

Estudio en trombosis venosa (de trombofilia)

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Thou art always figuring diseases in me, but
thou art full of error: I am sound

(Shakespeare W. Measure for measure 1604; Act I, Scene II)

Testing for thrombophilia

- Factor V Leiden worldwide most performed genetic test
- Often in combination with protein C, protein S, antithrombin, factor VIII, MTHFR 677T and homocysteine

Tests through history

- the very first test....





Eve tests Adam

(test of faith/love)

Georgio Giulio Clovio

Book of Hours (1546)



Titian (1550)



Judgement of Paris

(test of beauty)



Roman augur

(test for going to war)



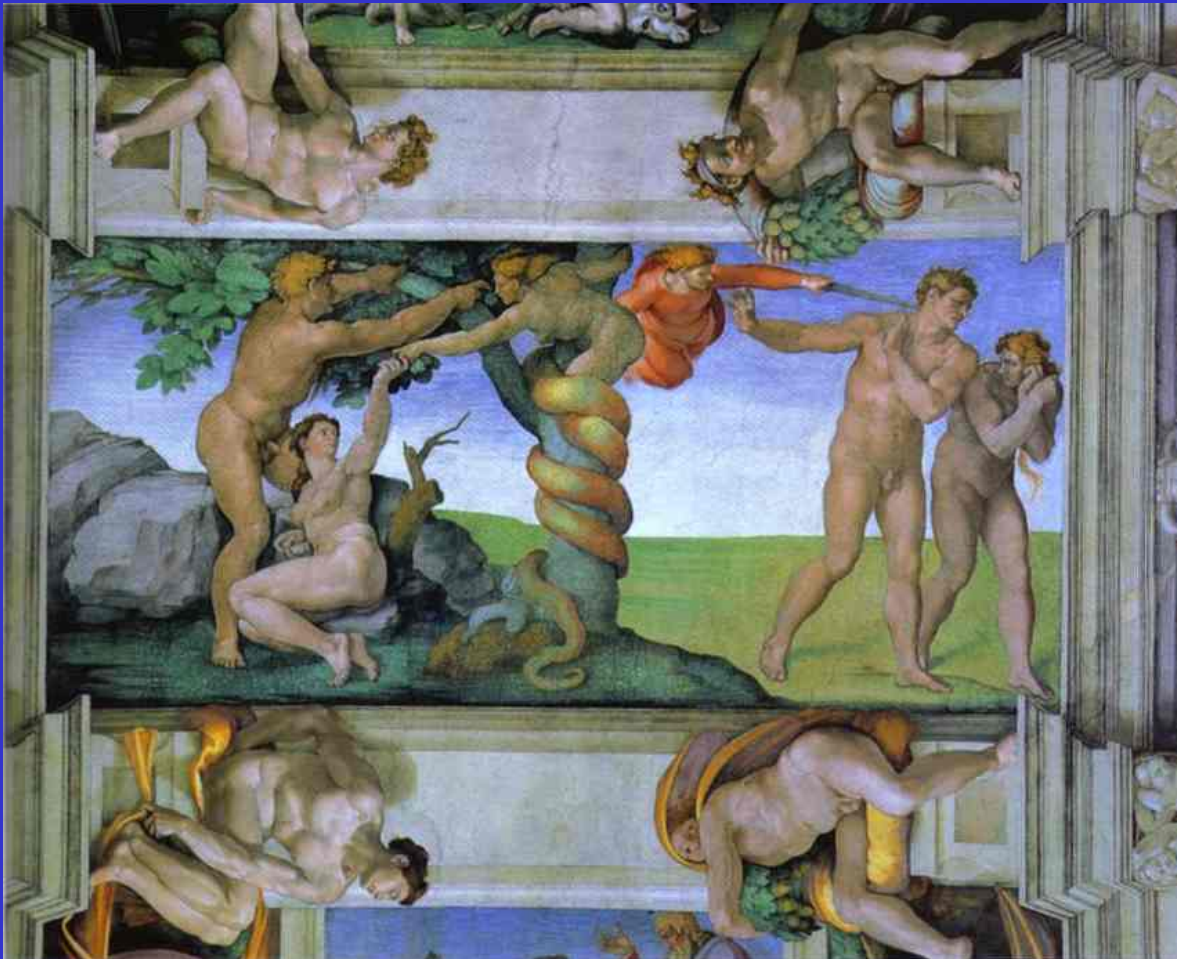
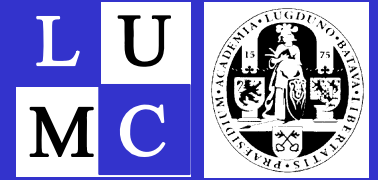
Rice water diarrhoea

(test for cholera)

