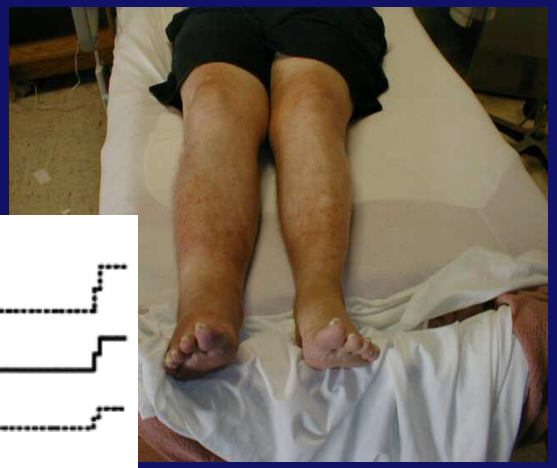
LEIDEN UNIVERSITY MEDICAL CENTER

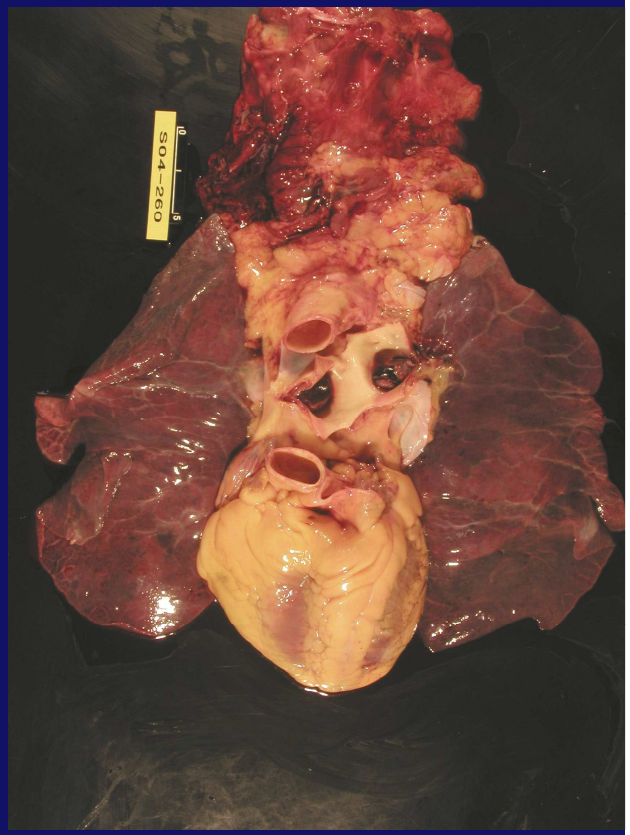
Klinische implicaties van trombofilie

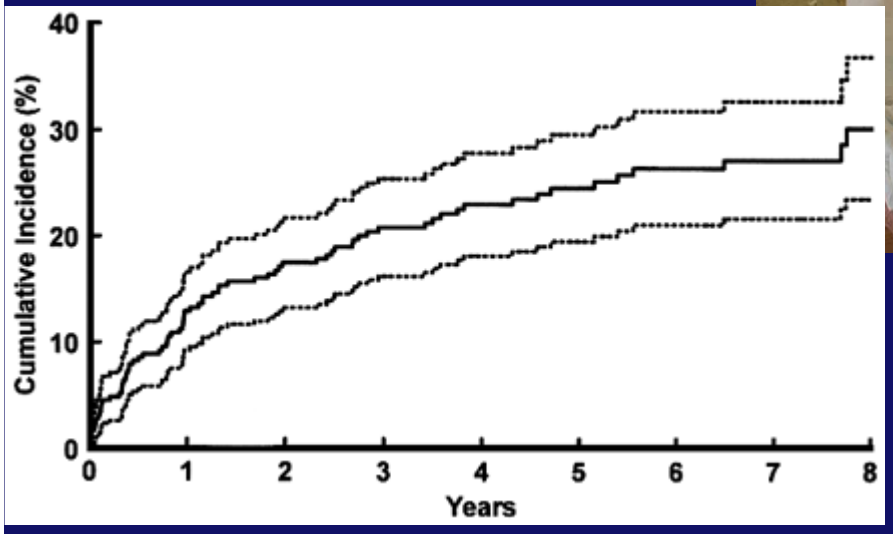
Saskia Middeldorp, M.D.

Venous thrombosis and pulmonary embolism

- 35,000 patients per year in The Netherlands
- 25-50% postthrombotic syndrome
- 25-30% recurs in the next 10 years
- Case fatality rate 5%







Hereditary thrombophilia

Increases the risk for venous thrombosis	RR
• Deficiencies of natural anticoagulants	8-10
• antithrombin, protein C, protein S	
• Gain of function mutations	3-7
• factor V Leiden (FVL, APC resistance)	
• prothrombin 20210A mutation	
• Elevated plasma levels of coagulation factors	4-5
• factor VIII:c	

