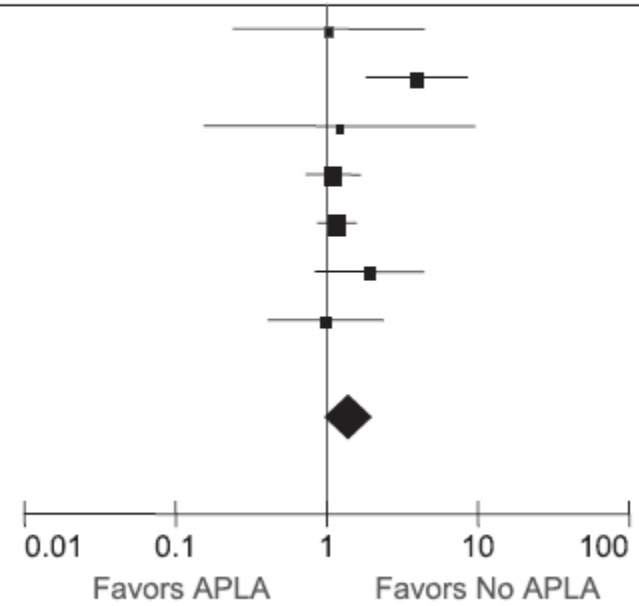


Figure 2. Relative risks for recurrent VTE after stopping anticoagulant therapy with APLA vs without APLA. M-H, Mantel–Haenszel.

Study or Subgroup	Lupus Anticoagulant Events	Total	No APLA Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Ginsberg 1995	2	9	6	34	46.3%	1.33 [0.22, 8.08]
Kearon 1999	2	3	12	71	24.5%	9.83 [0.82, 117.35]
Kearon 2004	1	7	6	124	29.2%	3.28 [0.34, 31.74]
Total (95% CI)		**19**		**229**	**100.0%**	**2.83 [0.83, 9.64]**
Total events	5		24			

Heterogeneity: Tau² = 0.00; Chi² = 1.66, df = 2 (P = 0.44); I² = 0%

Test for overall effect: Z = 1.66 (P = 0.10)

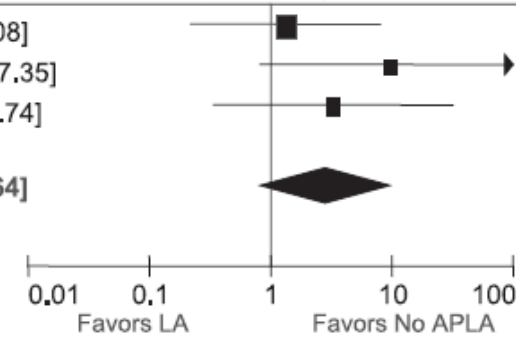


Figure 4. Relative risks for recurrent VTE after stopping anticoagulant therapy with an LA vs without APLA. M-H, Mantel–Haenszel.

Study or Subgroup	ACLA positive Events	Total	No APLA Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Kearon 1999	2	3	12	71	26.1%	3.94 [1.52, 10.22]
Schulman 2006	38	116	194	694	45.7%	1.17 [0.88, 1.56]
Wahlander 2005	5	48	49	465	28.2%	0.99 [0.41, 2.36]
Total (95% CI)		**167**		**1230**	**100.0%**	**1.53 [0.76, 3.11]**
Total events	45		255			

Heterogeneity: Tau² = 0.26; Chi² = 6.29, df = 2 (P = 0.04); I² = 68%

Test for overall effect: Z = 1.18 (P = 0.24)

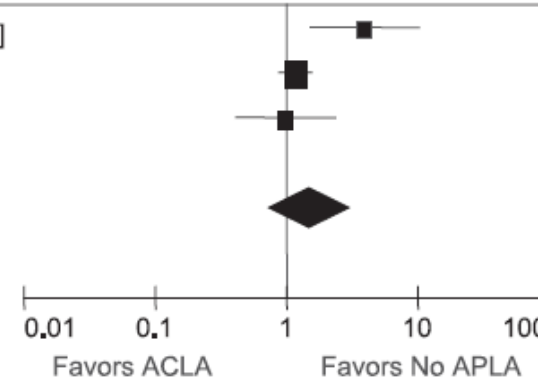


Figure 3. Relative risks for recurrent VTE after stopping anticoagulant therapy with ACLA vs without APLA. M-H, Mantel–Haenszel.

