



Groupe d'Étude de la Thrombose
de Bretagne Occidentale

UMR 1304

Importance du phénotype clinique de la MVTE sur l'identification des causes physiopathologiques sous- jacentes

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Disclosures

Dr. Couturaud reports having received:

- **Industrial**
 - research grant support from Pfizer, BMS
 - and fees for board memberships or symposia from Bayer, Astra Zeneka, BMS, Daiichi Sankyo, Boehringer, GSK, MSD
 - and having received travel support from Bayer, Boehringer Ingelheim, Daiichi Sankyo, Leo Pharma, Bristol-Myers Squibb, MSD, GSK, Roche, Novartis and Actelion.
- **Foundations, public:**
 - Fondation des maladies rares
 - PHRC nationaux, interrégionaux, ANR
 - Fonds de dotation INNOVEO, UBO, Archipel
 - Bourse nouveau souffle

HISTORIQUE DES THROMBOPHILIES

Phénotype clinique:

- MVTE sans facteur déclenchant, récidivante,
- jeune,
- histoire familiale

Découverte des thrombophilies (héréditaires):

Perte de fonction: rares

1965 : déficit antithrombine (1%)

1980 : déficits protéine C, S, dysfibrinogénémies (1-2%)

Gain de fonction: fréquents

1994 : Mutation Leiden sur le facteur V (20%)

Concept de MVTE génétique démontré

1995 : Mutation G20210A du gène de la prothrombine (5%)

Années 2000 : divers SNPs

2023 ?

MVTE non provoquée

Facteur « Transitoire » ou « réversible »

Récidive de MVTE après 1 à 6 mois de traitement

Etudes	N	Follow-up months	Recurrent VTE after stopping anticoagulation		Relative Risk
			<i>Reversible Risk Factors</i>	<i>No Reversible Risk Factors</i>	
Randomized Trials					
B.T.S., 1992	712	12	0.9%	6.9%	8
Levine, 1995	398	11	1.7%	13.0%	8
DURAC, Schulman 1995	898	24	6.7%	18.0%	2.7
DOTAVK, Pinède, 2001	720	15	5.1%	10.0%	2
WODIT-PE, Agnelli 2003	326	35	7.6%	12.2%	1.6
Prospective Cohorts					
Prandoni, 1996	250	24	4.8%	24.1%	5
Pini, 1994	570	12	1.5%	11.1%	7.3
Baglin, 2003	187	24	0%	11.2%	22

< 3%/year

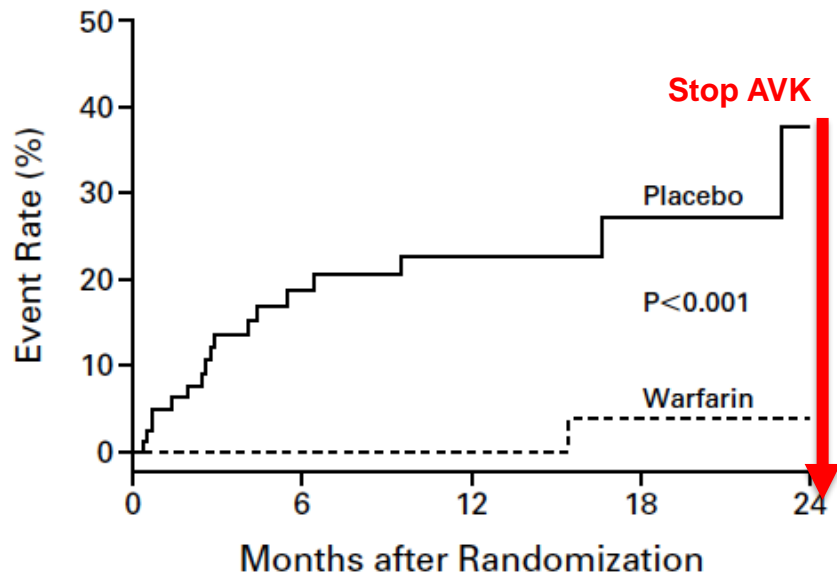
≥ 9%/year

Facteur transitoire/réversible
Traitement = 3 mois

Facteur persistant ou aucun facteur
Traitement > 3 mois ?

Durée minimale après une 1^{ère} MVTE non provoquée (3 vs 24 mois)

LAFIT STUDY



PATIENTS AT RISK

	0	6	12	18	24
Placebo	83	44	25	14	4
Warfarin	79	57	36	21	11

TABLE 3. RISK OF RECURRENCE OF VENOUS THROMBOEMBOLISM IN THE PLACEBO GROUP, ACCORDING TO SELECTED CHARACTERISTICS.*

CHARACTERISTIC	ALL PATIENTS (N=162)	PLACEBO GROUP (N=83)		
		PATIENTS WITH RECURRENCE (N=17)	PATIENTS WITHOUT RECURRENCE (N=66)	HAZARD RATIO (95% CI)†
		no./total no. (%)		
Hypercoagulable states				
Factor V Leiden	37/143 (26)	3/16 (19)	17/59 (29)	0.5 (0.1–1.8)
Homozygous	3/143 (2)	1/16 (6)	0/59	
Heterozygous	34/143 (24)	2/16 (13)	17/59 (29)	
Prothrombin gene mutation	7/141 (5)	1/16 (6)	2/59 (3)	2.2 (0.3–17)
Homozygous	2/141 (1)	0/16	0/59	
Heterozygous	5/141 (4)	1/16 (6)	2/59 (3)	
Antiphospholipid antibody	8/150 (5)	4/16 (25)	2/61 (3)	4.0 (1.2–13)
Lupus anticoagulant	4/150 (3)	2/16 (13)	1/61 (2)	6.8 (1.5–31)
Anticardiolipin antibody	4/148 (3)	2/16 (13)	1/61 (2)	2.3 (0.5–11)
Any state	48/150 (32)	7/16 (44)	20/61 (33)	1.4 (0.5–3.8)
Two or more states	4/150 (3)	1/16 (6)	1/61 (2)	2.0 (0.2–16)

Pas d'impact des thrombophilies héréditaire

Optimal term in 2000 ?

VTE with major transient (surgical) risk factor
= 3-fold lower risk of recurrence as compared to VTE with
persistent risk factor or no risk factor

- **Transient** vs **persistent** ?
→ *No inclusion of « no risk factors (idiopathic)»*
- **Reversible** vs non **reversible** ?
→ *No inclusion of « no risk factors (idiopathic)»*
- **Provoked** (or declenching = means “gun trigger effect”
and transient) vs **not provoked** (not declenched) VTE ?
→ *Acute transient risk factor versus other situations*

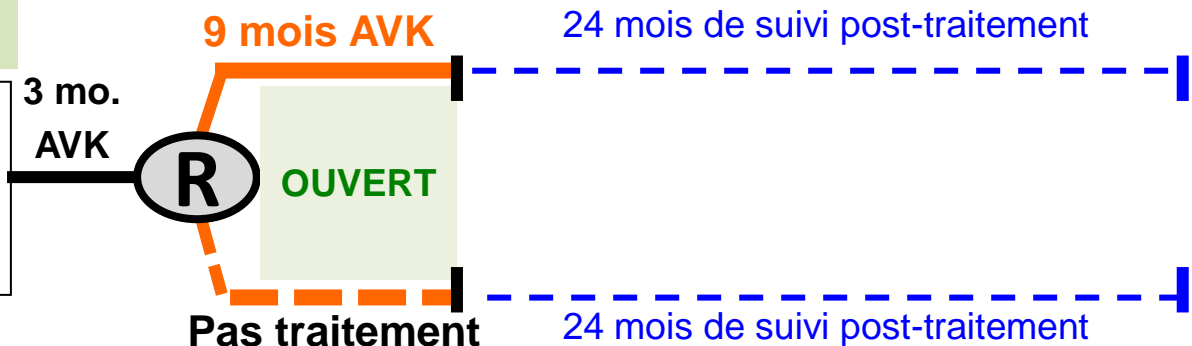


Clive Kearon

Etendre à 12 ou 24 mois après une 1^{ère} MVTE non provoquée

WODIT program

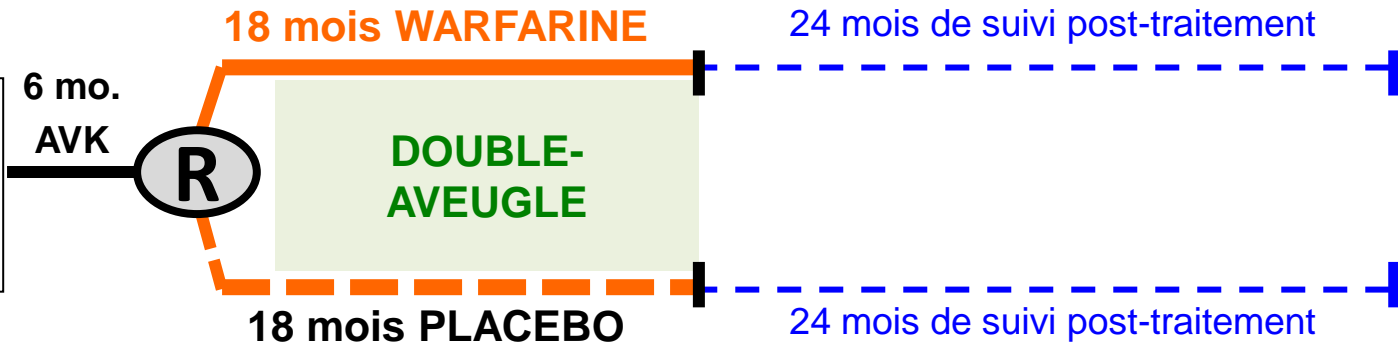
1^{ère} MVTE non provoquée
181 EP
267 TVP



Agnelli G et al, *NEJM* 2001
Agnelli G et al, *Ann Intern Med* 2003

PADIS program

1^{ère} MVTE non provoquée
371 EP
104 TVP

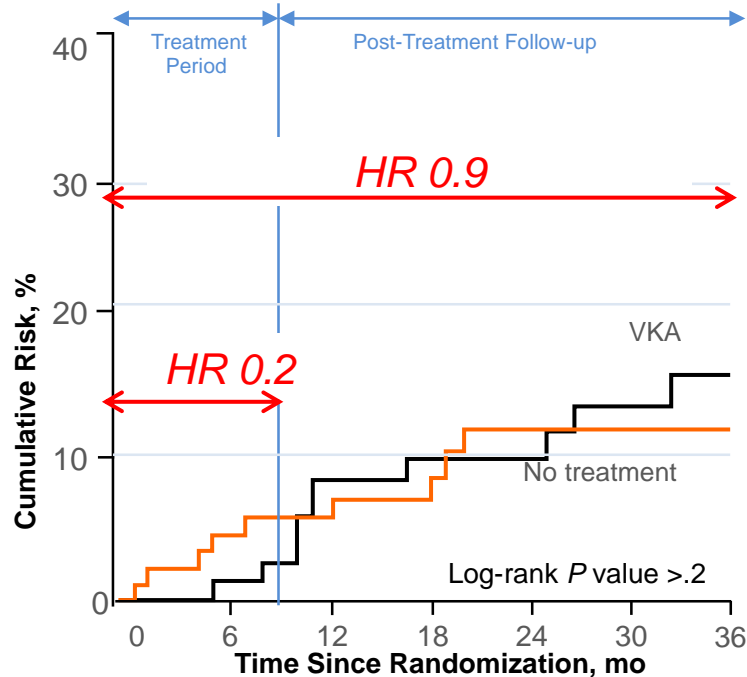


Couturaud F et al, *JAMA* 2015
Couturaud F et al, *Haematologica* 2019

Etendre à 12 ou 24 mois après une 1^{ère} EP non provoquée

WODIT PE (n=181) open RCT

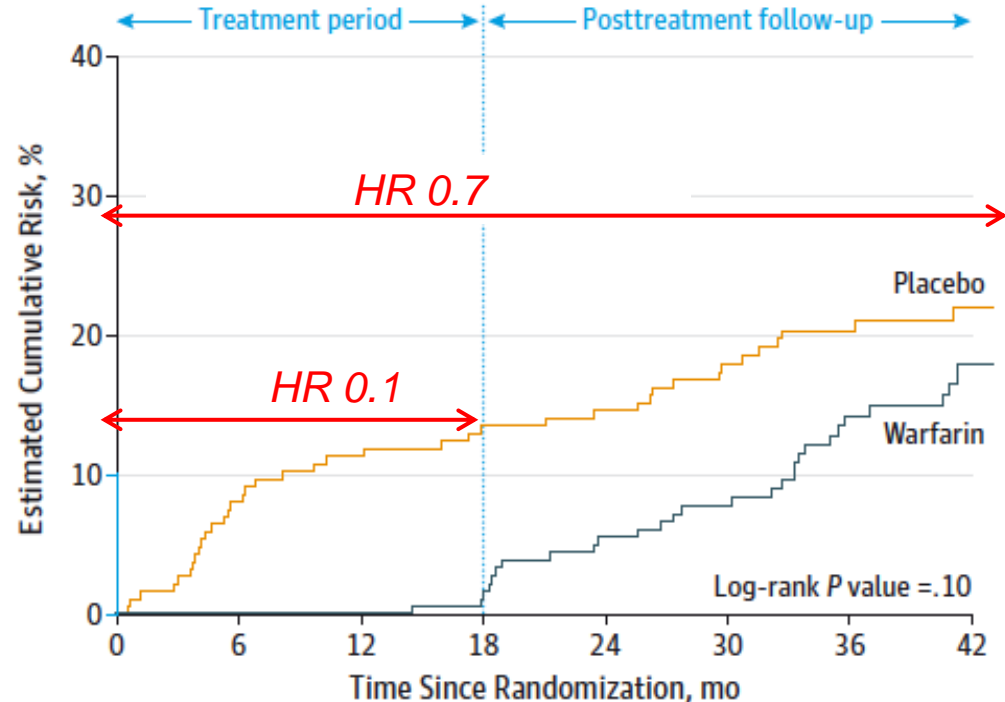
Après 3 mois: + 9 mois AVK vs pas de traitement



