

3° CONVEGNO DI ANTICOAGULAZIONE.it

ANTICOAGULAZIONE

Attualità cliniche e di laboratorio.
Aspetti sociali

BOLOGNA 25-26 GENNAIO 2018
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PROGRAMMA



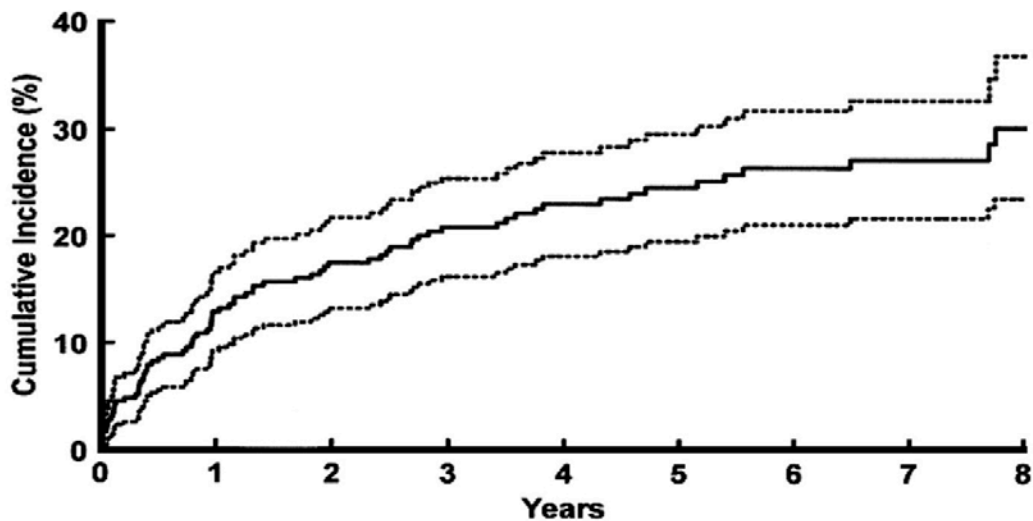
Trombofilia e Tromboembolismo Venoso Ricorrente

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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

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 probability at 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



Regular Article

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

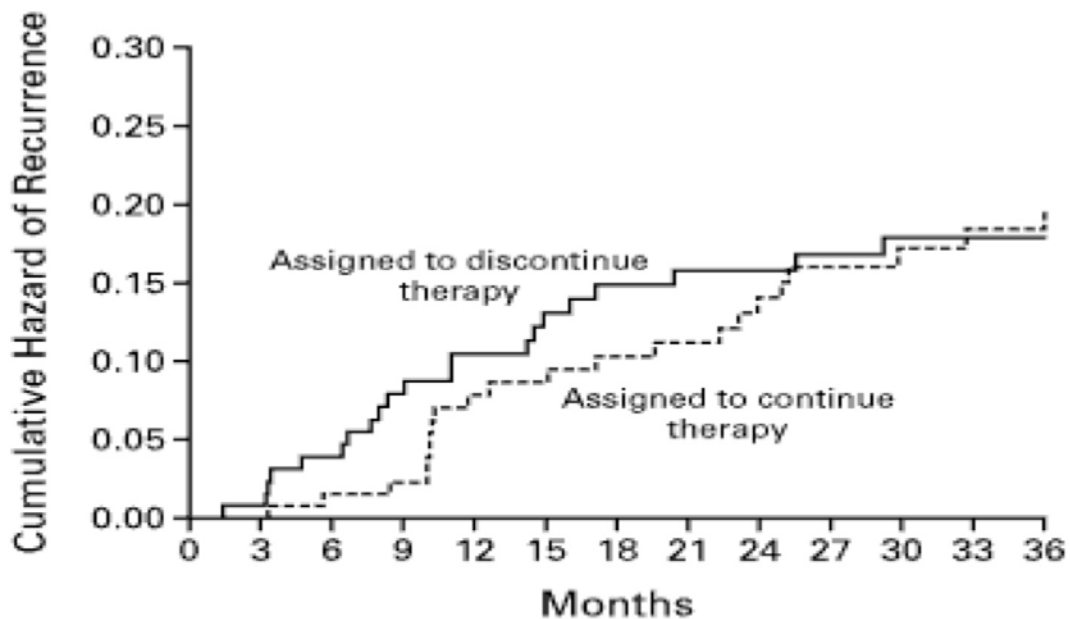
Cynthia Wu ^{a,*}, Ghazi S. Alotaibi ^a, Khalid Alsaleh ^b, Lori-Ann Linkins ^c, M. Sean McMurtry ^a^a Department of Medicine, University of Alberta, Edmonton, Alberta, Canada^b Department of Medicine, King Saud University, Riyadh, Saudi Arabia^c Department of Medicine, McMaster University, Hamilton, 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 ?



