Coagulopathies et AVC : Quel bilan ?

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Unité d'Hémostase Clinique
Université Lyon 1

Lyon, 16 10 2014

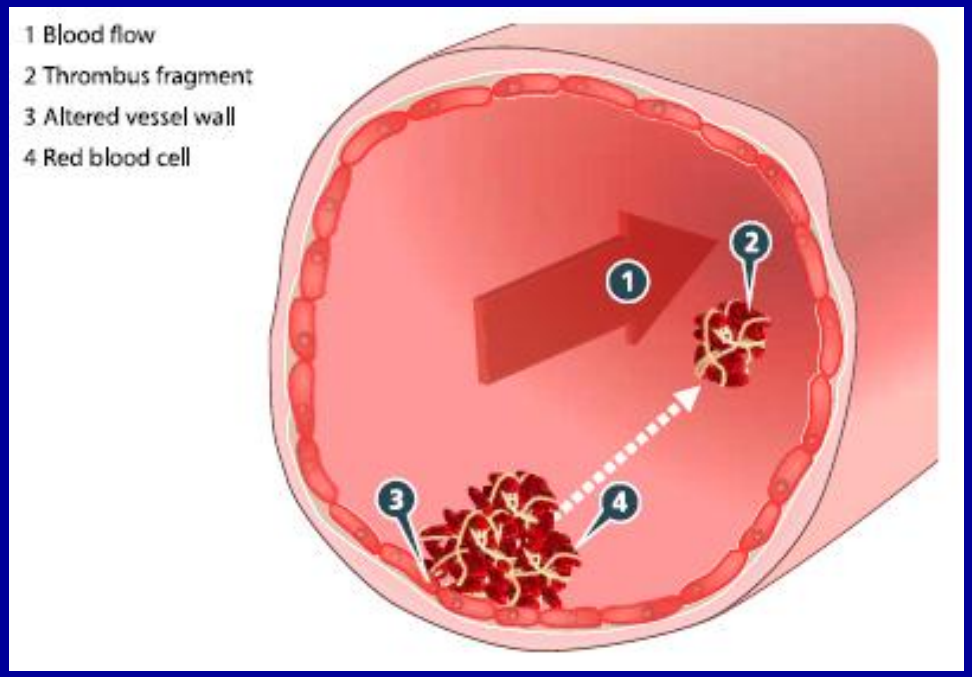
Venous Thrombosis

Vessel Wall Damage

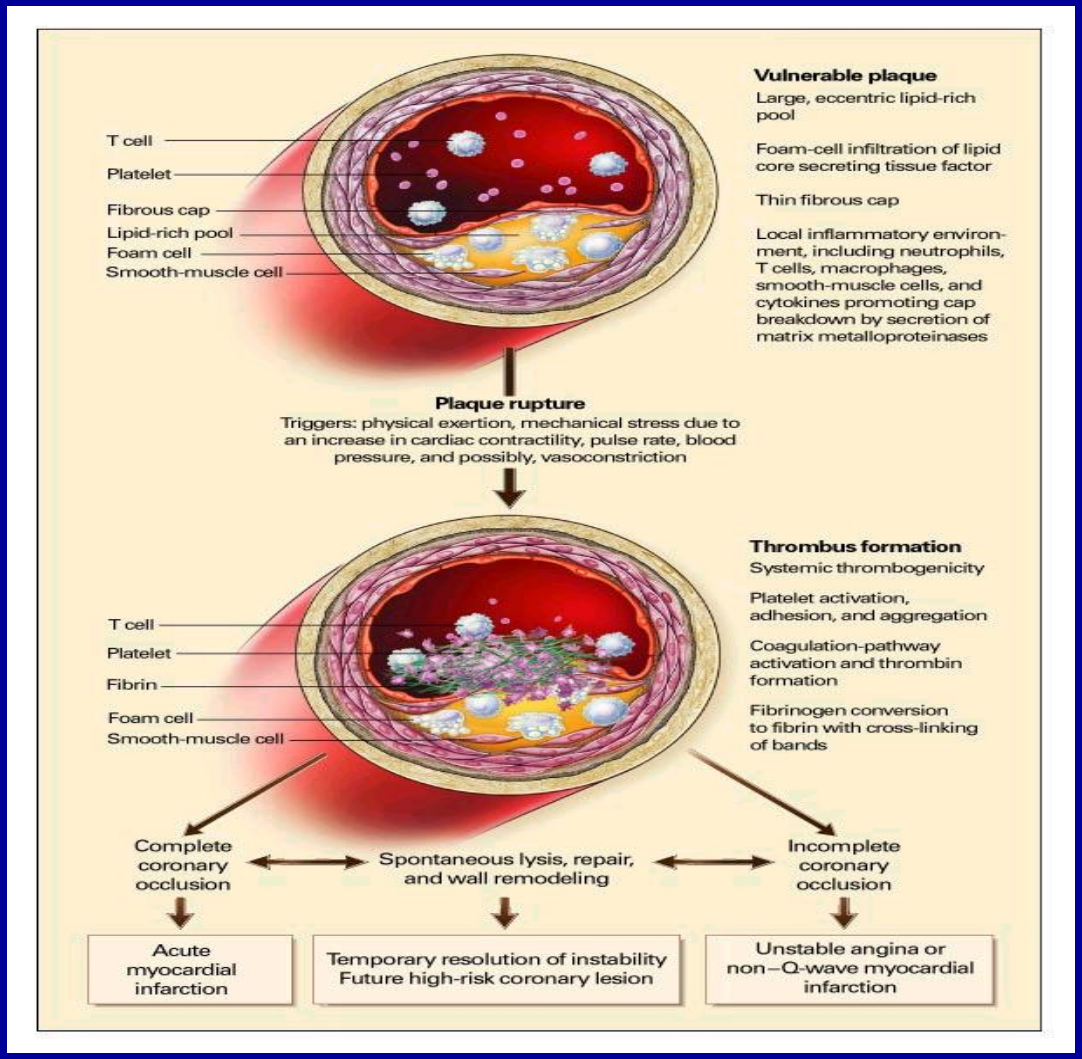
Altered Blood Flow

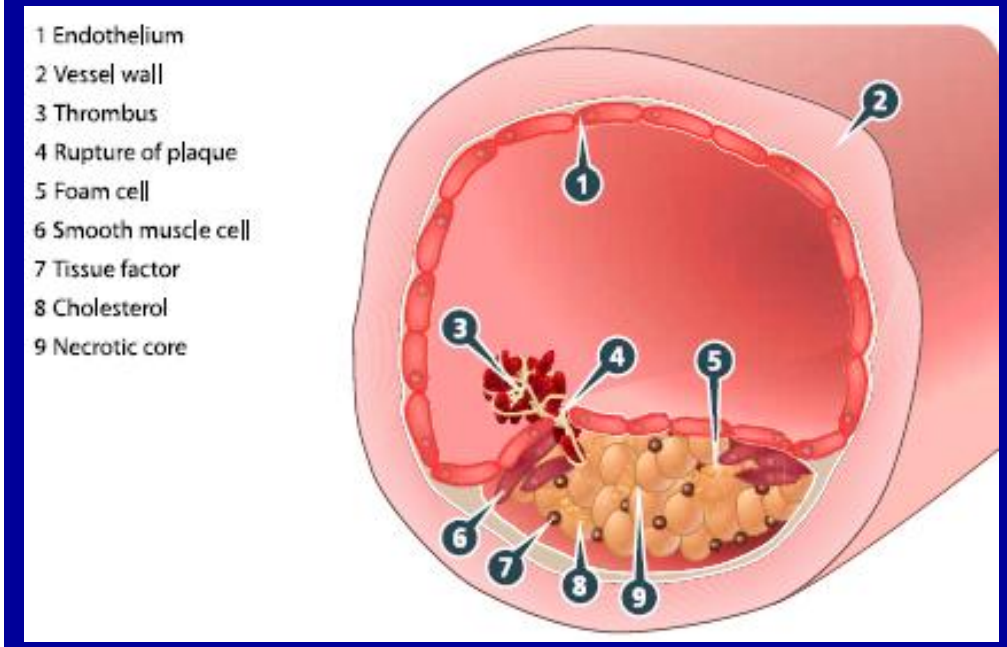
Factors Contributing to Thrombosis

Blood Coagulability



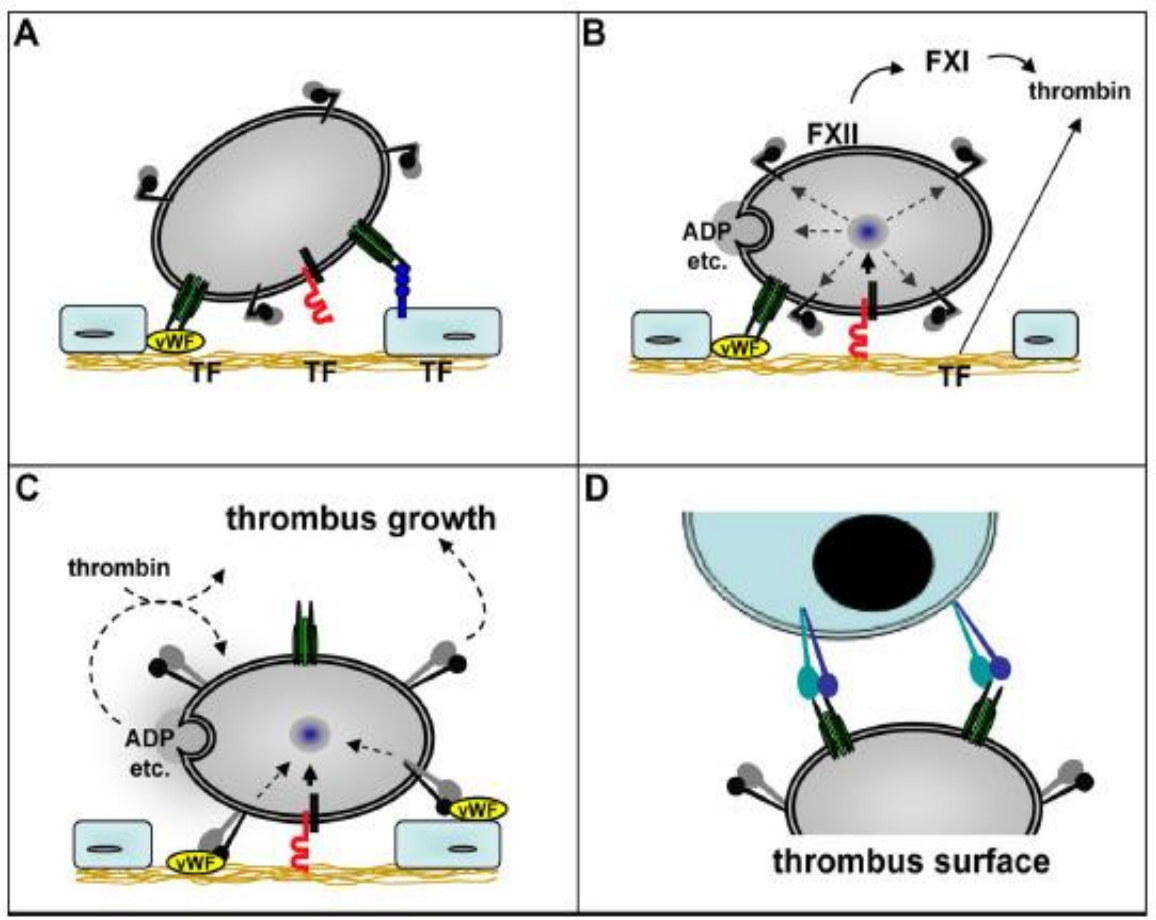
Arterial Thrombosis

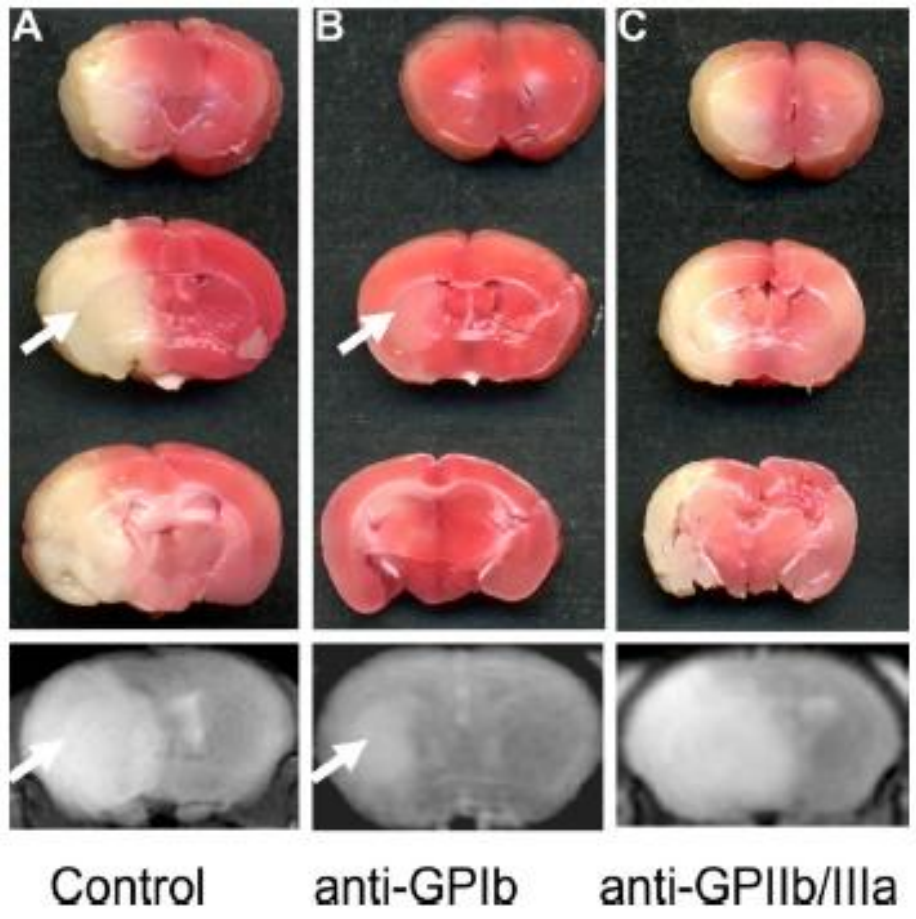




Ross R, N Engl J Med 1999