Slightly associated with pregnancy complications

No association with arterial diseases

Objectives of testing

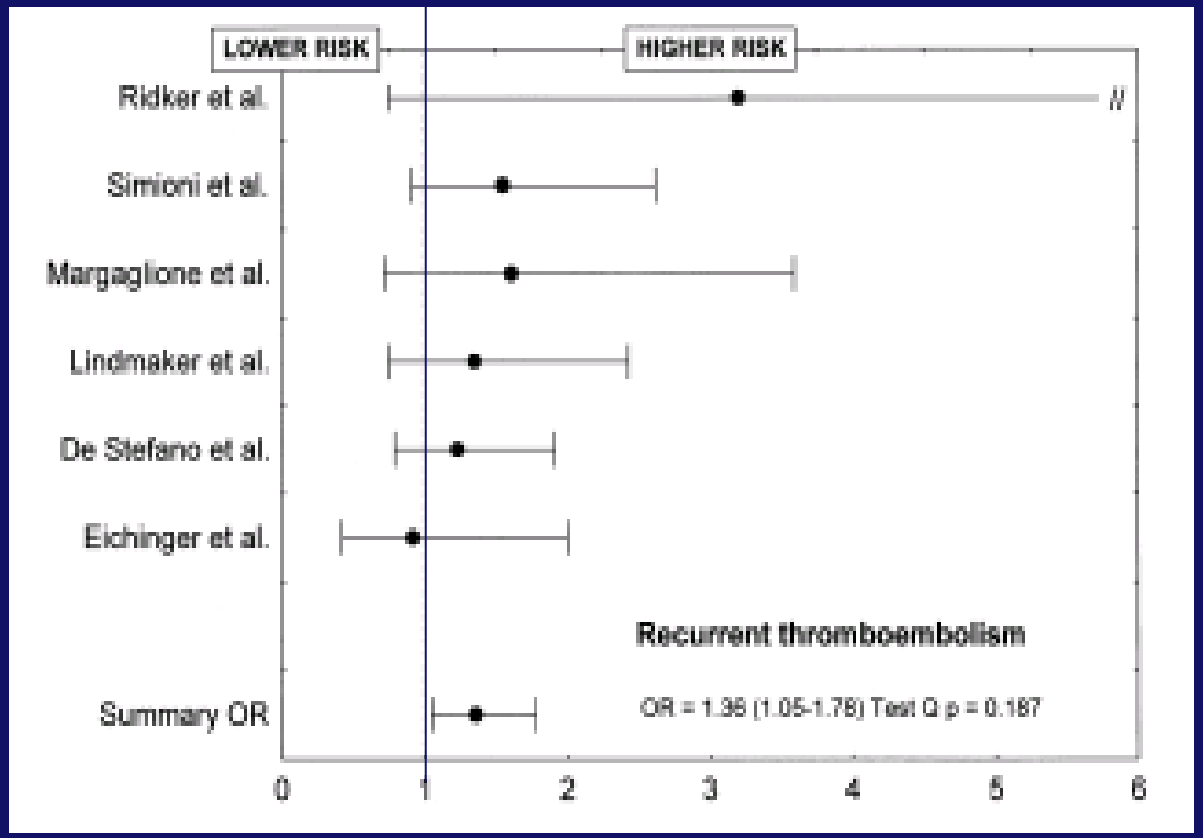
- (To have an explanation)
- To reduce morbidity and mortality

  In patients with venous thrombosis or pulmonary embolism
  - Modified treatment
  - Modified prophylaxis during high risk situations
  - Other preventive measures

  Primary prevention in relatives

Middeldorp NTvG 2001; Cohn Sem Thromb Haemost 2007

Thromphilia and the risk of recurrent VTE



Factor V Leiden:

OR 1.4 (1.1-1.8)

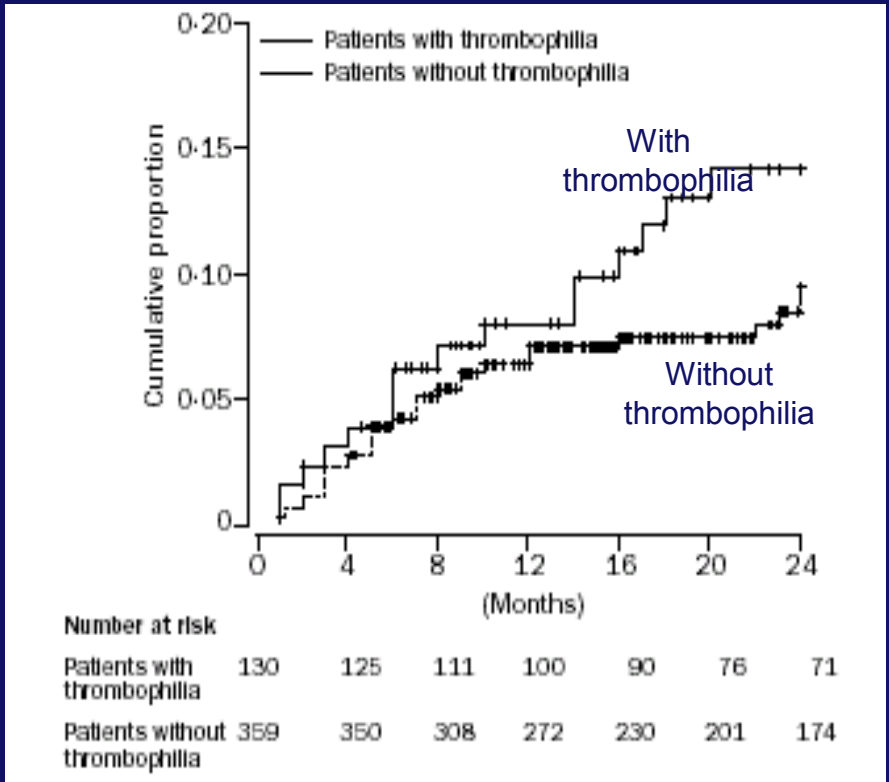
Prothrombin mutation:

