DO WE NEED THROMBOPHILIA SCREENING IN PRESENCE OF DVT?

SORBONNE UNIVERSITÉ

F-CRIN NETWORK
INNOVTE
INvestigation Network On Venous Thrombo-Embolism

Hôpitaux Universitaires Est Parisien
TENON
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THROMBOPHILIA : DEFINITION?

- **Thrombophilia** is a coagulation trouble inducing an increase of coagulation capacity

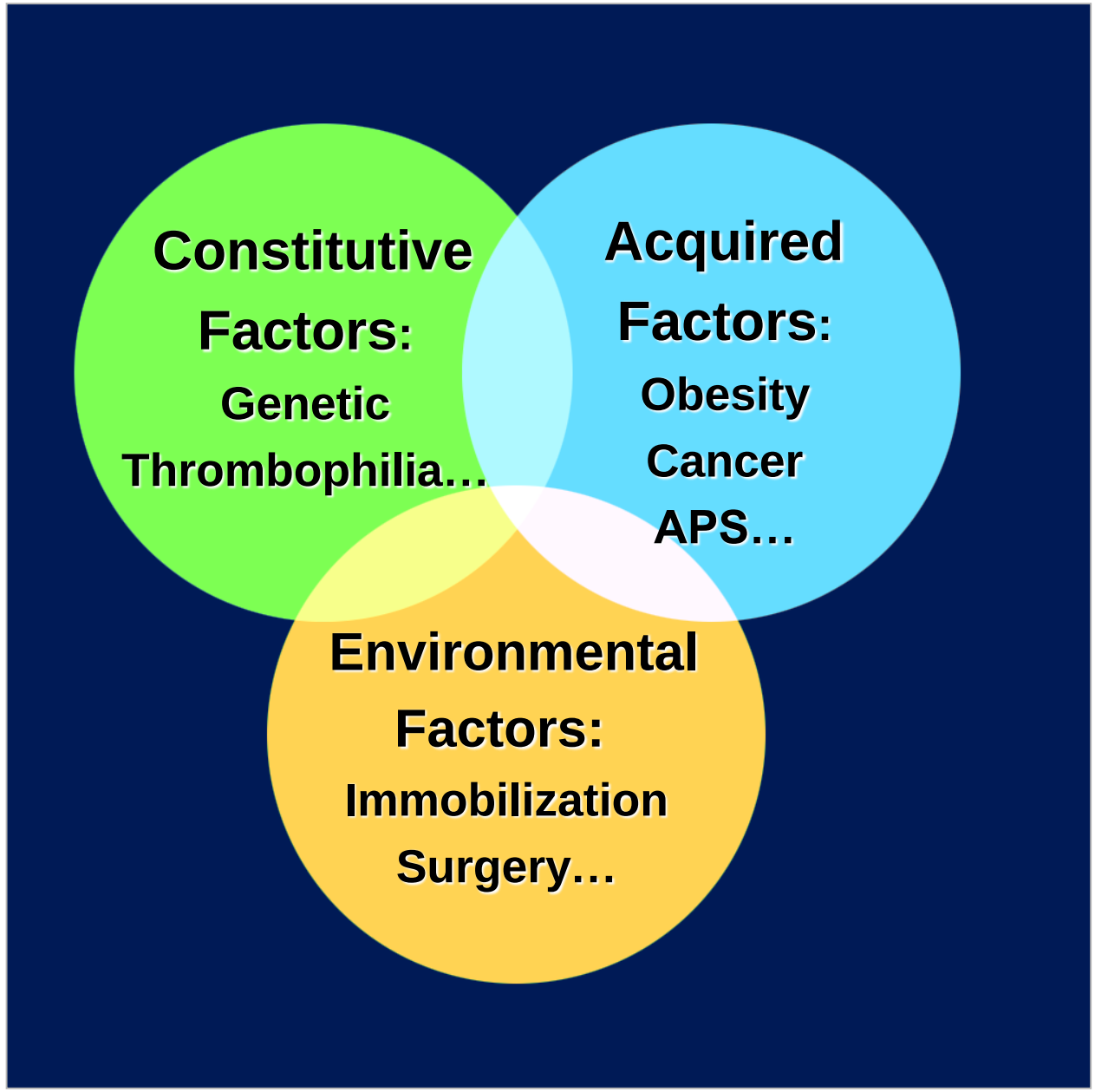
- **Thrombophilia** characterizes a person presenting an abnormality in the coagulation process

- **Thrombophilia**, constitutive or acquired, is a hemostatic disorder associated with a hypercoagulable state leading to thrombosis

- **Thrombophilia** is a patient status with a particular predisposition to present thrombotic episodes