Platelets and Ischemic Stroke





Summary of meta-analyses of circulating levels of haemostatic variables and Coronary Heart Disease risk

Variable	Cases (n)	Hazard ratio (95 CI)*
D-dimer	1535	1.7 (1.3-2.2)
Fibrinogen	7118	1.75 (1.59-1.92)
VWF	3969	1.23 (1.14-1.33)
PAI-1	833	0.98 (0.53-1.81)

* Top third vs bottom third

Lowe GDO, BJH 2006

Morange, ATVB 2006

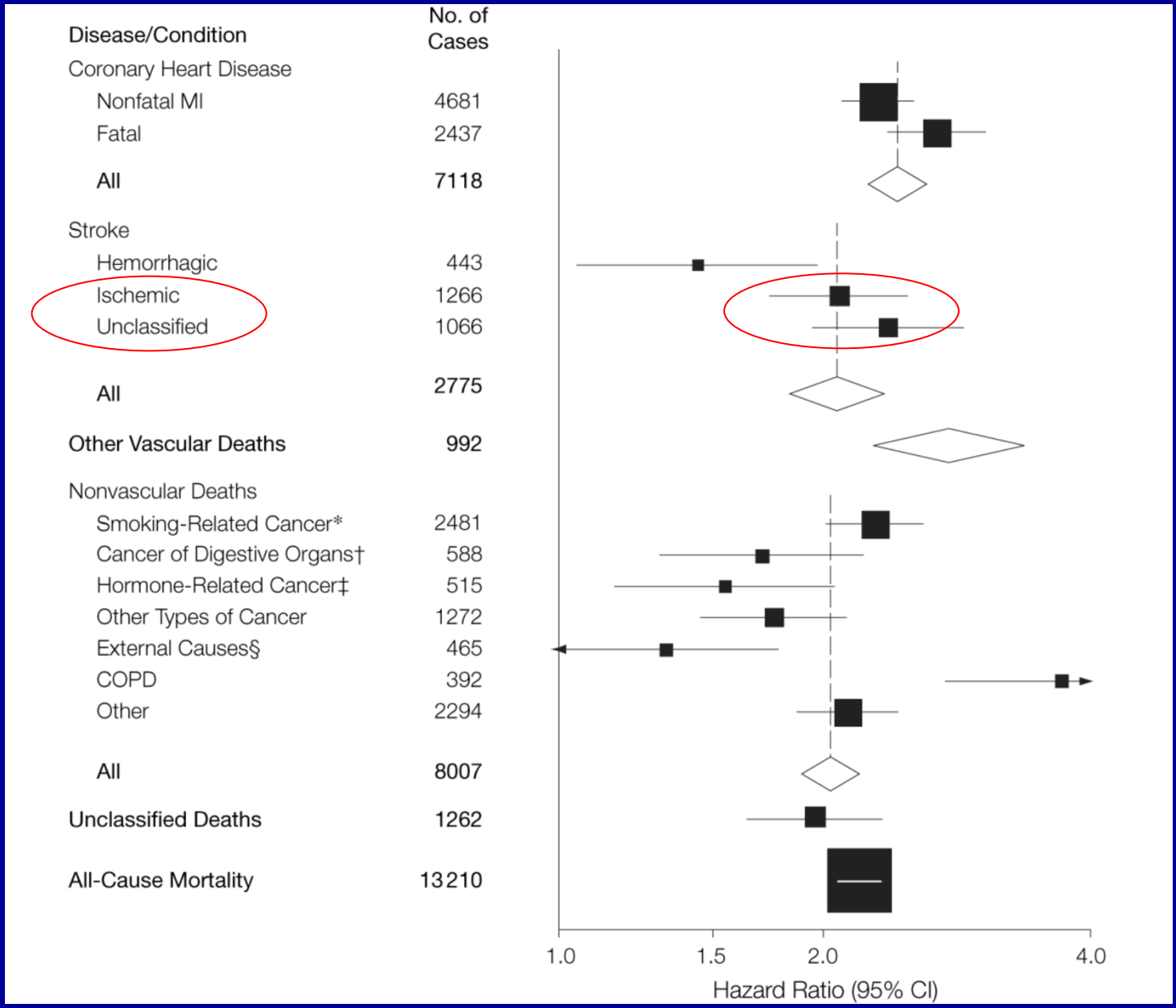
- Increase in coagulation marker is associated with a higher risk of arterial thrombosis

- Which factors of the coagulation pathway are involved?