Agnelli G et al, Ann Intern Med 2003

PADIS PE (n=371) double-blind RCT

Après 6 mois: + 18 mois Warfarine vs placebo

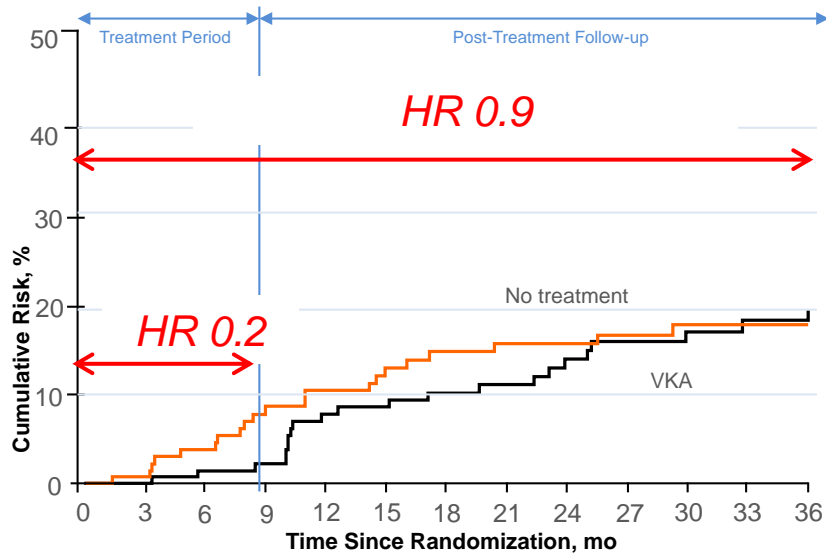


Couturaud F et al, JAMA 2015

Etendre à 12 ou 24 mois après une 1^{ère} TVP non provoquée

WODIT DVT (n=267) open RCT

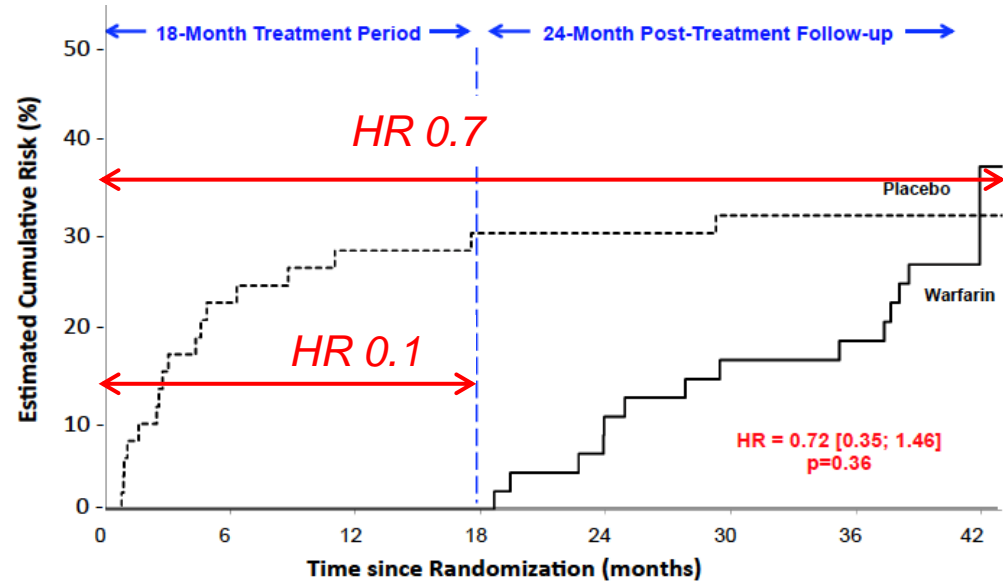
Après 3 mois: + 9 mois AVK vs pas de traitement



Agnelli G et al, NEJM 2001

PADIS DVT (n=104) double-blind RCT

Après 6 mois: + 18 mois Warfarine vs placebo



Couturaud F et al, Haematologica 2019

Impact d'un traitement étendu limité (1 à 2 ans)?

AUCUN

(en termes de récurrence de MVTE, létalité de la récurrence, mortalité)

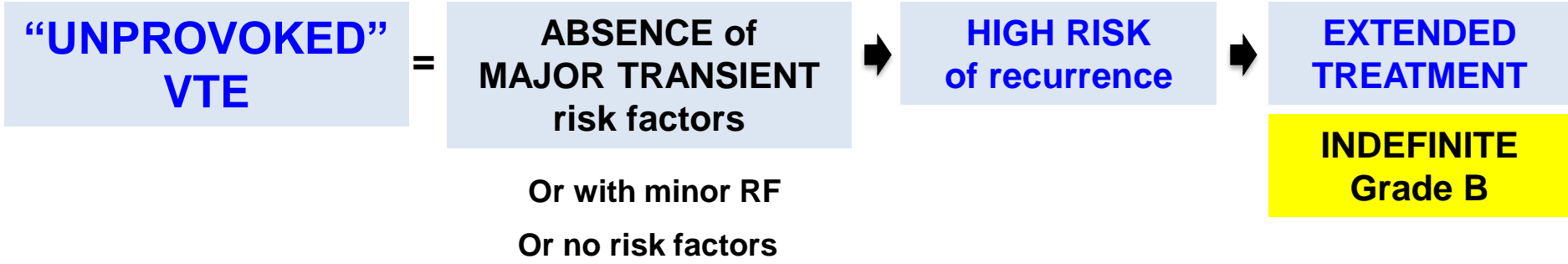
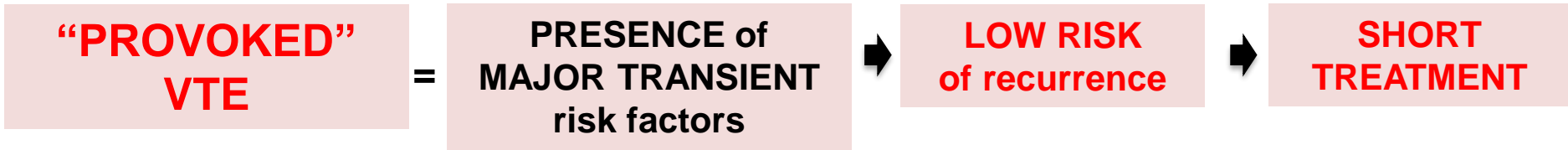
2 options seulement de traitement anticoagulant:

1- **Court** = 3 (≤ 6) mois

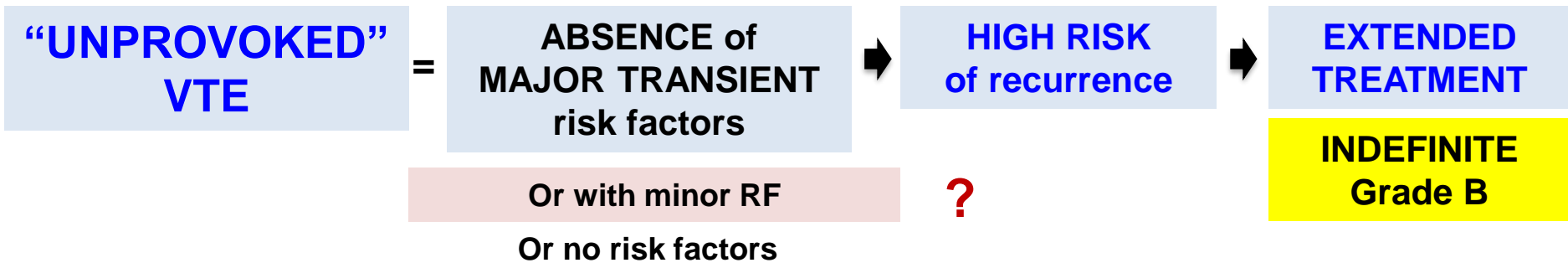
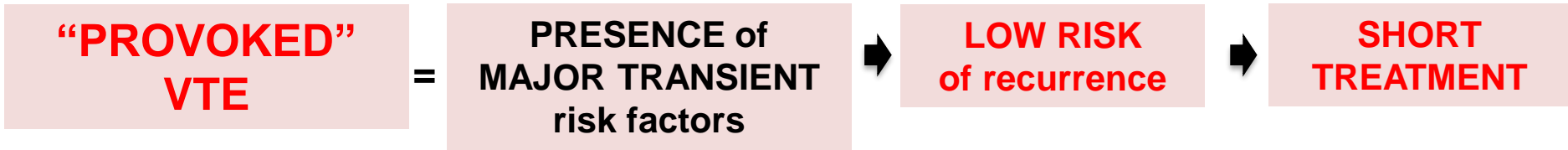
2- **Non limité**

ACCP 2016, ESC 2019, French Consensus 2019

Provoked vs Unprovoked VTE



Provoked vs Unprovoked VTE



Minor risk factors

Brest cohort (1881 patients)

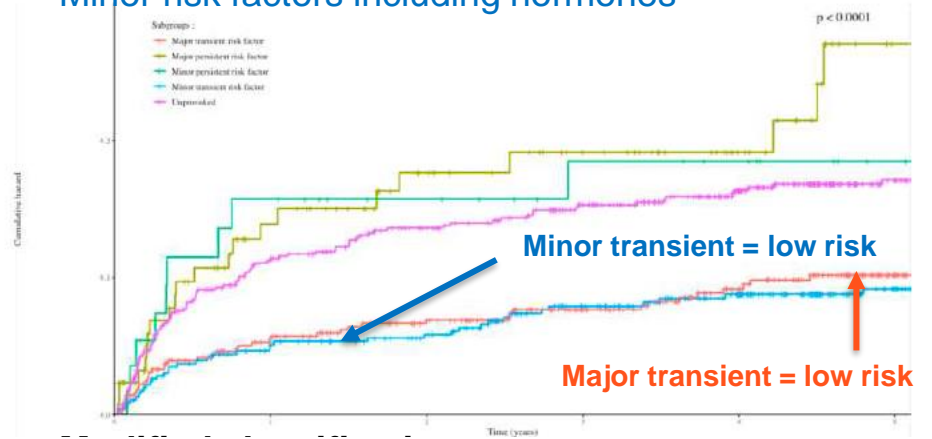
Aim:

- to validate ISTH risk classification
- To evaluate individual RF on recurrence
- To refine ISTH risk classification.

Variables	Univariable analysis HR (95%CI)	P-value	Multivariable Analysis (model 2) HR (95%CI)	P-value
MINOR TRANSIENT FACTOR^a				
Pregnancy or post-partum	0.26 (0.08-0.81)	0.021	0.26 (0.08-0.82)	0.02
Estrogen-containing pill	0.26 (0.14-0.47)	<0.001	0.25 (0.14-0.47)	<0.001
Hormonal replacement therapy	1.30 (0.60-2.57)	0.45		
Medically assisted procreation	3.67 (0.51-26.34)	0.20		
Travel in the past 3 months	0.90 (0.60-1.35)	0.615		
>6 hours	0.88 (0.37-2.11)	0.776		
Surgery with general anesthesia < 30 minutes	0.93 (0.44-1.98)	0.860		
Minor leg injury	0.00 (0.00-0.00)	0.99		

Original classification

Minor risk factors including hormones



PADIS-PE

Thrombophilia and recurrent VTE

	UNIVARIATE		MULTIVARIATE	
	OR (95% CI)	p	OR (95% CI)	p
Thrombophilia (total)	1.44 (0.85-2.42)	0.18		
Major Thrombophilia	1.83 (1.00-3.34)	0.049		
Minor Thrombophilia	1.17 (0.64-2.12)	0.61		

PADIS-PE

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Minor Thrombophilia	1.17 (0.64-2.12)	0.61		
FVL heterozygous	0.62 (0.23-1.71)	0.36		
G20210A heterozygous	1.52 (0.65-3.53)	0.33		
Elevated FVIII (90 th percent.)	2.30 (1.23-4.30)	0.01		

PADIS-PE

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Thrombophilia (total)	1.44 (0.85-2.42)	0.18		
Major Thrombophilia	1.83 (1.00-3.34)	0.049		
ACLAS (99 th percentile)	2.44 (0.59-9.98)	0.22		
Lupus Anticoagulant	2.21 (1.14-4.27)	0.02		
Antithrombin Deficiency	2.08 (0.51-8.51)	0.31		
Protein C deficiency	No recurrence	0.98		
Protein S deficiency	No recurrence	0.98		
FVL het. + G20210A het.	2.37 (0.32-17.3)	0.40		
FVL homozygous	No recurrence	0.98		
Minor Thrombophilia	1.17 (0.64-2.12)	0.61		
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ACLAS (99 th percentile)	2.44 (0.59-9.98)	0.22		
Lupus Anticoagulant	2.21 (1.14-4.27)	0.02	2.38 (1.15-4.89)	0.01
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G20210A heterozygous	1.52 (0.65-3.53)	0.33		
Elevated FVIII (90 th percent.)	2.30 (1.23-4.30)	0.01	1.07 (0.48-2.40)	0.86

MVTE non provoquée

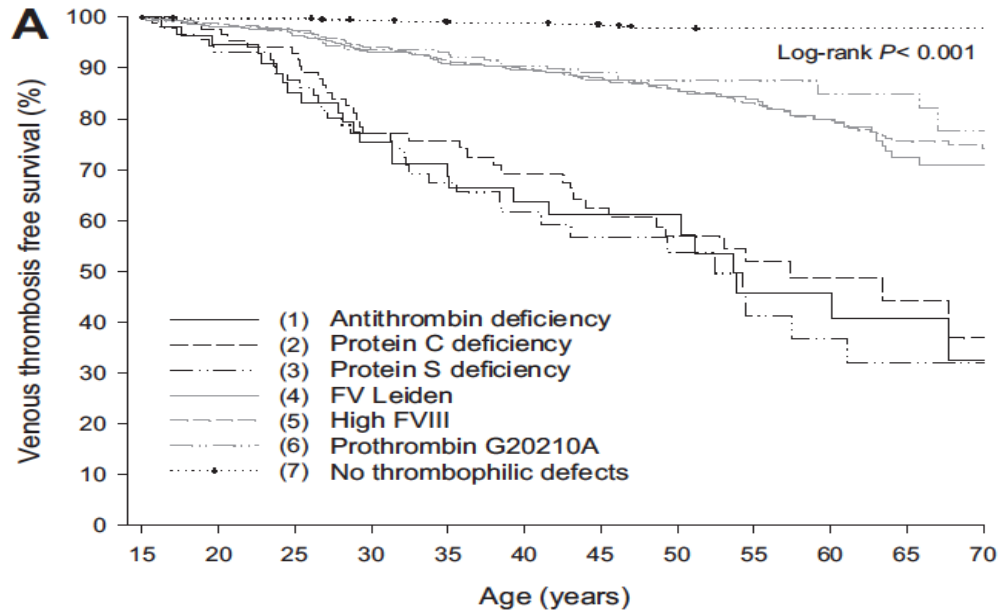
HYPOTHÈSE SCIENTIFIQUE: les patients sans thrombophilie détectables sont probablement porteurs d'une **thrombophilie non connue**

Cette thrombophilie non connue est probablement **héréditaire**

Quel risque familial de MVTE si le propositus:

1- A une MVTE **AVEC thrombophilie ?**

Présence ou non d'une thrombophilie héréditaire chez les membres de famille



No defect

FVL
PGM
FVIII

AT
PC
PS

OR 5-7
(incidence 4 ‰)