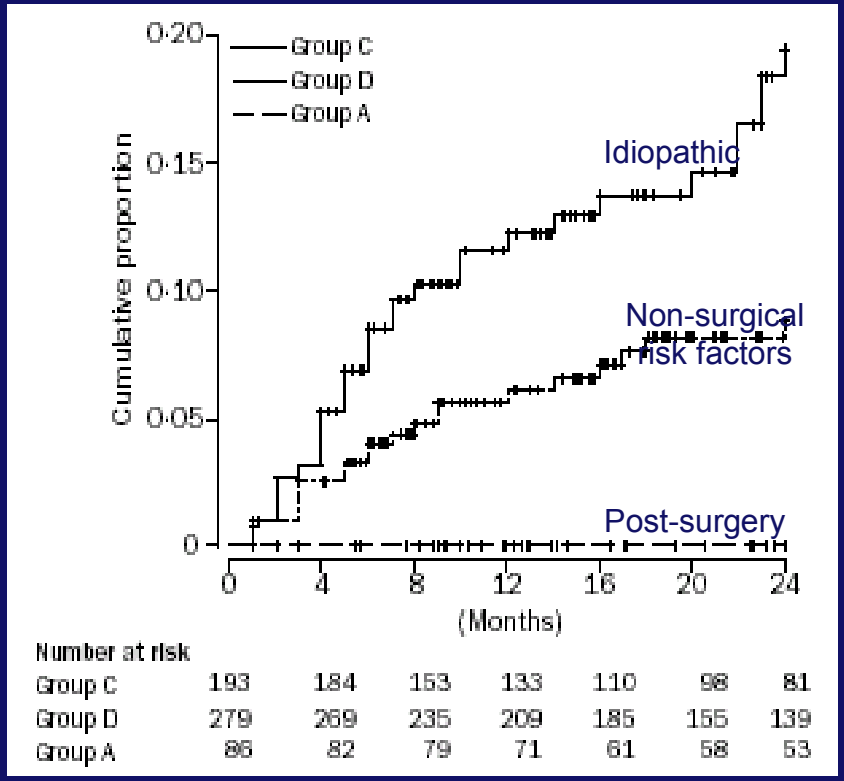
OR 1.4 (0.9-2.0)

Marchetti, Thromb Haemost 2000; Vink, J Thromb Haemost 2003

Thromphilia and the risk of recurrent VTE

- Thrombophilia versus clinical risk factors





Baglin, Lancet 2003

Aims of E. Dekker Stipend (2003T038)

Assessing the usefulness of screening for hereditary thrombophilia

1. To survey the current practice of thrombophilia testing in the Netherlands
2. To assess the effect of testing for thrombophilia on the risk of recurrent VT
3. To prepare a trial that provides grade 1 level of evidence on the usefulness of testing

funded by the Netherlands Heart Foundation

Acknowledgements

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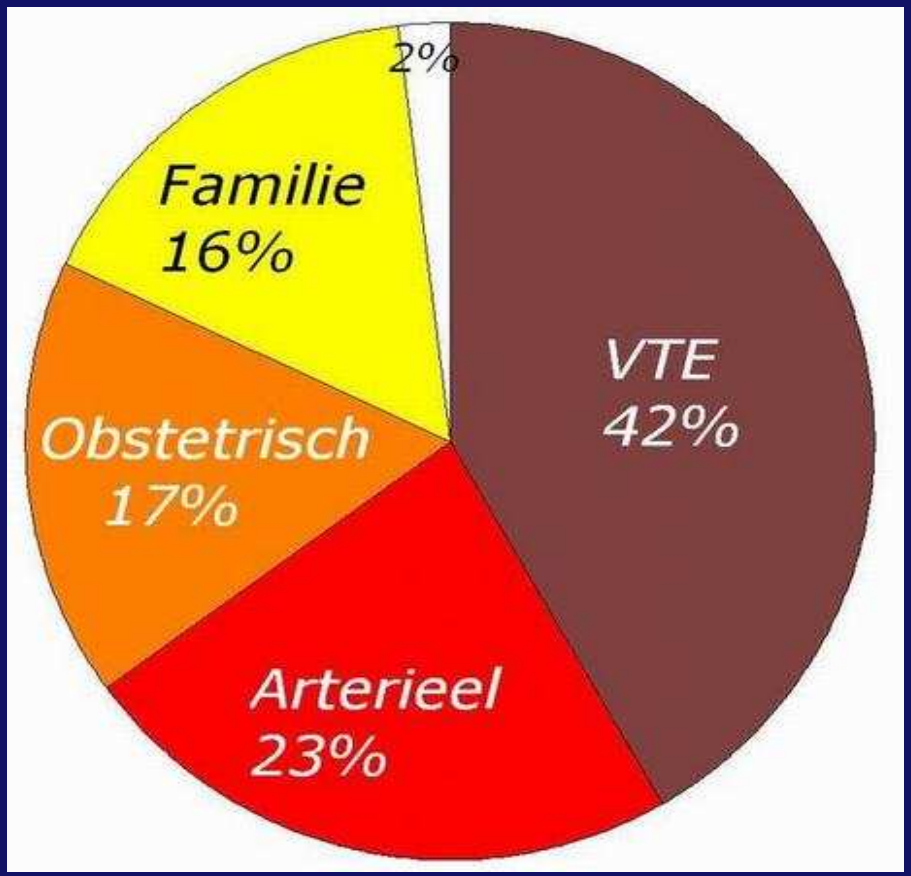
Nostradamus onderzoekers