Fibrinogen and CHD

Important role in physiology

- Final substrate of the coagulation cascade
- Role in platelet aggregation
- Determinant of blood viscosity

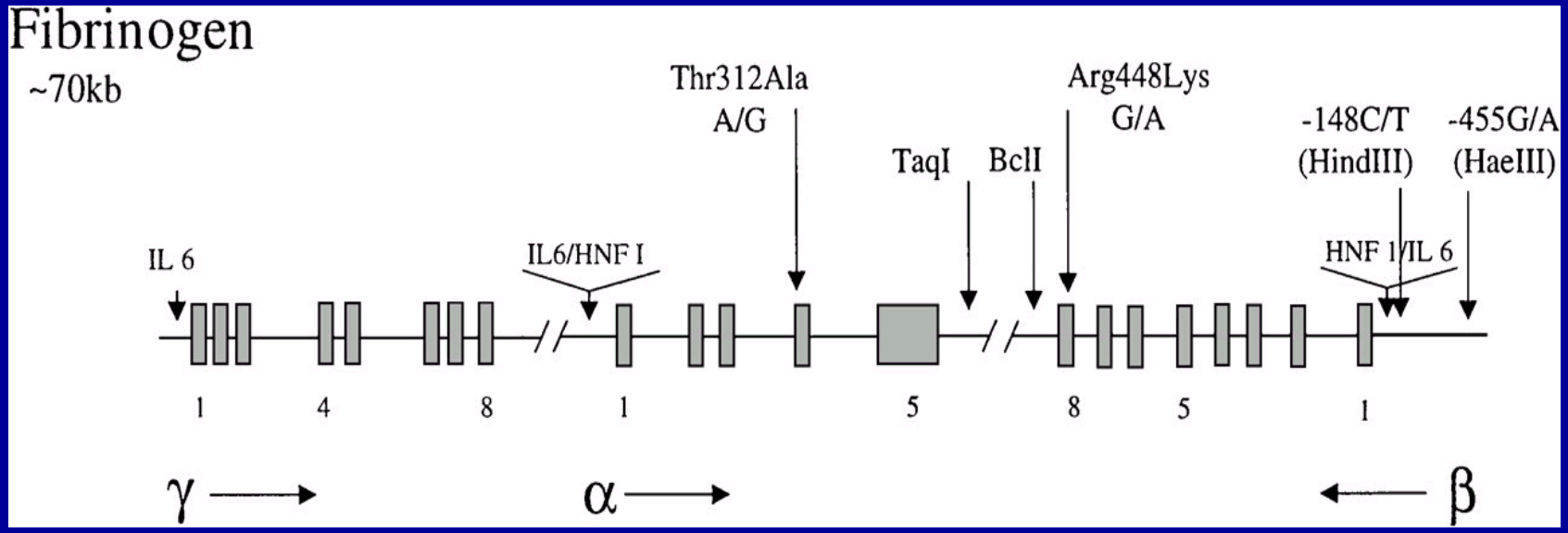


Fibrinogen studies collaboration JAMA 2005

Determinants of Fibrinogen plasma levels

- Age
- Smoking
- Obesity
- Lipid profile
- Inflammation…

Is Fibrinogen a marker or a risk factor for arterial thrombosis ?



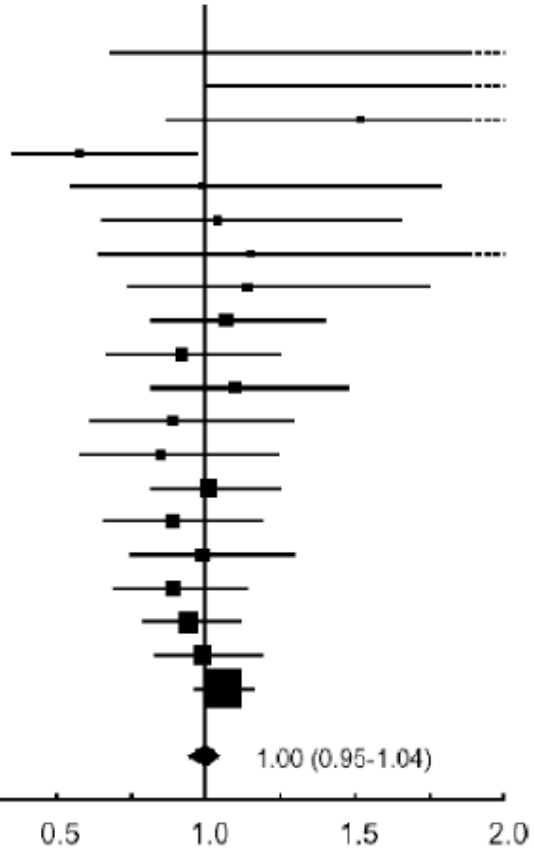
Gene β:

- polymorphisms - **455 G/A** and -148 C/T
- **Explain 14% of Fibrinogen variability**

→ (A allele carriers have higher levels)

Relation between -455G/A, and arterial thrombosis a meta-analysis

Study	Cases/ controls	Genotype frequency (cases vs controls) 1/1	1/2	2/2	Risk ratio per higher-fibrinogen allele (& CI)
Mean plasma fibrinogen (g/L):		3.34	3.48	3.60	
Volzke (2003)	26 / 185	42% v 54%	46% v 42%	12% v 4%	
Ma (1999)	66 / 53	55% v 77%	39% v 21%	6% v 2%	
Lee (1999)	95 / 393	65% v 56%	32% v 30%	3% v 3%	
Yu (1996)	103 / 331	71% v 54%	26% v 42%	3% v 4%	
Green (1993)	123 / 86	58% v 57%	38% v 36%	6% v 7%	
van der Bom (1998)	139 / 287	62% v 64%	35% v 32%	4% v 4%	
Wang (1997)	223 / 87	63% v 69%	34% v 46%	3% v 5%	
Lee (2001)	305 / 215	67% v 69%	30% v 29%	3% v 2%	
Blake (2001)	386 / 751	61% v 62%	33% v 32%	6% v 5%	
Folsom (2001)	398 / 498	69% v 65%	28% v 27%	3% v 5%	
Maghzal (2003)	432 / 490	60% v 63%	36% v 32%	4% v 5%	
Yamada (2002)	445 / 464	77% v 76%	22% v 22%	1% v 2%	
Gardemann (1997)	450 / 188	61% v 56%	34% v 38%	4% v 5%	
Tybjaerg-Hansen (1997)	489 / 6852	62% v 63%	34% v 33%	3% v 4%	
Tobin (2004)	546 / 505	70% v 67%	27% v 29%	3% v 4%	
Doggen (2000)	560 / 646	61% v 63%	36% v 33%	3% v 5%	
Behague (1996)	565 / 668	65% v 63%	31% v 32%	4% v 6%	
Leander (2002)	1169 / 1517	64% v 62%	32% v 34%	4% v 4%	
Italian Study Group (2003)	1210 / 1210	60% v 61%	35% v 33%	4% v 6%	
ISIS	4490 / 3290	65% v 66%	32% v 30%	3% v 4%	
Total	**12220 / 18716**				1.00 (0.95-1.04)



Danesh et al. Int J Epidemiol 2006

Summary of meta-analyses of circulating levels of haemostatic variables and CHD risk

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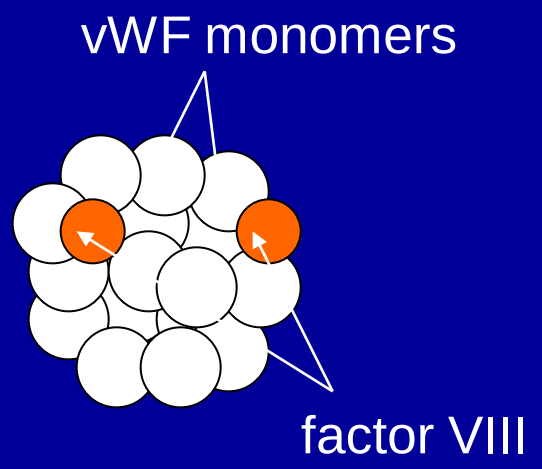
* Top third vs bottom third