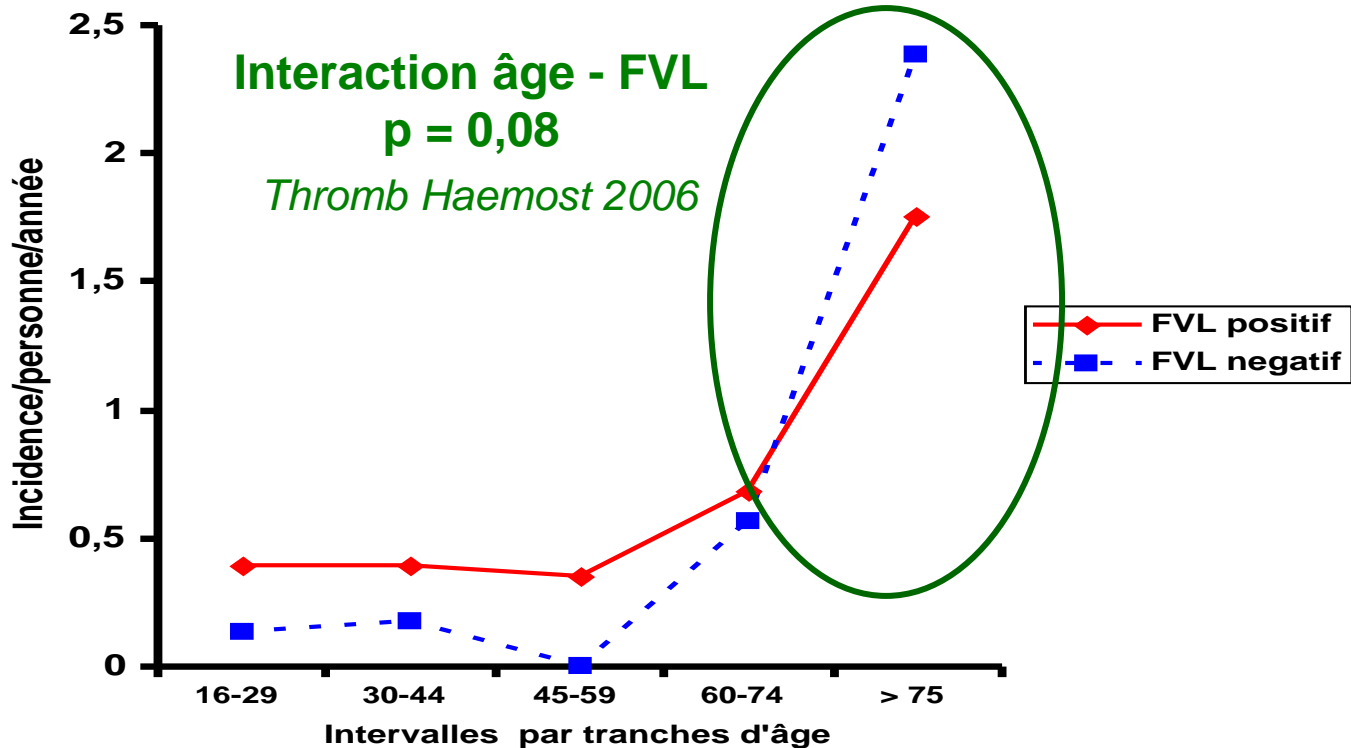
OR 24-30
(incidence 15-19 ‰)

Méta-analyse (Segal JB, et al. JAMA 2009)

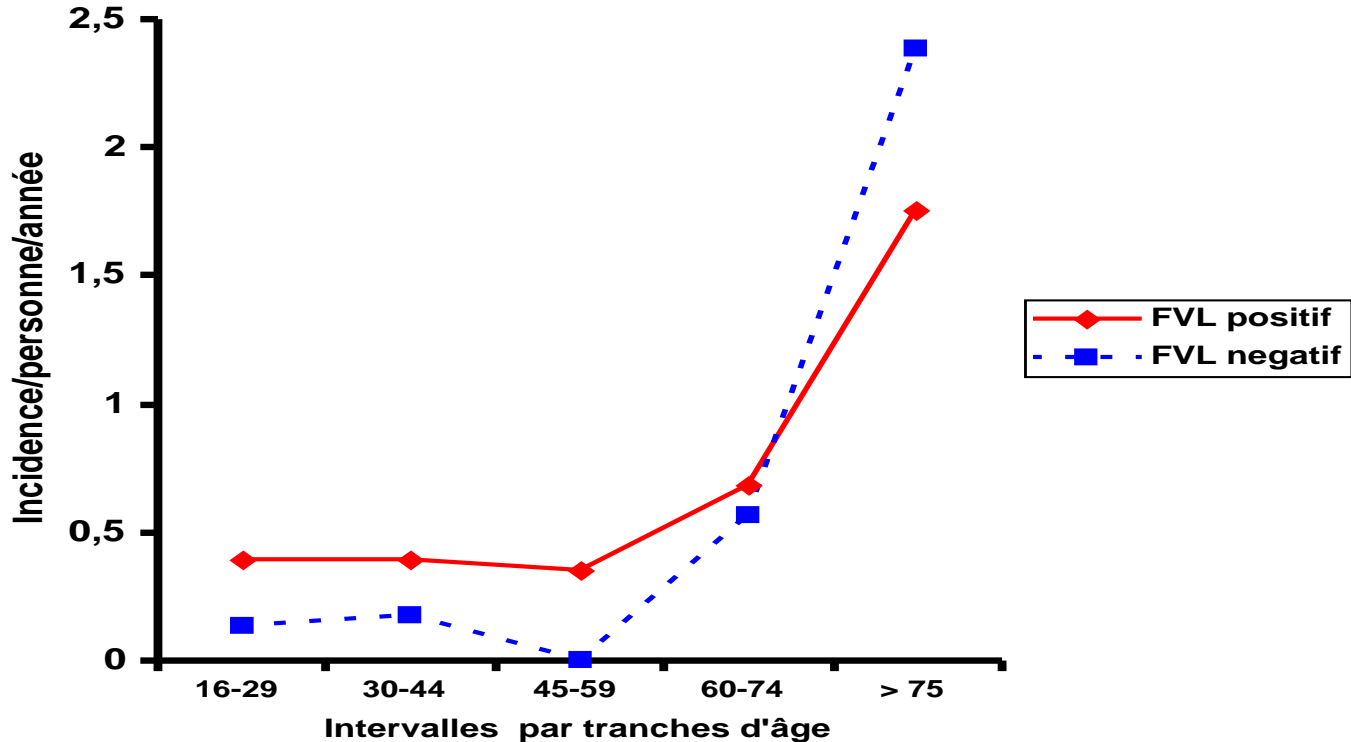
- OR si FVL hétérozygote = 3,5 (2,5-5,0)
- OR si FVL homozygote = 17,8 (8,0-39,9)

RISQUE FAMILIAL DE MVTE : exemple du Facteur V Leiden

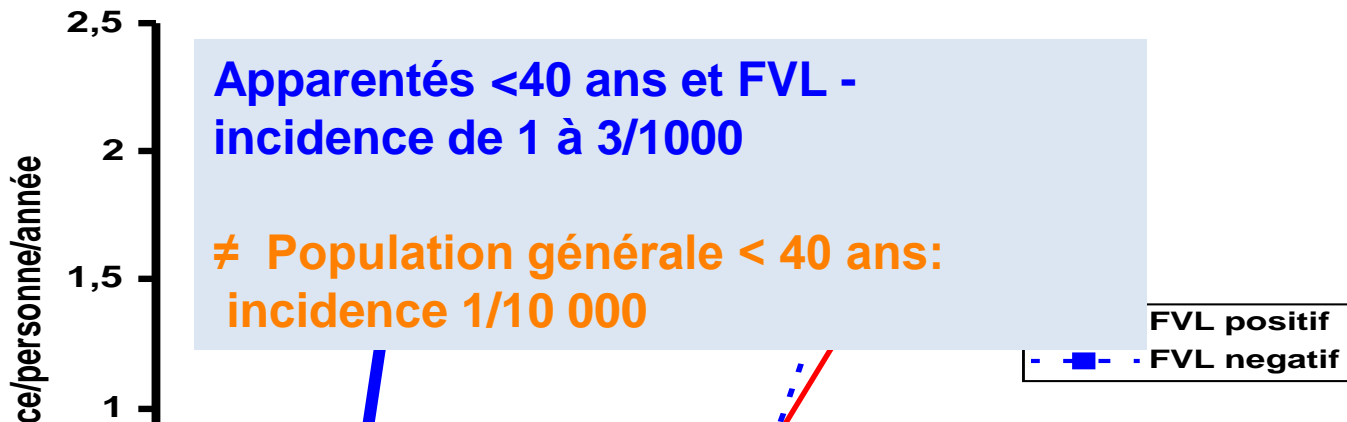
(F. Couturaud, *Thromb Haemost* 2006)



RISQUE FAMILIAL DE MVTE : exemple du Facteur V Leiden *(F. Couturaud, Thromb Haemost 2006)*



RISQUE FAMILIAL DE MVTE : exemple du Facteur V Leiden (F. Couturaud, Thromb Haemost 2006)



Thrombophilie héréditaire fréquente :

- peu discriminante au sein d'une même famille
- même si négative, risque > à la population générale

Thrombophilie et risque de MVTE pendant une contraception oestroprogestative

Incidence (%) d'une MVTE chez des femmes sous oestro-progestatifs apparentées à des propositi ayant une MVTE avec thrombophilie ou non

Thrombophilie	Incidence (%/année)
Propositus avec déficite Antithrombine, Protéine C ou S	
Apparenté AVEC déficit	43 / 1000
Apparenté SANS déficit	7 / 1000
Propositus avec FVLeiden ou G20210 PGM	
Apparenté AVEC déficit	5 / 1000
Apparenté SANS déficidit	2 / 1000
Histoire familiale de MVTE	
Population générale, AVEC histoire familiale de MVTE	0,8 / 1000
population générale, SANS histoire familiale de MVTE	0,4 / 1000

x 5

x 18

Quel risque familial de MVTE si le propositus:

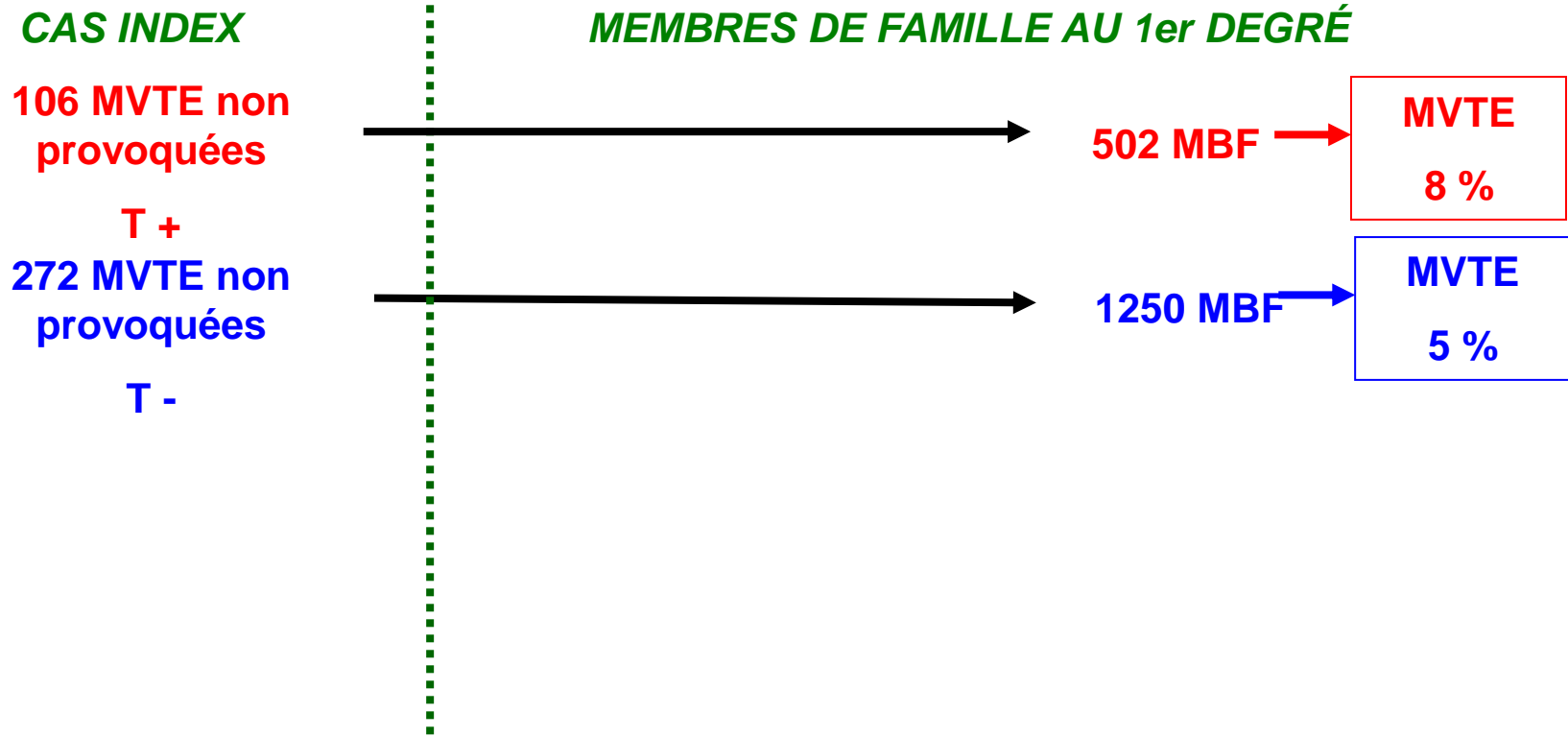
1- A une MVTE **AVEC thrombophilie ?**

Quel risque familial de MVTE si le propositus:

1- A une MVTE **AVEC thrombophilie ?**

2- A une MVTE **SANS thrombophilie ?**

Étude « FIT » (F. Couturaud et al., Blood 2014)



T = thrombophilie (FVL / PGM)

MBF : membre de famille au 1er degré

Étude « FIT » (F. Couturaud et al., Blood 2014)