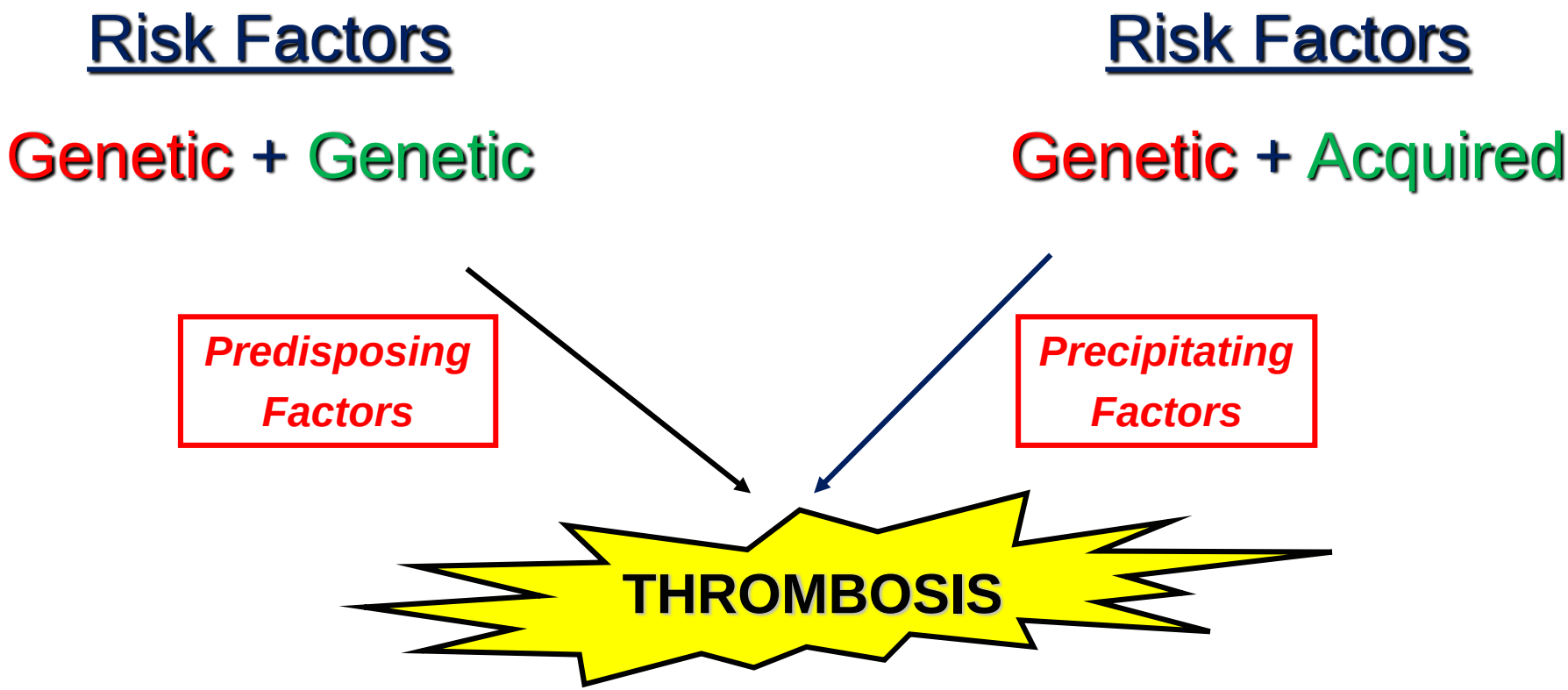
Wikipedia 2016

THROMBOSIS : MULTIFACTORIAL SOURCE



THROMBOSIS : MULTIFACTORIAL + MULTIGENIC

Interaction of Risk Factors



FAMILIAL THROMBOPHILIAS

- Deficiencies in Coagulation Inhibitors
  - AT 1965
  - PC 1981
  - PS 1982
- Resistance to Activated PC 1993
  Mutation R506Q FV Leiden 1994
- Facteur II G20210A Mutation 1996
- Polymorphisms ABO gene 2008
- Facteur IX Padua 2009
  (IX R338L ↑↑activity and X-linked transmission)
- Prothrombin Yukuhashi 2012
  (II R596L => resistance to AT and TM)
- ↑ FVIII, FIX,
- Dysfibrinogenemias
- FXIII 34val…

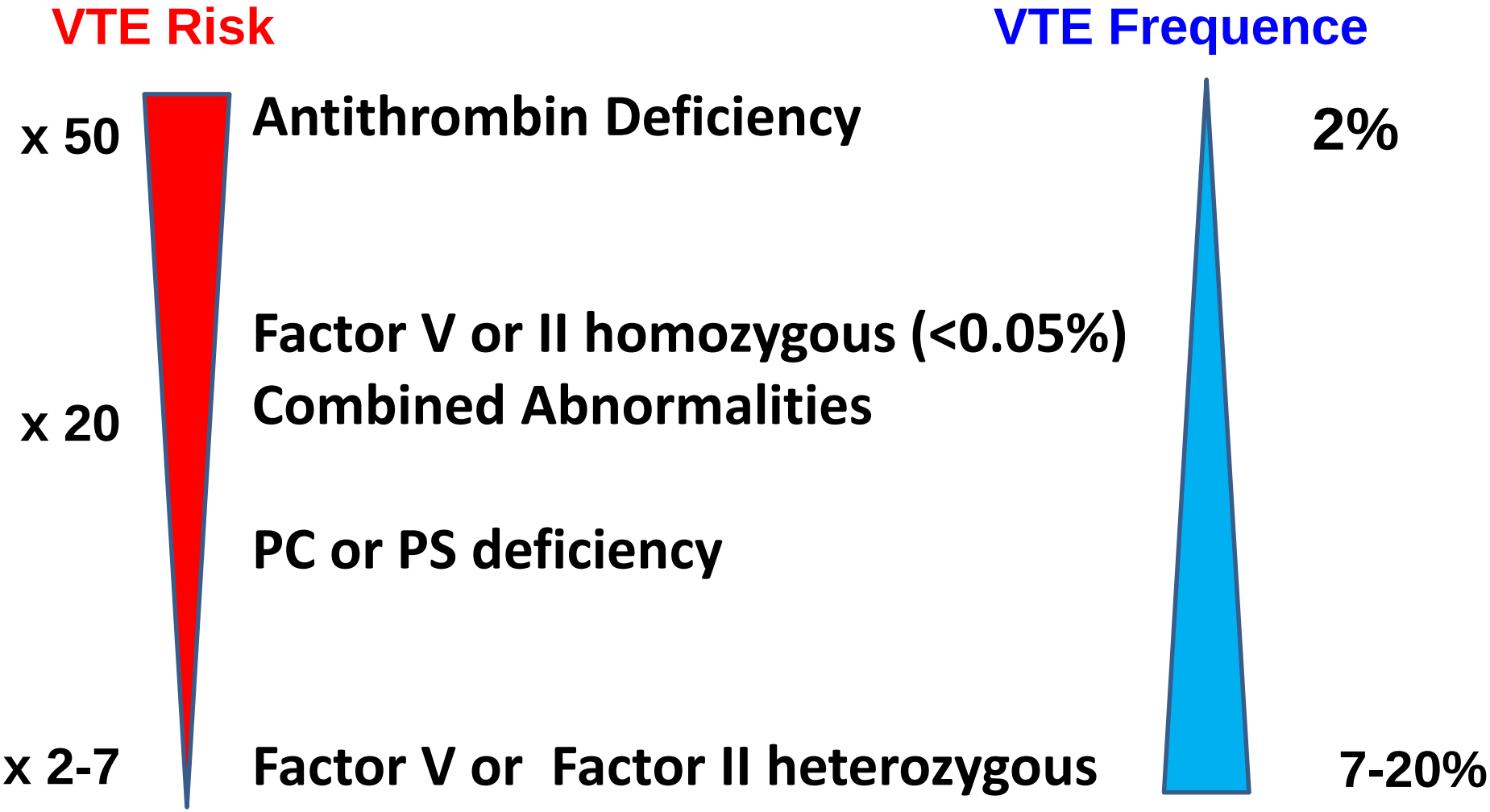
Tagagi et al, Thromb Haemost 2016

FAMILIAL THROMBOPHILIAS : PREVALENCE AND VASCULAR RISK

TYPE	Prevalence G^{I} population	Prevalence 1^{er} TEE	RR VTE
AT	0,02%-0,2%	1%	5-50
Protein C	0,1%-0,5%	3%	7-15
Protein S	0,1%-0,2%	1%-2%	6-10
FV Leiden	2%-18%	15%-20%	5-8
FII Leiden	2%-12%	6%-15%	2-4