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).

9th ACCP Conference updated Chest 2016

9. In patients with a first VTE that is an unprovoked proximal DVT of the leg or PE and who have a (i) low or moderate bleeding risk (see text), we suggest extended anticoagulant therapy (no scheduled stop date) over 3 months of therapy (Grade 2B), and (ii) high bleeding risk (see text), we recommend 3 months of anticoagulant therapy over extended therapy (no scheduled stop date) (Grade 1B).

Remarks: Patient sex and D-dimer level measured a month after stopping anticoagulant therapy may influence the decision to stop or extend anticoagulant therapy (see text). In all patients who receive extended anticoagulant therapy, the continuing use of treatment should be reassessed at periodic intervals (eg, annually).

- “ 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)

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

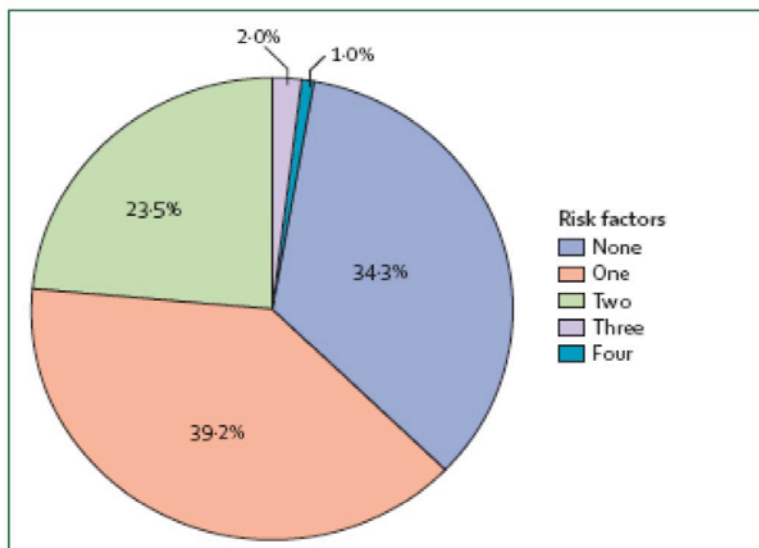


Figure 2: Number of risk factors identified by laboratory screening for thrombophilia in 158 patients without cancer with two episodes of unprovoked venous thrombosis