CAS INDEX

106 MVTE non provoquées

T +

272 MVTE non provoquées

T -

MEMBRES DE FAMILLE AU 1er DEGRÉ

502 MBF

MVTE
8 %

1250 MBF

MVTE
5 %

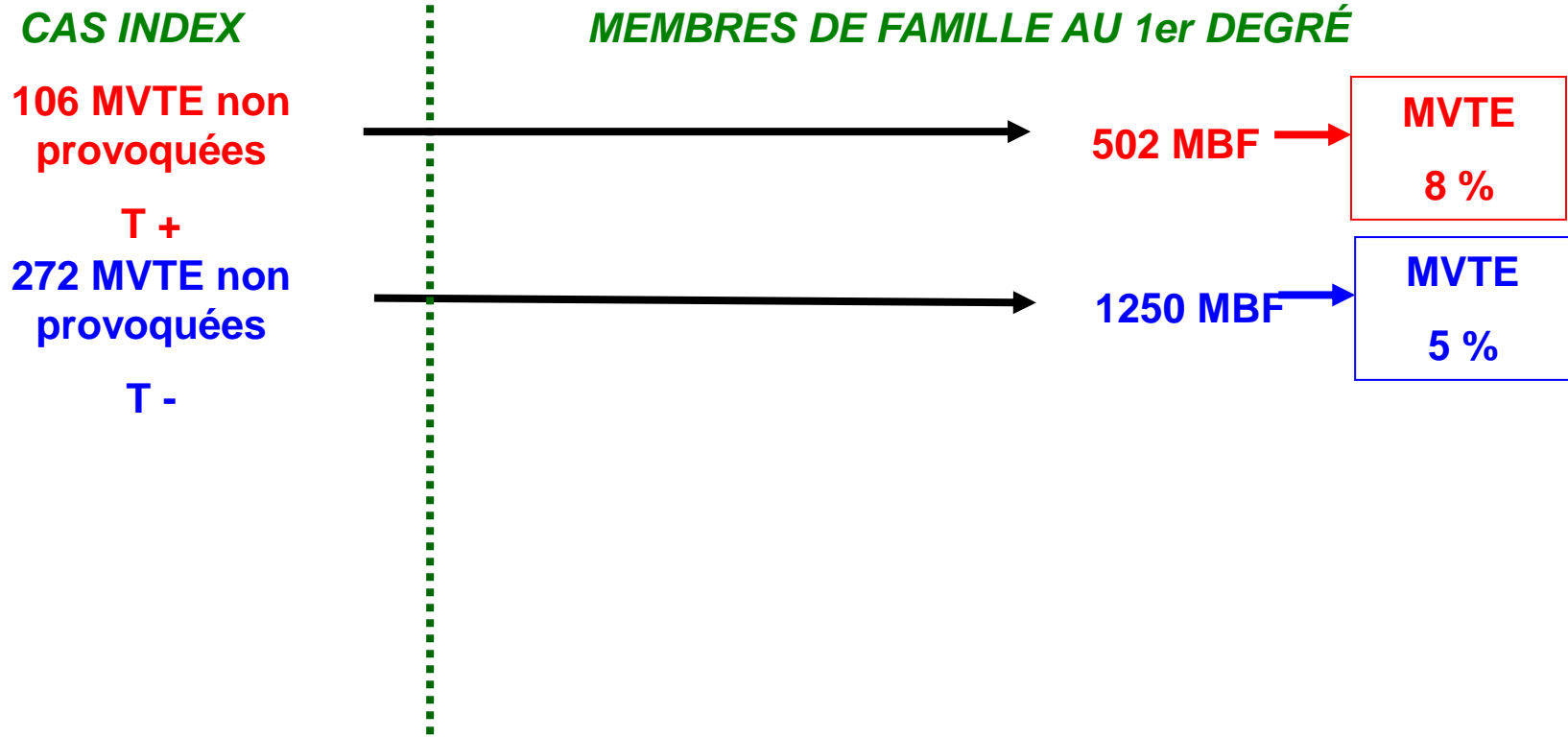
Cas Index	OR multivarié	p
- THROMBOPHILIE	1,5 [0,9- 2,3]	0,09
- AGE (en quartiles)		
16 - 44 ans	3,3 (1,7-6,4)	0,0005
45 - 60 ans	1,8 (0,9-3,4)	0,09
61 - 71 ans	1,9 (1,0-3,5)	0,062
> 71 ans	1,0 (référence)	

Est-ce vrai si le cas index a une MVTE provoquée ?

T = thrombophilie (FVL / PGM)

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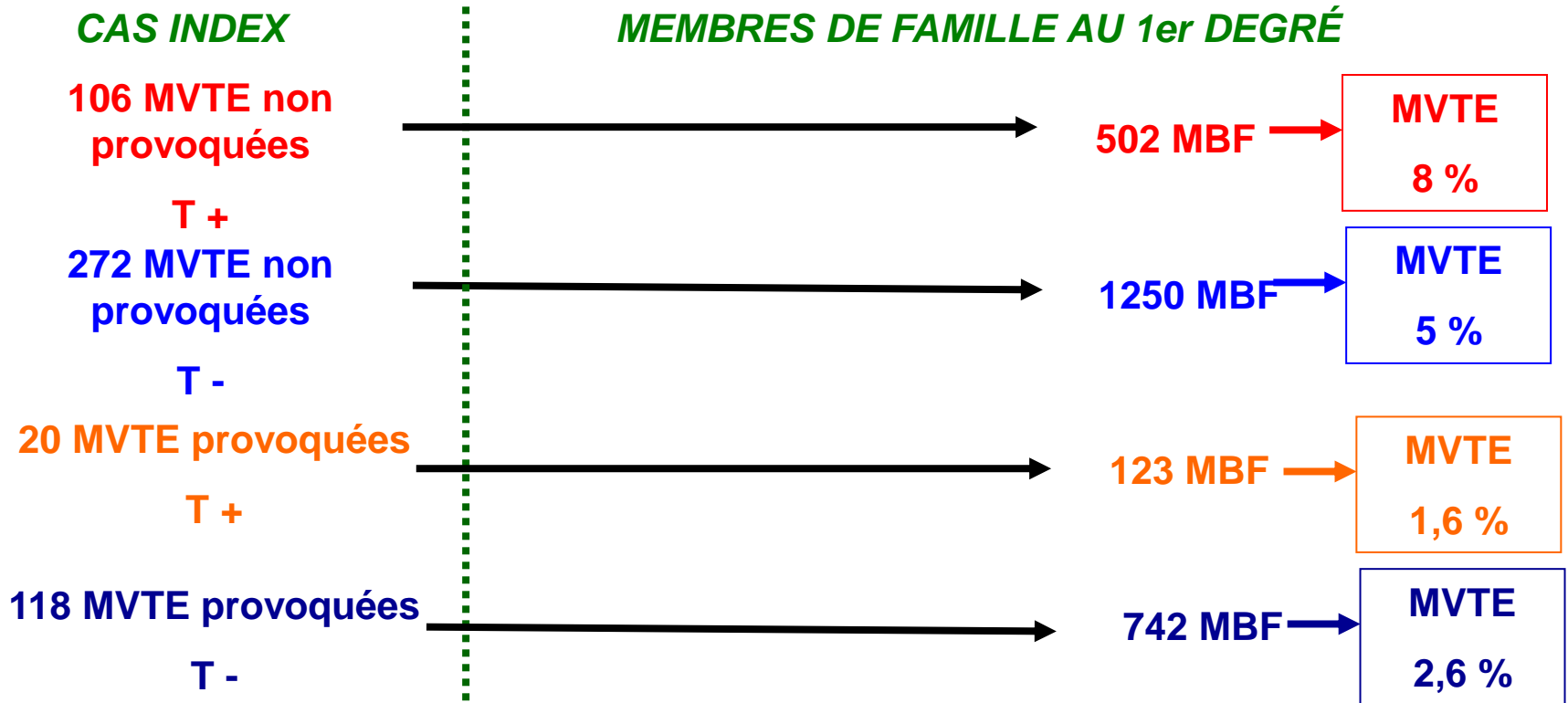
Étude « FIT » (F. Couturaud et al., Blood 2014)



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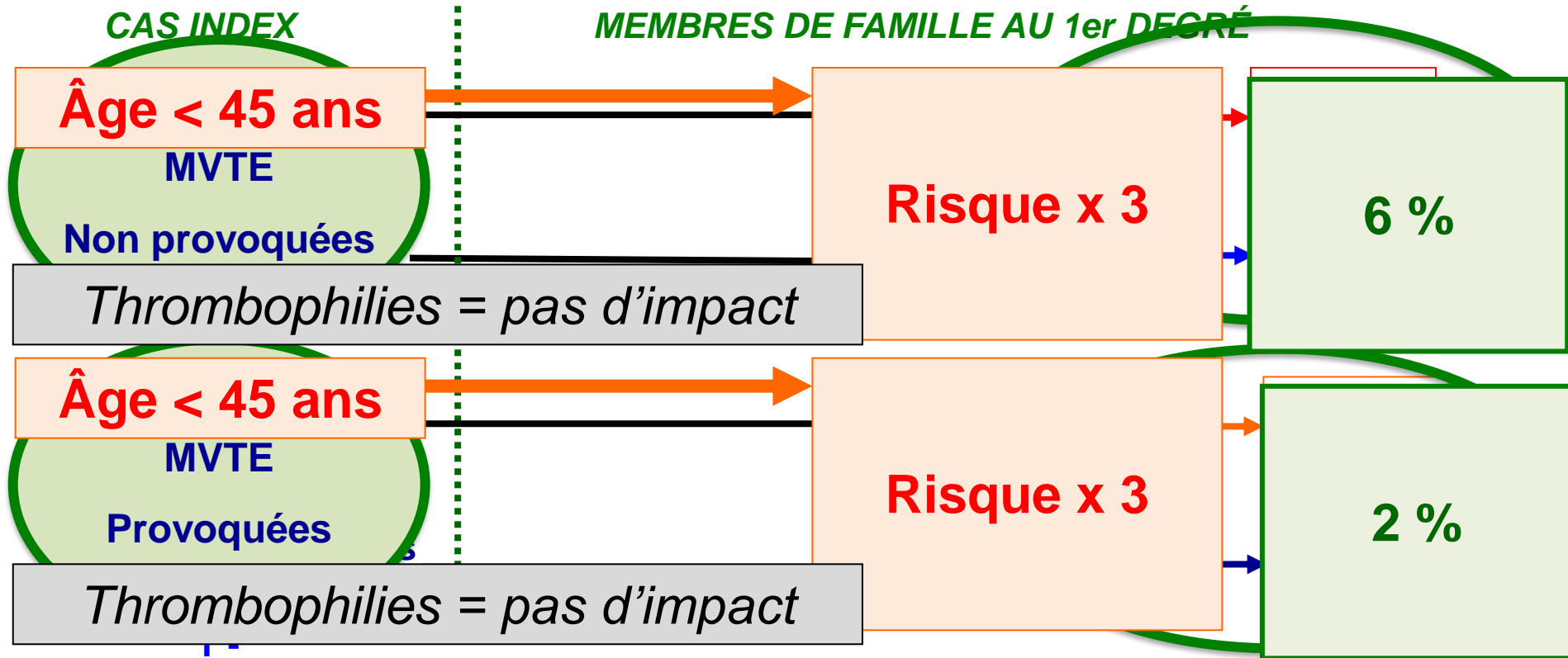
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Étude « FIT » (F. Couturaud et al., Blood 2014)



T = thrombophilie (FVL / PGM)

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Risque augmenté si ≥ 2 membres de familles atteints

Nb de membre de famille	Incidence annuelle	OR	p
1	4/1000	-	
≥ 2	8/1000	2,7 (2,2-3,3)	<0,001

Avec ou sans thrombophilie détectée

F. Couturaud et al., Blood 2014

Risque 1^{er}, 2^{ème}, 3^{ème} degré ? = Identique

Lien avec le propositus	OR
Membre famille 1 ^{er} degré	2,0 à 2,5
Membre famille 2 ^{ème} degré	1,5 à 2,3
Membre famille 3 ^{ème} degré	1,5

Van Vlijmen E., Blood 2013

Conclusions « Familles »

Chez les membres de famille au 1^{er} degré, le risque de MVTE est 2 à 4 fois plus élevé si:

- le cas index a eu une **MVTE avant 45 ans** (vs. >70 ans), ou
- le cas index a eu une **MVTE non provoquée ± hormones** (vs. provoquée), ou
- **au moins 2 membres de familles** ont eu une MVTE

→ **Non lié** à la présence d'une thrombophilie héréditaire commune chez le cas index

Conclusions valables pour les 2^{ème} et 3^{ème} degré

(Zöller B. et al. Thromb Haemost 2013)

Absence of thrombophilia in case of unprovoked VTE

Scientific hypothesis: patients with unprovoked VTE and without detectable thrombophilia are likely to have unknown thrombophilia, probably inherited

FIT 1 and 2 studies

“Familial risk of VTE according to probant characteristics”

(PHRC2001-2007, **2831** 1st degree relatives of **507** patients with VTE, **biobank**)



Selection of extreme phenotypes

INNOVTE “FAMILY-VTE”

“Discovering new inherited thrombophilia”
(PHRC 2009, **450** 1st to 4th degree relatives of 45 patients “extreme”, **biobank**)

Family selection:

- **PROBANTS**: unprovoked VTE < 50 years and **WITHOUT** detectable inherited thrombophilia
- **≥ 2 RELATIVES** (1st, 2nd, 3rd, 4th **WITH** unprovoked VTE < 50 years)

GENETICS

UMR 1078 (Ms E. Génin, Brest),
UMR1062 (Pr PE.Morange, Marseille)
UMR 1219 (Pr DA.Tregouët, Bordeaux).