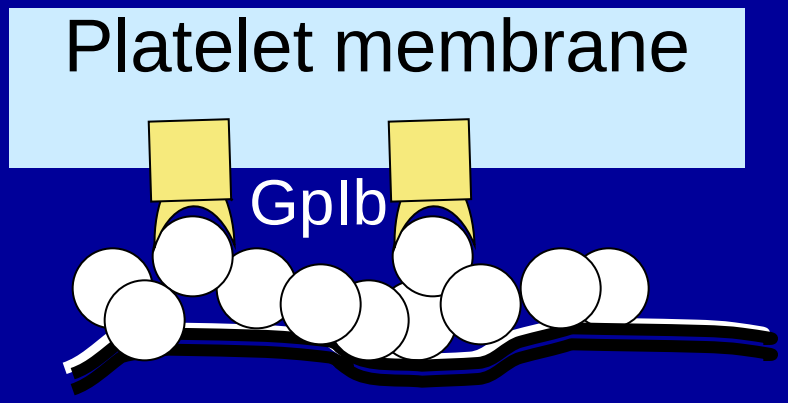
Lowe GDO, BJH 2006

2 physiological roles for VWF

Carrier of FVIII in plasma



Allow adhesion of platelets to subendothelial collagen



Journal of Thrombosis and Haemostasis, **11**: 845–854 DOI: 10.1111/jth.12194

ORIGINAL ARTICLE

Reduced prevalence of arterial thrombosis in von Willebrand disease

Y. V. SANDERS,* J. EIKENBOOM,†‡ E. M. DE WEE,* J. G. VAN DER BOM,§¶ M. H. CNOSSEN,** M. E. L. DEGENAAR-DUJARDIN,†† K. FIJNVANDRAAT,‡‡ P. W. KAMPHUISEN,§§ B. A. P. LAROS-VAN GORKOM,¶¶ K. MEIJER,*** E. P. MAUSER-BUNSCHOTEN,††† F. W. G. LEEBEEK* and ON BEHALF OF THE WIN STUDY GROUP1

635 adult patients aged 16-85 years

vWF <30%

2 control groups: Dutch National Healmth Compass

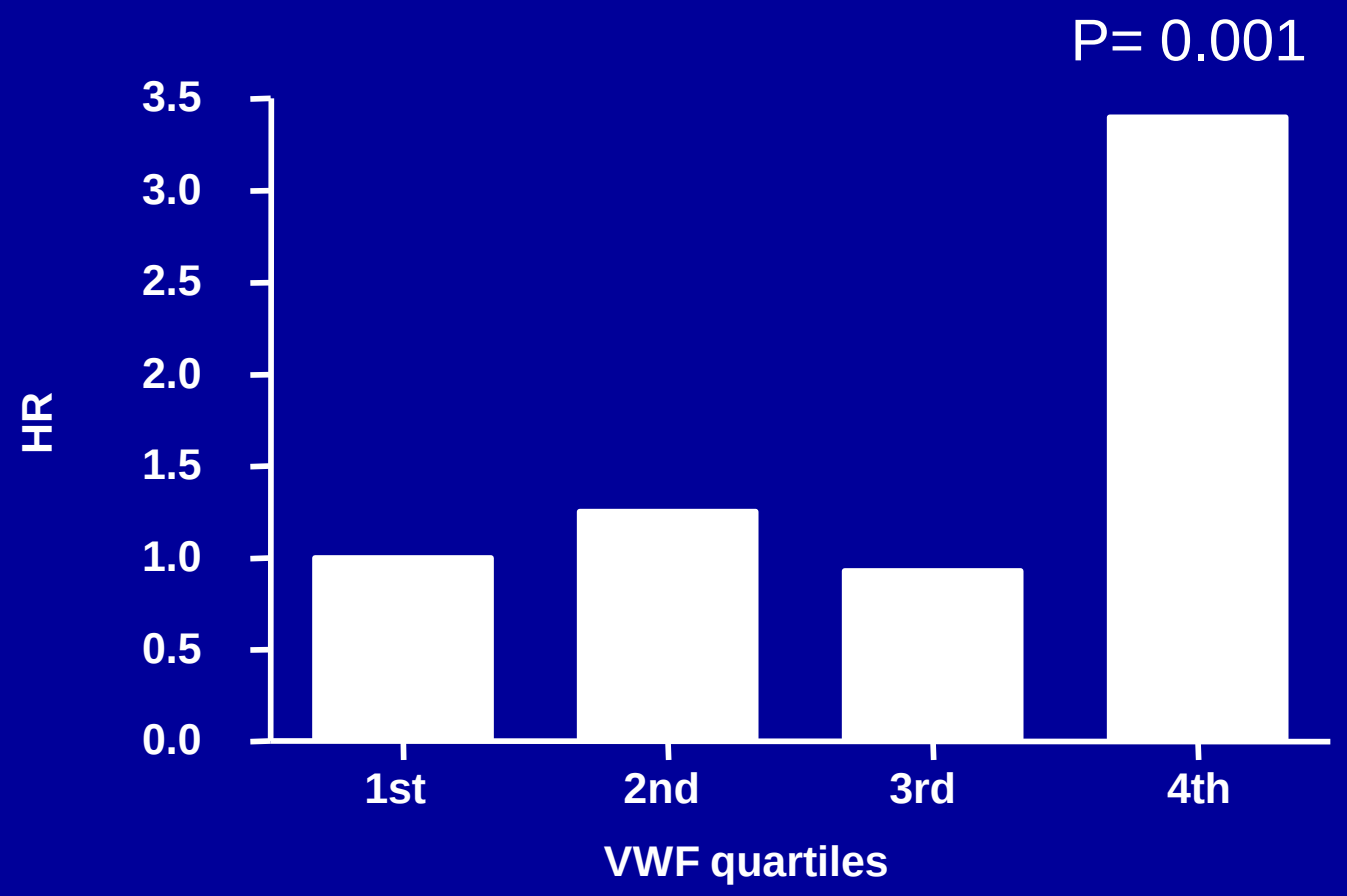
Central Bureau of Statistics Netherlands

Ischemic stroke : 39% lower than in the 2 reference populations

Coronary heart disease: 63% lower than in the 2 reference populations

J Thromb Haemost 2013

VWF and the risk of arterial thrombosis
The PRIME Study



Morange et al. Circulation 2004

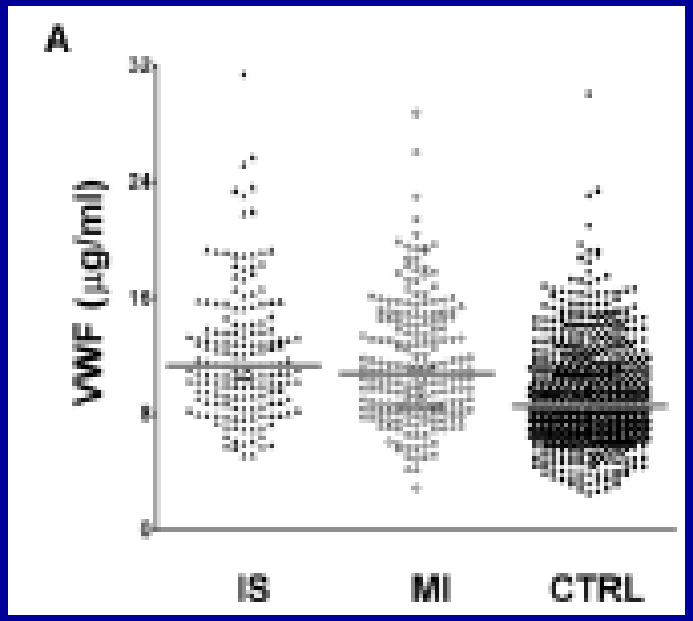
THROMBOSIS AND HEMOSTASIS

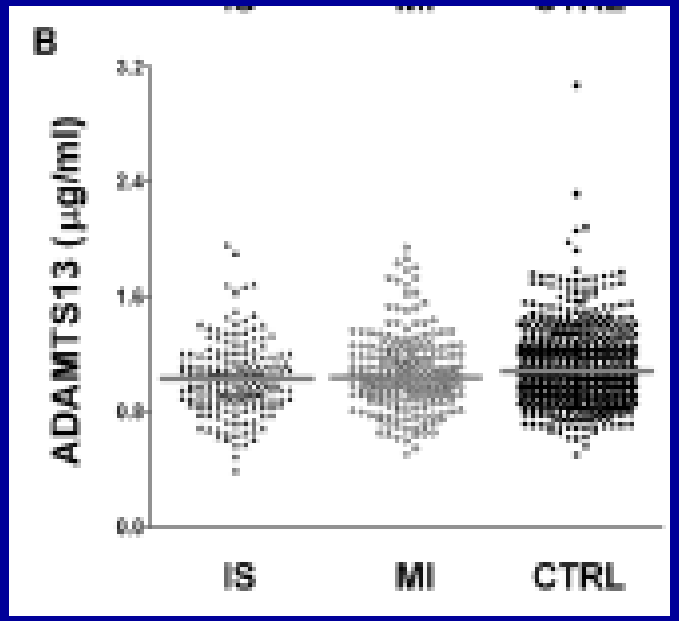
High VWF, low ADAMTS13, and oral contraceptives increase the risk of ischemic stroke and myocardial infarction in young women