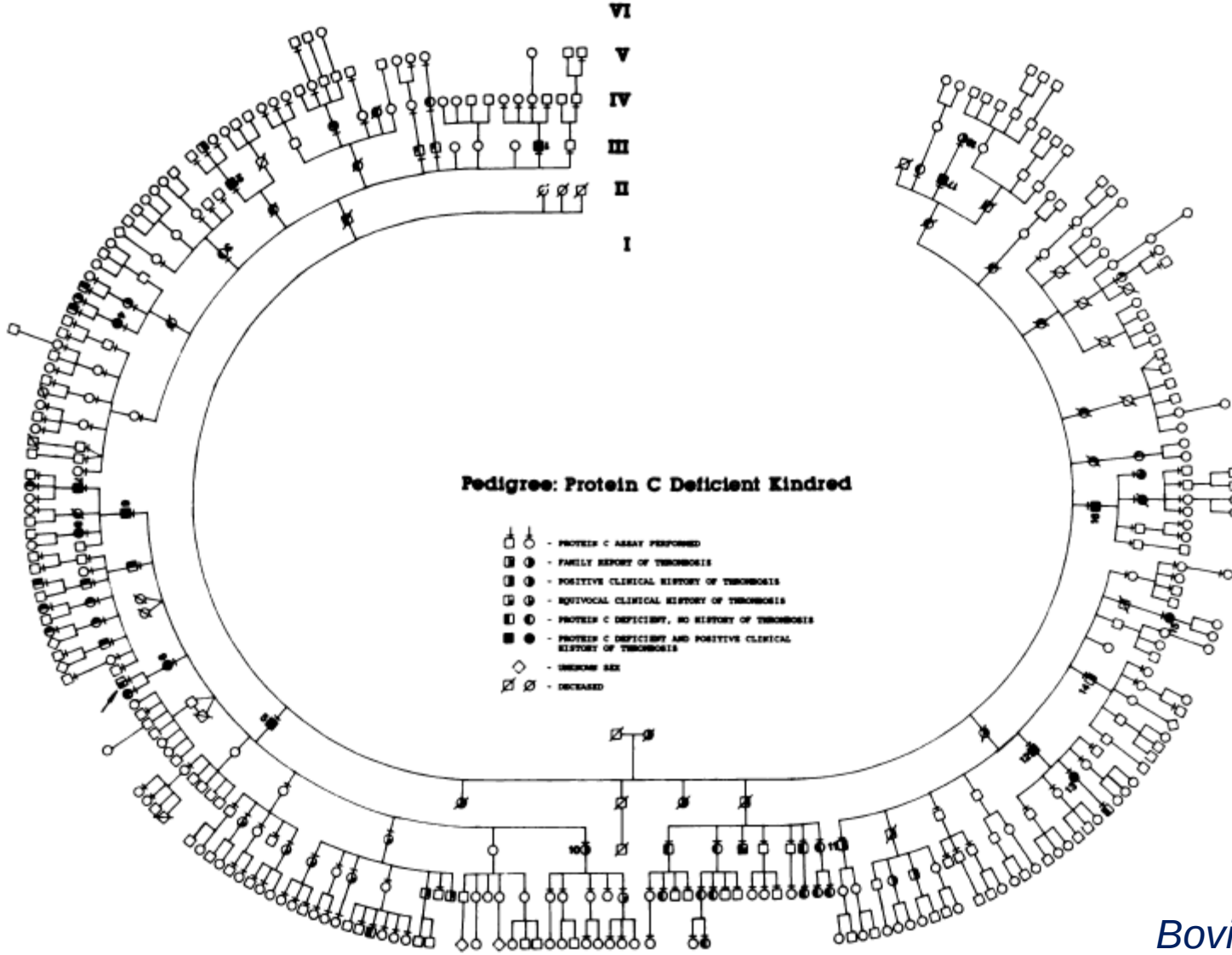
Blanco-Molina et al, Thromb Res 2012

DIFFERENCE OF RISK AND FREQUENCE



UTILITIES OF THROMBOPHILIA TESTING

- **Patient Explanation on the Reasons of Thrombosis?**



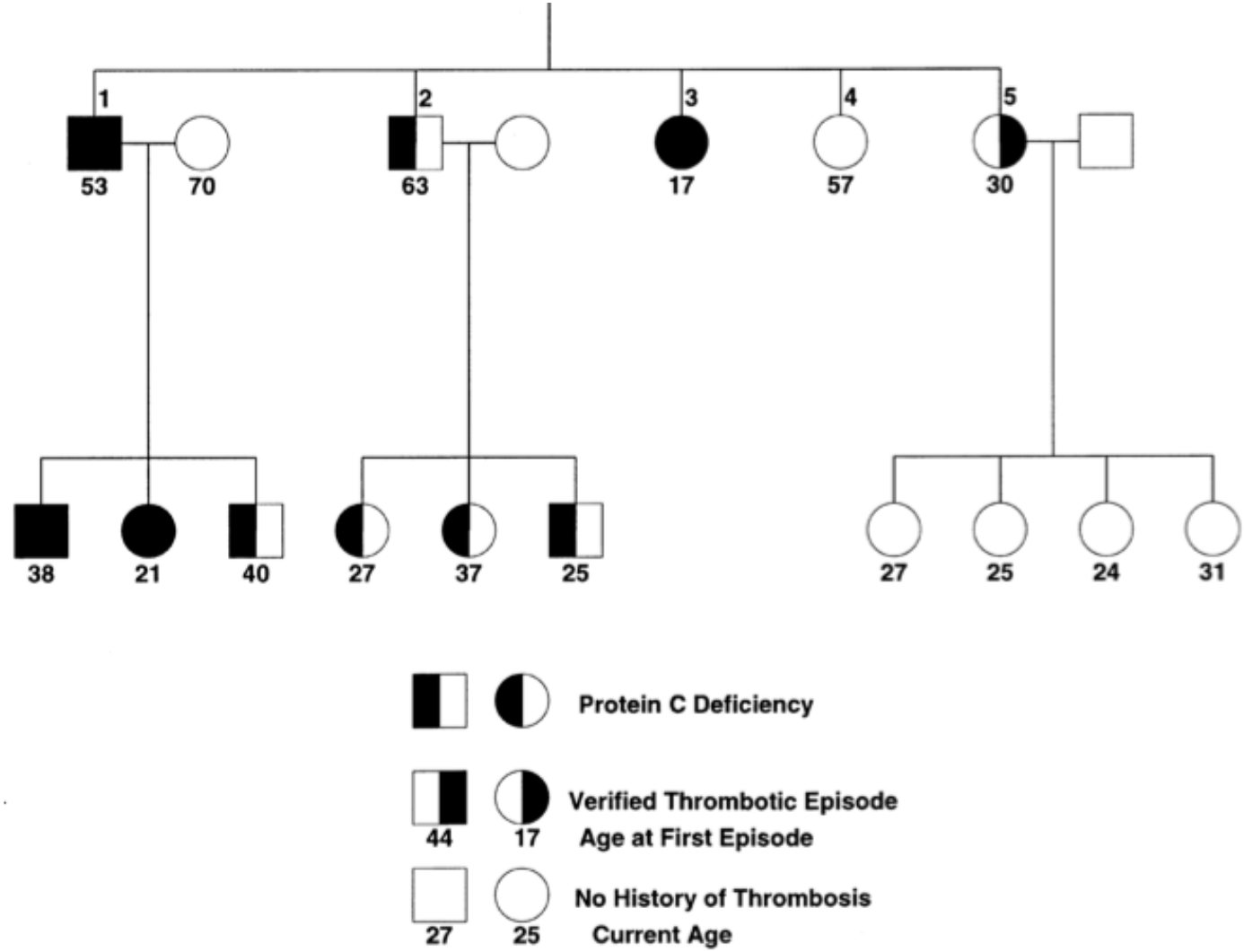
Bovill et al Blood 1989

Thrombophilic Family Franco-Canadian – 710 members

Heterozygous Deficiency in PC (Type 1 – His107Pro mutation exon 6)

28% of 144 mutation carriers had a DVT (60% < 40 yo)

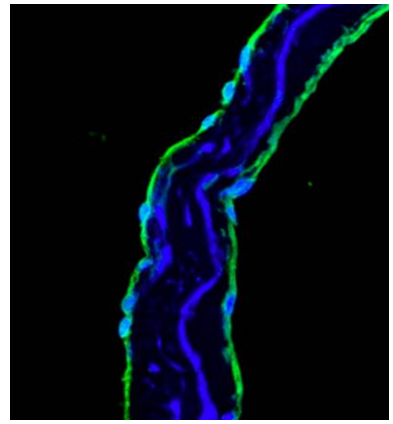
An Unknown Genetic Defect Increases Venous Thrombosis Risk, through Interaction with Protein C Deficiency



Haastedt et al Am J Hum Gen 1998

