



Ente Ospedaliero Cantonale

# Mio papà aveva una trombosi!

Quando cercare una trombofilia e quando no.

19. ottobre 2017

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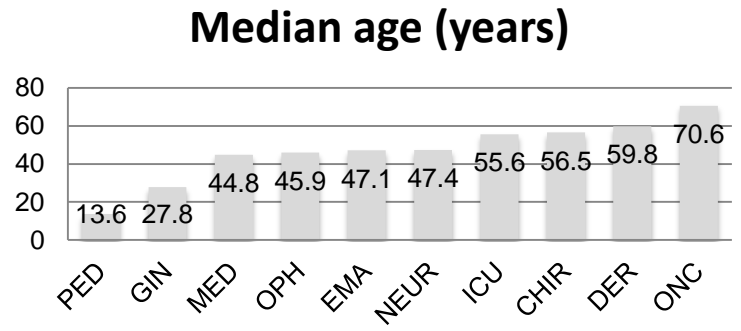
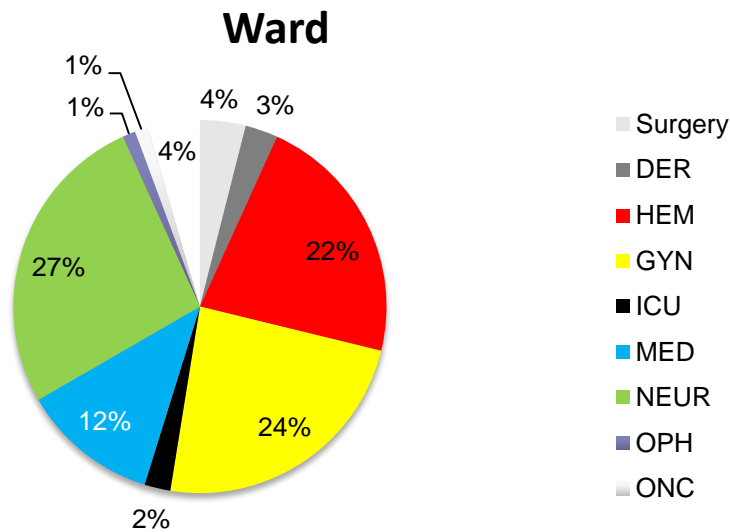
eoc

# My disclosures

I work for EOLAB

# EOLAB

## Thrombophilia tests EOLAB 12 months (n=177)



# Whom to test?

„Ordering thrombophilia tests is easy; determining whom to test and how to use the results is not.“

REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

## Thrombophilia Testing and Venous Thrombosis

Jean M. Connors, M.D.

J Thromb Thrombolysis (2016) 41:154–164  
DOI 10.1007/s11239-015-1316-1

## Guidance for the evaluation and treatment of hereditary and acquired thrombophilia

Scott M. Stevens<sup>1,2</sup> · Scott C. Woller<sup>1,2</sup> · Kenneth A. Bauer<sup>3</sup> · Raj Kasthuri<sup>4</sup> · Mary Cushman<sup>5</sup> · Michael Streiff<sup>6</sup> · Wendy Lim<sup>7</sup> · James D. Douketis<sup>7</sup>

# What are the problems?

## Estimating

- the thrombotic risk
- the benefit of a given intervention
- the bleeding risk
- psychological impact of testing
- cost

Am I changing my strategy based on the laboratory results?

# Case vignette

## Young lady 18 years

- Would like to start an oral contraceptive pill.
- Personal history: Suffering from acne. No VTE. Nonsmoker. BMI 19kg/m<sup>2</sup>.
- Family history: Mother with deep vein thrombosis during pregnancy (29 years). Heterozygous mutation R506Q of the coagulation factor V (Leiden).

## Gentleman 54 years

- DVT calf and popliteal vein 9 months ago ,out of the blue'. On a DOAC (direct oral anticoagulant).
- Personal history: customer advisor, travels a lot by car (Switzerland). Smoker, BMI 32 kg/m<sup>2</sup>. No other comorbidities.

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# What do you recommend?