LUMC Leiden
- Frits Rosendaal
- Carine Doggen
- Team MEGA studie

Sanquin Amsterdam
- Jan van Mourik
- Karel Eckmann

Indications for thrombophilia testing

- Survey in The Netherlands (2003-2004)



- Consecutive orders from November 1st 2003 at Sanquin Laboratories
- Mailed 2000 questionnaires to ordering physicians
- Response rate 63% (n=1132)

- Collection period 126 days
  - ≈ 5500-6000 orders/year

Coppens J Throm Haemost 2007

Ordering physicians

	Total (%)	VTE (%)	Arterial (%)	Obstetric (%)	Family (%)
Internal medicine	**37**	**68**	21	4	18
Gynecology	20	6	< 1	**95**	7
Neurology	15	2	**58**	0	4
General practitionars	14	4	2	1	**65**
Pulmonologists	6	13	0	0	< 1
Surgeons	5	3	14	0	1
Miscellaneous	3	4	4	<1	5

Consequences of tests

Management consequences	%
Patient management influenced by tests	71
Management implications present in this patient	23
Management implications only if thrombophilia was present	48
Nature of management decisions (> 1 answer possible)	
Altered duration of anticoagulant treatment	10
Intensified prophylaxis in high-risk episodes	12
Lifestyle changes (including withholding oral contraceptives)	11
Frequency of patient contact	2
Additional testing in family members	6
Not specified	43
No influence on patient management	24
Uncertain	5

Drawbacks of testing: psychological impact

Table 2 Methodology: used measurements and points in time

	Participants	Setting	Thrombophilic defects	Instruments	Point in time	Outcome
Hellmann 2003 [19]	110 consecutive individuals, 83 personal history of VTE, 27 reason for testing unknown	Clinical purposes	Factor V Leiden	1 not validated questionnaire, based on previous publications concerning other genetic tests	Mostly several years after disclosure of test results	Knowledge of genetic status increased awareness of thrombotic risk, but the magnitude of the risk is often overestimated. Knowledge of factor V Leiden status increased worry in 43% of the participants, although 88% of all participants were glad to know the outcome
Lindqvist 2003 [20]	4 personal history of VTE*, 211 healthy controls	Research purposes: to assess the incidence of APC resistance amongst pregnant women	Factor V Leiden* in case of altered test result of APC resistance	2 not validated questionnaires regarding satisfaction, the awareness and behaviour after receiving a positive test result	6–12 months after disclosure of test results	94% were satisfied with the awareness of being APC-resistant. 27% declared to be more worried
Bank 2004 [21]	17 asymptomatic relatives of individuals with factor V Leiden	Research purposes: to assess the incidence of VTE in individuals with thrombophilia	Factor V Leiden	Qualitative, semi-structured interviews	4–7 years after disclosure of test results	Asymptomatic carriership of factor V Leiden might influence daily life by concerns, stigmatization and problems with insurance eligibility
Van Korlaar 2005 [22]	168 family members of one kindred with a high incidence of protein C deficiency	Research purposes: to assess the heritability of a rare protein C deficiency	Protein C deficiency	Validated risk perception and worry scales and validated trait anxiety (STAI) questionnaire attitudes about testing	Mostly 10 years after disclosure of test results	Risk perception and worry increased in individuals with protein C deficiency, no significant differences in attitudes about genetic testing
Saukko 2006 [23]	42 participants, 10 personal history of VTE, 20 family history of VTE or thrombophilia, 12 other reason or unknown	Clinical purposes	Factor V Leiden Prothrombin mutation† Protein S deficiency† Protein C deficiency† Antithrombin deficiency†	Qualitative, semi-structured interviews	At most 2 years after testing for thrombophilia	Testing for thrombophilia was generally considered to be less serious than a genetic test for breast cancer or a non-genetic test for diabetes
Legnani 2006 [24]	140 participants, 63 personal history of VTE, 22 family history of VTE or thrombophilia, 55 apparently healthy individuals	Clinical purposes	Factor V Leiden Prothrombin mutation Protein S deficiency Protein C deficiency Antithrombin deficiency Hyperhomocysteinemia Lupus anticoagulant	Perceived Health Score and validated CBA scale A&B questionnaire	Prior to testing and 20 days after disclosure of test results	No (significant) harmful effects of genetic testing in individuals with thrombophilia. A non-significant decrease of Perceived Health Score in the subjects without a personal history of VTE

*Reported in correspondence by the authors; †self-reported by participants.

