Groupes sanguins et Thrombose

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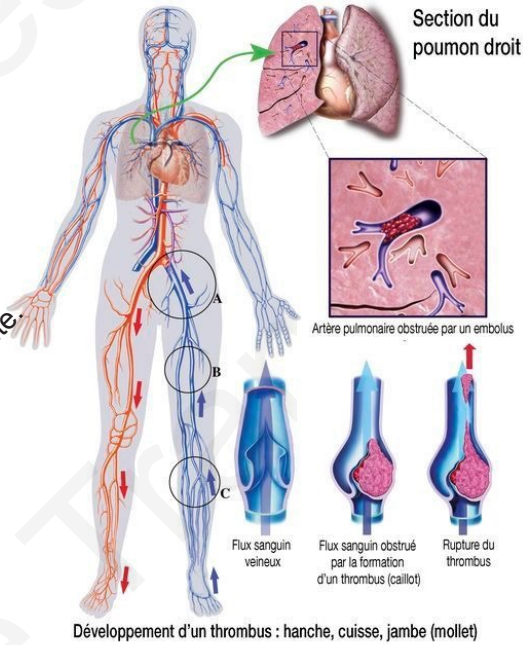
Venous ThromboEmbolism (VT)

VT includes Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE)

- Affects 0.2% individuals a year
- High Mortality rate 10%
- 30 % of unprovoked VT events will reocurr



Développement d'un thrombus : hanche, cuisse, jambe (mollet)

A common multifactorial disease

- Environmental origin

  sex, pregnancy, hormone therapy, immobilization, overweight…

- Genetic factors

  familial standardized incidence ratio of 2.45

Zoller, Circulation 2011

VENOUS THROMBOEMBOLIC DISEASE AND ABO BLOOD TYPE

A Cooperative Study

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SAMUEL SHAPIRO
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FROM THE DIVISION OF CLINICAL PHARMACOLOGY, LEMUEL SHATTUCK HOSPITAL AND TUFTS UNIVERSITY MEDICAL SCHOOL, BOSTON, MASSACHUSETTS; THE SWEDISH ADVERSE DRUG REACTION COMMITTEE; THE COMMITTEE ON SAFETY OF DRUGS, UNITED KINGDOM; THE MEDICAL RESEARCH COUNCIL'S STATISTICAL RESEARCH UNIT, LONDON; AND THE HARVARD SCHOOL OF PUBLIC HEALTH, CAMBRIDGE, MASSACHUSETTS