## Young lady 18 years

1. Call the patient and tell her that a consultation is not needed.
2. Prescribe a hormonal contraceptive pill not containing estrogens, without further testing
3. Test for factor V Leiden: If negative -> prescribe pill containing estrogen
4. Suggest a complete laboratoristic work-up and decide based on the results
5. Other

## Gentleman 54 years

1. The DVT is provoked, no testing needed, stop anticoagulation.
2. The DVT is not provoked, no testing needed, anticoagulation forever.
3. Complete work-up for thrombophilia warranted, discuss long-term DOAC based on the results.
4. Stop DOAC, measure D-dimer after 2-4 weeks. Decide according to the estimated risk for recurrence.
5. Other

# What do you recommend?

## Young lady 18 years

1. Call the patient and tell her that the consultation is not useful.
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# Risk factors for thrombosis

## HEREDITARY

- Age
- Gender
- Positive family history
- Hereditary thrombophilia

## ACQUIRED

- Post-partum > pregnancy
- Surgery, trauma and immobilization
- Obesity
- Certain drugs (estrogens, -imids, ...)
- Diseases such as cancer, myeloproliferative diseases, antiphospholipid syndrome, paroxysmal nocturnal hemoglobinuria (PNH)
- Prior VTE (PE/proximal > distal; unprovoked > provoked)

# Risk factors for thrombosis

## HEREDITARY

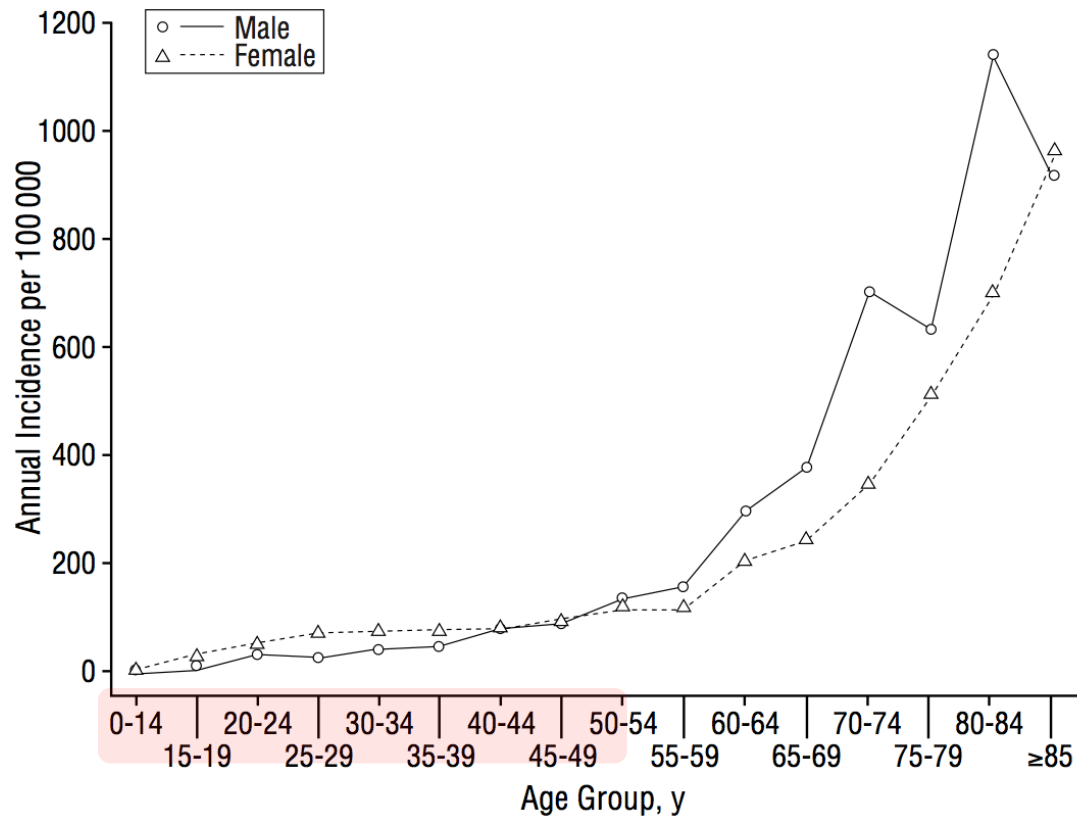
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# Age