Cell ADhesion Molecule 1: a Novel Risk Factor for VTE

"The interaction of abnormal or deficient endothelial CADM1 with PC deficiency suggests a novel mechanism of impaired endothelial barrier function conferring increased thrombosis risk in inherited thrombophilia that may shed light on the poorly understood third member of the Virchow triad : the vascular wall."

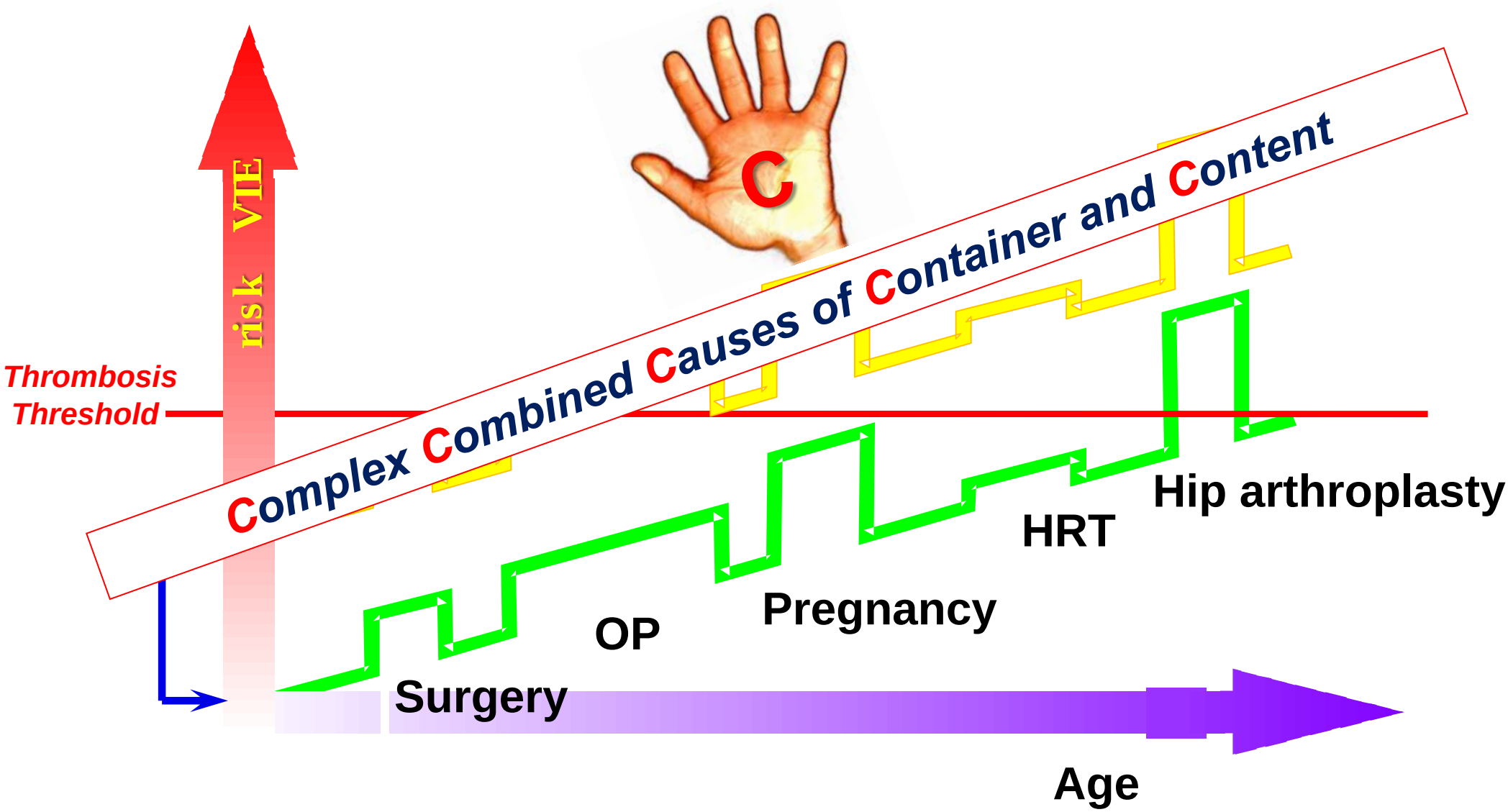


Haastedt et al Blood 2009

Genetic Variants in Cell ADhesion Molecule 1 (CADM1): A Validation Study of a Novel Endothelial Cell Venous Thrombosis Risk Factor

De Haan et al Thromb Res 2014

THROMBOPHILIA TO EXPLAIN DVT?