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

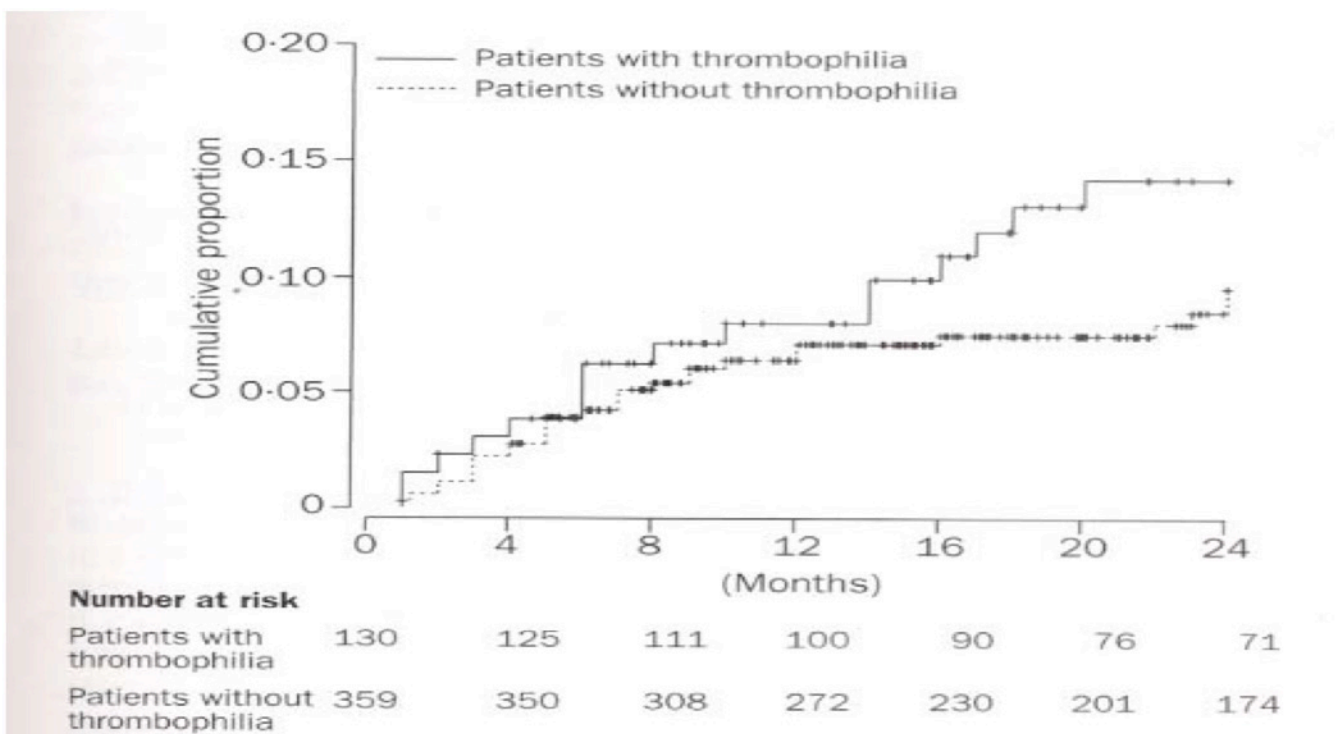
	Evidence	Clinical relevance
High concentrations of fibrinogen, factor VIII, or factor IX ^{24,51-55}	Strong	Uncertain
Hyperhomocysteinaemia ^{56,57}	Strong	Uncertain
Factor V Leiden ⁵⁸⁻⁶⁰	Strong	None
Factor II G20210A (prothrombin mutation) ⁵⁸⁻⁶⁰	Strong	None
High D-dimer ^{31,61-67}	Strong	To be confirmed
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

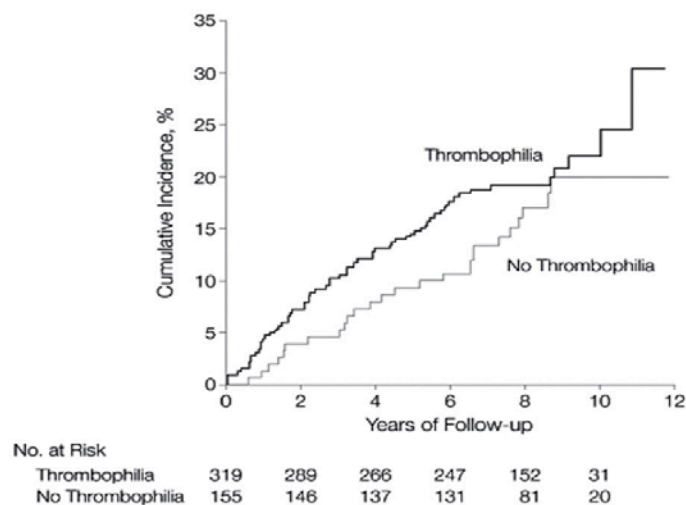
- There is no proof that thrombophilia screening helps patients, neither with regard to treatment of the acute event nor for prevention of recurrence.
- Routine screening for single laboratory markers should not be done in patients with a first venous thrombosis for various reasons. Venous thrombosis 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