## Population-based study Olmsted County, Minnesota



# Risk factors for thrombosis

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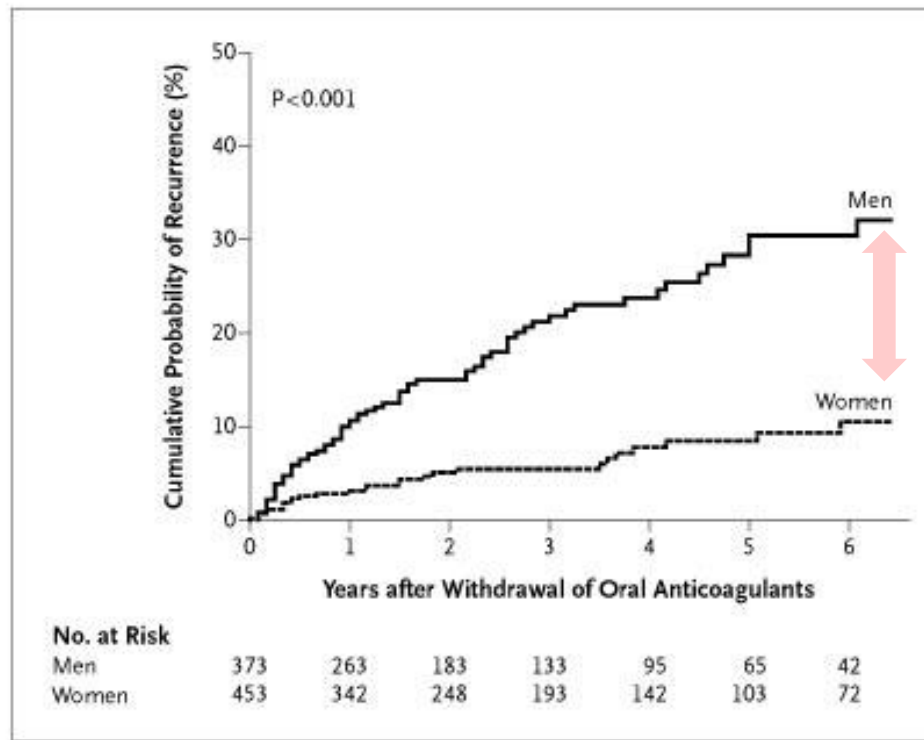
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# Gender

## Relapse-risk after first thromboembolic event



Male > female:  
3-fold elevated risk



# Risk factors for thrombosis

## HEREDITARY

- Age
- Gender
- **Positive family history**
- Hereditary thrombophilia

## ACQUIRED

- Post-partum > pregnancy
- Surgery, trauma and immobilization
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- Prior VTE (PE/proximal > distal; unprovoked > provoked)

# Family history

Only ~1/3 of the patients with a positive family history for TE have laboratory evidence of hereditary thrombophilia

TE-risk for first-degree family members are ~2-fold increased, even in the absence of an identifiable thrombophilia.

## Risk factors

- First degree relative (parents, siblings, children)
- Young age at diagnosis of the affected family member
- More than 1 family member
- Unprovoked thrombosis of the family member
- FV Leiden, prothrombin gene mutation

# Risk factors for thrombosis

## HEREDITARY

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# Hereditary thrombophilia

Table 1. Prevalence of thrombophilia and relative risk estimates for various clinical manifestations

	Antithrombin deficiency	Protein C deficiency	Protein S deficiency	Factor V Leiden	Prothrombin 20210A mutation	Acquired		
						Lupus anticoagulant*	Anti-cardiolipin antibodies*	Anti-β2 GPI antibodies
Prevalence in the general population	0.02%	0.2%	0.03%-0.13%	3-7%	0.7%-4%	1%-8 %	5	3.4
<b>Absolute annual risk ~0.05-0.2%</b>								
Relative risk for a first venous thrombosis	5-10	4-6.5	1-10	3-5	2-3	3-10	0.7	2.4
Relative risk for recurrent venous thrombosis	1.9-2.6	1.4-1.8	1.0-1.4	1.4	1.4	2-6	1-6	
Relative risk for arterial thrombosis	No association	No consistent association	No consistent association	1.3	0.9	10	1.5-10	
Relative risk for pregnancy complications	1.3-3.6	1.3-3.6	1.3-3.6	1.0-2.6	0.9-1.3	No consistent data	No consistent data	

Figures are derived from studies that are reviewed in detail elsewhere.<sup>2</sup>

\*In most studies, the presence of these thrombophilic risk factors was only assessed once.