Cohn, J Throm Haemost 2008

Drawbacks of testing: costs

• Full thrombophilia panel (excluding LAC/ACA)	150 (?)	
• Consultation with an expert	200	
Total/patient	350	
Spin-off costs		
• Consultation of 4 first degree relatives		800
• Lab costs targeted testing (4x 25)		100
• Intensified prophylaxis for 3 weeks (life-time estimation, 2x)		300
Total/4 relatives		1200
TOTAL		1550

Costs €

- Our survey
  - 126 days
  - Only regional care providers in The Netherlands
  - Partial thrombophilia screen in approx 50%
- 1000 * € 75 = 75,000
- 1000 * € 150 = 150,000
- Total costs € 225,000
- Annual (this lab only!): approx € 650,000

- Is it worthwhile? Does it reduce recurrent VTE?

Effect of testing on the risk of recurrent VT

- Case-cohort study of patients with recurrent VT
  - Multiple Environmental and Genetic Assessment of risk factors for venous thrombosis (MEGA) (NHS 98.113)
  - >5000 cases with first VT or PE, > 5000 controls
  - 1999-2004

- 197 cases with recurrent VT during follow-up
- 324 controls matched for age, sex, year of first VT and region

Coppens J Thromb Haemost 2008

Work load

- Selecting cases with recurrent VT from three anticoagulation clinics
- Selecting controls from the database

- Retrieving medical records from > 600 patients in 15 hospitals
  - Diagnosis verification
  - Thrombophilia testing yes/no

- Exposure: tested for thrombophilia after first VT
- Outcome: recurrent VT

Results

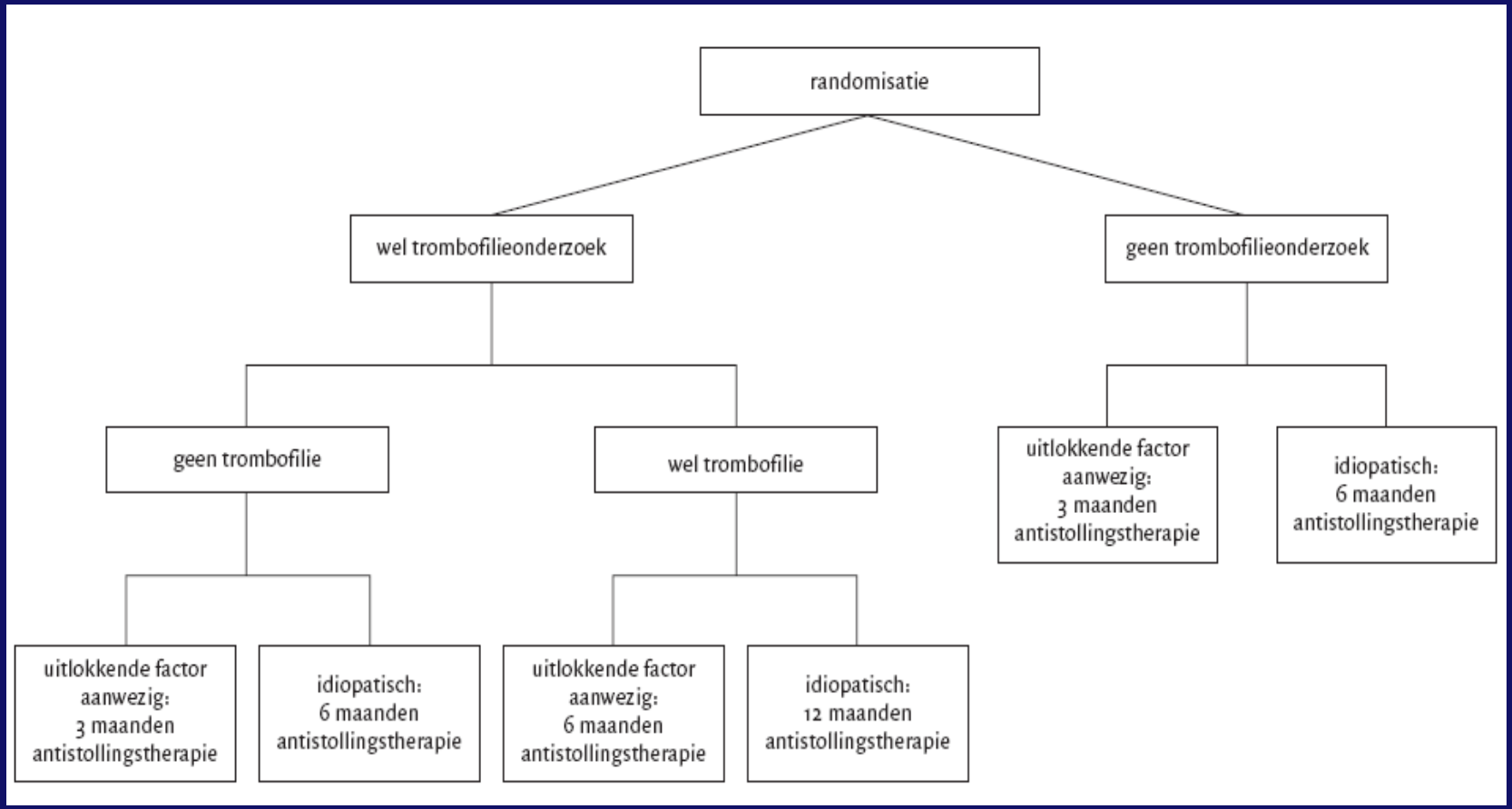
- Recurrent VT patients
  - 35% had been tested at the time of first VT
- Patients free from recurrence
  - 30% had been tested at the time of first VT

- Who were tested?
  - Women > men
  - Young > old
  - Positive family history of VT > no family history
  - Idiopathic or hormone-related > provoked by surgery/trauma

Effect of testing on recurrent risk

	% tested		OR for recurrent VT (tested vs not-tested)
	Recurrent VT (cases)	No recurrent VT (controls)	
all	35	30	1.2 (0.8-1.8)
women	41	35	1.4 (0.7-2.9)
First VT with OC use	60	32	3.4 (1.3-8.6)
Positive family history for VT	47	39	1.5 (0.7-3.1)

NOSTRADAMUS study - design



Has the issue now been settled?

