

# Thrombophilia testing: who is it good for?

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CHEST

Supplement

ANTITHROMBOTIC THERAPY AND PREVENTION OF THROMBOSIS, 9TH ED: ACCP GUIDELINES

**Ninth Edition**

**Antithrombotic Therapy and Prevention of Thrombosis,  
9th ed: American College of Chest Physicians  
Evidence-Based Clinical Practice Guidelines**

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To me, consensus seems to be the process of abandoning all beliefs, principles, values and policies. So it is something in which no one believes and to which no one objects.

(Margaret Thatcher)

# Two major distinctions

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- to prevent first or recurrent thrombosis
  - prevent first in asymptomatic, whole population
  - prevent recurrence after first thrombosis
  
- individuals from a 'thrombophilic family' or not
  - very specific rare families
  - general populaion

# Previous thrombosis

Additional factors for estimating risk of recurrence: Other factors predict risk of recurrence, but not strongly or consistently enough to influence recommendations on duration of therapy once the primary and secondary factors noted previously have been considered. These factors, which have mostly been evaluated in patients with unprovoked VTE, include negative D-dimer testing 1 month after withdrawal of VKA (risk ratio [RR],  $\sim 0.4$ ),<sup>148,176-181</sup> antiphospholipid antibody (RR,  $\sim 2$ ),<sup>182-185</sup> hereditary thrombophilia (RR,  $\sim 1.5$ ),<sup>162,163,174,177,180-182,185-190</sup> male vs female sex (RR,  $\sim 1.6$ ),<sup>191,192</sup> Asian ethnicity (RR,  $\sim 0.8$ ),<sup>193</sup> and residual thrombosis in the proximal veins (RR,  $\sim 1.5$ ).<sup>149,182,185,194-198</sup> Combinations

No recommendation on prevention based on risk factors

# No previous thrombosis

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surgical patients: no mention of thrombophilia

cancer: no mention of thrombophilia

pregnancy: prophylaxis in homozygous factor V Leiden or prothrombin mutation, or “other inherited thrombophilias and a positive family history”

- “serious consideration only”

# Medical patients

Padua score: >4 points is high risk

**Table 2—Risk Factors for VTE in Hospitalized Medical Patients<sup>9</sup>**

Risk Factor	Points
Active cancer <sup>a</sup>	3
Previous VTE (with the exclusion of superficial vein thrombosis)	3
Reduced mobility <sup>b</sup>	3
Already known thrombophilic condition <sup>c</sup>	3
Recent ( $\leq 1$ mo) trauma and/or surgery	2
Elderly age ( $\geq 70$ y)	1
Heart and/or respiratory failure	1
Acute myocardial infarction or ischemic stroke	1
Acute infection and/or rheumatologic disorder	1
Obesity (BMI $\geq 30$ )	1
Ongoing hormonal treatment	1

# Other conditions

**6.1.2. For long-distance travelers at increased risk of VTE (including previous VTE, recent surgery or trauma, active malignancy, pregnancy, estrogen use, advanced age, limited mobility, severe obesity, or known thrombophilic disorder), we suggest use of properly fitted, below-knee GCS providing 15 to 30 mm Hg of pressure at the ankle stockings during travel (Grade 2C). For all other long-distance travelers, we suggest against the use of GCS (Grade 2C).**



**7.1. In persons with asymptomatic thrombophilia (ie, without a previous history of VTE), we recommend against the long-term daily use of mechanical or pharmacologic thromboprophylaxis to prevent VTE (Grade 1C).**

# Conclusion ACCP

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- Previous thrombosis
  - thrombophilia does not affect strategy
  
- No previous thrombosis
  - 'serious consideration' in some pregnancies
  - acutely ill hospitalised patients with known thrombophilia may receive prophylaxis sooner
  - long distance travellers with known thrombophilia wear stockings

# Conclusion rephrased

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- 'known thrombophilia' may in rare cases affect therapy
- Since there is no advice to become knowledgeable on thrombophilia (testing), the guidelines see a thrombophilic test result as a mishap.