PATHOPHYSIOLOGY

UMR 1304 - GETBO (Ms C. Lemarié, Brest).
UMR 1062 (Pr PEMorange, Marseille)

Probants' characteristics associated with VTE in relatives	Risk of VTE in 1 st degree relatives
Age VTE < 47 years →	x 3
Unprovoked VTE →	x 3
Thrombophilia →	x 1

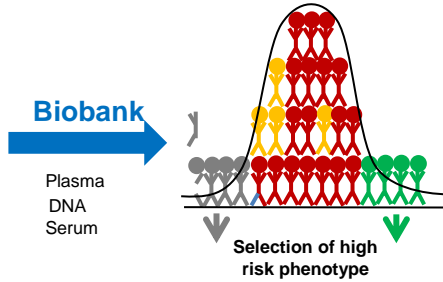
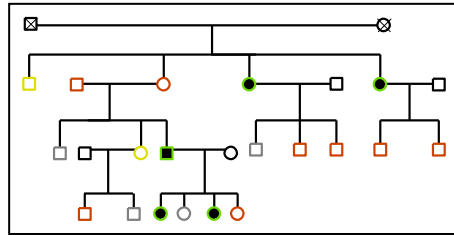
Couturaud F, et al. Chest 2009
Couturaud F, et al. BLOOD 2014

« **Prothrombin p.R541W** »: Fauche A et al. ECT congress 2021
« **MAST2 Arg89Gln variant** »: Morange PE et al. PLOS genet 2021
« **C4BPα**” (Rs776881743 **Glutamic acid** → **Glutamin** »: Lemarié C, ANR 2022
« **C4BPA** » Buil A et al. Blood 2010

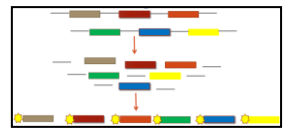
Découvrir de nouvelles thrombophilies héréditaires et mécanismes

INNOVTE "FAMILY-VTE" study

Families with very high VTE rate without known thrombophilia



RESEARCH ARTICLE
 A rare coding mutation in the MAST2 gene causes venous thrombosis in a French family with unexplained thrombophilia: The Breizh MAST2 Arg89Gln variant **PLOS GENETICS**
 Pierre-Emmanuel Morange^{1,2,*}, Franck Peiretti^{1*}, Lenaick Gourhant^{3,4}, Carole Proust^{5a,b}, Omar Soukarieh⁶, Anne-Sophie Pulcrano-Nicolas⁵, Ganapathi-Varma Saripella^{5a,b}, Luca Stefanucci^{7,8,9}, Romaric Lacroix¹, Manal Ibrahim-Kosta^{1,2}, Catherine A. Lemarié^{3,4}, Mattia Frontini^{7,8,9}, Marie-Christine Alessi^{1,2}, David-Alexandre Tréguët^{5a,b}, Francis Couturaud^{3,4}



Whole Exome Sequencing



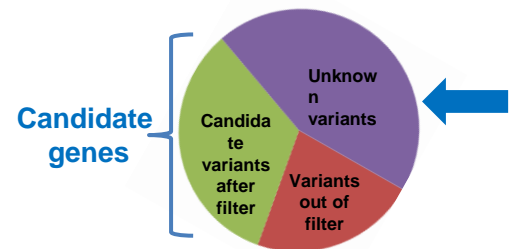
Bioinformatic Analyses

Variant calling
 Alignment to human reference

CTGTCACTCAAGCTGTGA	ACTCTGGGCCATGCCTCCAT
TTCTGTCACTCAAGCTGTG	ACTCTGGGCCATGCCTCCA
TTTCTGTCACTCAAGCTGTG	CTCACTCTGGGCCATGCCTC
TTTCTGTCACTCAAGCTGT	CTCACTCTGGGCCATGCCT
CTTTTCTGTCACTCAAGCTGTG	CTTCTACTCTGGGCCATGC
Reference genome sequence	
CTTTTCTGTCACTCAAGCTGTGA	CTTCTACTCTGGGCCATGCCTCCAT

Filtering variants :

- ✓ Compare non common variants between cases and controls
- ✓ Heterozygous variants
- ✓ Coding / splicing variants
- ✓ MAF <1% or unknown

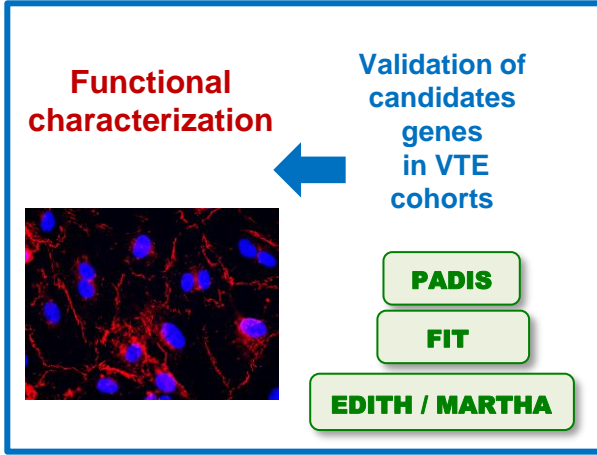
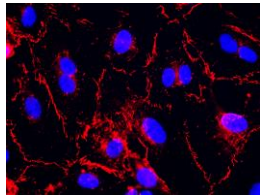


Candidate genes

Validation of candidates genes in VTE cohorts

- PADIS
- FIT
- EDITH / MARTHA

Functional characterization



Découvrir de nouvelles thrombophilies héréditaires et mécanismes

“Mast2” (MAST2 Arg89Gln variant)

- **Défaut de fibrinolyse**
- **Absent** sur les 10 000 patients inclus dans les cohortes du GETBO et MARTHA/Marseille)

PADIS

FIT 1&2

EDITH - MARTHA

- **Présent** dans 2 allèles sur ~ 345,000 séquences dans d'autres larges cohortes (i.e. 100,000 Genomes Project, gnomAD, NIHR BioResource-Rare Diseases, H3-Africa and GenomeAsia 100K)
- **Variant très rare**

“**Prothrombin p.R541W**”: Collaboration avec V. Muczynski and K. Gomez, from University College London.

- **Résistance à la thrombine**
- **Présente** dans 5 familles internationales, dont 3 en France (GETBO et MARTHA/Marseille)

PADIS

FIT 1&2

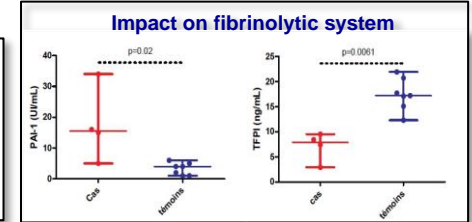
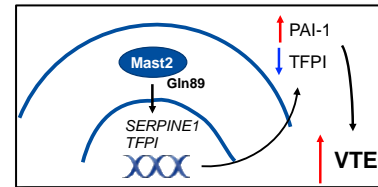
EDITH - MARTHA

- **Variant rare mais mécanisme probablement plus fréquent**

RESEARCH ARTICLE

A rare coding mutation in the MAST2 gene causes venous thrombosis in a French family with unexplained thrombophilia: The Breizh MAST2 Arg89Gln variant **PLOS GENETICS**

Pierre-Emmanuel Morange^{1,2,*}, Franck Peiretti^{1*}, Lенаick Gourhant^{3,4}, Carole Proust^{5a,b}, Omar Soukarieh⁶, Anne-Sophie Pulcrano-Nicolas⁵, Ganapathi-Varma Saripella^{5a,b}, Luca Stefanucci^{7,8,9}, Romaric Lacroix¹, Manal Ibrahim-Kosta^{1,2}, Catherine A. Lemarie^{3,4}, Mattia Frontini^{7,8,9}, Marie-Christine Alessi^{1,2}, David-Alexandre Trégouët^{5a,b}, Francis Couturaud^{3,4}



Thrombosis and genetics: is p.Arg541Trp the future Breizh prothrombin?

Alexandre FAUCHÉ^{1,2}, Catherine LEMARIE¹, Lенаick GOURHANT¹, Cédric LE MARECHAL², Francis COUTURAUD¹.

Localisation of Arg¹⁷⁸:

Thrombin heavy chain, exosite II.



Découvrir de nouvelles thrombophilies héréditaires et mécanismes

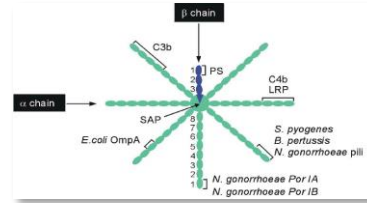
AGENCE NATIONALE DE LA RECHERCHE
ANR 2022
 Étude fonctionnelle de la mutation C4BPα
 Catherine LEMARIÉ

“**C4BPα**” (Rs776881743 Glutamic acid → Glutamin)
 Rare (3 familles)

PADIS

FIT 1&2

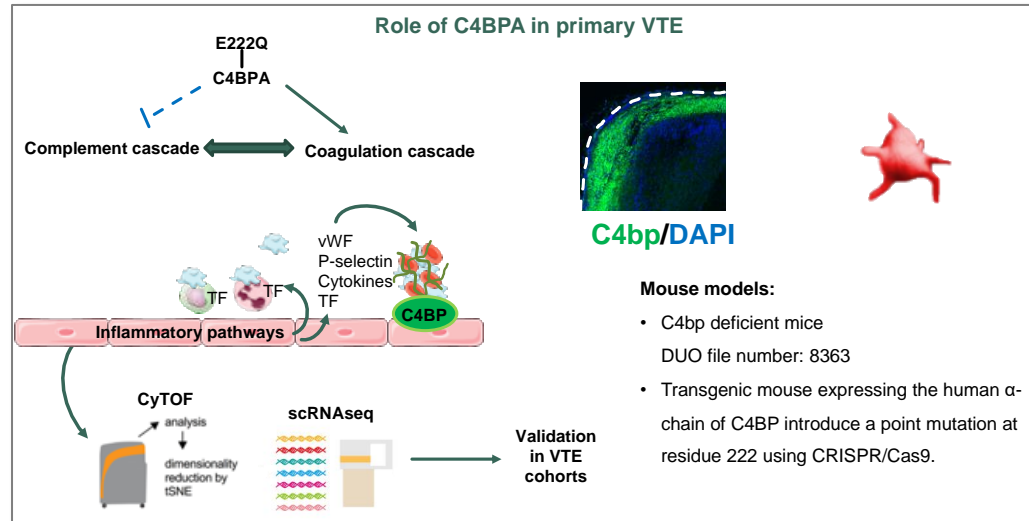
EDITH - MARTHA



Voie du complément

- Blocage complexe PC-PS?
- Dysfonction endothéliale?

→ **Recherche fonctionnelle mécanistique**

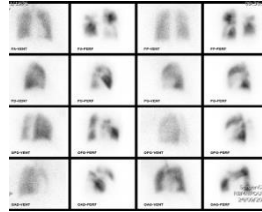


EP avec séquelle vasculaire obstructive

HYPOTHÈSE SCIENTIFIQUE: l'obstruction vasculaire résiduelle est liée à un défaut de fibrinolyse / dysfonction endothéliale

Vascular obstruction

≈ 6600 to 9900 / year*



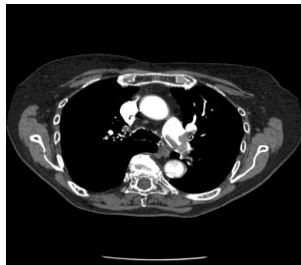
Residual obstruction

20-30% (CTED)

Becattini C et al. JTH 2019



Acute PE



≈ 33000 alive/year*

* In France

Other
predisposing
factors



CTEPH



≈ 150 TBE/year (KB)

≈ **250-300 new CTEPH/year** (60% operable) in French Registry

Cumulative incidence after PE: ≈ **2%** ≈ **600-700 new cases/year** => **CTEPH underdiagnosed**

Ende-Verhaar YM, et al. Eur Respir J 2017; 49: 1601792

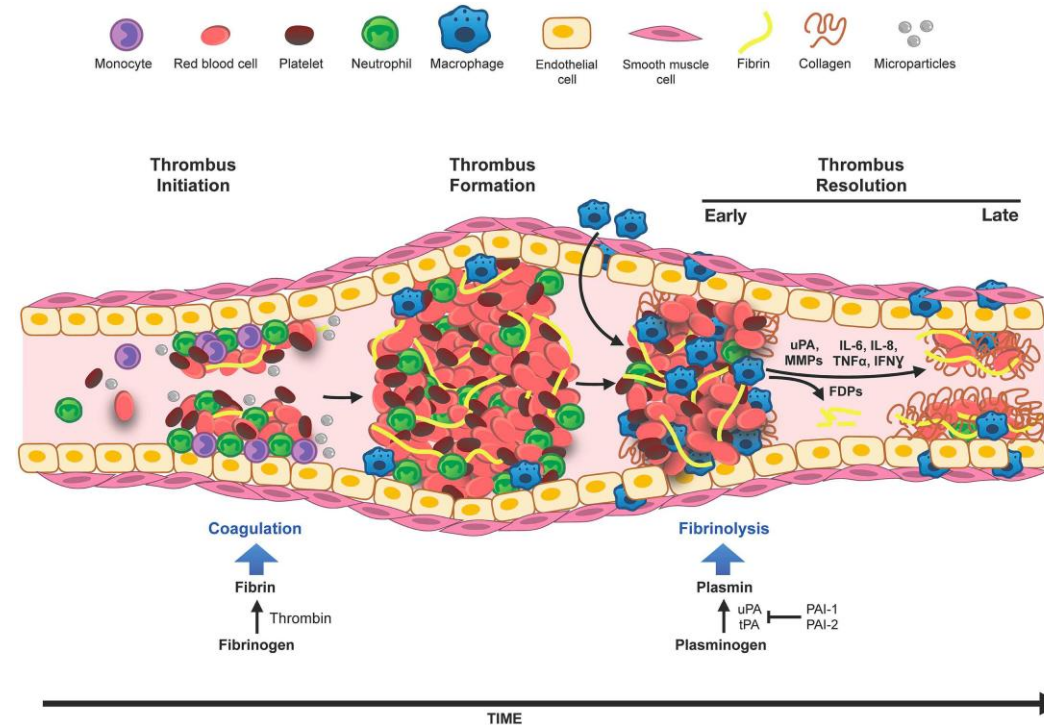
Quelle physiopathologie ?

Obstruction Vasculaire Pulmonaire (OVP)

- Initiale
- Résiduelle

Non résolution thrombus

- Défaut fibrinolyse
- Dysfonction endothélium
- Rôle inflammation



Risk factors of residual PVOI after PE. Results from the HEGP cohort study.