- Huge amount of money spent on testing
- No therapeutic consequences (observational evidence)
- Grade 1 evidence unlikely to ever become available

BRIEVEN AAN DE REDACTIE

Vroegtijdige beëindiging van het onderzoek naar het nut van trombofilietests bij een eerste veneuze trombo-embolie: het NOSTRADAMUS-onderzoek

D.M.Cohn en S.Middeldorp

Zie ook de artikelen op bl. 2053, 2057, 2062, 2065 en 2077.

Cohn, NTvG 2008

Family testing

- (To have an explanation)

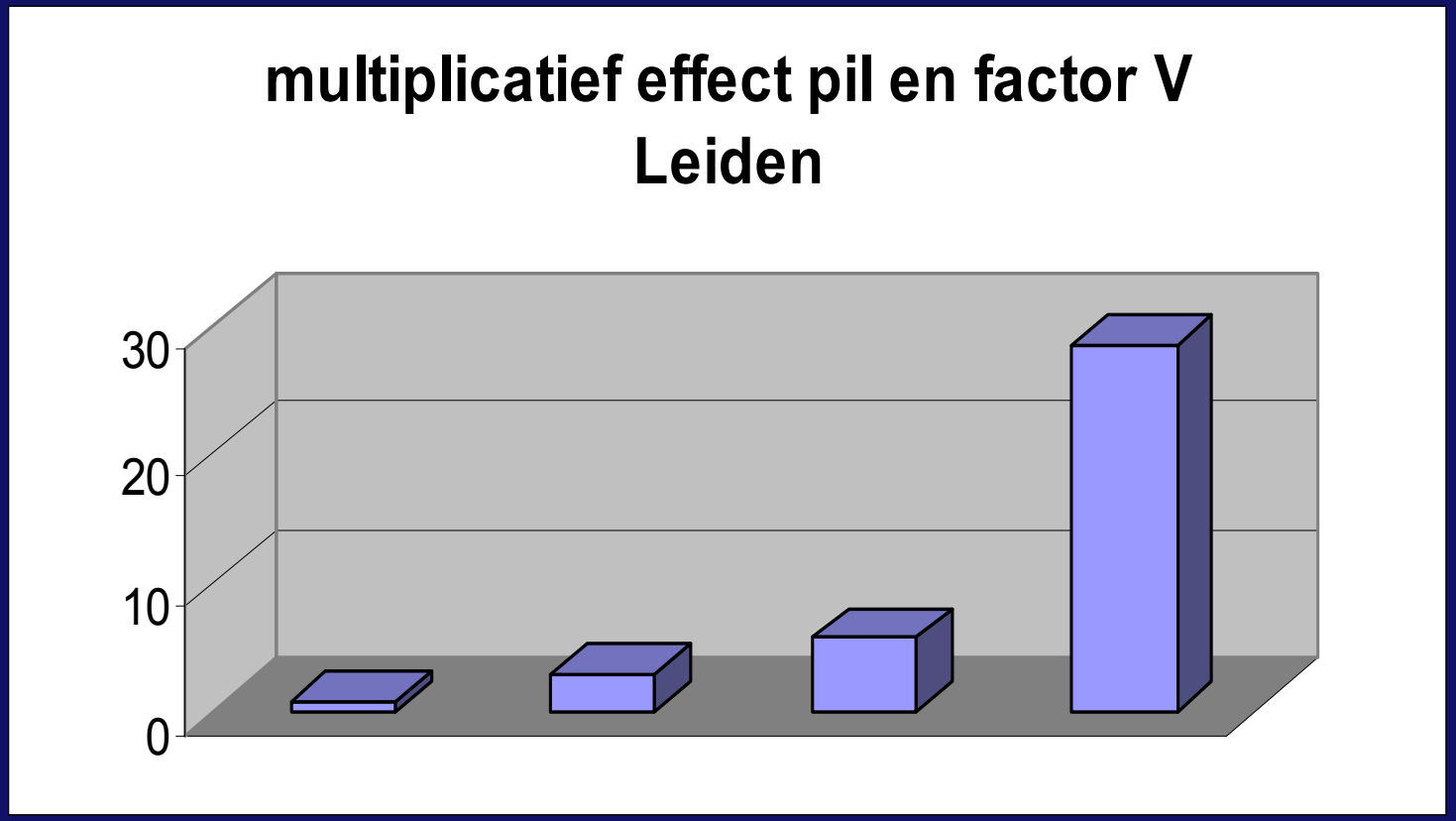
- To reduce morbidity and mortality

  In patients with venous thrombosis or pulmonary embolism

  - Modified treatment
  - Modified prophylaxis during high risk situations
  - Other preventive measures