# Hereditary thrombophilia

## 'High risk' for first VTE

- Deficiencies of antithrombin, protein C, protein S
- Homozygous for factor V Leiden mutation (FVL)
- Compound heterozygous for FVL and prothrombin gene mutation

## 'Low risk' for first VTE

- Heterozygous for FVL or for prothrombin gene mutation

# Risk factors for thrombosis

## HEREDITARY

- Age
- Gender
- Positive family history
- Hereditary thrombophilia

## ACQUIRED

- Post-partum > pregnancy
- Surgery, trauma and immobilization
- Obesity
- Certain drugs (estrogens, -imids, ...)
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- Prior VTE (PE/proximal > distal; unprovoked > provoked)

# Case vignette

## Young lady 18 years

### Risk factors

- Positive family history (RR 2)
- Young age of the affected family member, provoked by pregnancy, factor V Leiden mutation
- Oral contraceptive (RR 4)

### Estimated risk of first VTE event\*

- If negative for FVL: 0.2% per year
- If positive for FVL: 0.5% per year

\*healthy controls without oral contraceptive:  
0.01% per year

## Gentleman 54 years

### Risk factors

- Male
- Not provoked
- Proximal DVT (popliteal)

### Estimated risk of recurrence (first 5y)

- D-dimer 0.3 mg/l: 17.8%
- D-dimer 1.0 mg/l: 24.7%

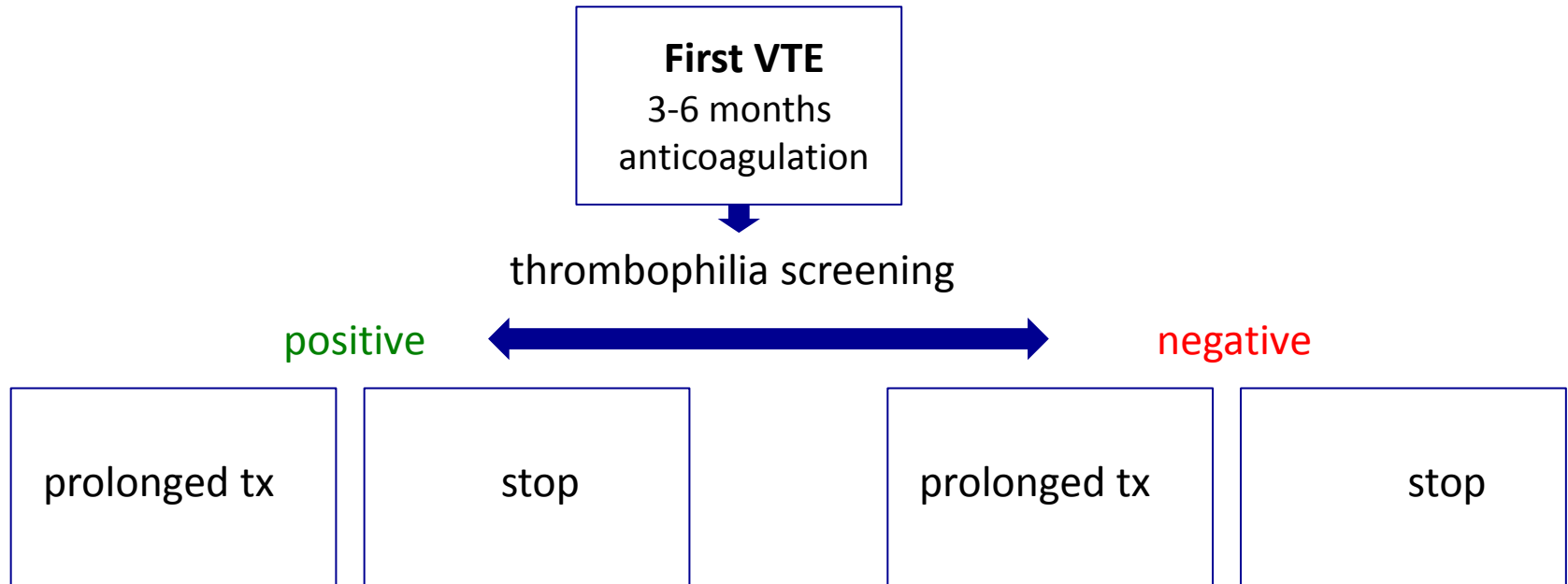
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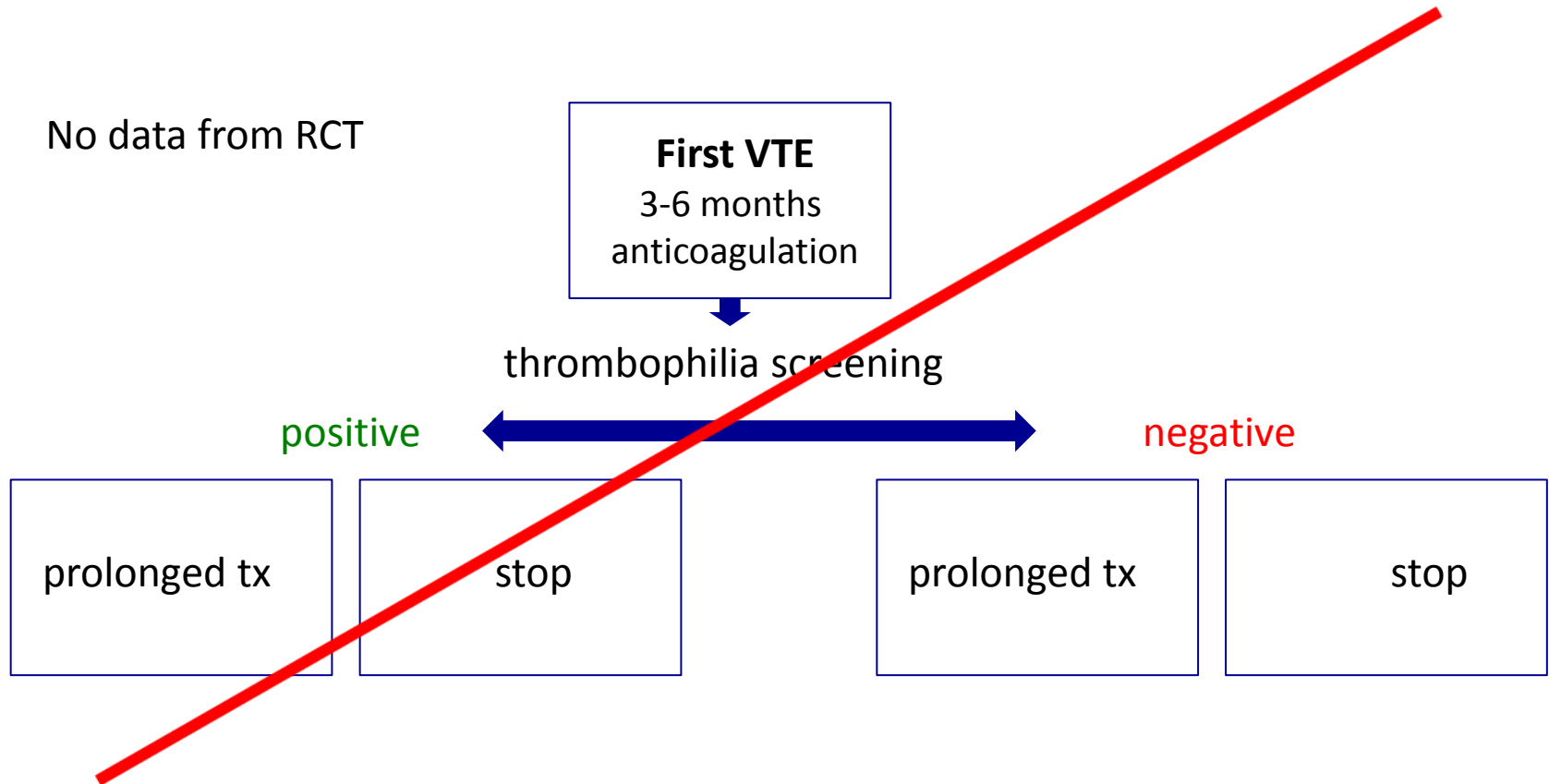
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- **the benefit of a given intervention**
- the bleeding risk
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# Benefit of a thrombophilia screening for relapse risk estimation