Modern tests

- Test for clinical disease (e.g. ECG)
- Test for early disease (e.g. Pap smear)
- Test for risk of disease (e.g. blood pressure)
- Test for fetal disease (e.g., amniocentesis)
- Test for risk of fetal disease (e.g. carrier testing)
- Test for past infection (e.g. Mantoux)
- Test for state (e.g. pregnancy test)
- etc

Not always happy end



Sistine Chapel
Michelangelo (1512)

Not always a happy end



.. a thousand ships
(film: Troy, 2004)

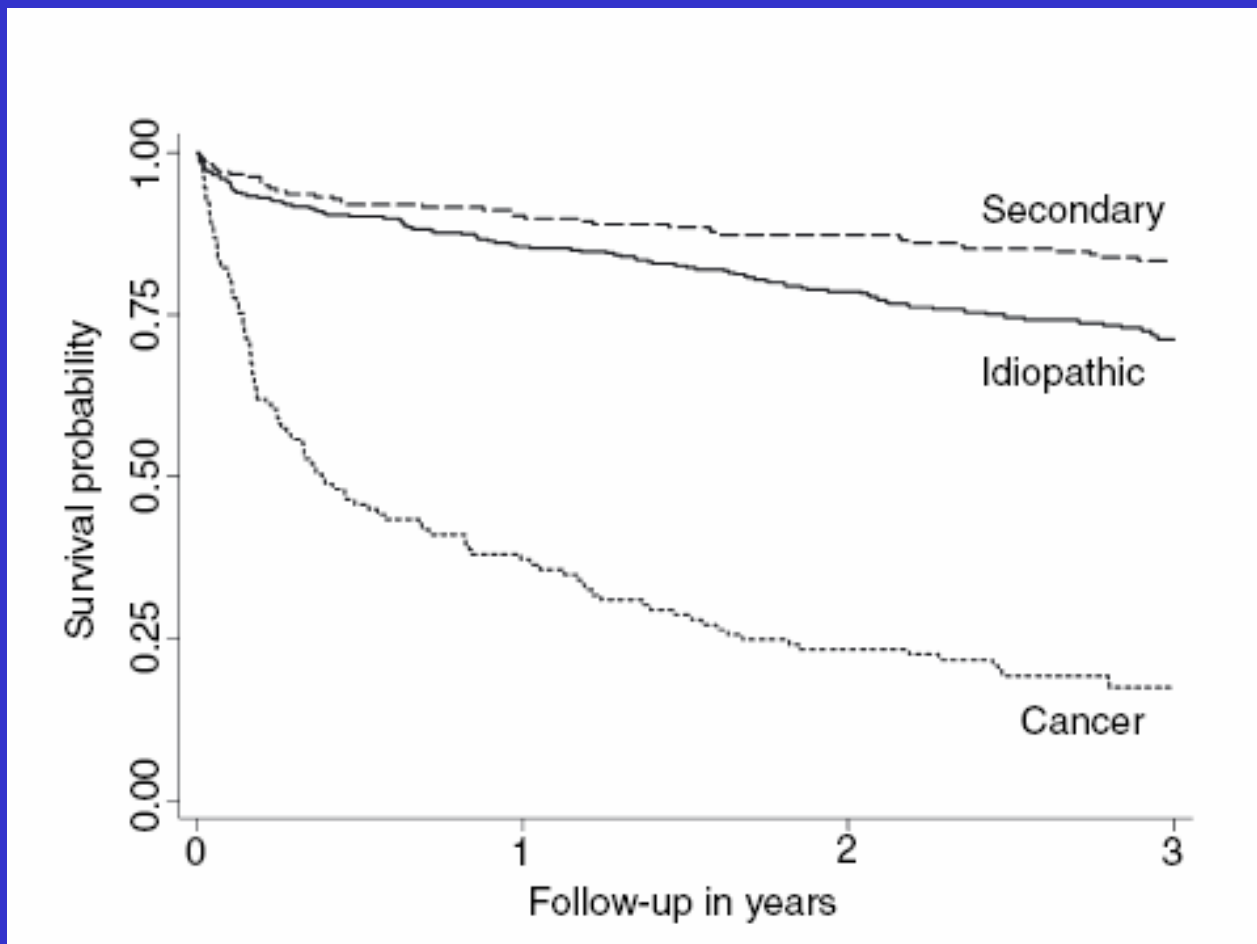


Brueghel, Jan the Elder. *The Burning of Troy* (c.1671-72)

Costs and benefits

- medical benefits (NNT, NNS)
- medical costs (side effects)
- psychosocial benefits (+ QoL)
- psychosocial costs (-QoL)
- economical benefits (+ €)
- economical costs (- €)

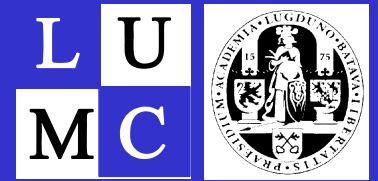
Death after venous thrombosis



1 yr mortality

	%
VT	21.6
idiop.	14.5
ca+	63.9
ca-	12.6

(Naess, J Thromb Haemost 2007)



If testing: for what?