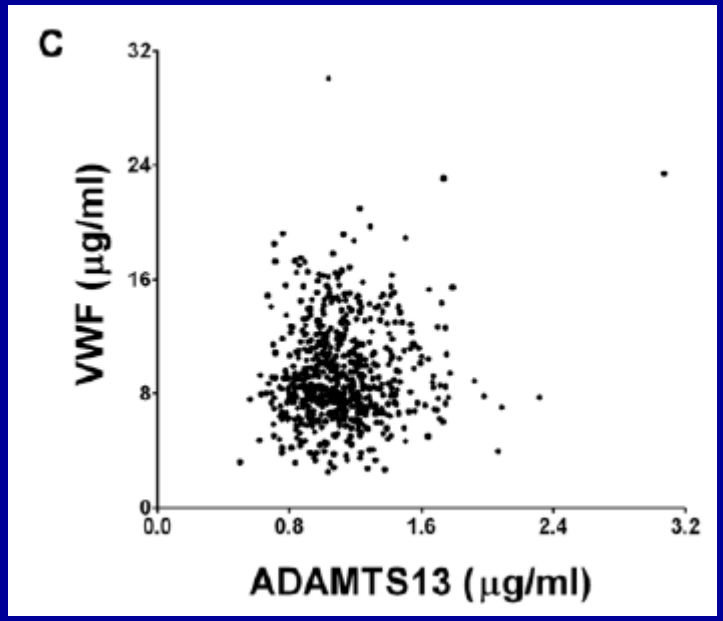
Helena M. Andersson,[1] Bob Siegerink,[2] Brenda M. Luken,[1] James T. B. Crawley,[1] Ale Algra,[2-4] David A. Lane,[1] and Frits R. Rosendaal[2,5]

High vWF and low ADAMTS 13 OR IS: 6,9 OR MI: 11,3

High vWF and low ADAMTS 13 + oral contraceptive OR IS: 7,5 OR MI: 12







Case control study

N= 1018 young women (18-49 yrs)

IS: 175 MI:205

Blood 2012

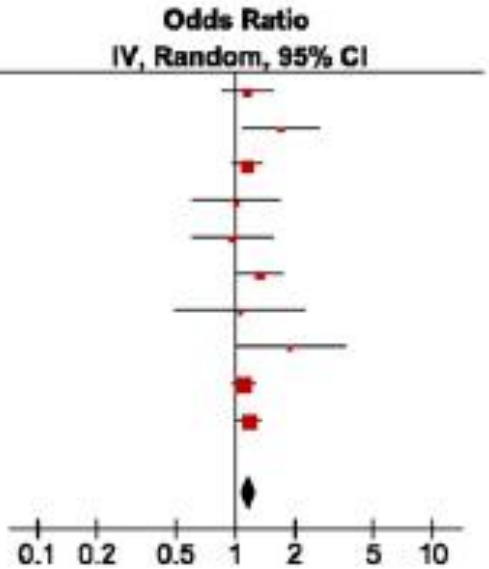
M.A.H. Sonneveld et al. / Blood Reviews 28 (2014) 167–178

Forest plot of the association between VWF and ischemic stroke

Study or Subgroup	Cases Total	Controls Total	Odds Ratio IV, Random, 95% CI
Smith 1997	45	1174	1.15 [0.85, 1.55]
Folsom 1999	191	14522	1.71 [1.09, 2.68]
Knuiman 2001	159	1234	1.15 [0.96, 1.37]
Johansson 2002	87	216	1.01 [0.61, 1.68]
Smith 2005	133	2090	0.97 [0.61, 1.55]
Tzoulaki 2007	168	177	1.33 [1.02, 1.73]
Carcaillon 2009	111	1055	1.06 [0.49, 2.28]
Gottesman 2009	196	214	1.90 [1.00, 3.61]
Wieberdink 2010	290	5960	1.10 [0.96, 1.26]
Wannamethee 2012	187	3171	1.18 [1.02, 1.36]
Total (95% CI)	**1567**	**29813**	**1.17 [1.08, 1.26]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 7.65$, df = 9 (P = 0.57); $I^2 = 0\%$

Test for overall effect: Z = 4.03 (P < 0.0001)



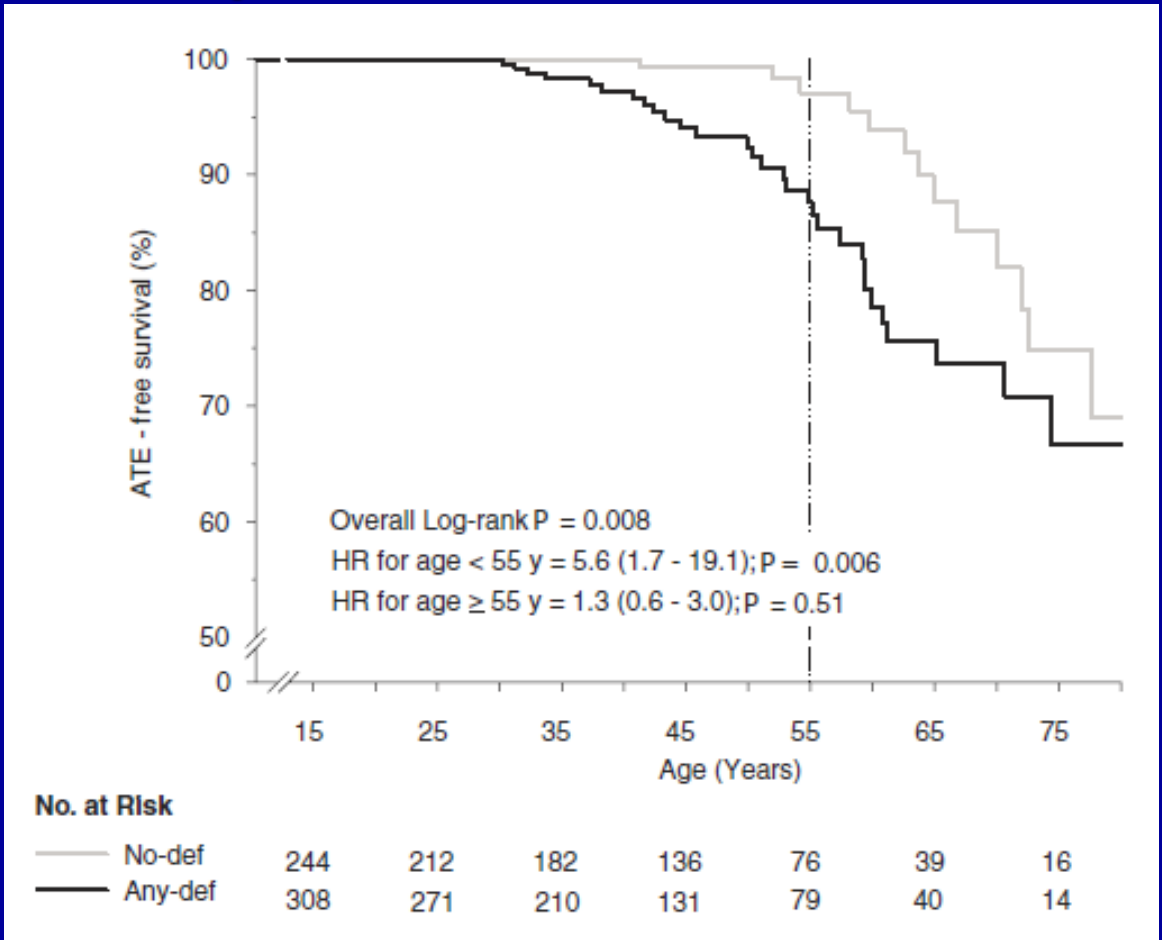
Thrombophilia and VTE

Year of description		Risk Factor	Prevalence % General population	Prevalence % VTE subjects	RR of VTE
1965	Egeberg	Antithrombin Def.	0.02	1	10
1981	Griffin	Protein C Def.	0.25	6	10
1984	Comp	Protein S Def.	0.25	6	10
1994	Bertina	Factor V Leiden	3	20	5
1996	Poort	Prothrombin 20210A mutation	3	20	3

Inhibitor deficiency and risk of arterial thromboembolism

Retrospective study from Netherlands :