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

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JAMA

Risk of recurrent VTE

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Table 1 The impact of thrombophilia on the risk of recurrent VTE

Study	Patients	Duration of follow up (months)	Thrombophilia Number of affected patients/total patients (%; 95 % CI)	Recurrent VTE (hazard ratio [95 % CI])
Baglin et al. [1]	570 first VTE	24	FVL 77/487 (16 %; 12.6–19.1) F2 20/476 (4 %; 2.6–6.4) AT 8/485 (2 %; 0.7–3.2) PC 5/431 (1 %; 0.4–2.7) PS 27/428 (6 %; 4.2–9.1)	15 % versus 10 % (HR 1.50 [0.82–2.77])
Christiansen et al. [4]	474 first DVT	87	FVL 92/474 (19 %) F2 29/474 (6 %) AT, PC, PS deficiency 25/474 (5 %) F8 110/474 (23 %) F9 86/474 (18 %) F11 92/474 (19 %) Fib 87/474 (18 %) HC 83/474 (18 %)	28 versus 22 per 1000 pt.-years. (HR 1.4 [0.9–2.2])
Prandoni et al. [2]	1626 first VTE	50	FVL 111/953 (11.6 %) F2 45/953 (4.7 %) AT 7/953 (0.7 %) PC 16/953 (1.7 %) PS 14/953 (1.5 %) LA 23/953 (2.4 %)	HR 2.02 (1.52–2.69)
Santamaria et al. [8]	267 first proximal DVT	47	FVL 15 (7.7 %) F2 14 (7.2 %) AT 3 (1.5 %) PC 2 (1.0 %) PS 2 (1.0 %) APS 4 (2.1 %) HC 7 (3.6 %)	HR 1.78 (1.002–3.14)
Ribierio et al. [9]	378 first VTE	43	FVL 37 (10 %) F2 20 (6 %) F8 47 (14 %) HC 13 (4 %) ABO Non-O 190 (73 %)	IRR 1.6 (0.5–5.5)

Streiff, J Thromb Thrombolys 2015

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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
<i>Prospective studies</i>								
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
Middelcorp (2001) ¹⁵⁹	855/470	1,564	NA	NA	NA	0.58 ^g	NA	NA
Simioni (2002) ¹⁶⁰	561/313	1,255	NA	NA	NA	0.67	NA	NA
Vossen (2005) ¹⁶¹	575 ^h	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 ^h (3.1)	NA
Mahmoodi (2010) ¹⁶³	382/149	3,472	2.29 ^h (10.2)	0.95 ^h (4.1)	1.55 ^h (9.6)	NA	NA	NA
<i>Retrospective studies</i>								
Lijfering (2009) ^{63*}	2,479/1,528	NA	1.77 ^h (28.2)	1.52 ^h (24.1)	1.90 ^h (30.6)	0.49 ^h (7.5)	0.34 ^h (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
Middelcorp (1998) ¹⁶⁵	437/236	12,240	NA	NA	NA	0.45 ^h (4.2)	NA	NA
Bucciarelli (1999) ¹⁶⁶	513 ^h	19,542	1.07	0.54	0.50	0.30	NA	0.67
Simioni (1999) ¹⁶⁷	793/405	19,685	0.87 (10.6) ^h	0.43 (10.6) ^h	1.65 (10.6) ^h	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) ^h	0.12 (5.1) ^h	0.14 (2.3) ^f	0.05 (0.6) ^g	0.24/0.19/0.58 ^g
Holzhauser (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. ^gObservation period starting from 14-15 years of age. ^hRelative risk calculated on the total carriers of antithrombin, protein C, and protein S deficiencies. ^fHomozygotes excluded. ^gIncidence 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