  Primary prevention in relatives

Interaction between FVL and oral contraceptive use



Vandenbroucke et al. Lancet 1994

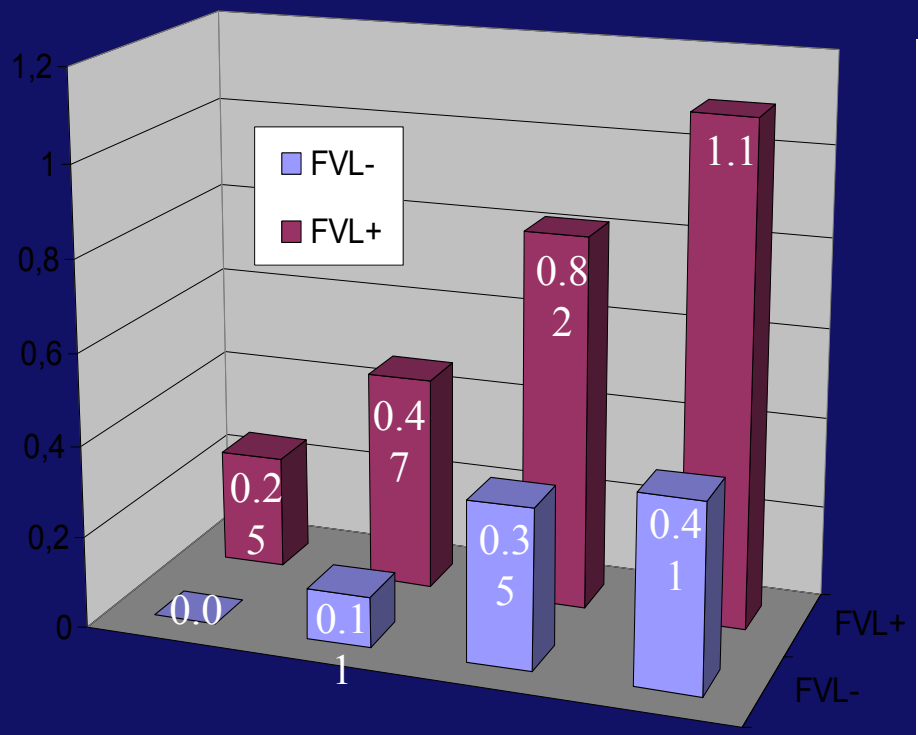
How does this translate to absolute risk?

- Overall (annual)
- Per high risk situation (including oral contraceptives)
- The setting matters
  - Family history of VTE?

Relatives of patients with a known defect – FV Leiden

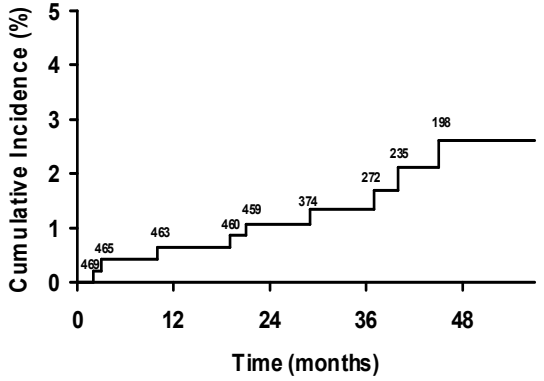
437 relatives of FVL + patients

All VTE



470 asymptomatic FVL carriers

Annual risk for spontaneous VTE 0.26% (0.07-0.65)



Middeldorp Ann Int Med 1998, Middeldorp Ann Int Med 2001

Solid risk estimates for high risk situations

- Setting of VTE family history

Incidences of first VTE in individuals who have inherited thrombophilia

	Antithrombin, protein S, or protein C deficiency	Factor V Leiden	Prothrombin 20210A	Elevated FVIII:c levels	Mild hyperhomocysteinemia
Overall (%/year)	1.5 (0.7–2.8) [89]	0.5 (0.1–1.3) [24,90]	0.4 (0.1–1.1) [91]	1.3 (0.5–2.7) [92]	0.2 (0.1–0.3) [93]
Surgery/trauma/immobilization (%/episode)	8.1 (4.5–13.2) [24]	1.8 (0.7–4.0) [23,24]	1.6 (0.5–3.8) [25]	1.2 (0.4–2.8) [15]	0.9 (0.1–3.4) [93]
Pregnancy (%/pregnancy)	4.1 (1.7–8.3) [24]	2.1 (0.7–4.9) [23,24]	2.3 (0.8–5.3) [25]	1.3 (0.4–3.4) [15]	0.5 (0.0–2.6) [93]
During pregnancy	1.2 (0.3–4.2)	0.4 (0.1–2.4)	0.5 (0.1–2.6)	0.3 (0.1–1.8)	0.0 (0.0–1.8)
Puerperium	3.0 (1.3–6.7)	1.7 (0.7–4.3)	1.9 (0.7–4.7)	1.0 (0.3–2.9)	0.5 (0.0–2.6)
Oral contraceptive use (%/year of use)	4.3 (1.4–9.7) [24]	0.5 (0.1–1.4) [23,24]	0.2 (0.0–0.9) [25]	0.6 (0.2–1.5) [15]	0.1 (0.0–0.7) [93]