UTILITIES OF THROMBOPHILIA TESTING

- **Patient Explanation on the Reasons of Thrombosis?**
- **Evaluation of Thrombosis Recurrence Risk?**
- **Determination of Treatment Duration?**

THROMBOPHILIA AND RELATIVE RISK

Thrombophilia	Risk relative to persons without the respective thrombophilia	
	First VTE	Recurrent VTE
Thrombophilia not present	Reference group	Reference group
Heterozygous II G20210A	3.8 (95 % CI 3.0–4.9) [34]	1.45 (95 % CI 0.96–2.21) [31]
Heterozygous FVL	4.9 (95 % CI 4.1–5.9) [34]	1.56 (95 % CI 1.14–2.12) [31]
Homozygous II G20210A	Insufficient data	Insufficient data
Heterozygous FVL + heterozygous II G20210A[a]	20 (95 % CI 11.1–36.1) [34]	1.0 (95 % CI 0.6–1.9) [32] or 4.81 (95 % CI 0.50–46.3) [31]
Homozygous FVL[a]	18 (95 % CI 4.1–41) [33]	1.2 (95 % CI 0.5–2.6) [32] or 2.65 (95 % CI 1.18–5.97) [31]
Protein S deficiency	30.6 (95 % CI 26.9–55.3) [30]	Increased, but insufficient data for accurate risk assessment
Protein C deficiency	24.1 (95 % CI 13.7–42.4) [30]	
Antithrombin deficiency	28.2 (95 % CI 13.5–58.6) [30]	

Moll J Thromb Thrombolysis 2015

Thrombosis Research 151, Suppl. 1 (2017) S11–S15

Contents lists available at ScienceDirect

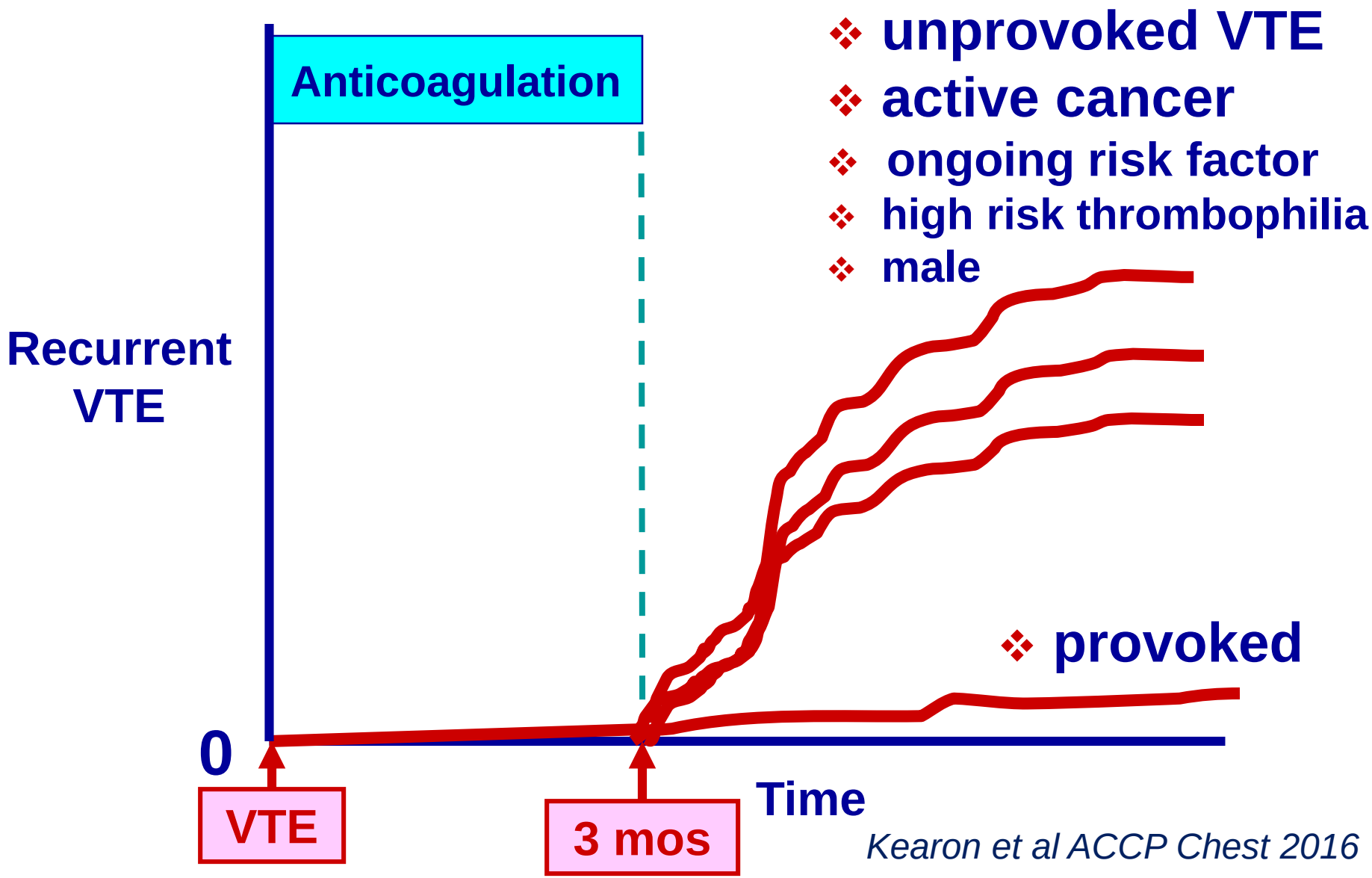
Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

	Hazard ratio (95% CI)
Factor V Leiden	
Patients, *N*	
Recurrent DVT	3.13 (1.79–5.67)
Recurrent PE	0.98 (0.40–2.35)
Major bleeding	–
Cerebral	–
Death	1.29 (0.38–4.59)
Prothrombin mutation	
Patients, *N*	
Recurrent DVT	1.89 (1.00–3.65)
Recurrent PE	1.82 (0.83–4.12)
Major bleeding	–
Death	0.61 (0.16–2.11)

Men with FVL or FIIL are at a much higher risk for VTE recurrences than Women.