558 subjects from 84 different kindreds



Mahmoodi, Circulation 2008

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association®

Hereditary Deficiency of Protein C or Protein S Confers Increased Risk of Arterial Thromboembolic Events at a Young Age: Results From a Large Family Cohort Study

Bakhtawar K. Mahmoodi, Jan-Leendert P. Brouwer, Nic J.G.M. Veeger and Jan van der Meer

Circulation. 2008;118:1659-1667; originally published online September 29, 2008;

	Arterial thromboembolism		
Variable	**HR (95% CI)**	**HR (95% CI)**	**P value**
PS, PC or AT deficiency (age < 55 y)	4.7 (1.5 - 14.2)		0.007
PS, PC or AT deficiency (age ≥ 55 y)	1.1 (0.5 - 2.6)		0.84
Hypertension	1.8 (1.1 - 3.0)		0.03
Hyperlipidemia	2.0 (1.1 - 3.7)		0.02
Smoking history	2.1 (1.1 - 3.6)		0.03

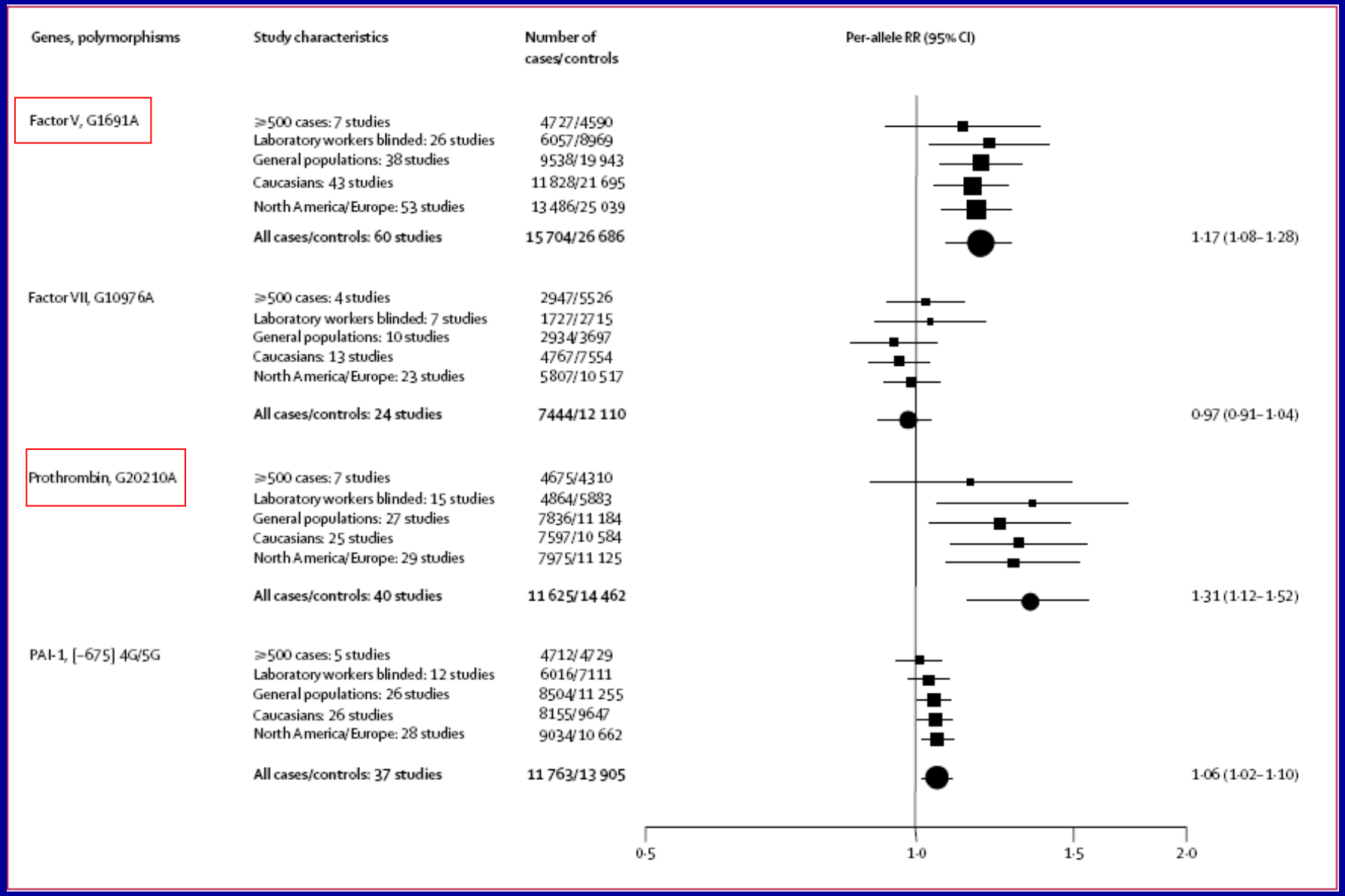
Table 1. Case-Control Studies of PC, PS, and AT in Patient With Ischemic Stroke

Reference	Age	N Cases and Controls	Thrombophilia Tested	% Identified in Cases	% Identified in Controls	Statistical Significance
Sastry (2006)[9]	16–39	101	PC, PS, AT	7.9	8.9	NS
		101				
Jerrard-Dunn (2003)[10]	≤65	130	PS, PC, AT	8.5*	6.3*	NS
		130				
Hankey (2001)[11]	Mean	219	PC, PS, AT	7.3	6.8	NS
	66	205				
Margaglione (1999)[12]	3–50	202	PC, PS, AT	0	0	NS
		1036				
De Stefano (1998)[13]	2–50	72	PC, PS, AT	1.4	0	NS
		198				
Mayer (1993)[14]	>39	94	PS	21	20	NS
		94				

Morris et al, Stroke 2010

Table 2. Case-Control Studies of FVL and PTM in Young Patients (Younger Than 60 Years) With Ischemic Stroke

Reference	Age	N Cases and Controls	Thrombophilia Tested	% Identified in Cases	% Identified in Controls	Statistica Significanc
Sastry (2006)[9]	16–39	101	FVL	4.0	7.9	NS
		101	PTM	2.0	0.0	NS
Slooter (2005)[18]	20–49 W	193	FVL	7.8	5.5	OR 1.8
		767	PTM	2.7	2.4	OR 1.0
Lalouschek (2005)[19]	<60	468	FVL	6.2	6.4	NS
		468	PTM	5.0	2.0	$P=0.032$
Madonna (2002)[20]	0.5–50	132	FVL	5.3	6.5	NS
		262	PTM	7.6	6.1	NS
Austin (2002)[21]	18–50	67	FVL	7.4	5.1	NS
		79	PTM	4.4	2.5	NS
Lopaciuk (2001)[22]*	≤45	100	FVL	3.0	4.2	NS
		238	PTM	2.0	2.1	NS
Voetsch (2000)[23]	15–45	153	FVL	3.3	3.6	NS
		225	PTM	4.6	2.2	NS
Margaglione (1999)[12]	3–50	202	FVL	14.9	4.2	$P<0.000$
		1036	PTM	5.0	4.2	NS
De Stefano (1998)[13]	2–50	72	FVL	5.5	2.5	NS
		198	PTM	12.5	2.5	$P=0.000$
Nabavi (1998)[24]	14–45	225	FVL	8.4	6.0	NS
		200				
Longstreth (1998)[25]*	18–44 W	106	FVL	0.9	4.1	NS
		391	PTM	1.9	1.6	NS
Bentolila (1997)[26]	18–49	125	FVL	6.7	5.9	NS
		134	PTM	6.4	3.7	NS
Martinelli (1997)[27]	43±13	155	FVL	3.2	1.3	NS
		155	PTM	3.8	3.2	NS
Sanchez (1997)[28]*	6–52	66	FVL	4.5	4.5	NS
		66				
Landi (1996)[29]	5–44	95	FVL	4.2	1.6	NS
		190				
Kontula (1995)[30]	<60	236	FVL	4.5	2.9	NS
		137				



Ye, Lancet 2006

Significant but modest effect :

Is that clinically useful ?

Stroke
Journal of the American Heart Association

Testing for Inherited Thrombophilias in Arterial Stroke: Can It Cause More Harm Than Good?