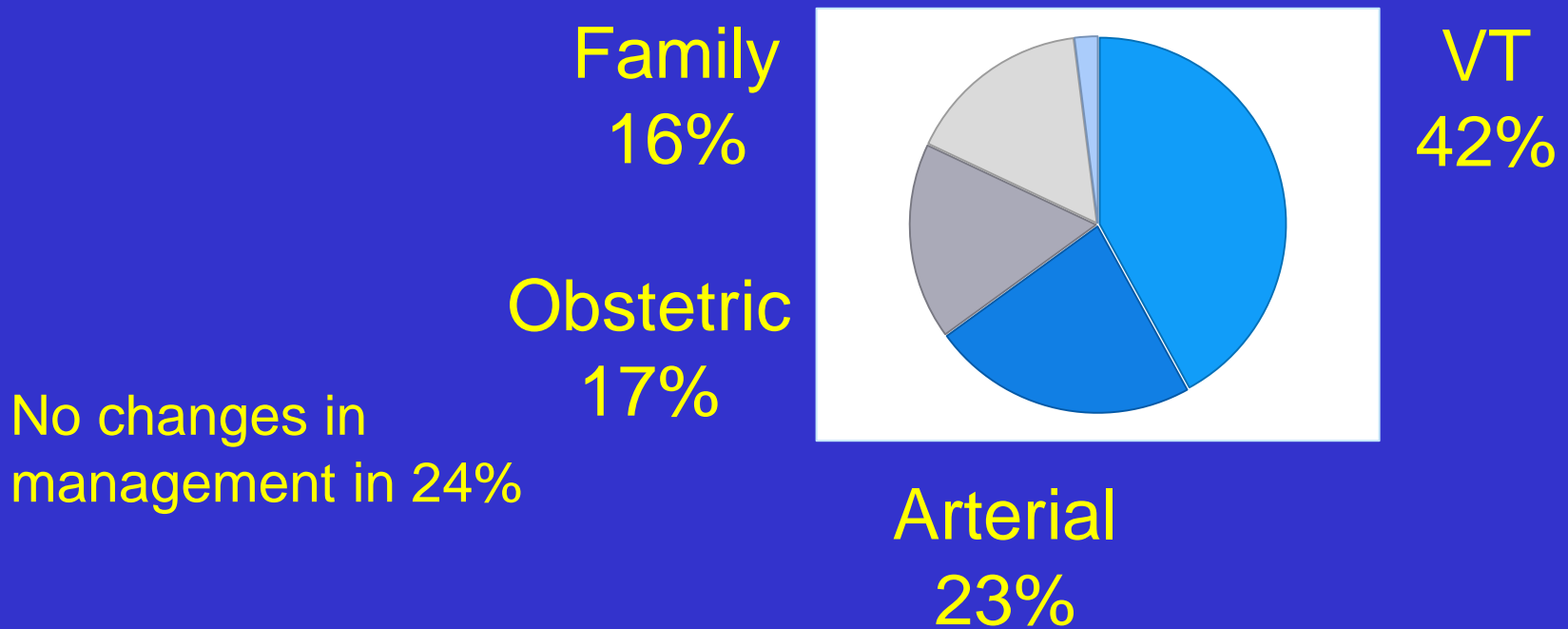
# Costs and benefits

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

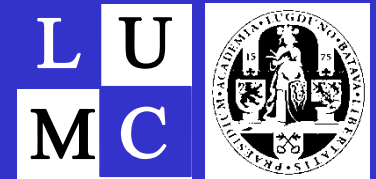
# Indications for testing

- Internal Medicine, Vascular Medicine, Hematology, Pulmonology, Cardiology, Surgery, Obstetrics, General Practitioners