Risk factors venous thrombosis

Stasis

Blood abnormalities

Genetic

venous mal-
formations

anticoagulant defects
procoagulant changes

thrombophilia

Acquired

age
immobilisation
surgery

female hormone use
cancer
pregnancy
lupus anticoagulant

Trombophilia: semantics

- Presence of high-penetrant familial tendency to venous thrombosis
- Presence prothrombotic defect
- Both

Testing for thrombophilia

- To be discussed
 - deficiencies of protein C, S or antithrombin
 - factor V Leiden
 - protrombin 20210A
 - high FVIII
 - high FIX
- all others too weak effect

Testing for thrombophilia

- Aim
 - prevent thrombosis
- Method
 - screening
 - intensified treatment or removal risk factors
- Target
 - asymptomatic patients (prevent 1st event)
 - symptomatic patients (prevent recurrence)

Major distinction

- unselected individuals and patients
- selected patients (familial thrombophilia)

Unselected individuals

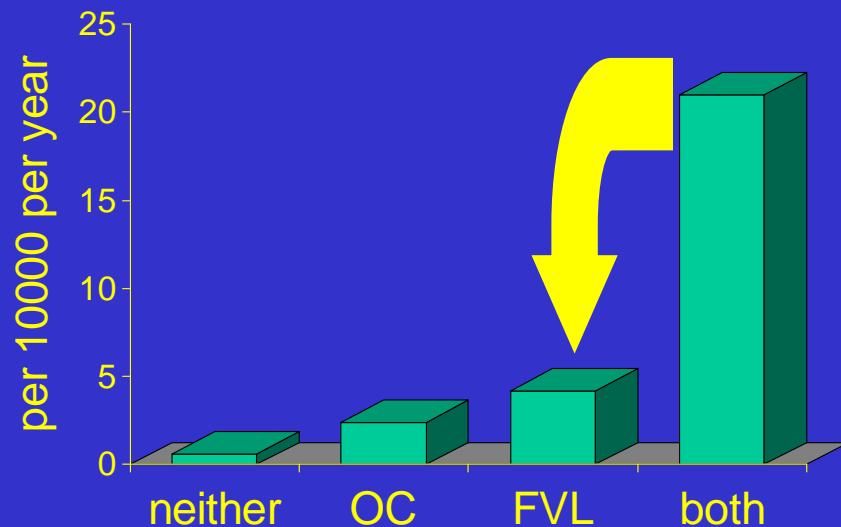
- screening of asymptomatic
 - prior to risk situations (surgery, OCs)
- testing of symptomatic
 - prevention of recurrences
 - prolonged anticoagulant treatment
 - liberal short-term prophylaxis

Testing for thrombophilia

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Screening of asymptomatics

Ex: Factor V Leiden and OCs



$$\begin{array}{r}
 20 \text{ per } 10000 \\
 5 \text{ per } 10000 \\
 \hline
 15 \text{ per } 10000 \\
 = \\
 1 \text{ per } 700 \text{ reduction}
 \end{array}$$

- FVL prev. 5%: to find 700, screen 14 000
- To prevent one thrombosis, screen 14 000 women (NNS)
- Costs: €/\$, QoL, suboptimal contraception