Table 5 Biological assessment at follow-up visit in 227 patients, as a function of residual pulmonary vascular obstruction

Variable	Available data, <i>n</i>	All (<i>n</i> = 227)	Residual perfusion defects		<i>P</i> *
			No (<i>n</i> = 160)	Yes (<i>n</i> = 67)	
Inherited thrombophilia, <i>n</i> (%)	206	42 (17)	34 (19)	8 (11)	0.15
Antiphospholipid antibodies, <i>n</i> (%)	200	26 (10)	15 (8)	11 (15)	0.44
Platelets, G/l, mean (SD)	227	239 (67)	237 (67)	200 (68)	0.41
D-dimers, (Liatest®) µg mL ⁻¹ , mean (SD)	227	0.5 (0.5)	0.5 (0.5)	0.5 (0.6)	0.47
D-dimers, (ELISA, µg mL ⁻¹) mean (SD)	224	0.6 (0.5)	0.5 (0.5)	0.6 (0.5)	0.23
TAFI antigen, µg mL ⁻¹ , mean (SD)	227	11.3 (1.9)	11.3 (1.8)	11.4 (2.1)	0.75
TAFI activity, %, mean (SD)	222	119.4 (26)	119.7 (25)	118.6 (27)	0.38
t-PA, ng mL ⁻¹ , mean (SD)	227	12.3 (8)	12.0 (8)	13.2 (7)	0.53
PAI-1 antigen, ng mL ⁻¹ , mean (SD)	227	42.0 (40)	42.2 (38)	41.5 (45)	0.60
PAI activity, U mL ⁻¹ , mean (SD)	227	18.2 (11)	18.3 (10)	18.2 (11)	0.66
s-EPCR, ng mL ⁻¹ , mean (SD)	227	120 (74)	125 (78)	109 (62)	0.21
s-TM, ng mL ⁻¹ , mean (SD)	227	57.9 (35)	58.8 (40)	55.9 (19.8)	0.42
Free TFPI, ng mL ⁻¹ , mean (SD)	226	13.7 (6)	13.2 (6)	14.8 (5)	0.02
Total TFPI, ng mL ⁻¹ , mean (SD)	227	82.2 (18)	80.5 (16)	86.5 (19)	0.00
TAT, µg L ⁻¹ , mean (SD)	215	4.7 (33)	5.7 (39)	2.4 (3)	0.69
F1 + 2, nmol L ⁻¹ , mean (SD)	227	0.8 (0.8)	0.9 (0.9)	0.6 (0.4)	0.51
Factor VIII activity, %, mean (SD)	210	172.1 (54.9)	164.5 (51.0)	192.9 (60.2)	0.00

RVPO factors

Thrombophilia = no risk

Impaired fibrinolysis = no risk

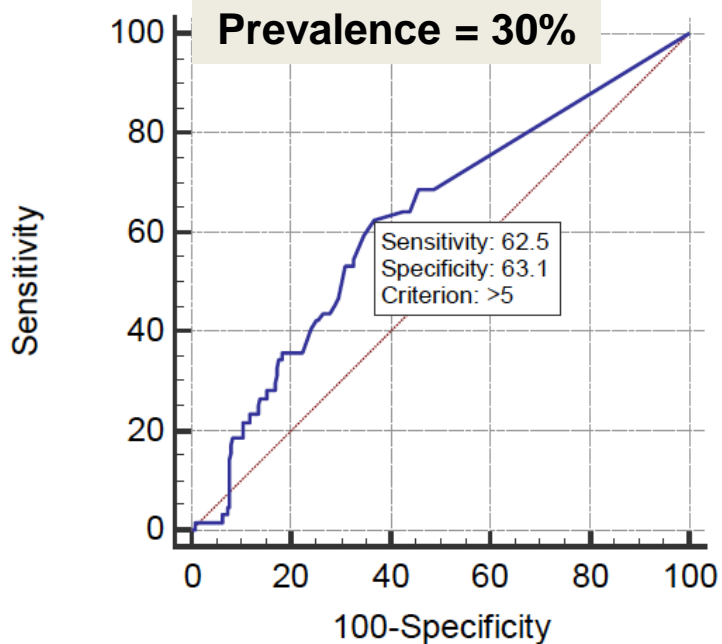
TFPI

Elevated FVIII

t-PA, tissue plasminogen activator; PAI-1, plasminogen activator inhibitor-1; TFPI, tissue factor Pathway inhibitor; TAFI, thrombin-activatable fibrinolysis inhibitor; s-EPCR, soluble endothelial protein C receptor; s-TM, soluble thrombomodulin; F1 + 2, prothrombin fragment F1 + 2; TAT, thrombin-antithrombin complexes; F VIII, blood coagulation factor VIII.

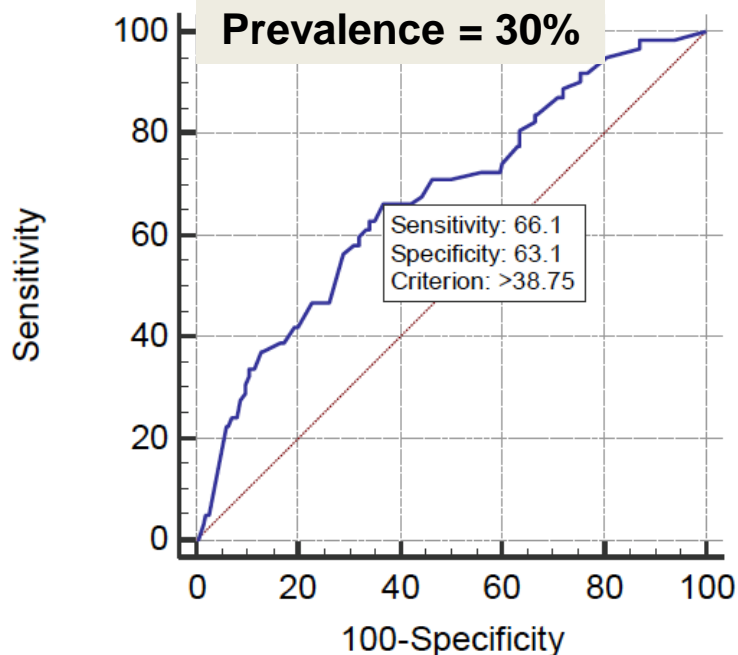
Initial and residual pulmonary vascular obstruction to predict recurrence risk in PADIS-PE trial

Residual PVOI (at 6 months) $\geq 5\%$



Area under the ROC curve (AUC)	
Area under the ROC curve (AUC)	0.623
Standard Error ^a	0.0381
95% Confidence interval ^b	0.565 to 0.678
z statistic	3.225
Significance level P (Area=0.5)	0.0013

Initial PVOI (PE Dx) $\geq 40\%$



Area under the ROC curve (AUC)	
Area under the ROC curve (AUC)	0.672
Standard Error ^a	0.0397
95% Confidence interval ^b	0.612 to 0.728
z statistic	4.342
Significance level P (Area=0.5)	<0.0001

Correlation
 $r=0.6$ $p<0.001$

but also

Interaction
 $p<0.001$

PADIS-PE

Risk factors of recurrent VTE

Variables		Main Multivariate Model		Second Multivariate Model		Third Multivariate Model		Point
		HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	
Age	<50 y.	Ref.	0.008					
	50-65 y.	3.65 (1.33-9.99)						2
	>65 y.	4.70 (1.78-12.4)						3
PVOI								
-1st model: PVOI at 6 months ≥5%		2.06 (1.14-3.72)	0.016	-	-	-	-	2
-2nd model: PVOI at diagnosis ≥40%		-	-					
-3rd model: PVOI at diagnosis ≥40% and/or PVOI at 6 months ≥5%		-	-	-	-			
APLA (LA and/or CLAs)		2.38 (1.15-4.89)	0.01					2

*PVOI, pulmonary vascular obstruction index;
APLA, antiphospholipid antibodies;*

PADIS-PE

Risk factors of recurrent VTE

Variables		Main Multivariate Model		Second Multivariate Model		Third Multivariate Model		Point
		HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	
Age	<50 y.	Ref.	0.008					
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PVOI								
-1st model: PVOI at 6 months ≥5%		2.06 (1.14-3.72)	0.016	-	-	-	-	2
-2nd model: PVOI at diagnosis ≥40%		-	-	2.36 (1.34-4.17)	<0.01	-	-	2
-3rd model: PVOI at diagnosis ≥40% and/or PVOI at 6 months ≥5%		-	-	-	-	-	-	
APLA (LA and/or CLAs)		2.38 (1.15-4.89)	0.01					2

PVOI, pulmonary vascular obstruction index;
APLA, antiphospholipid antibodies;

PADIS-PE

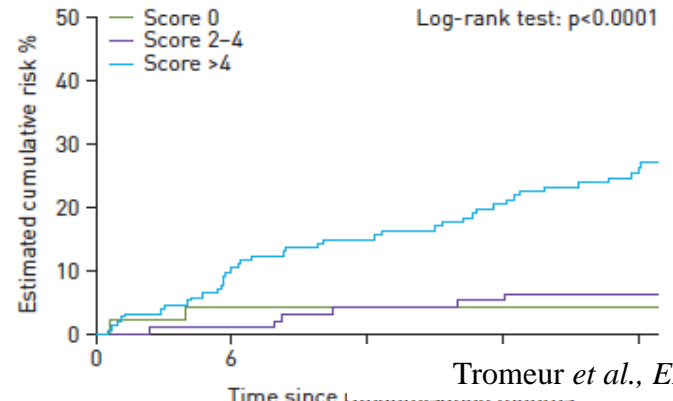
Risk factors of recurrent VTE

Variables	Main Multivariate Model		Second Multivariate Model		Third Multivariate Model		Point
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	
Age							
<50 y.	Ref.	0.008					
50-65 y.	3.65 (1.33-9.99)						2
>65 y.	4.70 (1.78-12.4)						3
PVOI							
-1 st model: PVOI at 6 months ≥5%	2.06 (1.14-3.72)	0.016	-	-			2
-2 nd model: PVOI at diagnosis ≥40%	-	-	2.36 (1.34-4.17)	<0.01	Additive effect		2
-3 rd model: PVOI at diagnosis ≥40% and/or PVOI at 6 months ≥5%	-	-	-	-	4.73 (1.99-11.2)	<0.01	4
APLA (LA and/or CLAs)	2.38 (1.15-4.89)	0.01					2

If PVOI <40% at diagnosis **AND** <5% at 6 months

Score Values	Incidence Rate of Recurrent VTE
Low Risk = 0*	1.4 %/year
Intermediate Risk = 2 or 4	3.2 %/year
High Risk > 3	14 %/year

* Sensitivity 97% Negative Predictive Value 94%



Initial / Residual pulmonary vascular obstruction added to validated scores ? PADIS-PE trial

	Variables	OR	p
Modèle 1	HERDOO2 ≥ 2	2.3	p=0.04
	PVO residual $\geq 5\%$	2.5	p<0.001
Modèle 2	HERDOO2 ≥ 2	2.4	p=0.03
	PVO initiale $\geq 40\%$	2.9	p<0.0001
Modèle 3	HERDOO2 ≥ 2	2.3	p=0.04
	PVO initiale $\geq 40\%$ + residual $\geq 5\%$	4.8	p<0.0001

Adding Vascular obstruction :

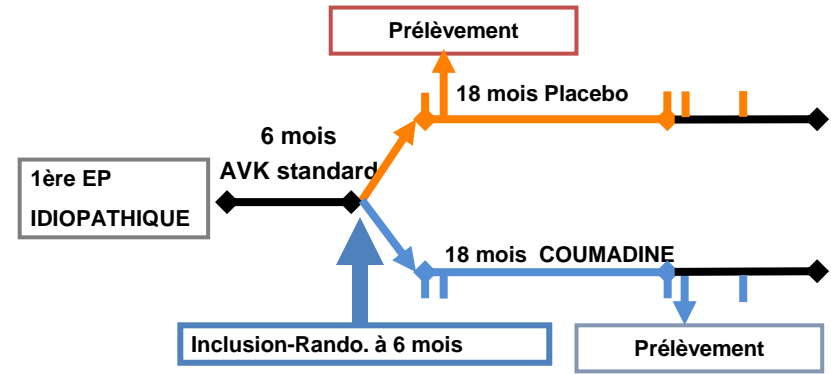
- reclassifies 70% of patients with low risk HERDOO2 → HIGH RISK
- reclassifies 30% of patients with high-risk HERDOO2 → LOW RISK

Découvrir le mécanisme de l'obstruction vasculaire résiduelle:

Cohorte PADIS-EP

Phénotype extrême

- 18 – 60 ans
- OVP initiale > 30 %



OVPR < 5% sans
récidive (10)

OVPR < 5% avec
récidive (10)

OVPR > 5% avec
récidive (6)

OVPR > 5% sans
récidive (9)

Bilan biologique M+1 arrêt AVK

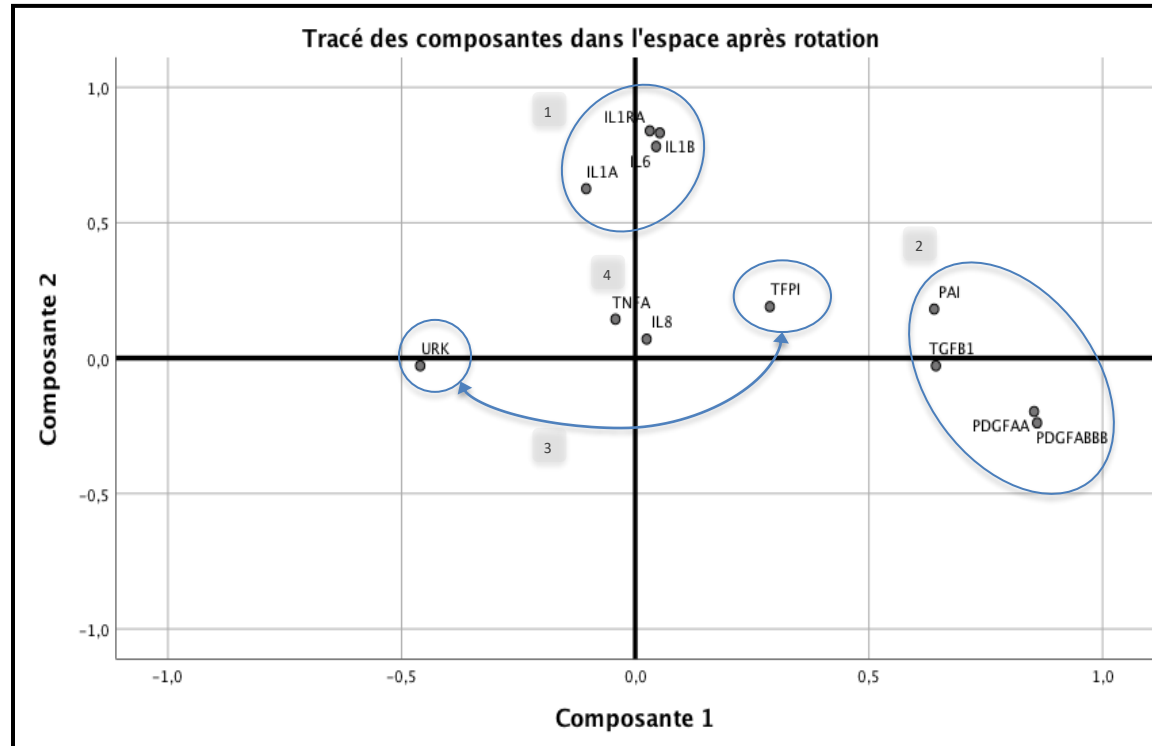
- LUMINEX (IL-1,6,8, IFN γ , TNF α , CXCL-5, MIF, TGF β , PDGF, VEGF, PAI-1)
- ELISA (TFPI, uPA)

Unpublished data

Découvrir le mécanisme de l'obstruction vasculaire résiduelle: Défaut de fibrinolyse – dysfonction endothéliale - inflammation

Analyse en composante principale

Fibrinolyse
Endothélium
inflammation



Unpublished data

Au delà de la veine

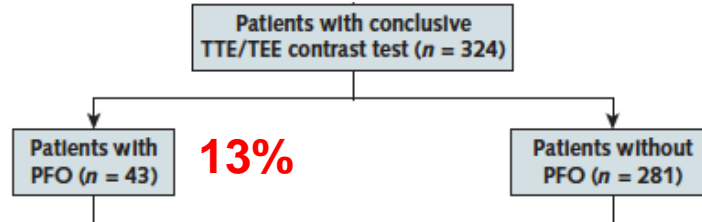
lien artère-veine

Résultat intrigant

Foramen Ovale perméable ?