# If testing: for what?

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# Confirmed genetic risk factors

		patients (%)	pop. (%)	RR	PAR (%)
AT/PC/PS deficiency		3	<1	>10	1
Factor V Leiden	rs6025	19	3	7.9	17
PT 20210A	rs1799963	6	2	2.8	3
FGG C10034T	rs2066865	12	6	2.4	8
non-00 bloodgroup		71	57	1.8	31
FGB his95arg	rs6003	19	14	1.5	7
FXIII leu34val (rec.)	rs5985	96	94	1.4	27
PROC A2418G	rs1799809	22	19	1.3	5
FGA Thr312Ala	rs6050	29	26	1.2	5
FGB 455 G/A	rs1800788	26	21	1.3	6
F11	rs2289252	48	41	1.3	13
F5	rs4524	79	73	1.3	19
GP6	rs1613662	84	82	1.2	11
SERPINC1	rs2227589	17	10	1.3	3

# Testing for genetic variants

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



# Unselected individuals

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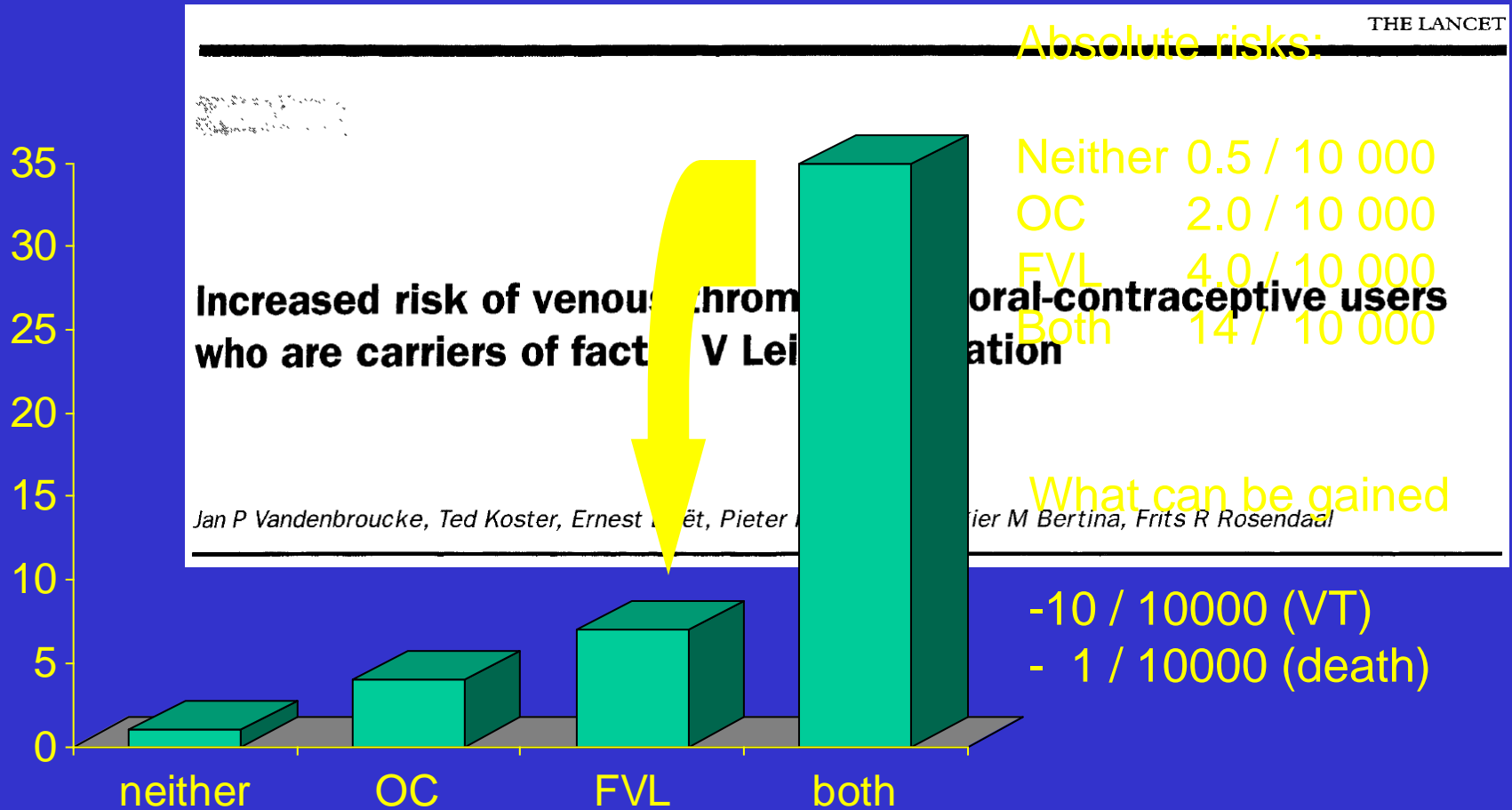
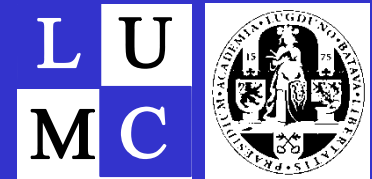
- screening of asymptomatics
  - everybody
  - prior to risk situations (surgery, OCs)
    - all
    - relatives of patients
  