Screening asymptomatics

- Risk reduction too low to render it cost-effective
- Not rational

Testing for thrombophilia

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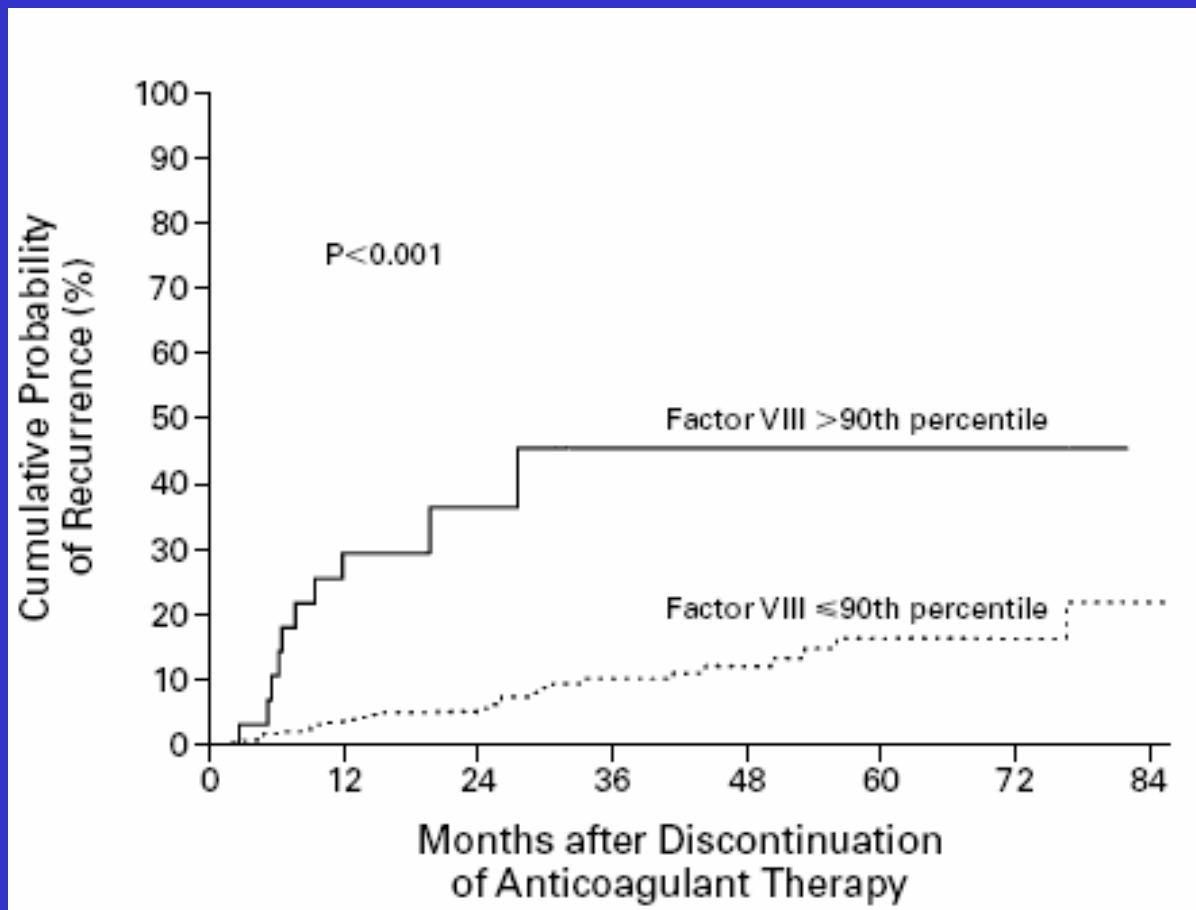
Testing thrombosis patients

- testing of unselected patients
- can only be useful if
 - patients with positive test have higher recurrence risk than those without
 - there are ways to reduce this risk with a positive risk-benefit ratio (side-effects)

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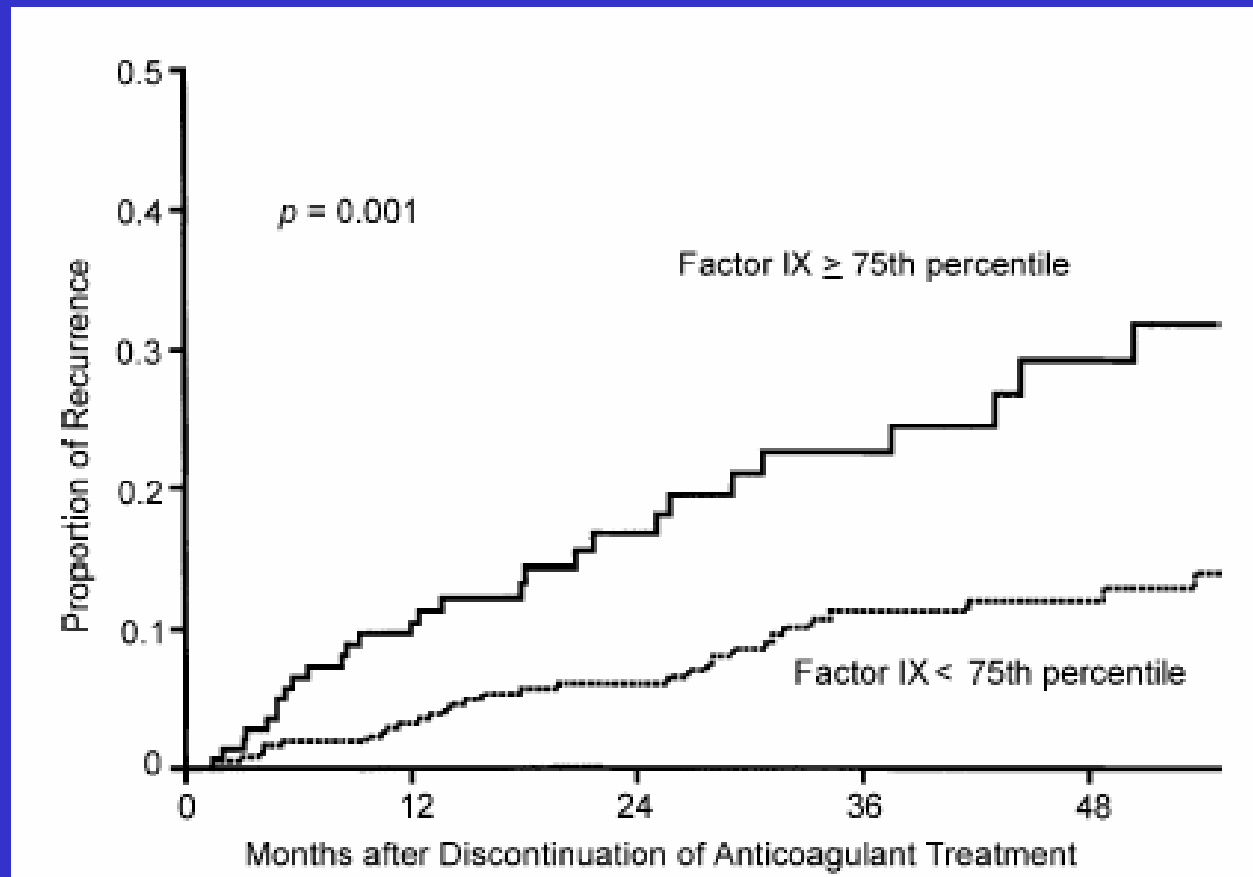
High levels of FVIII