EPIC-FOP study design

ETT + IRM cérébrale
systématiques à la phase
aiguë de l'EP



Characteristic of Recent Ischemic Stroke	PFO (n = 42), n (%)	Non-PFO (n = 273), n (%)	Relative Risk (95% CI)
Symptomatic or silent	9 (21.4)	15 (5.5)	3.90 (1.62 to 8.67)
Symptomatic	4 (9.5)	4 (1.5)	6.50 (1.08 to 45.50)
Silent	5 (11.9)	11 (4.0)	2.95 (0.72 to 7.95)
Cryptogenic	7 (16.7)	5 (1.8)	9.10 (2.89 to 39.00)

Interest of systematic TTE for reason other than CTED/CTEPH?

Argue for **indefinite anticoagulation** if unprovoked PE ?

PFO = patent foramen ovale.

Risque d'évènement artériel après une MVTE

Méta-analyse

Des facteurs artériels

Des facteurs veineux

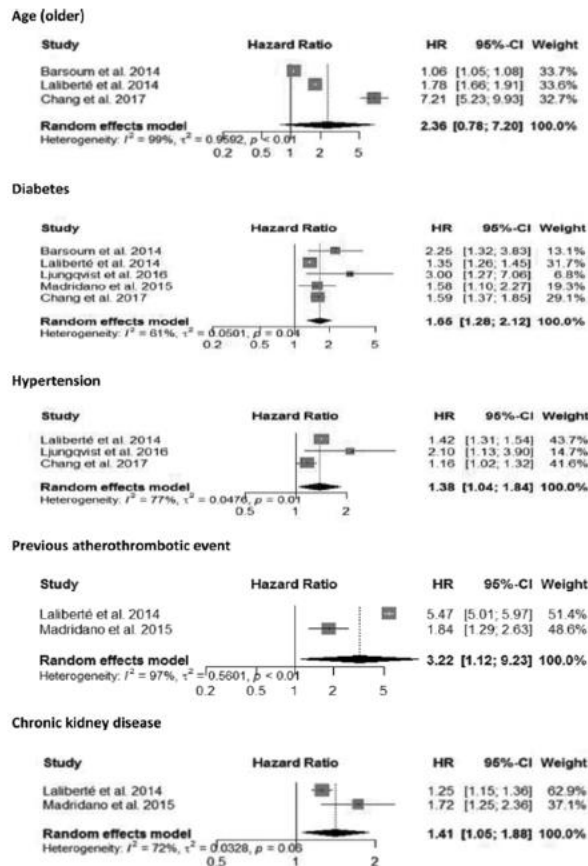


Fig. 2 Arterial risk factors reported in meta-analysis with substantial heterogeneity. CI, confidence interval; HR, hazard ratio.

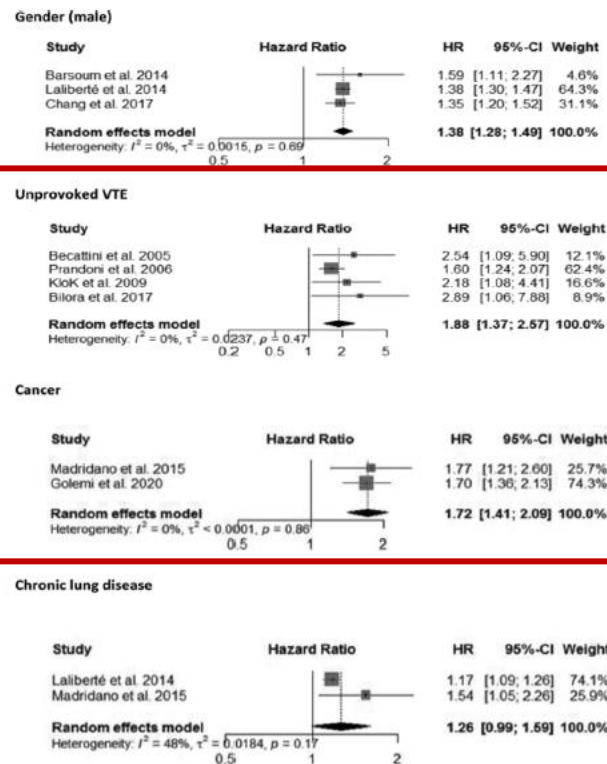


Fig. 3 Arterial risk factors reported in meta-analysis without substantial heterogeneity. CI, confidence interval; HR, hazard ratio; VTE, venous thromboembolism.

Risque d'évènement artériel après une MVTE

	Univariable analysis		Multivariable analysis	
	Unadjusted HR (95% CI)	p-Value	Adjusted HR (95% CI)	p-Value
General characteristics				
Sex (male)	1.13 (0.97–1.30)	0.11	1.03 (0.84–1.25)	0.78
Age				
< 50 y	–	ref	–	ref
50 to 65 y	2.58 (1.92–3.48)	< 0.001	2.00 (1.38–2.91)	< 0.001
> 65 y	7.25 (5.65–9.30)	< 0.001	4.85 (3.35–7.02)	< 0.001
Personal past history of VTE	1.25 (1.06–1.48)	0.01	1.02 (0.83–1.25)	0.88
Blood group				
O group	–	ref		
Non-O group	0.77 (0.64–0.93)	0.01		
Characteristics of VTE				
Type of VTE				
DVT only	–	ref	–	ref
PE only	1.14 (0.94–1.40)	0.90	0.99 (0.77–1.26)	0.94
DVT and PE	1.73 (1.47–2.05)	< 0.001	1.25 (1.02–1.55)	0.03
Location of DVT (only)				
Distal DVT	–	ref		
Proximal DVT	1.21 (0.93–1.59)	0.15		
Type of VTE according to provoking factors				
Transient factors associated VTE, n (%)	–	ref	–	ref
Cancer associated VTE, n (%)	2.23 (1.80–2.76)	< 0.001	1.21 (0.92–1.59)	0.18
Unprovoked VTE, n (%)	1.79 (1.50–2.13)	< 0.001	1.29 (1.04–1.59)	0.01
Minor thrombophilia				
Heterozygous factor V Leiden	0.67 (0.52–0.86)	0.001	0.78 (0.58–1.05)	0.11
Heterozygous G20210A prothrombin gene variant	0.98 (0.72–1.33)	0.89		
Homozygous factor V Leiden	0.45 (0.11–1.79)	0.26		
Homozygous G20210A prothrombin gene variant	–	–		
Heterozygous factor V Leiden and heterozygous G20210A prothrombin gene variant	0.96 (0.42–2.19)	0.92		

	Univariable analysis		Multivariable analysis	
	Unadjusted HR (95% CI)	p-Value	Adjusted HR (95% CI)	p-Value
Others classic cardiovascular risk factors				
Tobacco use				
Never,	–	ref	–	ref
Past	1.32 (1.10–1.57)	0.002	1.15 (0.93–1.42)	0.21
Current	0.64 (0.49–0.83)	< 0.001	1.45 (1.07–1.98)	0.01
Diabetes	1.57 (1.17–2.12)	0.002	0.91 (0.64–1.28)	0.59
Hypertension	2.32 (2.01–2.69)	< 0.001	1.61 (1.30–1.98)	< 0.001
Dyslipidemia	1.31 (1.09–1.57)	0.004	0.77 (0.57–1.05)	0.09
Obesity	0.93 (0.76–1.13)	0.44		
History of symptomatic atherosclerosis	2.88 (2.44–3.41)	< 0.001	1.52 (1.17–1.98)	0.002
Other comorbidities at the diagnosis of VTE				
Heart failure	4.10 (3.27–5.14)	< 0.001	1.71 (1.21–2.42)	0.002
Chronic respiratory failure	2.73 (2.09–3.55)	< 0.001	1.31 (0.89–1.91)	0.17
Atrial fibrillation	3.33 (2.57–4.30)	< 0.001	1.55 (1.15–2.08)	< 0.001
Concomitant treatment at VTE diagnosis				
Anticoagulant therapy	2.80 (1.89–4.15)	< 0.001		
Antiplatelet therapy	2.52 (2.08–3.04)	< 0.001	1.11 (0.86–1.44)	0.44
Statin therapy	1.45 (1.14–1.83)	0.002	1.08 (0.74–1.57)	0.69

Cohorte EDITH 5000 patients

Des facteurs artériels

Des facteurs liés au phénotype de MVTE

- MVTE non provoquée et cancer
- EP + TVP

Pas d'impact des thrombophilies

**Au delà des approches
biomoléculaires**

phénotype du caillot

Approche physico-chimique

UMR 1304 - GETTBO

UBO, Brest, « THROMBOSIS CHAIR » GETTBO-UBO-PFIZER

LGC Toulouse

UMR 5503 (CNRS, INP, UPS)
Génie des Interfaces et Milieux Divisés –
GIMD - Ingénierie de la Matière Molle
Pr. Patrice Bacchin

Duke University

Pr. Mark Wiesner's Group
Member of National Academy of Engineering,
Risk modelisation.

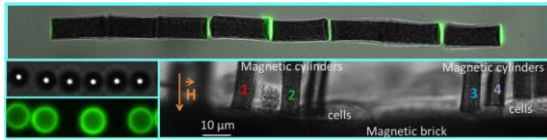
ESPCI Paris (6 Nobels)

Physique et mécanique
des milieux hétérogènes UMR 7636
Anke Lindner group Complex solutions
Pr. Anke Lindner

Cinétique de formation et de lyse des caillots

- Microrhéologie
- Diffusing Wave Spectroscopy
- Taille : diffusion dynamique de la lumière
- Potentiel zéta
- Laser Speckle
- Small angle X-Ray scattering (SAXS)

Micro-rheology



SAXS

Structure et propriétés des caillots

Mesures fondamentales et complexe :

- Propriétés mécaniques
 - Rheologie/micro-rheologie (micro-barreau aimanté)
 - Microfluidique
- Propriétés structurales à différentes échelles
 - Microscopie électronique (SEM/MET), optique et confocale.
 - Moléculaires : Small angle X-Ray scattering (SAXS)
 - Multi échelle : Small angle neutron scattering (SANS)

Fluides étudiés

Plasma frais congelés Boostés

- Facteurs de la coagulation
- Anticoagulants

Plasma patients

- Phénotypes forts comparés à témoins
- Sous groupes
 - Cancer
 - Thrombophilie
 - Maladies inflammatoires
 - MTEV non provoquée
 - EP ou TVP isolées
 - EP+TVP vs. EP seules
 - Sujets Agés >75ans

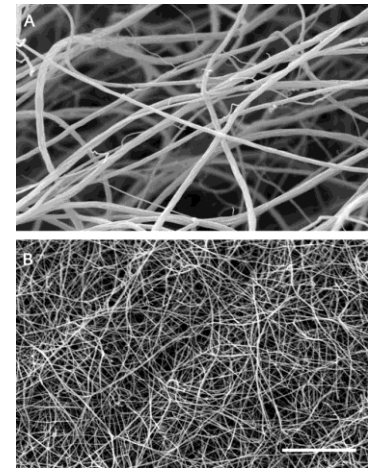


Fig. 4. Scanning electron micrographs of fibrin clots. (A) Clot with thick fibers and few branch points made from recalcified plasma with low thrombin concentration. (B) Clot with thin fibers and many branch points made from recalcified plasma at high thrombin concentration. Magnification bar=5 µm.

Corrélations avec des phénotypes de MVTE "expliquées" avec physiopath.

Distribution dans les MVTE non provoquées

Validation and translation into clinical practice

(EDITH, PADIS-PE-DVT, MARTHA, FIT-INNOVTE.

Generating new hypotheses:

- Guide basic research on new inherited thrombophilia
- Improve patient management

S'affranchir du phenotype ?

**Scores, big data, “intelligence”
artificielle**

Méthode scientifique: ne prendre ne compte que les faits avérés

« Un fait scientifique est une **hypothèse qui a été corroborée** par sa confrontation à la réalité dans une expérience spécifique » (Karl Popper)

≠ d'une théorie spéculative

= PREUVES

Médecine expérimentale:

« Il faut admettre comme un axiome expérimental que chez les êtres vivants aussi bien que dans les corps bruts les **conditions d'existence de tout phénomène sont déterminées** d'une manière absolue. » (Claude Bernard)

= lorsque la condition d'un phénomène est connue et remplie, le phénomène doit se **reproduire** toujours et nécessairement, à la volonté de l'expérimentateur.