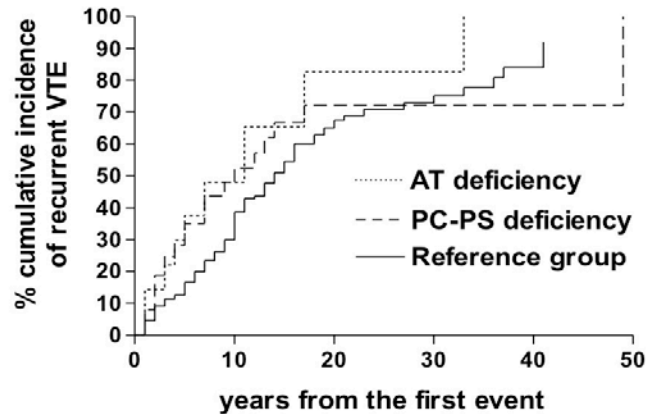
The risk of recurrent venous thromboembolism in patients with inherited deficiency of natural anticoagulants antithrombin, protein C and protein S

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

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Summary

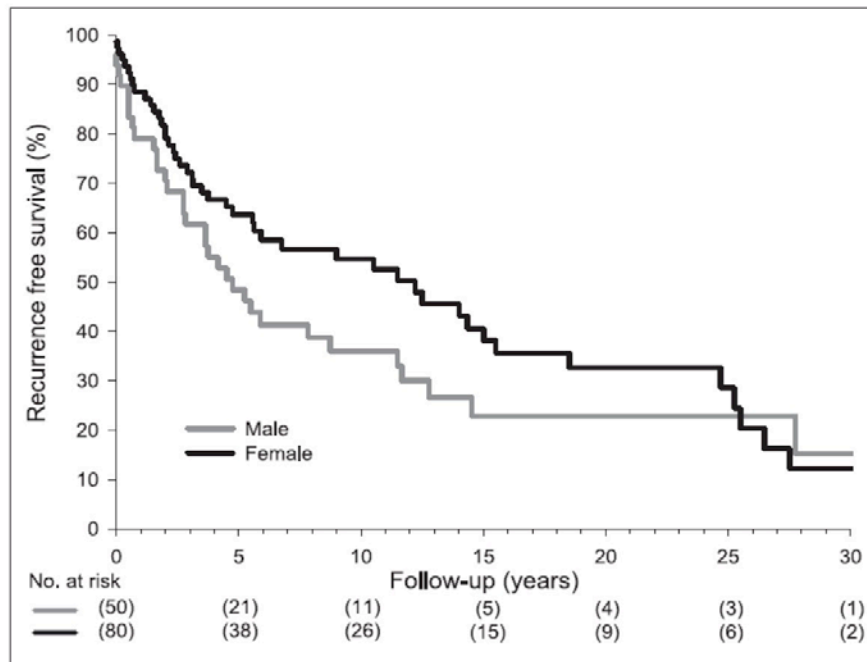
Hereditary deficiencies of protein S, protein C and antithrombin are known risk factors for first venous thromboembolism. We assessed the absolute risk of recurrence, and the contribution of concomitant thrombophilic defects in a large cohort of families with these deficiencies. Annual incidence of recurrence 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 defi-

ciency, 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)



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Regular Article

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



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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



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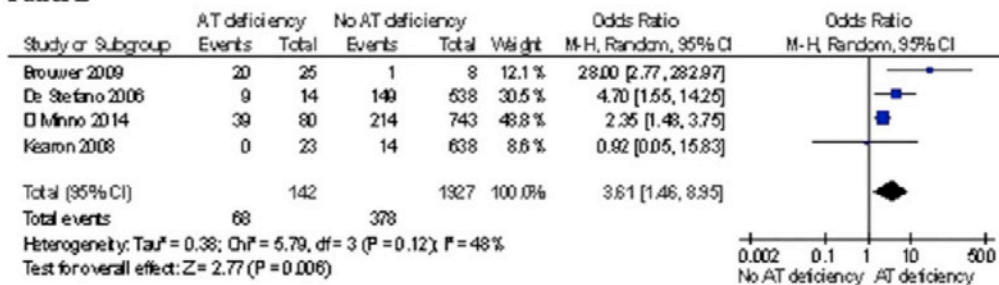
^a Department of Clinical Medicine and Surgery, Reference Centre for Coagulation Disorders, Federico II University, Naples, Italy