- N=360
- 30 months
- RR= 6.6
- per year:
18.5% vs 2.5%

(Kyrle, N Engl J Med 2000)

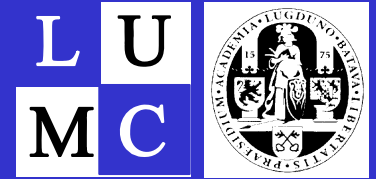
High levels of FIX



- N=546
- 31 months
- RR= 2.2
- per year:
7.7% vs 3.7%

(Weltermann, J Thromb Haemost 2003)

Austrian Study on Recurrent Venous Thromboembolism



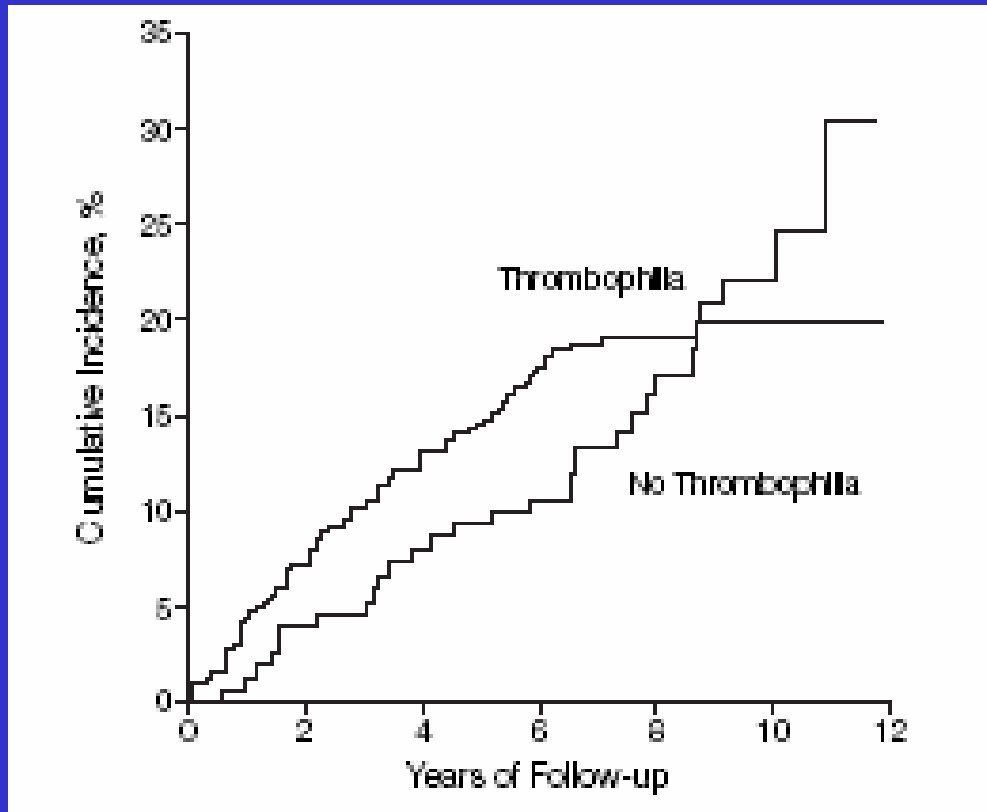
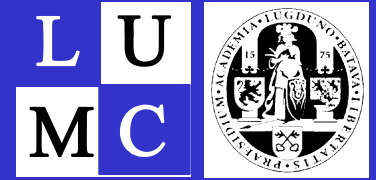
- FVL -
- PT20210A -
- high FVIII +
- high FIX +
- hyperhomocysteinemia +