- testing of symptomatics
  - prevention of recurrences
    - prolonged anticoagulant treatment
    - liberal short-term prophylaxis

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# Gene-environment interaction



(Vandenbroucke, Lancet 1994)

# How many to test to prevent one

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Risk: 10/10 000

- 1000 with FVL should not take OCs to prevent one VT
- 10000 with FVL should not take OCs to prevent one death

How to find 1000 women with factor V Leiden

- Population (5%) : test 20 000
- Relatives (20%): test 10 000

# Screening asymptomatics

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- risk reduction too low to render it cost-effective
- not rational
- this includes screening looking for relatives of patients

# Testing for genetic variants

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# Testing thrombosis patients

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- 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)

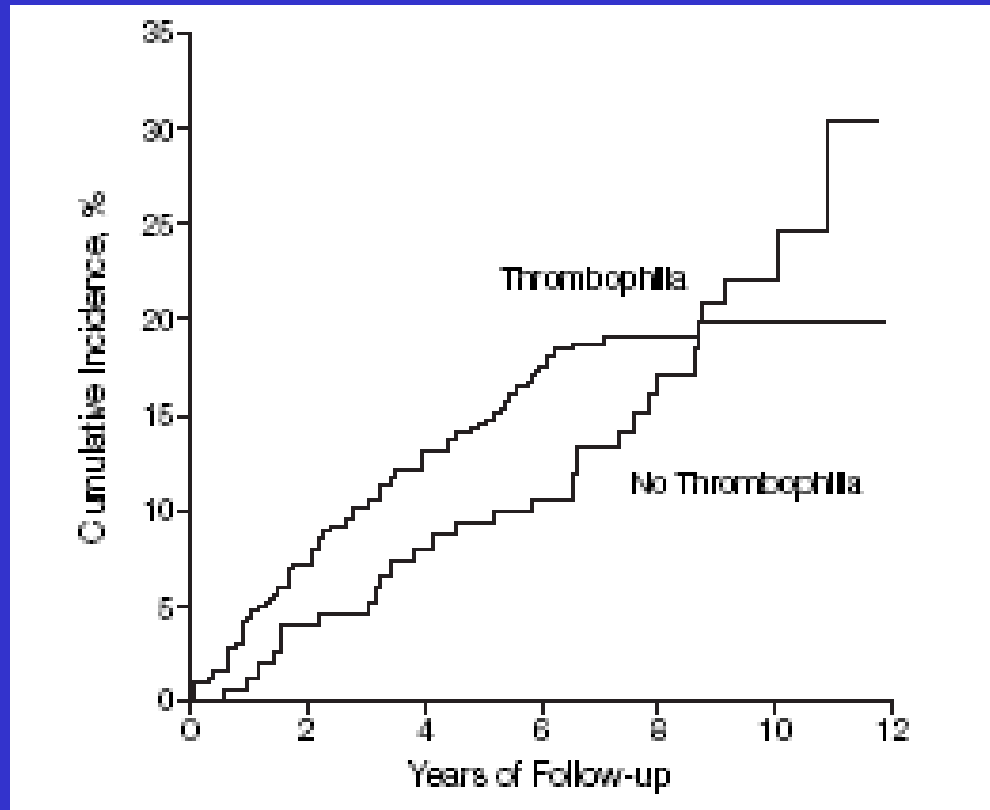
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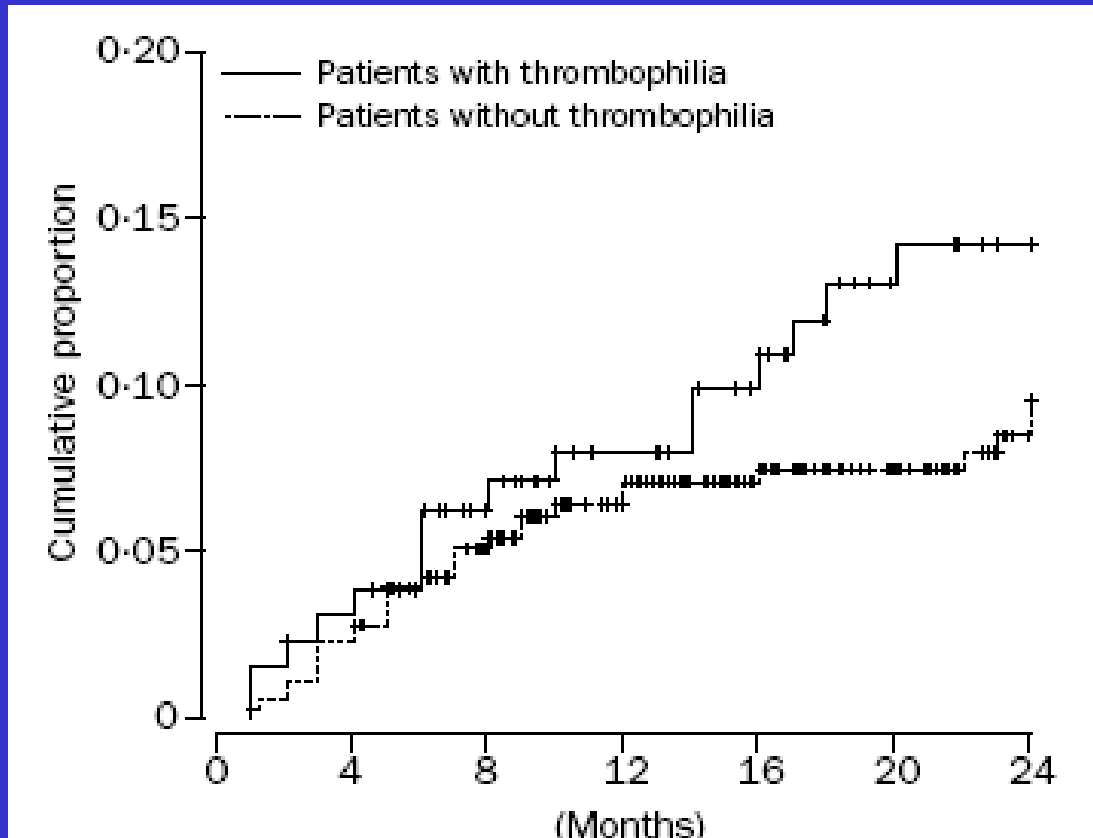
# No long-term effect thrombophilia



- abnormalities
  - PC, PS, AT
  - FVL, PT20210A
  - FVIII, FIX, FXI
  - homocysteine
- HR: 1.4 (CI95: 0.9-2.2)

(Christiansen, JAMA 2005)