Journal of Thrombosis and Haemostasis, **8**: 237–242 DOI: 10.1111/j.1538-7836.2009.03674.x

IN FOCUS

Clinical course of high-risk patients diagnosed with antiphospholipid syndrome

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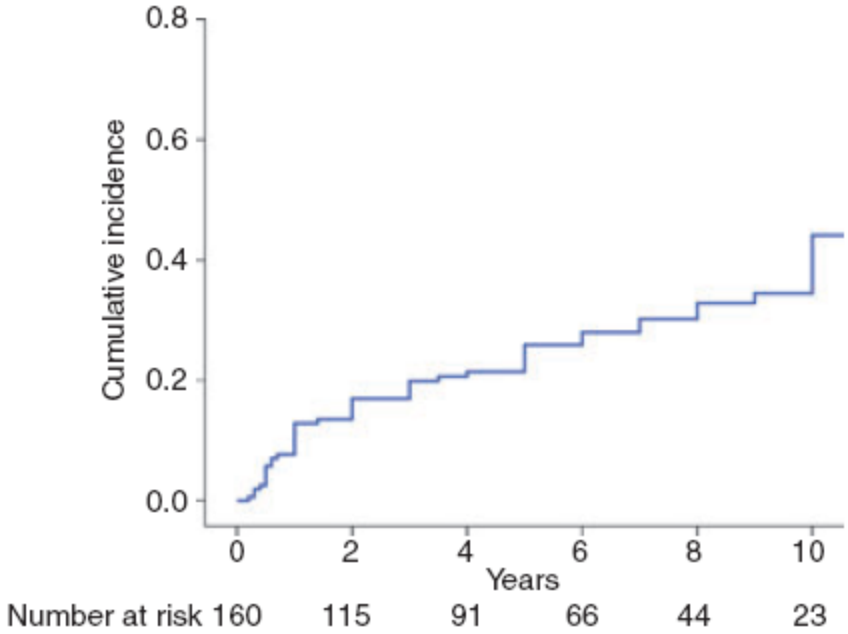


Fig. 1. Cumulative incidence of thromboembolic events [25 venous thromboembolism (VTE) and 30 arterial thromboembolism (ATE)] in 160 patients with antiphospholipid syndrome (APS) and triple laboratory positivity (figure reports data of 10-years follow-up).

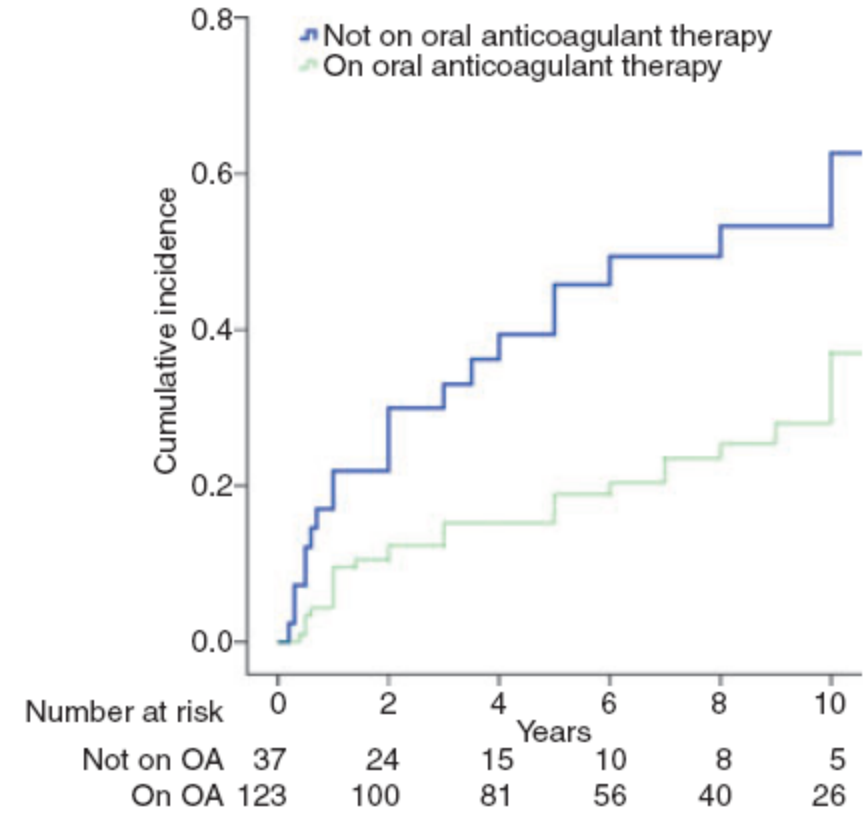


Fig. 3. Cumulative incidence of thromboembolic events in patients with antiphospholipid syndrome (APS) and triple laboratory positivity according to treatment with oral anticoagulants during follow-up (OA, oral anticoagulants).