(Eichinger, Thromb Haemost 1998; Kyrle, N Eng J Med 2000; Eichinger, Arch Intern Med 2002; Weltermann, J Thromb Haemost 2003; Eichinger, Thromb Haemost 1997)

Leiden Thrombophilia Study

- 474 consecutive patients with DVT
 - exclusion: malignancy
- prospective follow-up
- mean follow-up 7.3 yr (max 12 yr)
- 90 recurrent thrombotic event
- event rate 2.6 percent per year

No long-term effect thrombophilia



- abnormalities

PC, PS, AT

FVL, PT20210A

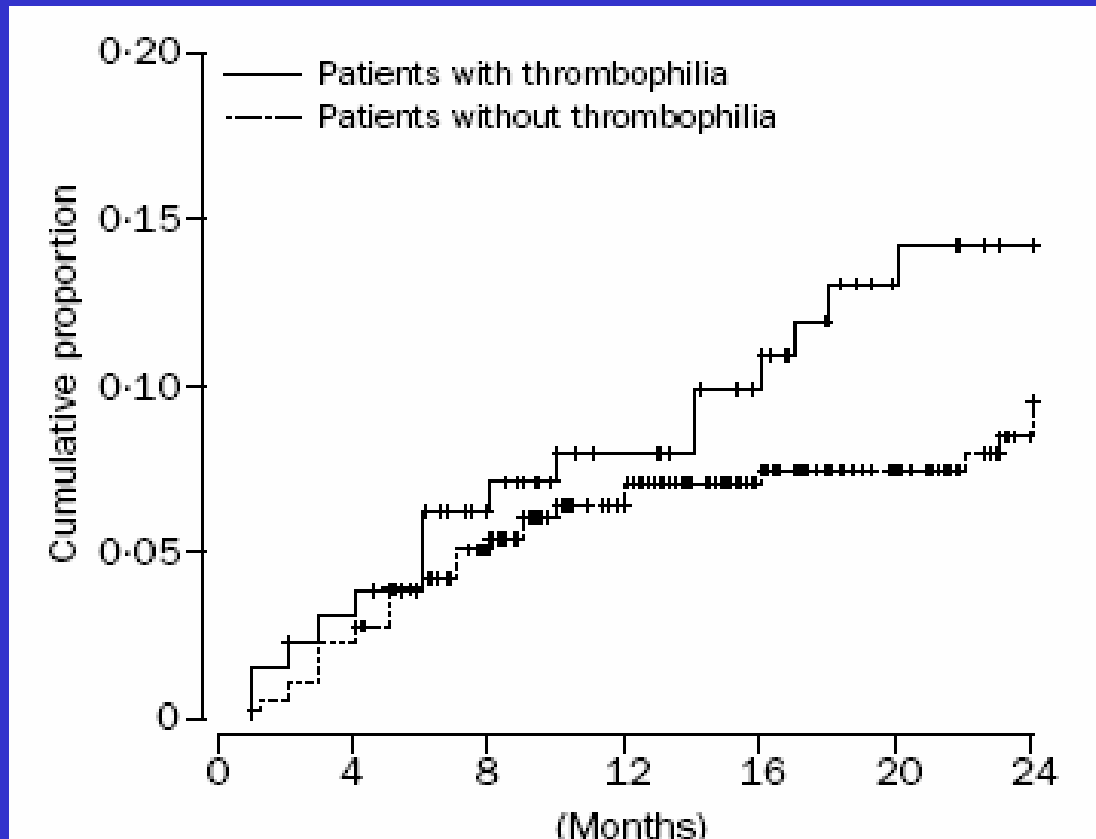
FVIII, FIX, FXI

homocysteine

- HR: 1.4 (CI95: 0.9-2.2)

(Christiansen, JAMA 2005)

Cambridge study



- N=489
- 2 yr follow-up
- anticoagulant defects
PC, PS, AT
FVL, PT20210A
- HR 1.50 (CI95 0.8-2.8)

(Baglin, Lancet 2003)