INDIVIDUALIZED TREATMENT DURATION



Kearon et al ACCP Chest 2016

DURATION OF TREATMENT FOR VTE

	duration
Provoked (transient, reversed risk)	3 months
Unprovoked	indefinite*
Continuing risk (unresolved cancer, AT deficiency, APLS)	indefinite*

*Periodic reassessment re:

1) New patient risk factors for bleeding, thrombosis
2) New knowledge
3) Patient preference

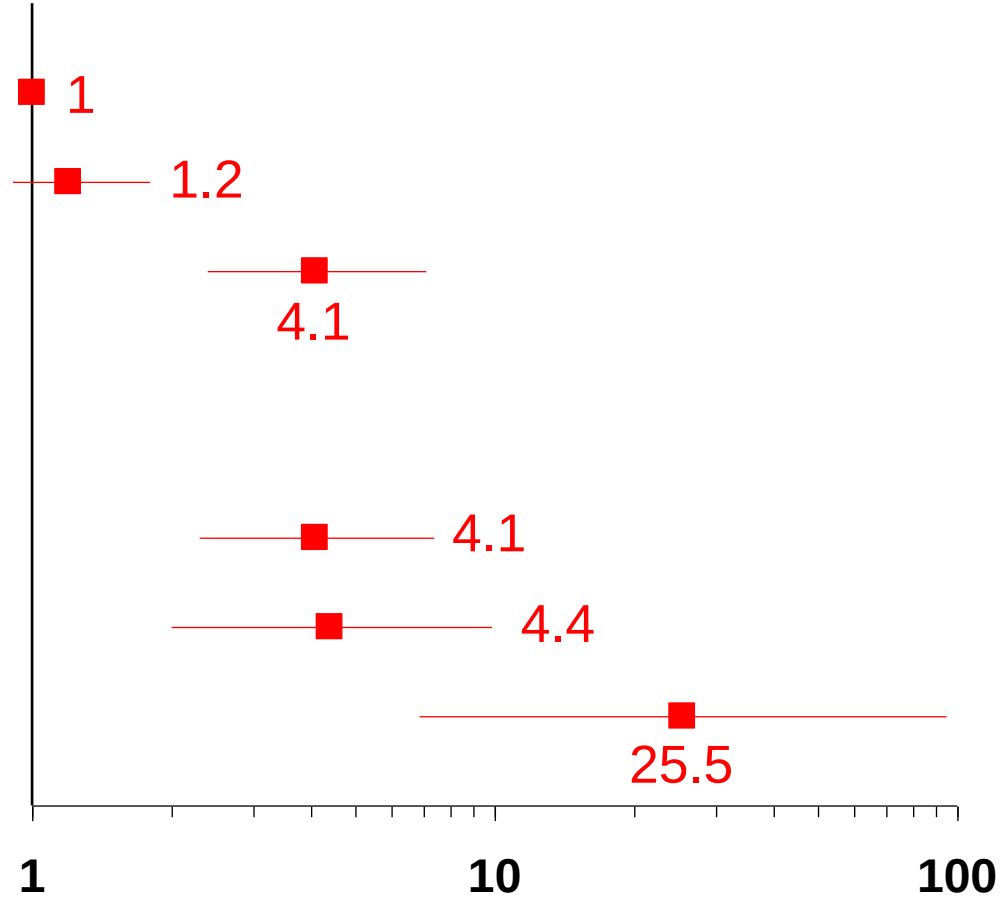
Kearon et al ACCP Chest 2016

UTILITIES OF THROMBOPHILIA TESTING

- Explaining to the patient the reasons of thrombosis occurrence?
- Evaluation of the risk of Thrombosis recurrence?
- Determination of treatment duration?
- Protective strategy for targeted siblings in risky situations?

HRT AND DVT : MUTATIONS IMPACT
ESTHER STUDY

Estrogen	*Mutation*	*Cases/Controls*	*Odds ratios (95 % CI) **
No E	no	*93/316*	1
Transdermal E	no	*46/156*	1.2
Oral E	no	*37/41*	4.1
No E	yes	*31/25*	4.1
Transdermal E	yes	*14/13*	4.4
Oral E	yes	*14/3*	25.5



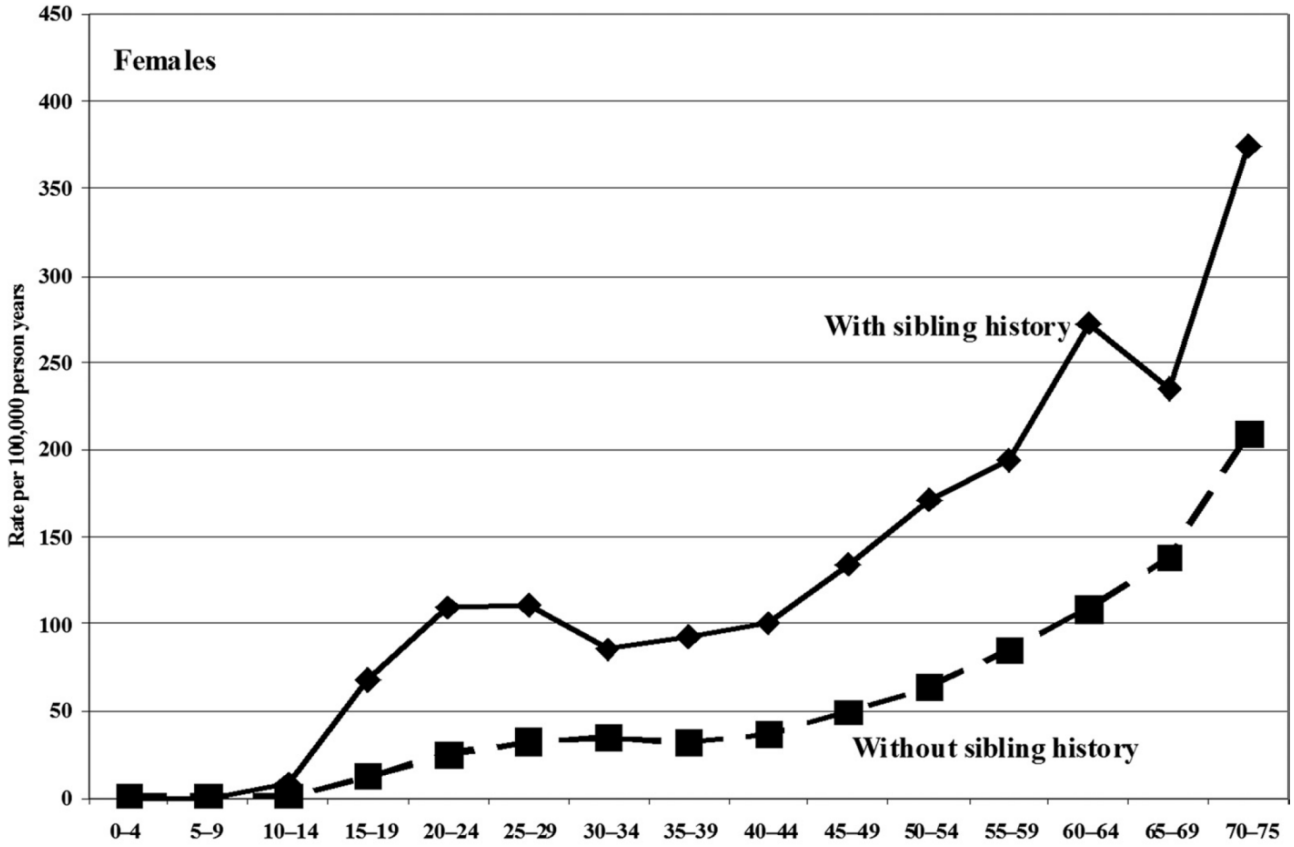
£ Either FVL or Prothrombin 20210

** Adjusted for BMI, family history of VTE and varicose veins*

Straczek et al., Circulation, 2005

THROMBOTIC RISK NOT EQUAL IN CASE OF FAMILY HISTORY

- Positive Familial History



45 362 patients ETEV+
2393 membres de la fratrie ETEV+ femmes

Zoller et al Circulation 2011

PERSONAL DISPOSITIONS …

- **Testing only for heritable biological thrombophilia will provide an uncertain estimate of risk…**