- Primauté de l'hypothèse scientifique
- Reproductibilité de l'expérience et du résultat

Recurrent VTE / Bleeding - concept

VTE-PREDICT to predict risks of recurrent VTE, bleeding and individual benefits, and harms of extended anticoagulation

Development

Competing risk-adjusted models for

- Recurrent VTE
- Clinically relevant bleeding

were derived in combined individual patient data (n = 15,141)



Bleeding Risk Study, Hokusai-VTE, RE-MEDY, RE-SONATE, PREFER in VTE Registry

Validation

External validation (n = 59,257) showed agreement between predicted and observed risks up to 5 years



Danish VTE Cohort, EINSTEIN-CHOICE, GARFIELD-VTE, Tromsø study, MEGA study

Key features of the VTE-PREDICT risk score

- Suitable for all adult patients with VTE without active cancer for whom the decision to stop or continue anticoagulation is yet to be made
- Uses 14 simple, readily available patient characteristics
- Available worldwide through <https://vtepredict.com>

Individual patient example



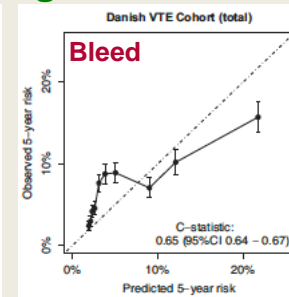
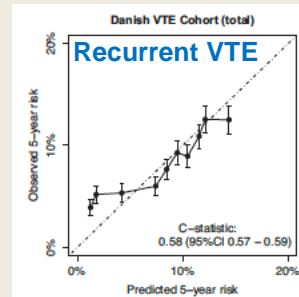
Healthy male patient
60 years old
Unprovoked DVT
BMI 29.8 kg/m²
Hb 15 g/dL
SBP 135 mmHg

VKA	1.6%	9.8%
DOAC (full dose)	2.8%	5.2%
DOAC (reduced)	2.3%	2.3%
Aspirin	7.5%	2.9%

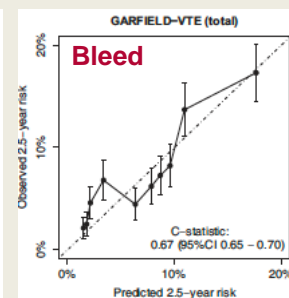
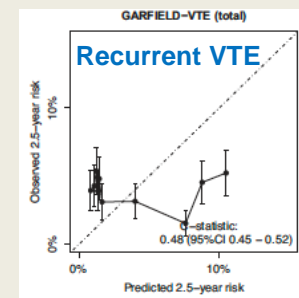
5-year risk with extended treatment


10.3% (Recurrent VTE)
2.0% (Bleeding)
5-year risk without extended treatment

Danish Register



Gardfield cohort



- Discriminant power of 50% to 60%** on academic registries
= similar to other pre-existing scores,
= **No added value**
- Only clinical variables:** derived from industrial studies 
with selected patients

Omics (biology, imagerie)
Patient's perception
Time dependant variable

Conclusions

Importance du phénotype clinique → **observation, génération d'hypothèse**

Sélection de phénotypes extrêmes → **augmentation des chances de découvertes physiopathologiques**

MVTE non provoquée:

- un modèle d'étude avec impact sur les facteurs biologiques héréditaires
- découverte de nouveaux mécanismes

EP avec séquelle vasculaire obstructive résiduelle:

- élargit le champ des mécanismes physiopathologiques
- étude du contenant (endothélium)
- rôle de l'environnement (inflammation loco-régionale/poumon, général)

Recurrent VTE / Bleeding - concept

VTE PREDICT scores et grandes bases de données

Table 2 Prediction models for recurrent VTE and bleeding

	Predictor	Recurrent VTE		Bleeding	
		sHR (95% CI)	χ^2 statistic	sHR (95% CI)	χ^2 statistic
Demographics and physical examination	Age (per decade)	1.01 (0.97–1.06)	0.20	1.05 (1.03–1.08)	7.95
	Female sex	0.86 (0.75–0.98)	2.38	1.14 (1.05–1.24)	4.87
	BMI (kg/m ² ; per 1 unit increase)	1.00 (0.99–1.02)	0.21		
	Systolic blood pressure (per 10 mmHg)			1.07 (1.03–1.10)	14.36
Index event	PE	1.02 (0.89–1.18)	0.05	1.07 (0.98–1.17)	1.47
	Provoked by surgery, trauma or immobilization	0.81 (0.68–0.98)	3.16		
	Provoked by oestrogen therapy	0.68 (0.47–1.00)	2.53		
Medical history	History of cancer	1.53 (1.14–2.06)	6.44	2.48 (2.00–3.07)	128.44
	History of VTE	1.13 (0.97–1.32)	1.10		
	History of bleeding			1.26 (1.11–1.44)	4.57
	Stroke			1.26 (1.08–1.46)	3.72
Lab values	Hb (g/dL; per 1 unit increase)			0.95 (0.93–0.97)	9.69
Co-medication	NSAIDs			1.22 (1.08–1.38)	5.92

“MORPHEUS” project

EUROPEAN PROJECT (HORIZON-HLTH-2023-TOOL-01-05)



- Direction, coordination: **F-CRIN INNOVTE**

- International (8 countries): The Netherlands, Sweden, Germany, Italy, Spain, Denmark, Switzerland, Polonia



Phase I: Preparation

Ph
int

Time-dependent multicomponent tool

PHYSICIAN

Outcomes
Predictors (precision
medicine)

Treatment options

PATIENTS

Outcomes
Predictors (patient's
centred medicine)

Treatment options

INTEGRATED IN SHARED MEDICAL DECISION

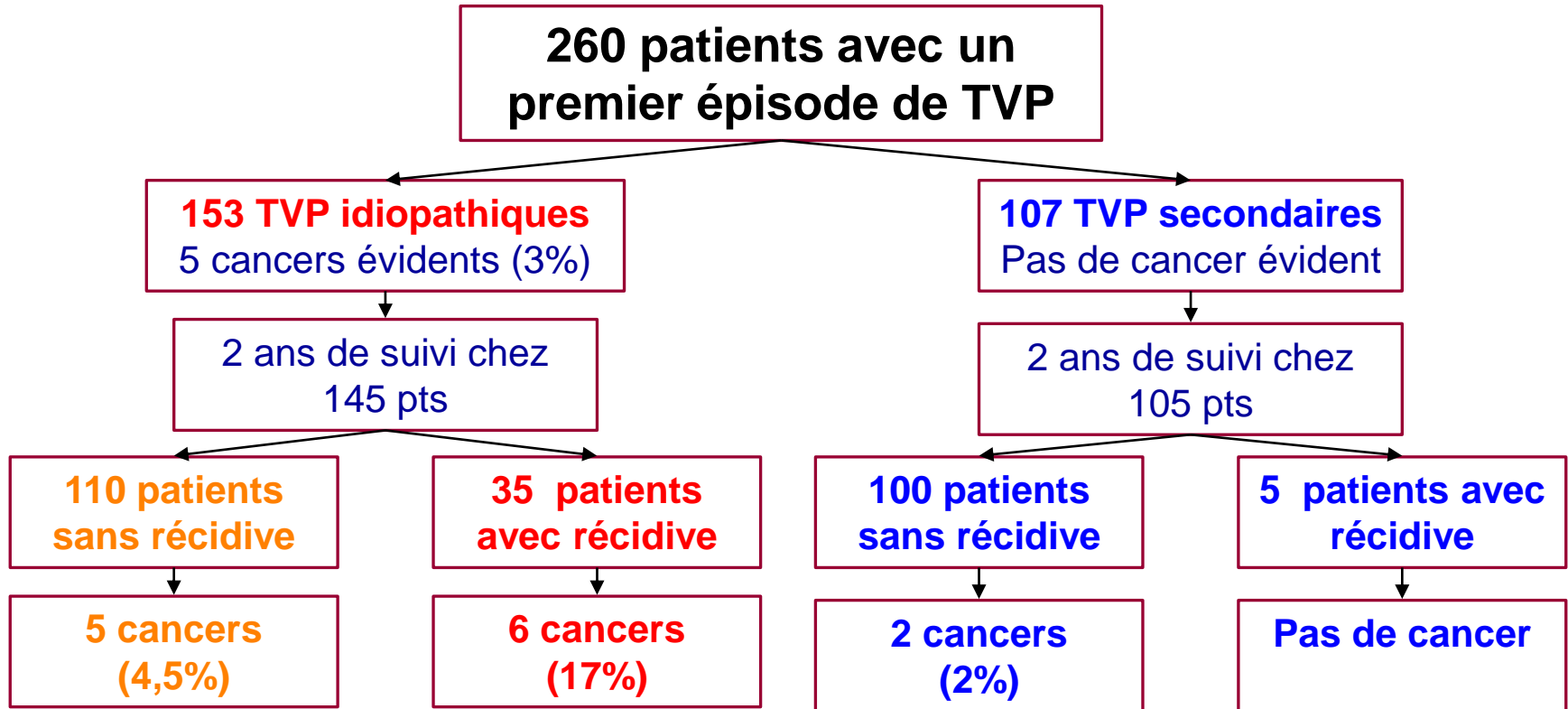
Cluster randomized trial

ETHNOGRAPHY

- Clinical
- Biological
- Imaging

- Psycho-sociological
- Anthropological
- Economic

Chez qui rechercher un cancer occulte?



Les patients les plus jeunes vont-ils bénéficier d'un dépistage intensif du cancer ?

Age	Cancer	Nombre de patients à dépister
<40	0	-
41-50	6,3%	16
51-60	5,4%	18,5
61-70	17,3	5,8
71-80	13,1	7,6
>80	14,8	6,8

Cible > 60 ans

Screening for Occult Cancer in Patients With Unprovoked Venous Thromboembolism

A Systematic Review and Meta-analysis of Individual Patient Data

Nick van Es, MD; Grégoire Le Gal, MD, PhD; Hans-Martin Otten, MD, PhD; Philippe Robin, MD, PhD; Andrea Piccioli, MD, PhD; Ramón Lecumberri, MD, PhD; Luis Jara-Palomares, MD; Piotr Religa, MD, PhD; Virginie Rieu, MD; Matthew Rondina, MD; Mariëlle M. Beckers, MD, PhD; Paolo Prandoni, MD, PhD; Pierre-Yves Salaun, MD, PhD; Marcello Di Nisio, MD, PhD; Patrick M. Bossuyt, PhD; Harry R. Büller, MD, PhD; and Marc Carrier, MD

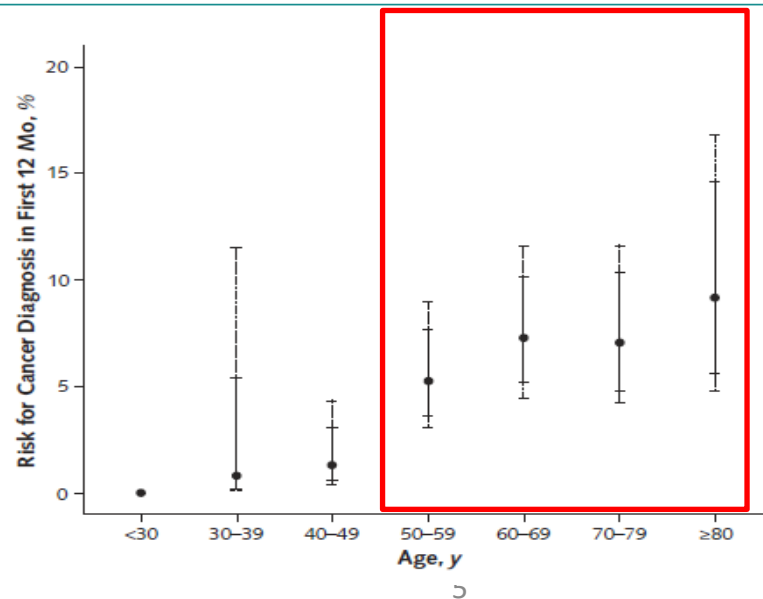
Table 2. 12-Month Prevalence of Cancer in Subgroups*

Subgroup	Patients With Cancer, %	Patients, n	Estimated 12-Mo Prevalence (95% CI), %
Age			
≥50 y	6	592	6.7 (5.5–8.2)
<50 y	95	1409	1.0 (0.46–2.2)
Sex			
Female	38	758	5.0 (3.4–7.5)
Male	63	1243	5.7 (3.8–8.5)
Estrogen use			
Yes	2	151	1.3 (0.33–5.1)
No	35	602	5.8 (3.8–8.8)
Smoking history			
Current or former smoker	51	901	5.7 (4.3–7.4)
Never smoked	38	989	3.9 (2.5–6.0)
Index VTE			
PE with or without DVT	42	950	5.2 (3.2–8.2)
DVT only	59	1051	5.6 (4.4–7.2)
Previous VTE			
Yes	12	187	6.4 (3.7–11)
No	89	1814	5.2 (3.8–7.1)

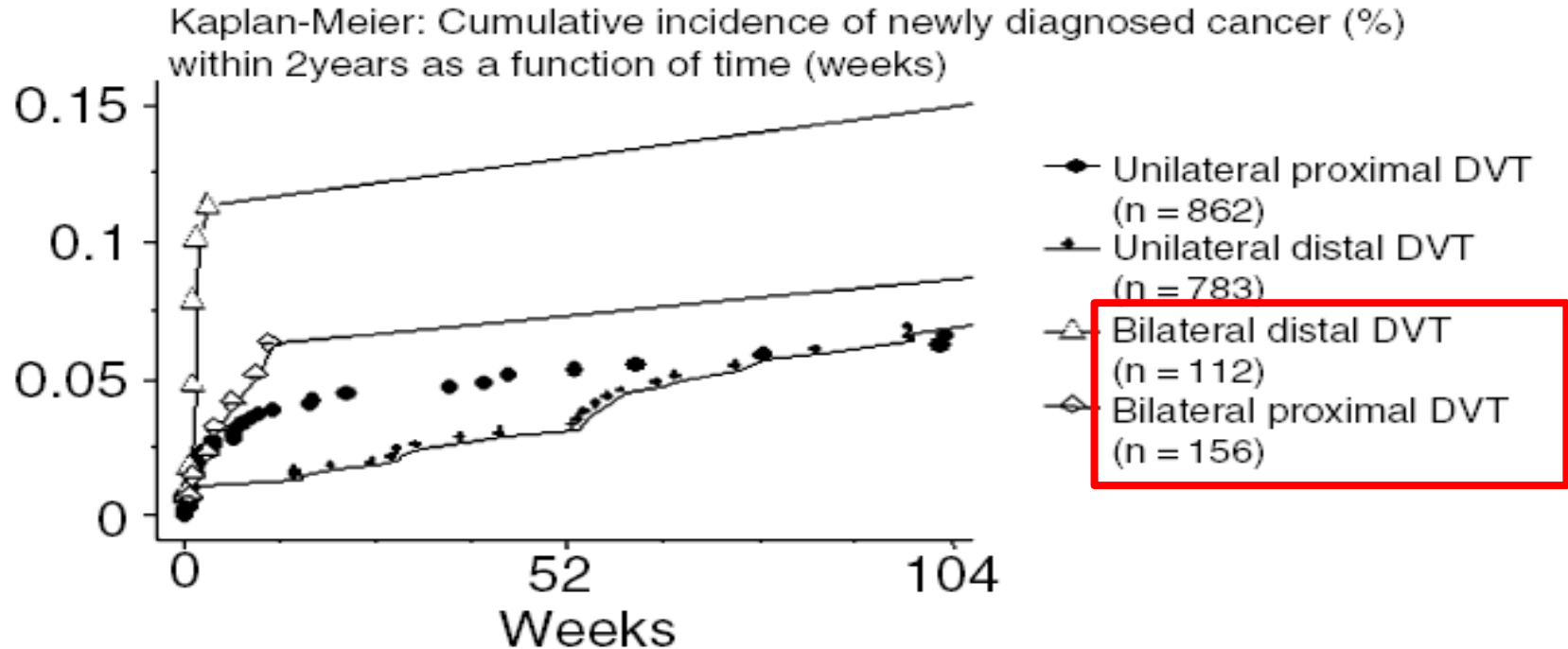
Identification de patients à risque:

- Age +++
- Risque cancer < 40ans: 0.5%
- Risque cancer > 80 ans: 9.2%

Figure 4. Point prevalence of cancer at 12 months, stratified by age cohorts.



MTEV idiopathique quand penser au cancer?



Autres contextes

- **Thrombose récidivante** (sous anticoagulants)
 - Récidive sans anticoagulant : **cancer 4,3% à 17%**
 - Récidive sous anticoagulant : **cancer 30%**
- **Thrombose de site inhabituel**