Jane G. Morris, Swaraj Singh and Marc Fisher

Stroke. 2010;41:2985-2990; originally published online October 14, 2010;

- **Potential risk to patients related to inappropriate use of long term anticoagulants**

- **Significant costs to the health care system:**
  Patient 35 yo person with a life expectancy of 80 years
  Costs warfarin + INR monitoring + 18 000 USD
  Bleeding risk: fatal bleeding risk 2,7%, major bleed 13,5%, minor bleeds 100%
  2800 – 5800 USD/year

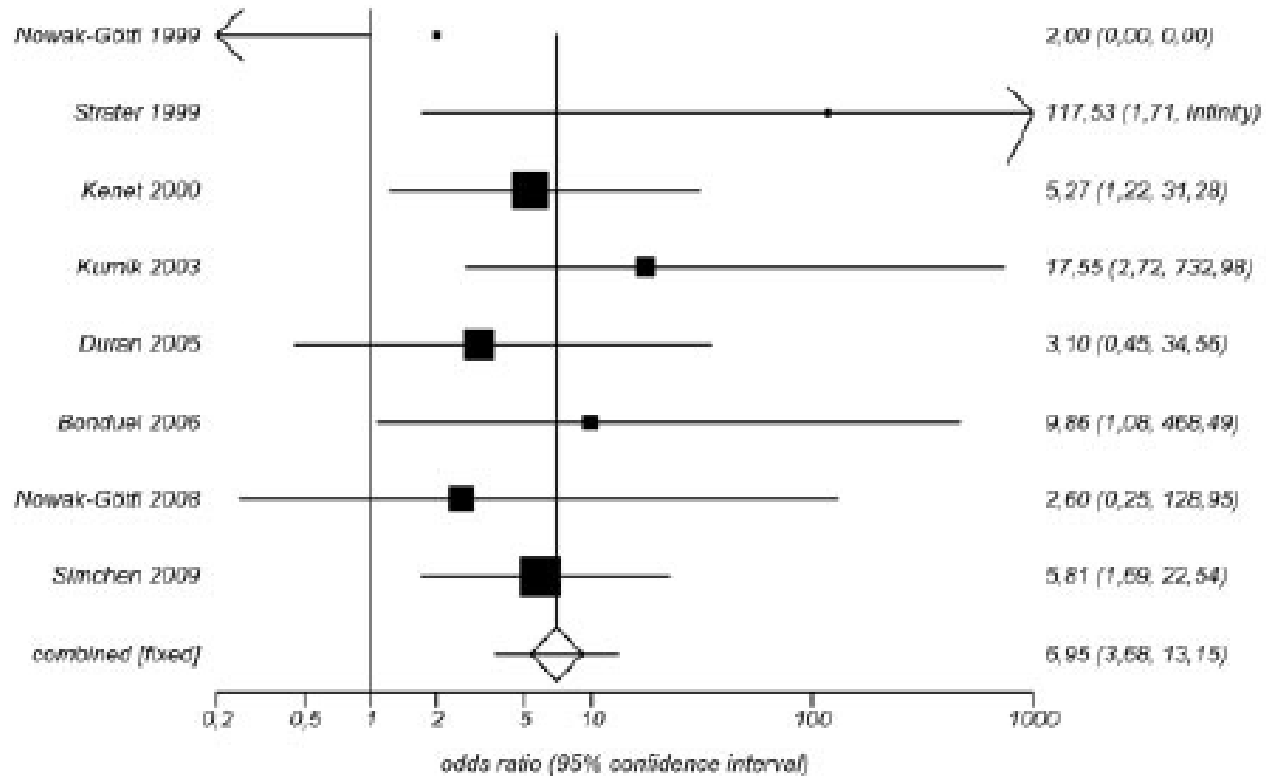
Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association®

Impact of Thrombophilia on Risk of Arterial Ischemic Stroke or Cerebral Sinovenous Thrombosis in Neonates and Children: A Systematic Review and Meta-Analysis of Observational Studies

Gili Kenet, Lisa K. Lütkhoff, Manuela Albisetti, Timothy Bernard, Mariana Bonduel, Leonardo Brandao, Stephane Chabrier, Anthony C
Fullerton, Neil A. Goldenberg, Eric Gra
Holzhauer, Alfonso Iorio, Janna Journey
John K. Lynch, Christoph Male, Marily
Heleen van Ommen, Leslie Raffini, Ke
Young an

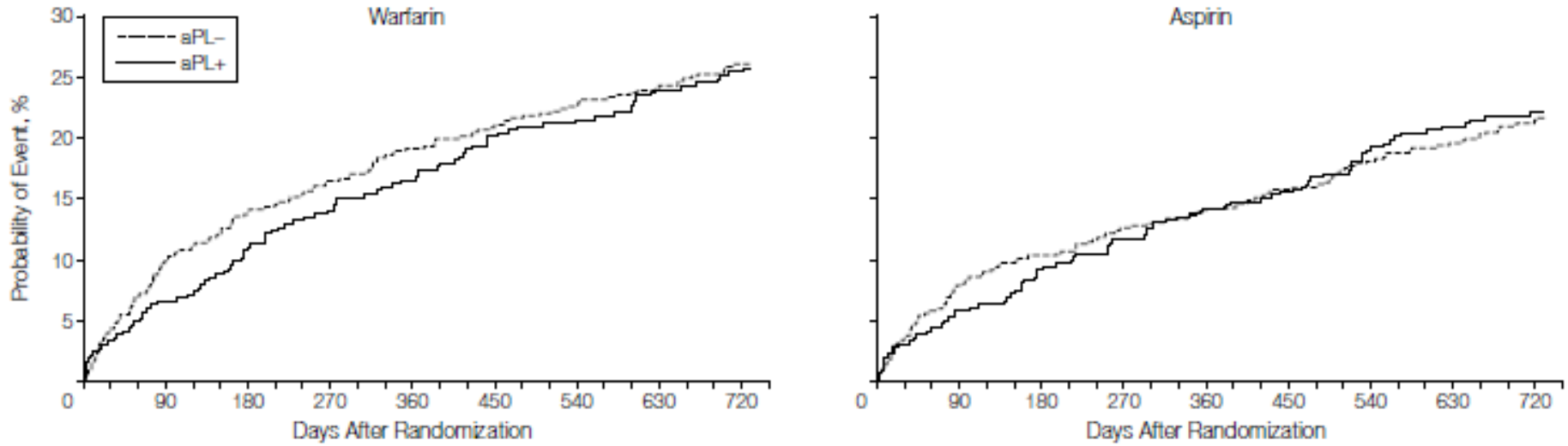
Circulation. 2010;121:1838-184



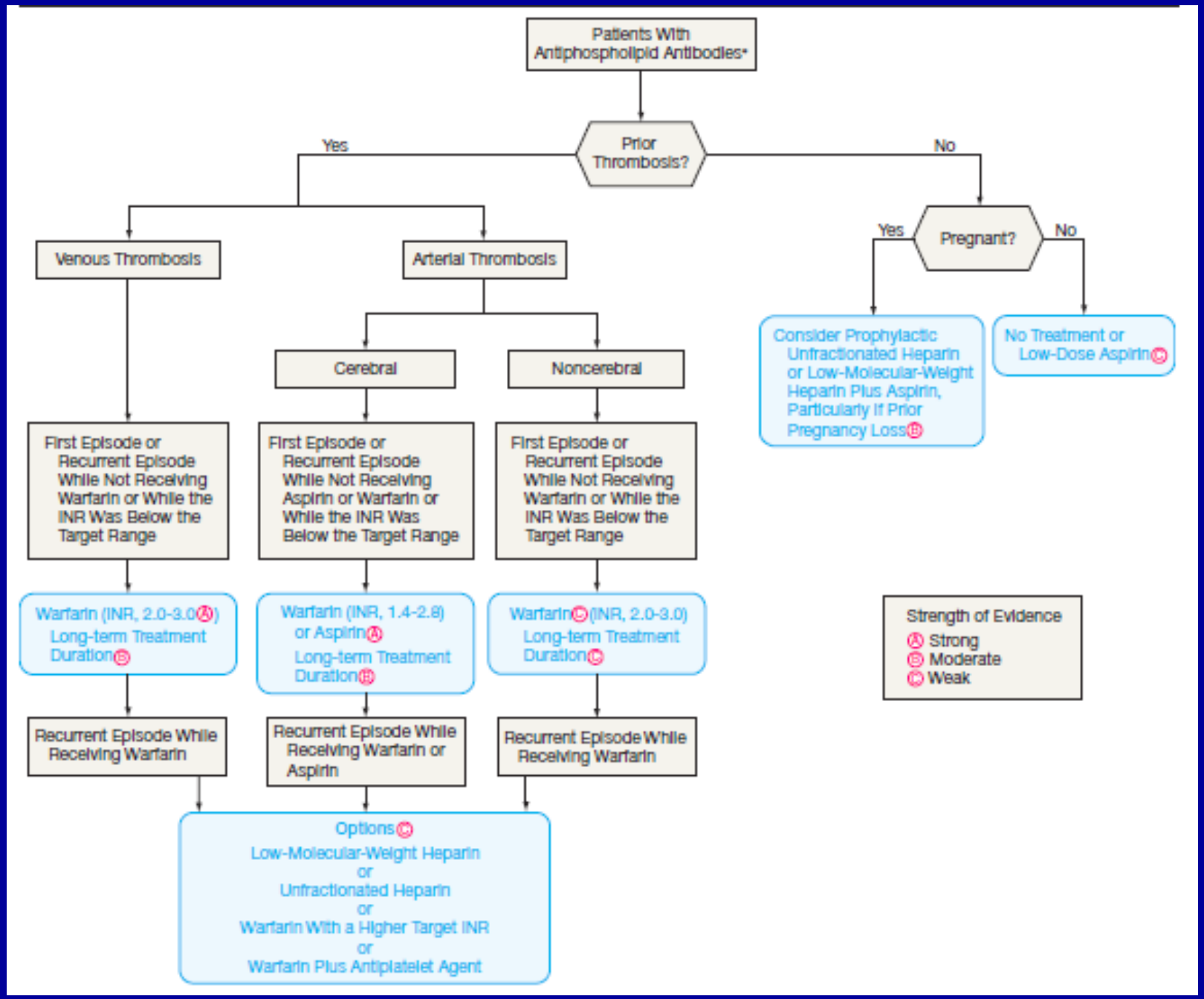
OR 6,95 (95% CI, 3,67-13,14)