VTE PROPHYLAXIS AND PREGNANCY : RECOMMENDATIONS

- **SFAR** **France (2010)**
- **ACCP** **USA (2012)**
- **ACOG** **USA (2013)**
- **ABM** **France (2013)**
- **SOGC** **Canada (2014)**
- **RCOG** **UK (2015)**

- No Randomized Trials
- Low Level of Evidence
- Contradictions between various Recommendations

Multidisciplinary Approach

Thrombophilia, Pregnancy and Thrombotic Risk

Coagulation Defect	Women with History of Thromboembolism during Pregnancy and Puerperium (n=243) % (no. with defect/total no.)		Control Women (n=243) % (no. with defect/total no.)		P Value	Odds Ratio	95%CI†
Genetic defects ‡ §							
FVL heterozygous	28.44	60/211	8.02	19/237	<0.0001	**4.6**	2.65-7.95
FVL homozygous	2.58	4/155	0.15 ¶		<0.0001	**17.2**	6.3-47
Prothrombin G20210A heterozygous	7.93	13/164	2.68	6/224	0.029	**3.1**	1.16-8.41
FVL and prothrombin G20210A (compound heterozygous)	7.93	13/164	0.18 ¶		<0.0001	**47**	26-84
Antithrombin deficiency (activity)							
Mild deficiency (cut-off <90%)	9.18	19/207	4.83	10/207	0.083	**2.0**	0.9-4.93
Severe deficiency (cut-off <60%)	0.97	2/207	0.02‖		<0.0001	**49**	11.5-204
Protein C deficiency (activity)							
Mild deficiency (cut-off <76%)	10.67	19/178	4.98	10/201	0.037	**2.3**	1.03-5.1
Severe deficiency (cut-off <50%)	1.69	3/178	0.31¶		0.019	**5.5**	1.8-17.3
Protein S deficiency (activity)							
Mild deficiency (cut-off <56%)	10.73	19/177	4.50	9/200	0.021	**2.6**	1.12-5.8
Severe deficiency (cut-off <40%)	3.95	7/177	1.0	2/200	0.089	**4.1**	0.84-19.9
Free protein S deficiency (concentration)							
Mild deficiency (cut-off <57%)	12.1	19/157	4.17	6/144	0.02	**3.2**	1.23-8.17
Severe deficiency (cut-off <40%)	6.37	10/157	0.69	1/144	0.011	**9.7**	1.2-76.9
Family history of VTE in first-degree relatives ‖	39.1	95/243	16.5	40/243	<0.0001	**3.3**	2.2-5.0

Gerhardt et al, Blood 2016

Thrombophilia, Pregnancy and Thrombotic Risk

- **1 – Major Risk**

Clinical Risk	Biological Risk
Recurrent DVT On-Going Indefinite AC Treatment	AT* Deficiency non HBS type 1 ou 2 APLS*

  - Expert Follow-Up
    - Echo-Doppler (basal status)
    - LMWH at **curative dosage** during **all pregnancy and post-partum period**
    - adjusted to body weight
    - Stockings during pregnancy and post-partum
    - VKA or DOACs in post-partum

1. Agence de biomédecine 2013, 2. RCOG 2015
3. ACCP 2012

Thrombophilia, Pregnancy and Thrombotic Risk

- **2 – High Risk**

Clinical Risk	Biological Risk
- Previous proximal DVT idiopathic - Previous DVT assoicated with pregnancy or OP contraceptive	With ou without biological thrombophilia
- Previous personal DVT with transient risk factor - Familial DVT but no personal DVT	Major Thrombophilia: FV ou FII homozygous gene mutation, Combined heterozygous thrombophilias

  - Expert Follow-Up
    - Echo-Doppler (basal status)
    - LMWH at **prophylactic dosage** during **all pregnancy and post-partum period**
    - adjusted to body weight
    - Stockings during pregnancy and post-partum

1. Agence de biomédecine 2013, 2. RCOG 2015
3. ACCP 2012

Thrombophilia, Pregnancy and Thrombotic Risk

- **3 – Moderate Risk**

Clinical Risk	Biological Risk
- Previous DVT with transient risk factor (no pregnancy and no OPC pill) - Familial DVT and ni personal DVT - Association with minor risk factors (Table)	Non Major Biological Thrombophilia Detected in Familial survey

- LMWH at **prophylactic dosage in post-partum period**
  - Stockings during pregnancy and post-partum
  - France ABM 2013 : Start during 2nd or 3rd trimester if combined to > 2 RF
  - UK RCOG 2015 : LMWH > 28 weeks (recommandation level D)

OR >10 = High Risk

1. Agence de biomédecine 2013, 2. RCOG 2015
3. ACCP 2012

Risk Factors For Maternal VTE Absolute Risk < 1%

Risk Factors	Adjusted OR
• Lupus Erythémateux Disséminé	8
• Cardiopathie majeure	7
• Maladie inflammatoire de l'intestin	4
• Drépanocytose	4
• Grossesse obtenue par PMA	4
• Prééclampsie avec RCIU	4
• Grossesse multiple	4
• Infection du post-partum	4
• Obésité IMC>30 ou poids > 120 kg	4
• Tabagisme (>10 cig/j avant grossesse ou persistant)	3
• **Thrombophilie bas risque asymptomatique***	**3**
• Anémie durant grossesse	3
• Hémorragie grave du post-partum (> 1L et/ou transfusion)	3
• Accouchement prématuré < 37SA	3
• Césarienne en urgence	3
• Parité > 3	2
• Varices importantes	2
• Age> 35 ans	1.5

Additive Evaluation
OR>10 => Absolute Risk >1%

- ***Heterozygous FVL or FIIL***
- ***Heterozygous PC or PS Deficiency***

Sénat et al J Gyn Obst Biol Reprod 2015
Recommandation du post-partum

DEDICATED STRATEGY

FVL heterozygous
No family history

- **Other Risk Factor**
  - **None**

Score 3

Florence

Moderate Risk

Stockings
LMWH Prophylaxis
Only in post-partum
6 to 8 weeks

FVL heterozygous
No family history

- **Other Risk Factor**
  - **Age>35 yo**
  - **Obesity**
  - **Smoking**
  - **Varicosis…**

Score 13,5

Catherine

High Risk

Echo-Doppler
Stockings
LMWH Prophylaxis
Pregnancy + post-partum
6 to 8 weeks

WHO… WHY?