# Cambridge study

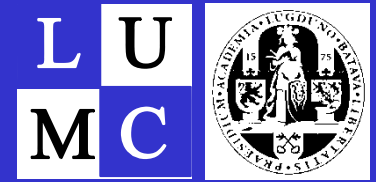


- N=489
- 2 yr follow-up
- anticoagulant defects  
PC, PS, AT  
FVL, PT20210A
- HR 1.50 (CI95 0.8-2.8)

( Baglin, Lancet 2003)

# Conclusion

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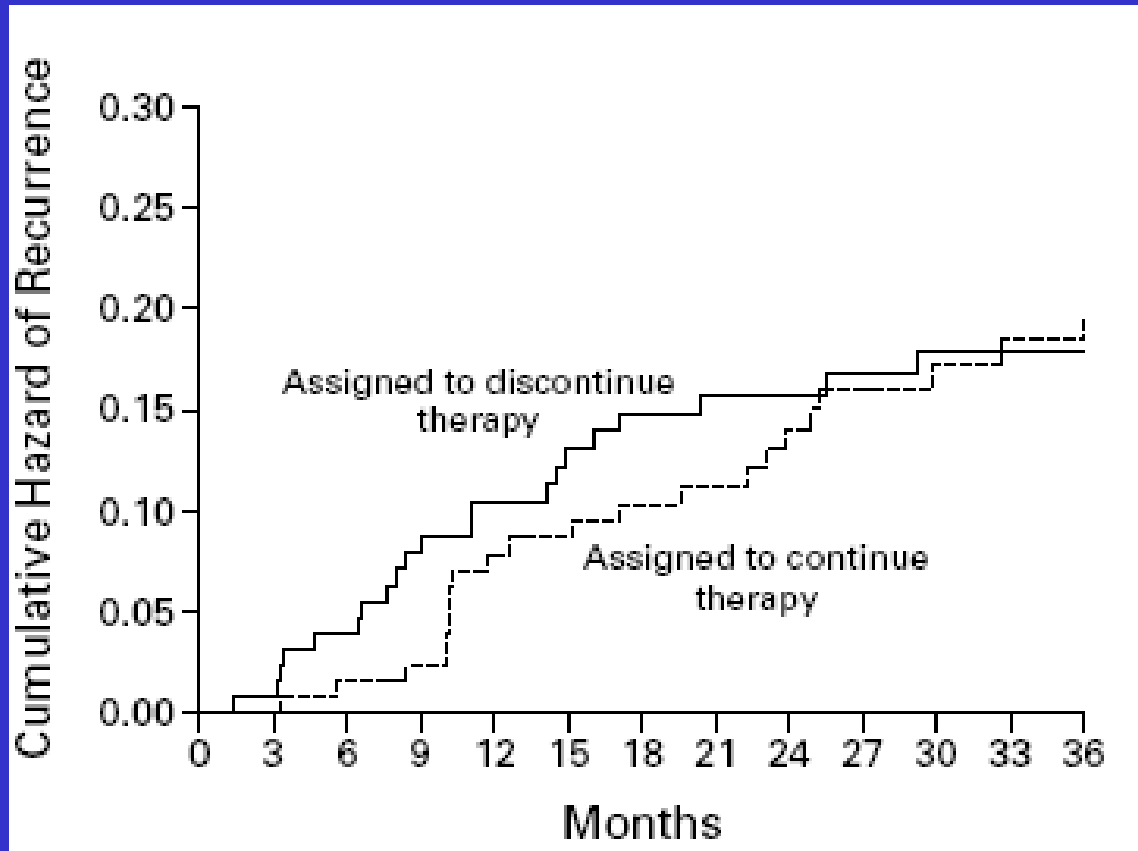
- effect of laboratory abnormalities on recurrence small or absent
- test result does not predict who is at increased risk