Recurrence risk by defect

	RR	CI95
factor V Leiden	1.2	0.7 - 1.9
prothrombin 20210A	0.7	0.3 - 2.0
PC/PS/AT deficiency	1.8	0.9 - 3.7
high FVIII	1.1	0.7 - 1.8
high FIX	0.9	0.5 - 1.7
high FXI	0.6	0.3 - 1.1
hyperhomocysteinemia	0.9	0.5 - 1.6

(Christiansen, JAMA 2005)

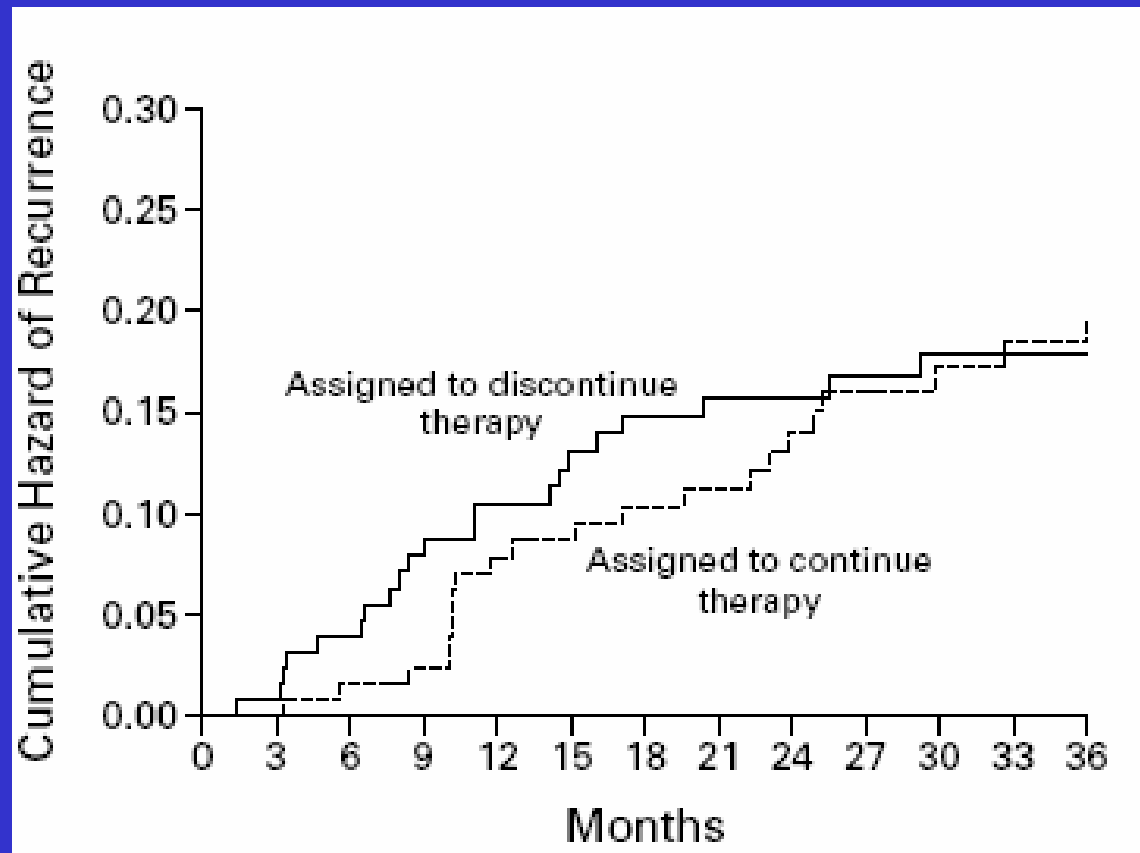
Conclusion

- Effect of laboratory abnormalities on recurrence small or absent
- Test result does not predict who is at increased risk

Testing thrombosis patients

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Prolonged anticoagulation



- idiopathic VT
- N=267
- 3 vs 12 months
- catch-up
- no benefit

(Agnelli, N Engl J Med 2001)

Conclusion

- Effect of laboratory abnormalities on recurrence probably small
- No clear strategy to reduce risk except life-long anticoagulation
 - risk of severe hemorrhage 1-2 percent per year

Real predictors

Relative risk

sex

men vs women

3- to 4-fold

type of first event

idiopathic vs secondary

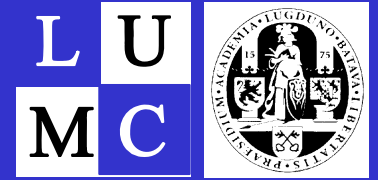
2- to 3-fold

(Baglin, Lancet 2003; Baglin, JTH 2004; Kyrle, NEJM 2004; Christiansen, JAMA 2005)

Unselected individuals

- Screening asymptomatic individuals
 - risk reduction too low to render it cost-effective
 - not rational

- screening symptomatic patients
 - does not identify those at high risk of recurrence
 - does not open treatment options
 - not rational