Risk factors could produce a prediction score ?

Table 1: Models to predict recurrent VTE.

	Men continue and HER D002 (44)	Vienna Prediction Model (45)	DASH-score (46)
Study design	Prospective cohort	Prospective cohort	Patient level meta-analysis
Patients	646	929	1818
Predictive variables	Men: none Women: • age ≥ 60 years • signs of PTS • BMI ≥ 30 kg/m^2 • D-dimer > 250 µg/l during anticoagulation	• Sex • Location of first VTE • D-dimer after anticoagulation	• Abnormal D-dimer after anticoagulation • Age < 50 years • Male sex • Hormonal therapy
Increased risk of recurrent VTE	>1 point	> 180 points (according to a nomogram)	> 1 point
Recurrence rate in patients at low risk	1.6% (95% CI, 0.3–4.6)	4.4% (95% CI, 2.7–6.2)	3.1% (95% CI, 2.3–3.9)

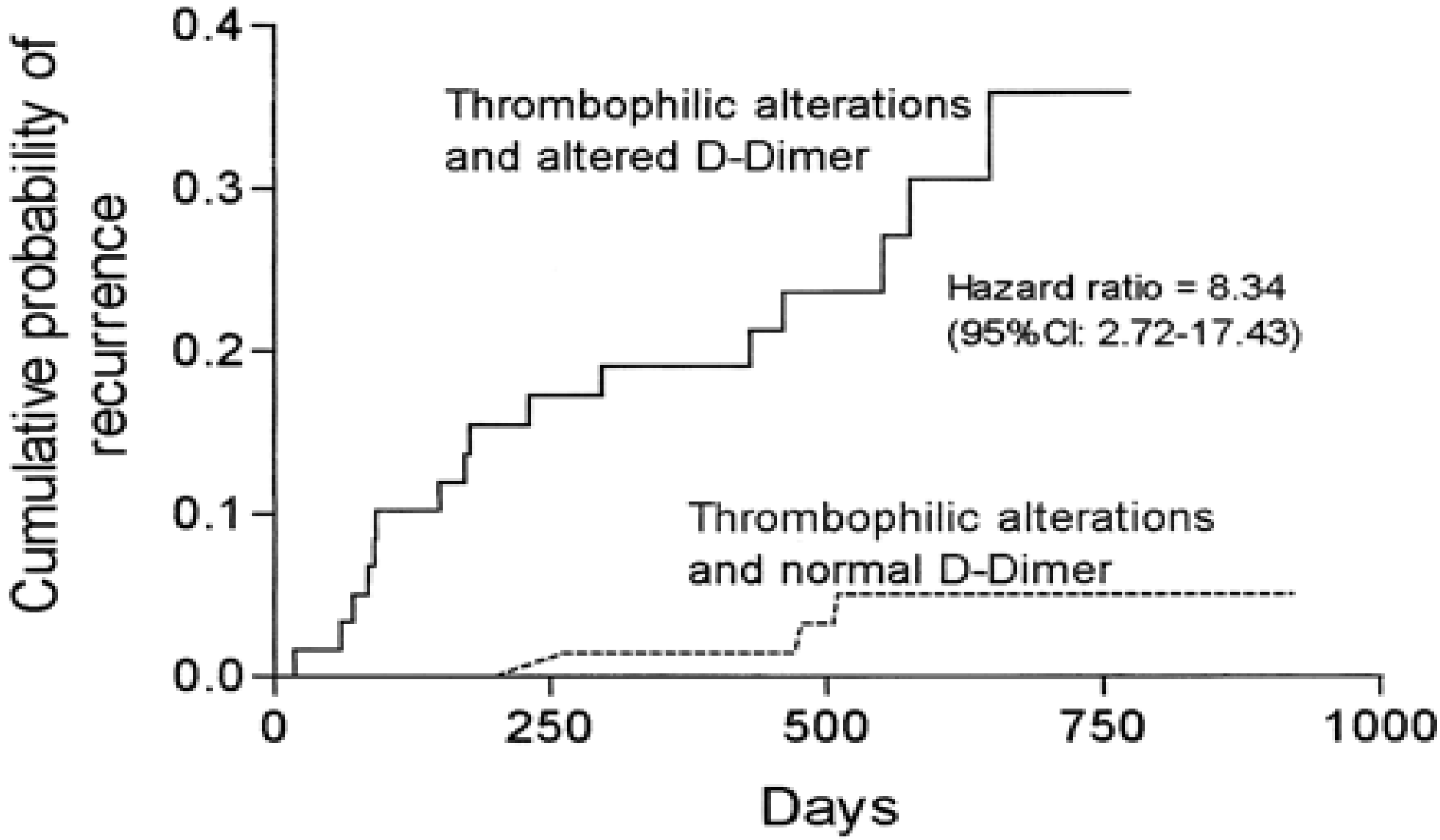
Thromb Hemostas 2015

Conclusions ?

- **Additional factors considered strong enough to modify duration of therapy after VTE are:**
- isolated calf DVT versus proximal DVT (relative risk, RR, approximately 0.5); one or more previous episodes of VTE (RR, approximately 1.5).

- **Other additional factors predicting the risk of recurrent VTE include:**
- negative d-dimer 1 month after withdrawal of VKA (RR, approximately 0.4);
- **presence of antiphospholipid antibodies (APLA) (RR, approximately 2);**
- **inherited thrombophilia (RR, approximately 1.5);**
- males vs females (RR, approximately 1.6);
- Asian ethnicity (RR, approximately 0.8);
- residual thrombosis in the proximal veins (RR, approximately 1.5).

ACCP Guidelines, Chest 2008 – Chest 2012



Palareti et al, Circulation 2003

CASO CLINICO – FAM 6/21

- Femmina, 42 anni