Antiphospholipid Antibodies and Subsequent Thrombo-occlusive Events in Patients With Ischemic Stroke

Figure 2. Kaplan-Meier Analysis of the Time to Thrombo-occlusive Event, by aPL Status of APASS Patients Receiving Warfarin (n=881) or Aspirin (n=889)



Levine et al JAMA 2004

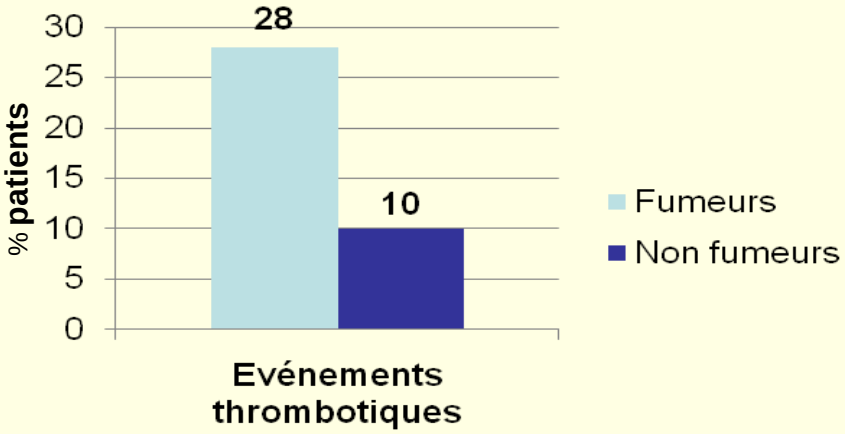

Patients With Antiphospholipid Antibodies*
Prior Thrombosis?
Yes
No
Venous Thrombosis
Arterial Thrombosis
Cerebral
Noncerebral
Pregnant?
Yes
No
Consider Prophylactic Unfractionated Heparin or Low-Molecular-Weight Heparin Plus Aspirin, Particularly if Prior Pregnancy Loss B
No Treatment or Low-Dose Aspirin C
First Episode or Recurrent Episode While Not Receiving Warfarin or While the INR Was Below the Target Range
First Episode or Recurrent Episode While Not Receiving Aspirin or Warfarin or While the INR Was Below the Target Range
First Episode or Recurrent Episode While Not Receiving Warfarin or While the INR Was Below the Target Range
Warfarin (INR, 2.0-3.0 A) Long-term Treatment Duration B
Warfarin (INR, 1.4-2.8) or Aspirin A Long-term Treatment Duration B
Warfarin C (INR, 2.0-3.0) Long-term Treatment Duration C
Recurrent Episode While Receiving Warfarin
Recurrent Episode While Receiving Warfarin or Aspirin
Recurrent Episode While Receiving Warfarin
Options C
Low-Molecular-Weight Heparin
or
Unfractionated Heparin
or
Warfarin With a Higher Target INR
or
Warfarin Plus Antiplatelet Agent
Strength of Evidence
A Strong
B Moderate
C Weak

2- TE et facteurs de risque vasculaire
Résultats: attention au tabac

SMP ET THROMBOSE

31
événements thrombotiques*
(16% à 10 ans)

Influence marquée du tabagisme



11
saignements majeurs**
(8% à 10 ans)

- **Numération plaquettaire très élevé** (1 279 G/L, 424-1 922)

- **Mutation *Jak2* chez 42% des patients**
  - Sans relation avec les complications thrombotiques
  - Retrouvée chez les 5 patients ayant évolué vers une polyglobulie de Vaquez

TE= thrombocytémie essentielle
(*) fréquence élevée des événements thrombotiques chez ces sujets jeunes, proche de celle observée chez les sujets âgés.
(**) dont 3 patients sous antiplaquettaire

A. Alvarez-Larran et al. (Barcelone, Espagne)
ASH 2006, résumé 3598,

Hyperhomocystinurie

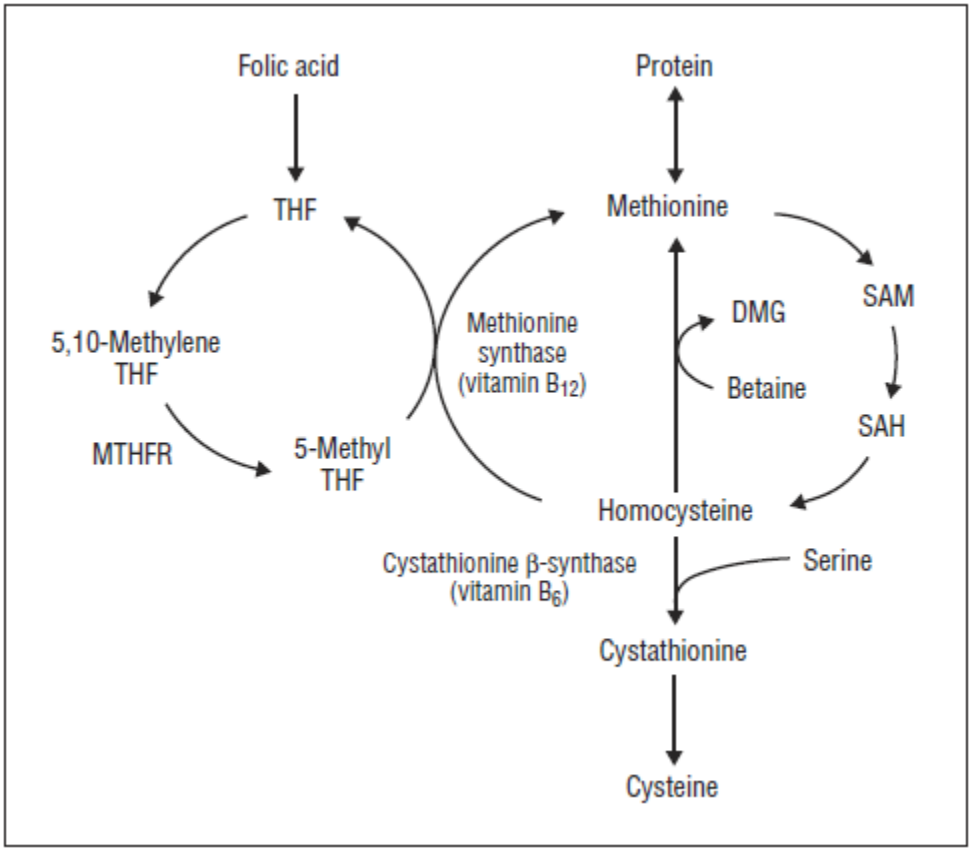


Table 1. Clinical Manifestations of Homocystinuria

Organ	Manifestation
Skin	Hypopigmentation, malar flush, livedo reticularis
Central nervous system	Mental retardation, developmental delay, seizures, ischemic stroke
Psychiatric disorders	Personality disorder, behavior disorder, depression
Skeletal system	Osteoporosis, pectus excavatum or carinatum, genu valgum, scoliosis, dolichostenomelia with marfanoid appearance (rarely, arachnodactyly)
Eye	Extopia lentis, myopia, glaucoma, cataracts, retinal detachment, optic atrophy
Vascular system	Thromboembolism
Kidney	Foul odor of the urine
Gastrointestinal	Pancreatitis

Fernando et al Arch. Neurol. 2010

Conclusions

- From a scientific point of view :

  These data ‘prove’ that the hemostatic system is important to arterial thrombosis.

- From a clinical point of view:

  Clinical utility of a marker depends on :

  Whether or not the obtained information affects clinical decision making?

  Evaluation of coagulation markers in unselected patient populations with arterial thrombosis is not yet justified

En Pratique:

Devant un AVC ischémique, envisager un bilan de thrombophilie si:

- Sujet jeune <50 ans
- Pas de facteur de risque cardiovasculaire
- ATCD personnel de MTEV ou thrombose artérielle inexpliquée

Bilan à envisager:

- **NFP :** syndrome myéloprolifératif
- **Syndrome des anti-phospholipides**: Lupus anticoagulant
  Ac anti-cardiolipines
  Ac anti-beta 2 GPI
- **Homocystéine**: hyperhomocystinurie