^b Unit of cell and molecular biology in cardiovascular diseases, Centro Cardiologico Monzino, IRCCS, Milan, Italy

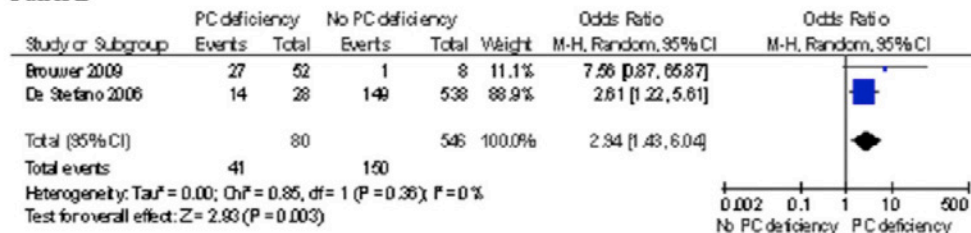
^c Department of Clinical and Experimental Medicine, University of Insubria, Varese, Italy

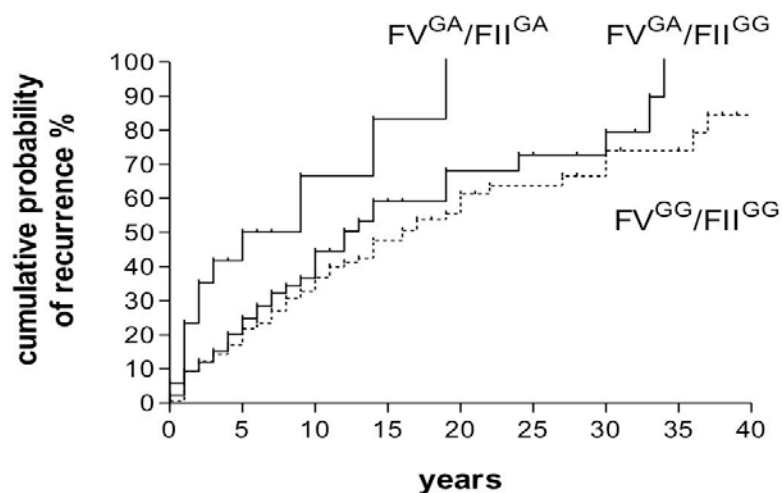
^d Department of Thrombosis and Hemostasis, Leiden University, Leiden, The Netherlands

Panel B



Panel B





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

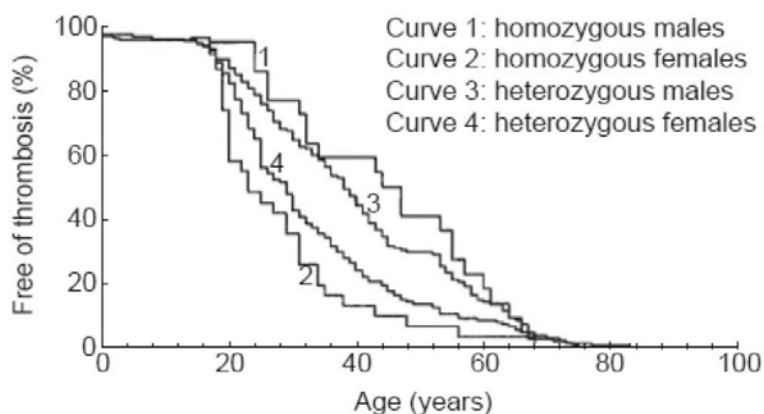


Figure 1. The probability of being free from thrombosis at a certain age (Kaplan–Meier analysis) for 59 homozygotes (25 males, 34 females) and 296 heterozygotes (142 males, 154 females) for the R506Q mutation. The Kaplan–Meier analysis has been carried out on symptomatic individuals. Difference between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

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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)†	Referent	1.2 (0.7-2.0)	1.4 (0.8-2.3)	1.3 (0.8-2.0)
Hazard ratio (95% CI)‡	Referent	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.