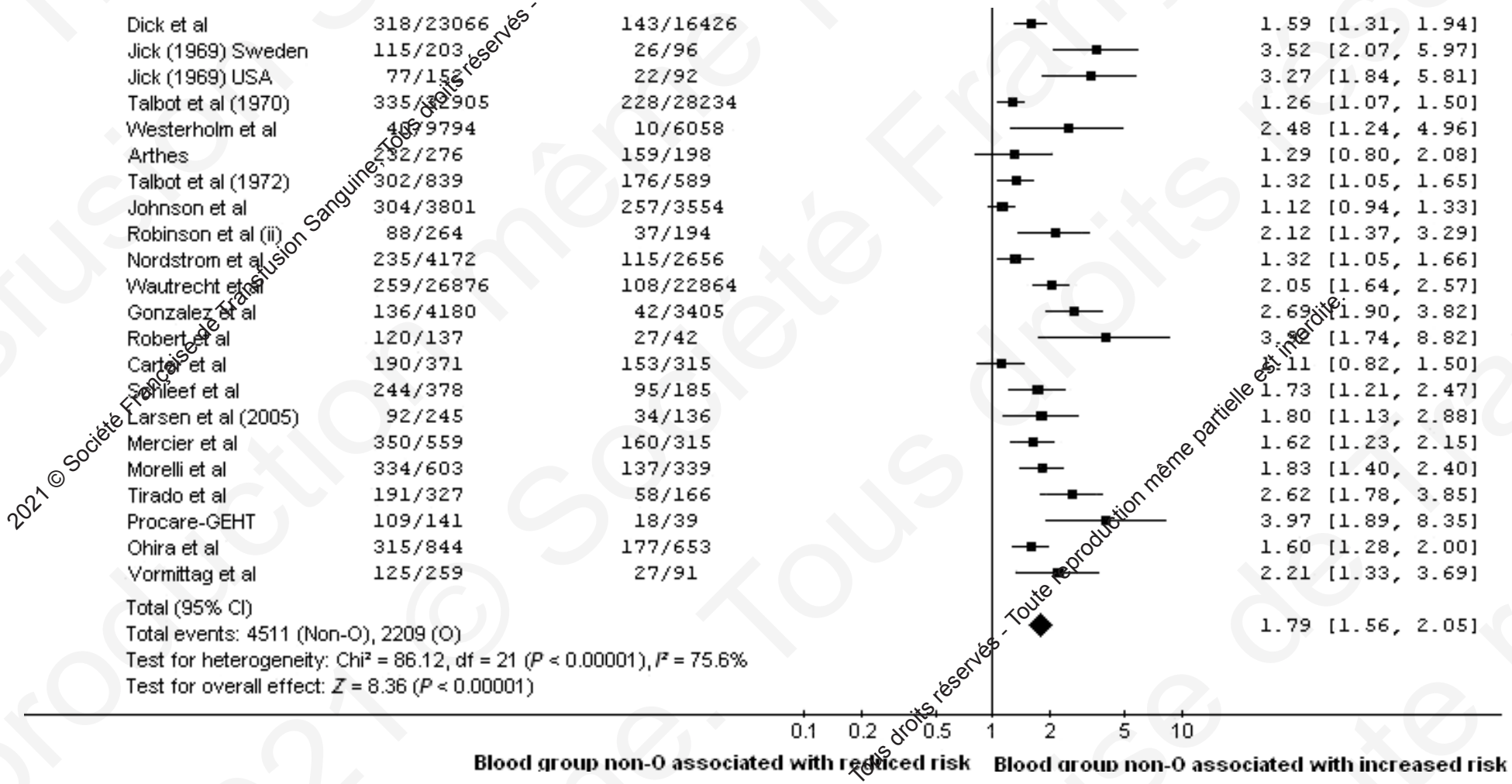
TABLE IV—RELATIVE RISKS A/O AND (A + B + AB)/O IN EACH SERIES OF PATIENTS

Type of patient with thromboembolism	Comparison	Country				Pooled estimate of risk‡	Approximate 95% confidence limits for pooled estimate of risk
		U.S.A.	Sweden	U.K.*	U.K.†		
Medical patients (both sexes)	A/O	1·9	..	..	..	1·9	1·1–3·2
	(A+B+AB)/O	1·6	..	..	..	1·6	1·0–2·6
Non-pregnant women not using oral contraceptives	A/O	1·9	..	..	1·7	1·8	0·9–3·4
	(A+B+AB)/O	2·0	..	..	1·7	1·8	0·9–3·2
Pregnant or puerperal women	A/O	2·5	2·7	..	1·4	2·1	1·5–3·1
	(A+B+AB)/O	2·2	2·7	..	1·4	2·1	1·5–3·0
Women using oral contraceptives	A/O	4·6	3·2	2·8	2·6	3·2	2·2–4·7
	(A+B+AB)/O	4·6	3·2	2·7	2·9	3·3	2·3–4·8

* Committee on Safety of Drugs. † Medical Research Council's Statistical Research Unit. ‡ Woolf's method (Woolf 1955).