# Testing thrombosis patients

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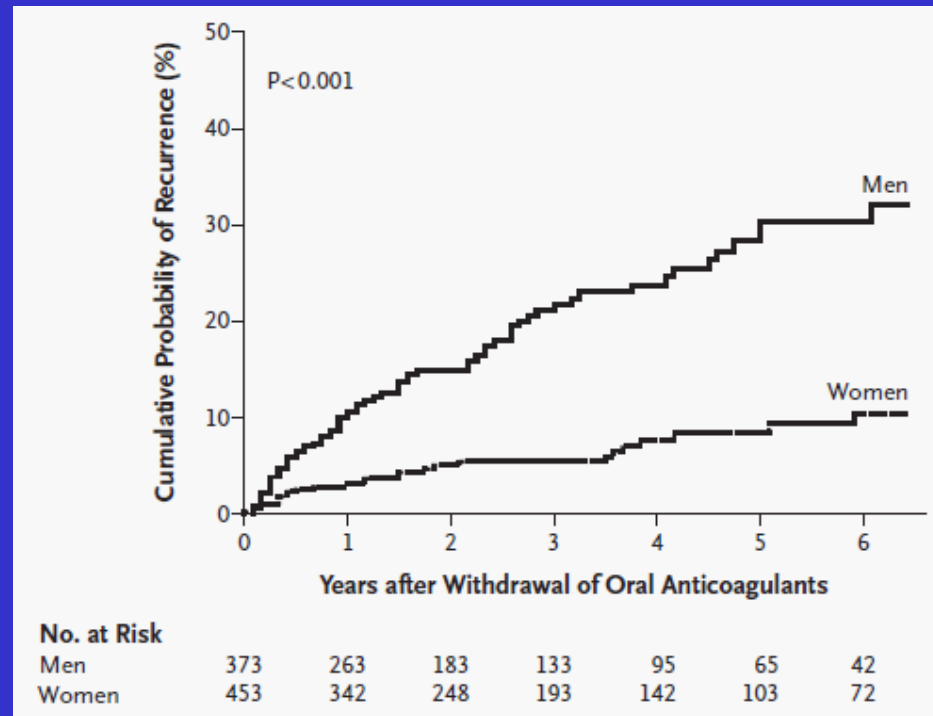
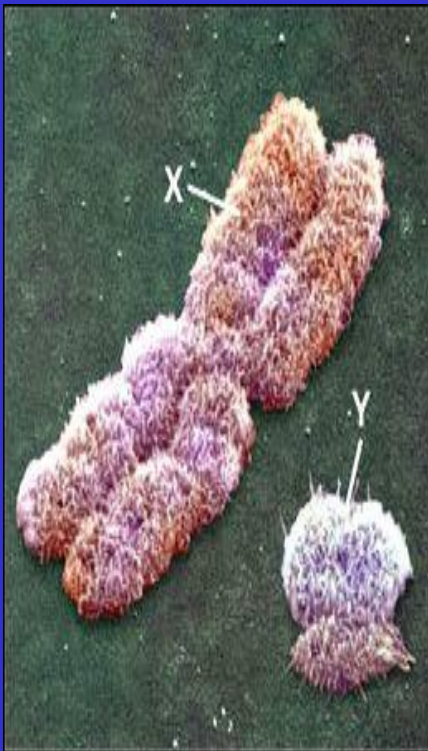
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# Prolonged anticoagulation



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

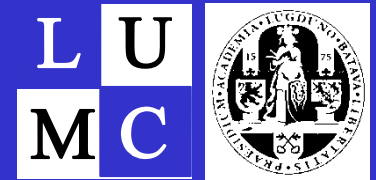
# Strongest genetic risk factor for recurrence



(Kyrle, N Engl J Med 2004; Roach, unpublished observations)