- Figlio di 17 anni con TVP + EP e diagnosi di difetto di AT tipo I
- Viene identificata per indagine familiare

- La mutazione è TGG>TGA con stop codon in posizione 307

CASO CLINICO 4 – (2)

- In anamnesi:
- 25 anni preeclampsia prima gravidanza
- 30 anni seconda gravidanza (ASA)
- 36 anni terza gravidanza TVP femorale sn alla 33a settimana.
- Ha effettuato TAO fino a 37 anni.

- All’epoca risultava un difetto di AT in cartella ma la paziente non è stata informata.
- Doppler attuale: ricanalizzazione completa a sinistra

CASO CLINICO 4 – (3)

- Viene deciso di non effettuare ripresa TAO

- Un anno dopo dopo viaggio in camper di 12 ore

  TFS safena sn, con testa del trombo a 2 cm dallo sbocco in VFC. D-D 1206. Dubbio su nuovo evento a livello VFS.

- Clexane 6000 U x 2 s.c. e TAO fino a ?

CASO CLINICO 4 – (4)

- Sospende TAO dopo 3 mesi
- Dopo sospensione D-Dimero nei limiti
- Doppler: sindrome post-trombotica VFS (risalente al primo episodio e misconosciuta in precedenza) e poplitea. Insufficienza safena.

CASO CLINICO 4 – (5)

- Dopo 4 mesi dalla sospensione TAO trombosi safena interna gamba sinistra dopo un viaggio (non profilassato)
- Clexane 8000 U x 2 s.c. e TAO fino a ?

CASO CLINICO 4 – (6)

- Dopo 3 mesi sospensione TAO
- Dopo un mese dalla sospensione TFS safena interna sinistra
- Riprende Clexane 8000 U x 2 e TAO.
- Si valuta per safenectomia

CASO CLINICO 4 – (7)

- Dopo un mese di TAO INR 2.01 e D-dimero 442
- Torna dopo 5 giorni: INR 2.61 e D-dimero 312
- Doppler: TFS safena in ricalizzazione

- Si invia comunque in PS per modica dispnea.
- TAC: microembolia polmonare
- Ecocardiogramma: n.d.p.

- TAO a tempo indeterminato