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- 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.

Risk factors could produce a prediction score ?

Table 1: Models to predict recurrent VTE.

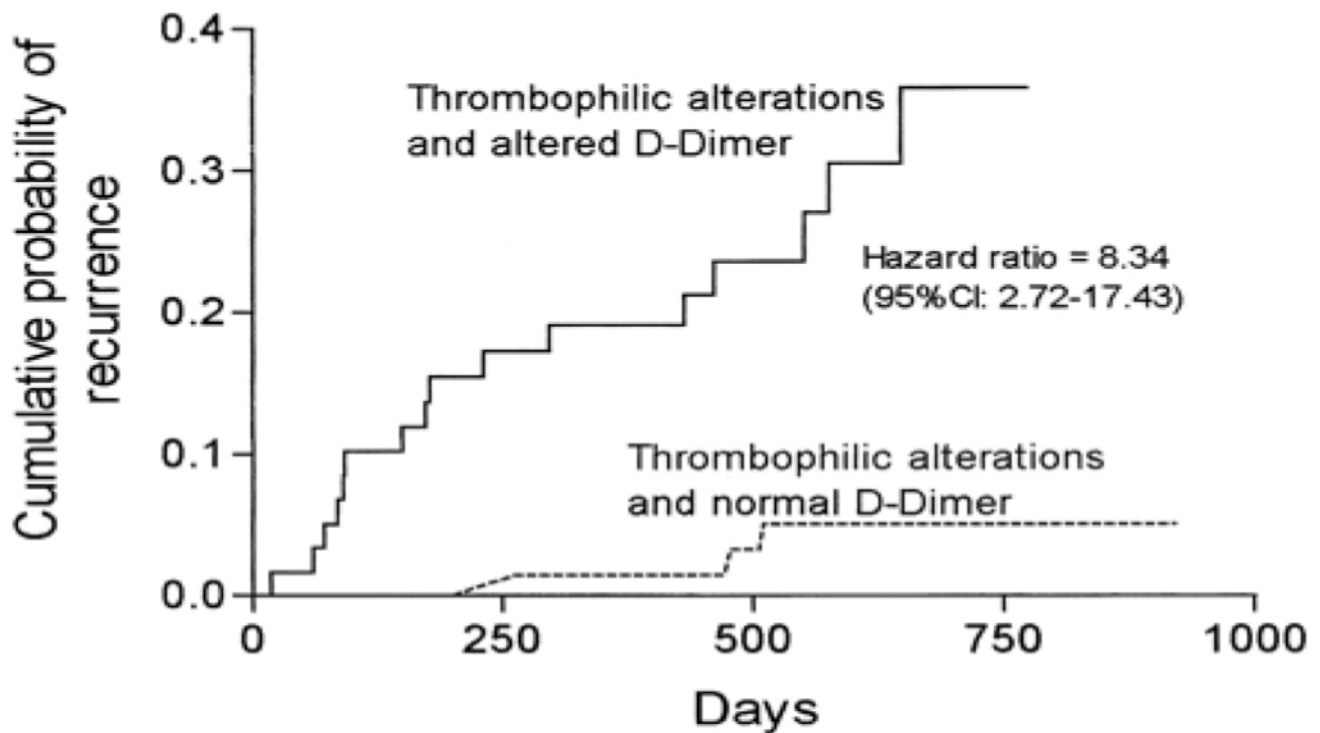
	Men continue and HER D002 (44)	Vienna Prediction Model (45)	DASH-score (46)
Study design	Prospective cohort	Prospective cohort	Patient level meta-analysis
Patients	646	929	1818
Predictive variables	Men: none Women: <ul style="list-style-type: none"> • age ≥ 60 years • signs of PTS • BMI ≥ 30 kg/m² • D-dimer > 250 µg/l during anticoagulation 	<ul style="list-style-type: none"> • Sex • Location of first VTE • D-dimer after anticoagulation 	<ul style="list-style-type: none"> • 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