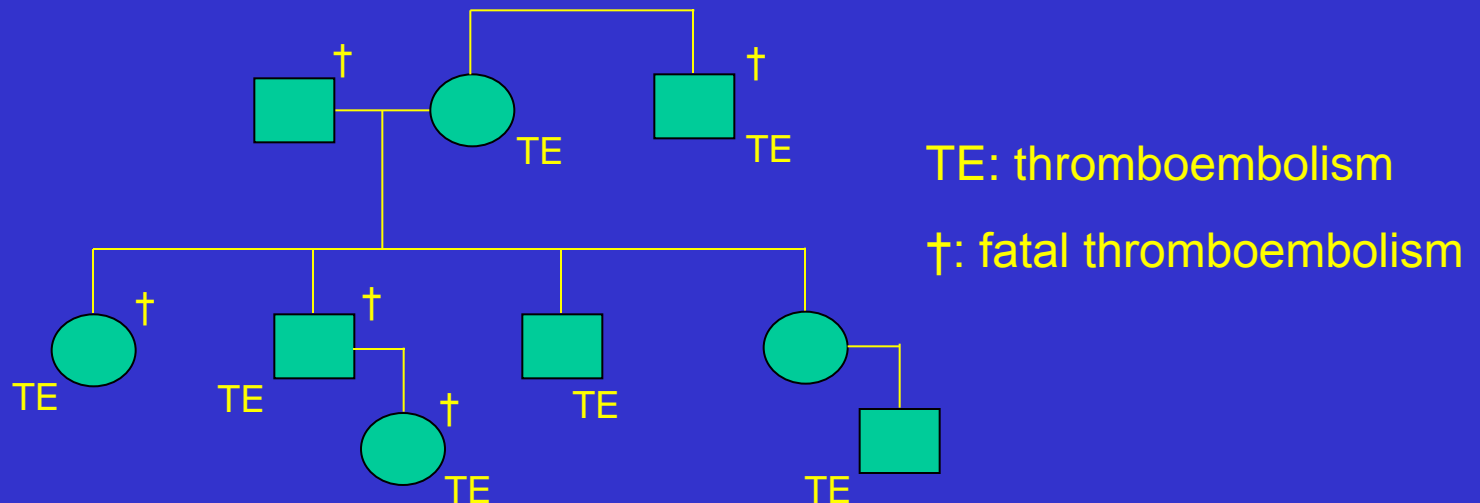
# Selected individuals

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# 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)





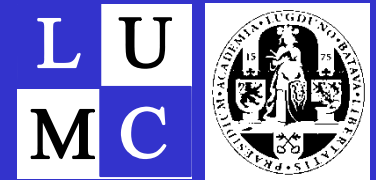
# Selected individuals

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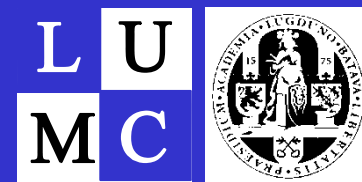
- Asymptomatic individuals
  - incidence 0.8% per year
- Symptomatic individuals
  - recurrence risk 5% per year
  - low for all defects except antithrombin deficiency (10% per year)

# Conclusion

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- testing may identify people at slightly higher risk but this is not relevant
- there is zero evidence of a benefit of testing

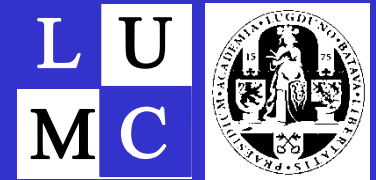


# Does testing do any good?

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- case-cohort study of patients with recurrent VT
  - MEGA: 5000 cases with first VT or PE
  - 1999-2004
  
- 197 patients with recurrent VT during follow-up
- 324 patients without recurrence
  
- physicians: in 76% testing had changed management
- if beneficial: most testing in patients without recurrence

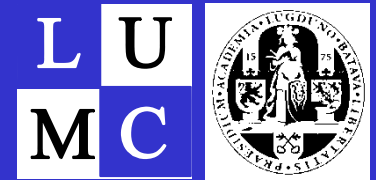
# No benefit



	% 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)

# Conclusion

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- thrombophilia testing medically not rational
- thrombophilia testing exceedingly costly
- psychological impact unknown
- psychological benefit: for whom?