Jick, Lancet 1969

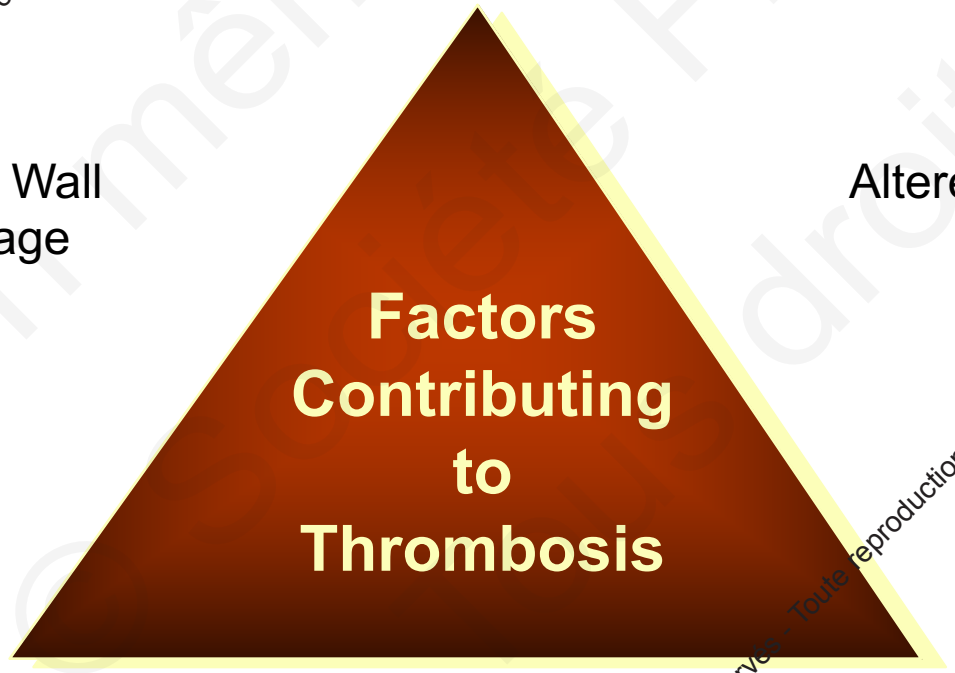
ABO blood group and VT



Wu, J Thromb Heamost 2008

Virchow's Triad
1850

Venous Thrombosis



Vessel Wall Damage

Altered Blood Flow (Stasis)

Blood Coagulability

Associations between ABO blood group and VWF

Relationship between ABO blood group phenotype and plasma vWF:Ag levels (IU dL^{-1}).

Authors	*n*	Group O	Group A	Group B	Group AB	*P*
McCallum *et al.* (1983)	136	89·7	129·2	135·0	139·0	< 0·001
Mohanty *et al.* (1984)	96	99·7 ± 9·1	113·8 ± 6·7	90·3 ± 16·4	118·3 ± 16·9	< 0·05
Orstavik *et al.* (1988)	167	65·4	96·7	102·5	119·1	< 0·01
Gill *et al.* (1987)	1117	74·8	105·9	116·9	123·3	< 0·01
Shima *et al.* (1995)	330	80·9 ± 14·1	107·3	103·8	113·8 ± 17·2	< 0·001
Souto *et al.* (2000)	328	77·3 ± 27·4	114·7	102·8 ± 30·2	136·7 ± 33·7	< 0·001

All values are given as mean ± 1 SD where possible. *P*-values are for group O vWF:Ag levels compared to vWF:Ag levels in the other blood groups.