# Benefit of a thrombophilia screening for relapse risk estimation



# Benefit of a thrombophilia screening?

- **Primary prophylaxis:** Might help to identify family members at high-risk (e.g. antithrombin deficiency, FVL homozygous). Patient education.

- **Secondary prophylaxis:** Personal history much more important than the lab results.

- FVL heterozygous HR 1.3
- FII 20210A HR 0.7
- ....
- Non provoked vs provoked HR 1.9
- Male vs female HR 1.9 - 2.7
- PE vs distal DVT HR 2.6

Online score for *non provoked* TE based on localization, gender, D-dimer 3 weeks after discontinuation of anticoagulation: '[Vienna Prediction Model](#)'

# Benefit of a thrombophilia screening?

So far, thrombophilia screening in relatives of patients with thrombophilia has not shown to significantly reduce VTE incidence.

So far thrombophilia testing has not led to reduction of VTE relapse in patients with a first VTE.

# Case vignette

## Young lady 18 years

A positive result would strongly argue against the use of the estrogen containing contraception.

A negative result could wrongly reassure the patient. She is at higher risk than others, even if testing is negative.

## Gentleman 54 years

Do not test for hereditary thrombophilia, as it does not reliably predict relapse risk

# Case vignette

## Young lady 18 years

A positive result would strongly argue against the use of the estrogen containing contraception.

A negative result could wrongly reassure the patient. She is at higher risk than others, even if testing is negative.

## Gentleman 54 years

Do not test for hereditary thrombophilia, as it does not reliably predict relapse risk

### However

- I would test for acquired thrombophilia (antiphospholipid syndrome). Make a physical examination and a chest XR (smoker).
- > 50 years: candidate for lower GI cancer screening.

debatable



# What are the problems?

## Estimating

- the thrombotic risk
- the benefit of a given intervention
- **the bleeding risk**
- psychological impact of testing
- cost

# Bleeding risk long-term DVT/PE treatment

## Major bleeding after the acute phase of DVT/PE treatment (per year)

• Placebo	0.5%
• Aspirin	0.3%
• Vitamin K antagonist	≈2%
• DOAC	0.1-0.5%

## Bleeding Risk Scores (atrial fibrillation, VKA)

- HEMORR<sub>2</sub>HAGES Score
- HAS-BLED
- ATRIA, ORBIT, ....



# Case vignette

## Young lady 18 years

No primary prophylaxis with anticoagulation as the bleeding risk outweighs the thrombosis risk).

## Gentleman 54 years

Relatively low bleeding risk is helpful when recommending long-term anticoagulation.

# What are the problems?

## Estimating



- the thrombotic risk
- the benefit of a given intervention
- the bleeding risk
- **psychological impact of testing**
- cost

# What are the problems?

## Estimating

- the thrombotic risk
- the benefit of a given intervention
- the bleeding risk
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- **cost**

# Costs

Dipartimento di medicina di laboratorio  

EMATOLOGIA IOSI  
LABORATORIO DI EMATOLOGIA EOLAB

PD Dr. med. Georg Stüssi  
Primario

COGNOME NOME  
DATA NASCITA

**SCREENING TROMBOFILIA**

Richiedente: ?  
Copia a: -  
Data prelievo: ?      Data entrata: ?      Data referto: ?  
Numero richiesta ?

Indicazione: Testo

Analisi	Valore	Unità di misura	Valori di riferimento
Quick		%	70-130
aPTT		secondi	25-37
Fibrinogeno		g/l	1.7 – 4.5
Tempo di trombina		secondi	10.3 – 16.6
D-dimeri		mg/l	<0.50
Fattore VIII attività		%	50 – 150
Antitrombina funzionale		%	83 – 128
Antitrombina immunologica		%	80 – 120
Proteina C funzionale		%	70 – 140
Proteina S libera funzionale		%	64 – 149
Proteina S libera immunologica		%	♀ 55-124 / ♂ 74-146
Fattore V Leiden			negativo
Protrombina G202010A			negativo
Lupus anticoagulans		rapporto	<1.2
Anticorpi anti-cardiolipine			
IgG		U/ml	<10*
IgM		U/ml	<10*
Anticorpi anti-b2-glicoproteina 1			
IgG		U/ml	<7**
IgM		U/ml	<7**

\*10-40 zona grigia, >40 positivo  
\*\*7-10 zona grigia, >10 positivo

**COMMENTO FINALE**  
Testo

Health care insurance does not have to cover costs for genetic testing in asymptomatic individuals in Switzerland.

Complete panel:  
~ 750 PT (punto tariffario)

Incidence of hormone associated TE is very low (0.04%). Almost 100'000 asymptomatic women would need to be screened for FVL to prevent one death from TE.

# Thrombophilia testing – my view

## Whom?

- First spontaneous TE in individuals < 45 years
- Recurrent TE
- Positive family history (first-degree relatives)
- Atypical localization: e.g CNS venous, abdominal (*JAK2*, ev PNH)
- Recurrent miscarriage with or without thrombosis (APL-Abs)
- Thrombosis despite anticoagulation (heparin -> HIT)
- Skin necrosis during anticoagulation (protein C/S, HIT)

## When?

- Not in the acute phase of the event. If you plan to alter your strategy genetic testing, searching for *JAK2* mutation, APL-Abs, and PNH is possible.
- >2 weeks after suspension of VKA, > 3 days after DOAC or heparin suspension
- Protein S > 3 months after giving birth or after suspension of the contraceptive pill.

# THANK YOU

Young lady 18 years

Gentleman 54 years