	1st episode	Recurrence risk	Asympto. Relatives	Pop. Gal
French Consensus Guideline, 2009 (11)	Yes, in patients with a single unprovoked proximal DVT and/or PE < 60 years, in patients with recurrent proximal DVT and/or PE, and in patients with recurrent unprovoked distal DVT < 60 years)	Yes (testing for deficiency of AT, PC, PS, homozygosity, and double heterozygosity for FVL and PT20210A)	Yes (possible exception for relatives of probands who are isolated heterozygotes for FVL and PT20210A)	No
British Committee for Standards in Haematology, 2010 (12)	No (possible exception for those with a strong family history of unprovoked recurrent VTE)	No (possible exception for those with a strong family history of unprovoked recurrent VTE)	No (possible exception for relatives of probands with deficiency of AT, PC, PS)	No
National Institute for Health and Clinical Excellence (NICE), 2012 (14)	Yes, in patients with unprovoked VTE and with a first-degree relative with VTE < 50 years (testing for deficiency of AT, PC, PS)	Yes, in patients with a first-degree relative with VTE < 50 years if anticoagulation treatment is to be discontinued (testing for deficiency of AT, PC, PS)	No (possible exception for females of childbearing age who are first-degree relatives of patients with VTE and known thrombophilia and are planning oral contraception or pregnancy)	Not analysed

De Stephano et al Thromb Haemost 2013

CANDIDATES FOR THROMBOPHILIA TESTING

TABLEAU 3

Bilan étiologique d'une maladie veineuse thromboembolique

	Examen clinique
MTEV provoquée	Pas d'exploration complémentaire
Thrombose proximale ou embolie pulmonaire non provoquée (1er événement), ou de thromboses veineuses profondes récidivantes	Recherche d'un SAPL
MTEV non provoquée < 40 ans et antécédent familial non provoqué de 1er degré jeune	Bilan de thrombophilie
MTEV non provoquée < 40 ans chez la femme	Bilan de thrombophilie en cas de désir de grossesse (pour gestion éventuelle de la prévention)
MTEV non provoquée > 50 ans	Bilan hépatique, radiographie pulmonaire, hémogramme, mise à jour des dépistages carcinologiques (Hemoccult, frottis cervico-vaginaux, mammographie, PSA) Si point d'appel carcinologique : cibler Si thrombose récidivante dans l'année, ou récidivante sous traitement, ou bilatérale (ou D-dimères > 4 ng/mL au diagnostic ?) : dépistage de cancer (TDM)
Si stigmate d'hémolyse intravasculaire	Recherche HPN
Hyperplaquettose ou polyglobulie	Recherche d'un syndrome myéloprolifératif (mutation JAK2, culture de progéniteurs hématopoïétique)

Luxembourg et al Thromb Haemost 2014; Pernod G, Précis MTEV SFMV 2015

WHICH EXAMS…?

Juste prescription des examens de biologie
http://dommed.aphp.fr:4567/jpbio

- Hemogram
- PT ApTT,
- Lupus Anticoagulant
- AT,PC,PS Activities
- APCR and mutation FV Leiden
- Mutation G20210A FII
- Anticardiolipins, anti-β2GPI (IgG, IgM)
- Anti-PT, Anti-ET, Anti-Annexin V…

(Informed and Signed Consent)

WHEN…?

Test	Acute thrombosis	Unfractionated heparin	Low molecular weight heparin	Vitamin K antagonists	DOACs
Factor V Leiden genetic test	Reliable	Reliable	Reliable	Reliable	Reliable
APC resistance assay	Reliable[a]	???[a]	???[b]	Reliable[a]	Unreliable[h]
Prothrombin G20210A genetic test	Reliable	Reliable	Reliable	Reliable	Reliable
Protein C activity	???[c]	Reliable	Reliable	Low	Elevated[f]
Protein C antigen	???[c]	Reliable	Reliable	Low	Reliable
Protein S activity	May be low	Reliable	Reliable	Low	Elevated[f]
Protein S antigen	May be low	Reliable	Reliable	Low	Reliable
Antithrombin activity	May be low	May be low	May be low	May be elevated[h]	Elevated[g]
Lupus anticoagulant	Accurate[d]	???[e]	???[e]	???[e]	False positive[i]
Anticardiolipin antibodies	Accurate[d]	Reliable	Reliable	Reliable	Reliable
Anti-$ß_2$-glycoprotein-I antibodies	Accurate[d]	Reliable	Reliable	Reliable	Reliable
Homocysteine	Reliable	Reliable	Reliable	Reliable	Reliable

Far from the Acute Phase…

Moll et al J Thromb Thrombolysis 2015

Rule Out High Risk Thrombophilias…

DOACS AND THROMBOPHILIA TESTING

GEHT, http://www.geht.org

Tests pouvant être réalisés chez les patients traités par dabigatran, rivaroxaban et apixaban	
Antithrombine	**Activité :** - basé sur activité anti-Xa (dabigatran) - basé sur activité anti-IIa (rivaroxaban et apixaban) **Antigène**
Protéine C	**Activité amidolytique** **Antigène**
Protéine S	**Antigène libre**
Résistance à la protéine Ca	**Mutation Q506 du facteur V**
Mutation G20210A du gène de la prothrombine	**Mutation G20210A du gène de la prothrombine**
Recherche de SAPL	**Anticorps anticardiolipine** **Anticorps anti-bêta2GPI**

THROMBOPHILIA IS CLINICO-BIOLOGICAL

- 50% of clinical thrombophilias with negative biological audit
- 40 % of idiopathic VTE are associated with a genetic factor
- 40% of familial VTE history are associated with a genetic factor
- 30% of unprovoked VTE got 1st degree relatives with VTE history
- Impact in asymptomatic relatives : OPC, contextualized prophylaxis

Allain et al Rev Med Interne 2016

THROMBOPHILIA TESTING : UTILITY NOT FUTILITY

- All thrombophilias and all patients are not associated with the same risk of VTE
  - combined thrombophilia, AT deficiency, APLS…
  - heterozygous FV Leiden, PS deficiency…

- Thrombophilia identification may allow
  - Prophylaxis in situations at risk
  - Optimisation of antithrombotic strategy
  - Improvement of lifestyle habits
  - Patient motivation for personal and familial primary prevention

- Don’t neglect a « negative biological audit»

SEE RIGHT TO PROTECT RIGH