Middeldorp et al, Colman & Hirsh Ed 2001; Coppens et al, Obstet Gynecol Clin N Am 2006

General conclusion

- No indication for thrombophilia testing of relatives
  - Potential exception: women who intend to become pregnant or are ambivalent to use oral contraceptives
  - Beware of false reassurance!
- Think before you test, and counsel

Middeldorp, Ned Tijdschr Geneesk 2001

Pregnancy loss

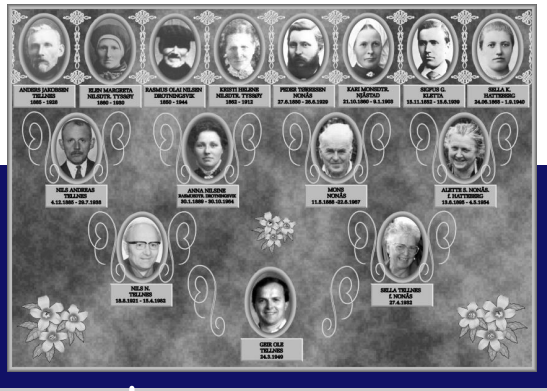
Recurrent miscarriage prevalent

- 0.5-1% of couples (3 or more)
- 3% of couples (2 or more)

Revised nomenclature (2005)

- Recurrent miscarriage
  - 3 early consecutive losses or 2 late pregnancy losses
- Early or late pregnancy loss
  - Before or after 12 weeks gestation
  - Ultrasound criteria

Rai, Lancet 2006; Farquharson, Hum Reprod 2005; “Miscarriage” Rachel Dolezal



Family studies

Thrombophilia defect	Sporadic miscarriage OR	Recurrent miscarriage OR	Intra-uterine fetal death OR
AT, PC, or PS deficiency	2.0 1.3	2.6	3.6
Factor V Leiden mutation	1.0 2.0	2.6	1.4
Prothrombin 20210A mutation	1.3	0.9	-
Homozygous defects or combinations of defects	0.8 2.9	-	14.3 6.4
Mild hyperhomocysteinemia	0.8	1.1	-
Elevated FVIII:c levels	1.2	1.1	-

Sanson, Thromb Haemost 1996; Preston, Lancet 1996; Meinardi, Ann Int Med 1999; Tormene, Thromb Haemost 1999; Bank, Arch Int Med 2004; Middeldorp, J Thromb Haemost 2004

Thrombophilia defect	Sporadic miscarriage OR	Recurrent miscarriage OR	Intra-uterine fetal death OR
Lupus anticoagulant	3.0	7.8	2.4
Anticardiolipin antibodies	3.4	3.6 - 5.1	3.3
AT deficiency	1.5	0.9	7.6 (0.3-196)
PC deficiency	1.4	1.6	3.1
PS deficiency	Heterogeneous data	14.7 (1.0-218.0)	7.4 (1.3-42.8) 20.1 (3.7-109.2)
Factor V Leiden	1.7	2.0	2.1 - 3.3
Prothrombin 20210A	2.1	2.3 - 2.7	2.3 – 2.7
Homozygous / combined defects	2.7	-	-
Hyperhomocysteinemia	6.3	2.7 – 4.2	1.0

Rey, Lancet 2003; Robertson, Br J Haematol 2006; Nelen et al, Fertil Steril 2000

Effect of heparin in trombophilia - more observations

EPCOT cohort study

131 pregnant women with hereditary thrombophilia

- No thrombosis prophylaxis n=48 (9 prior fetal loss)
  - Live birth rate 67-79% with/without fetal loss history
- With thrombosis prophylaxis started early n=21
  - Live birth rate 76%

Single center Dutch study

37 women with AT/C/S deficiency, mainly asymptomatic

- No thrombosis prophylaxis n=11
  - Live birth rate 55%
- With thrombosis prophylaxis n=26
  - Live birth rate 100%

Vossen, J Thromb Haemost 2004; Folkeringa Br J Haematol 2007

Recent trials – none with placebo or no treatment

Gris (Blood 2004)

- At least 1 single late fetal loss and thrombophilia
- LMWH versus aspirin

Live-enox (Brenner, JTH 2005)

- Women with at least 3 losses 1st trimester, 2 2nd trimester, or 1 IUFD (3rd trimester) and hereditary thrombophilia
- 2 doses of LMWH

Ongoing trials

TIPPS study (M. Rodger, Canada)
- Recurrent fetal loss and other pregnancy complications + thrombophilia
- No treatment vs LMWH

ALIFE study (S. Middeldorp, The Netherlands)
- Recurrent fetal loss - unexplained or with hereditary thrombophilia
- Placebo (for aspirin) vs aspirin vs aspirin + LMWH

SPIN study (P. Clark, UK)
- Recurrent fetal loss - unexplained
- No treatment vs aspirin + LMWH

HAPPY study (I. Martinelli, Italy)
- Pregnancy complications
- No treatment vs LMWH

Conclusions

- Patients with VTE
- Family testing
- Pregnancy complications (recurrent miscarriage)

Thrombophilia testing only serves limited purpose and should not be performed on a routine basis

Middeldorp & Van Hylckama Vlieg, Br J Haematol 2008