Selected individuals



Selected individuals

Age at first thrombosis:

- Consecutive patients with 1st VT (N=378)
 - protein C deficiency 47 yr
 - no defect found 43 yr

- Familial thrombophilia (24 families, N=229)
 - protein C deficiency 35 yr
 - no defect found 33 yr

EPCOT study

- 9 centres in Europe
- all their patients with familial thrombophilia
- prospective follow-up (1995-2001)
- 1626 patients (proband and relatives)
- AT/PC/PS deficiency or FVL

(Leiden, Barcelona, Glasgow, Sheffield, Frankfurt, Vienna, Malmö, Bologna, Paris)

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EPCOT: asymptomatic people

- incidence of venous thrombosis (no AC)
 - 0.8 % per year (CI95 0.5-1.2%)
- majority of events spontaneous
- risk not greater than that of anticoagulation
- Testing will not affect management

EPCOT: symptomatic patients

- patients with one prior event
- divided in those +/- long-term anticoagulation
- incidence of venous thrombosis
 - long term AC: 1.1 % per year
 - no AC: 5.3 % per year
- gradient of risk over type of thrombophilia
 - AT-def: 10.5%/yr (2.7 on AC), FVL: 3.8%/yr (0.0 on AC)
- incidence of major hemorrhage: 0.6%/yr

Familial thrombophilia

- Asymptomatic people (relatives)
 - no obvious advantage of screening
 - no obvious management choices
- Symptomatic patients
 - suggestive of benefit of long-term anticoagulation (esp. AT-deficiency)

Testing for thrombophilia

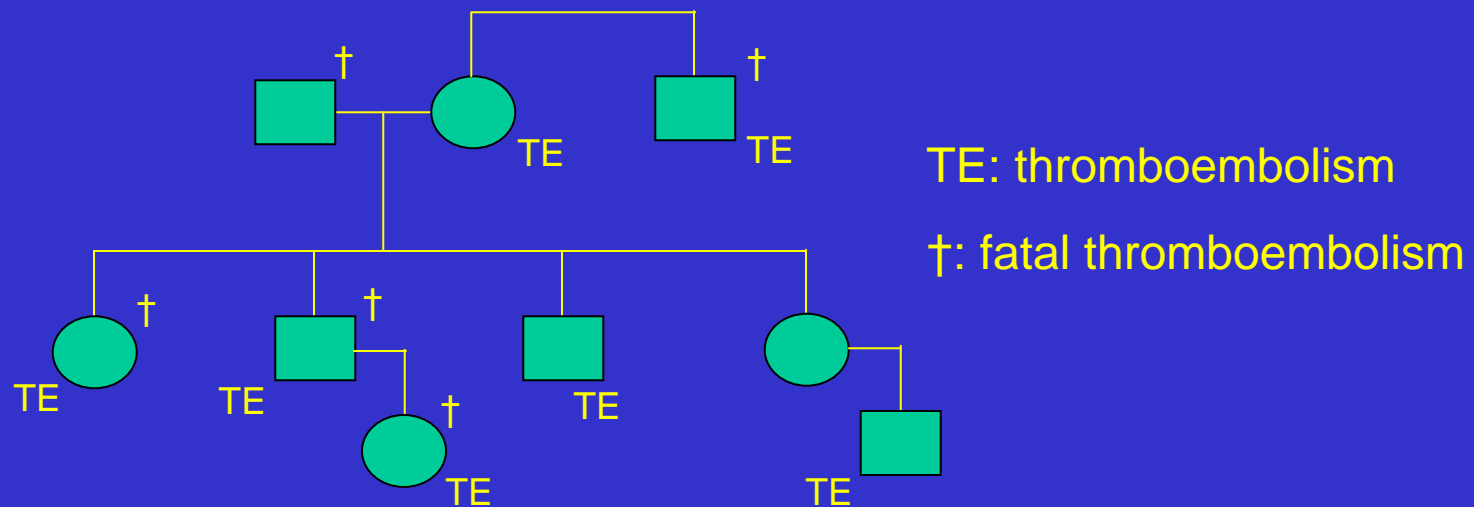
- Screening in unselected individuals or patients with thrombosis not indicated
- Screening symptomatic individuals in highly penetrant familial thrombophilia may be indicated
 - only antithrombin deficiency
 - no studies that prove positive benefit-risk-ratio

Testing in selected patients

- Symptomatic patients with familial thrombophilia: very small group

Familial thrombosis

It is probably more than coincidence when six or more members of the same family each develop from one to five thromboembolic conditions and when most of them eventually die of such conditions (Wright, 1952)



Conclusion: we test too much!

- Seems natural 'to want to know'
- Wanting to know not always a good idea



(film: Troy, 2004)