→ Taux de VWF plus élevés chez les porteurs de groupes sanguins non-O

O'Donnell, Transfus Med 2001

Association between ABO blood group and VWF

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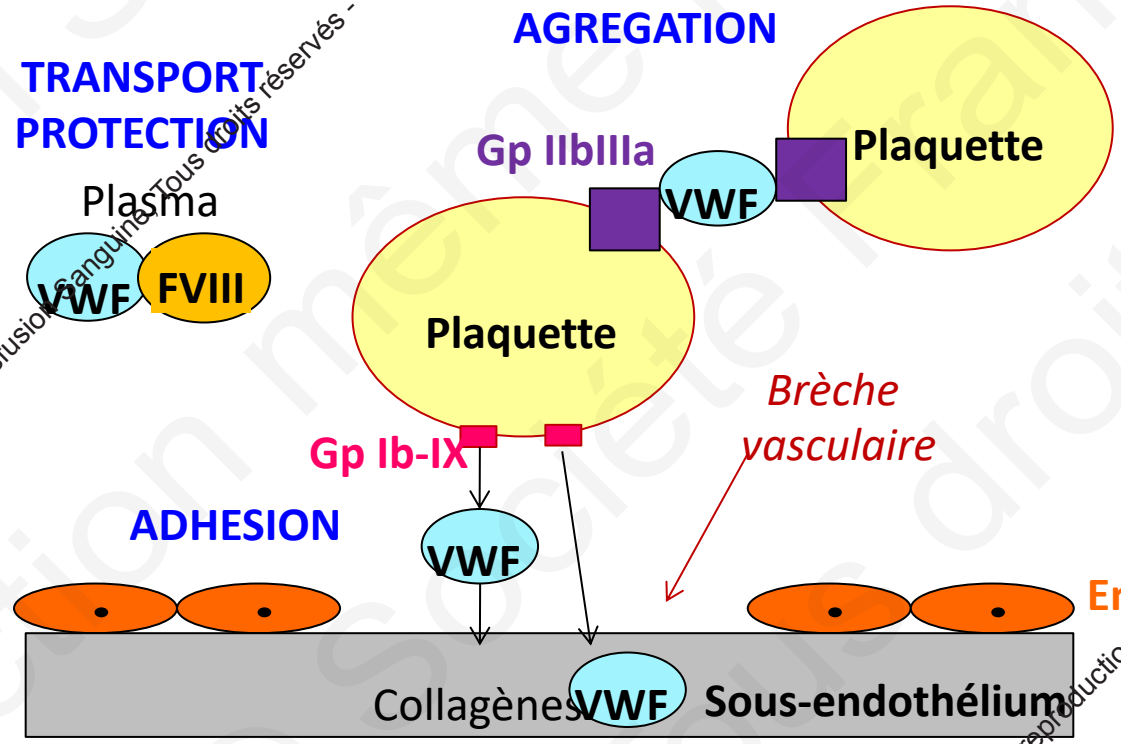
→ Taux de VWF 25-30% moins élevés chez les porteurs du groupes sanguins O

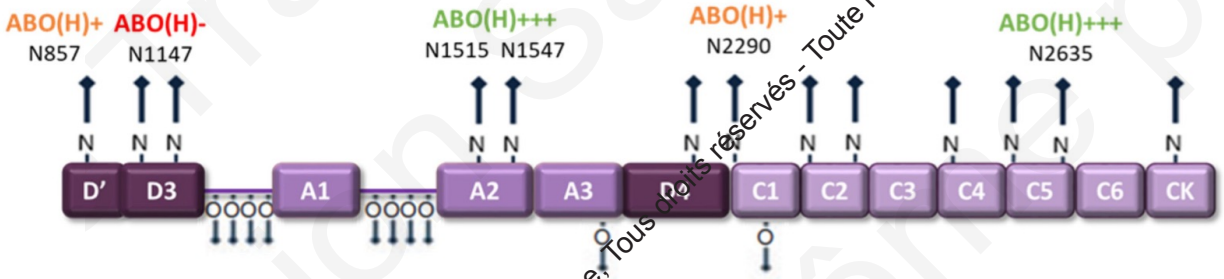
O'Donnell, Transfus Med 2001

Relations between ABO and VT



1. Hémostase primaire: adhésion plaquettaire
2. Coagulation: transporteur et stabilisateur des taux plasmatiques de facteur VIII (FVIII)

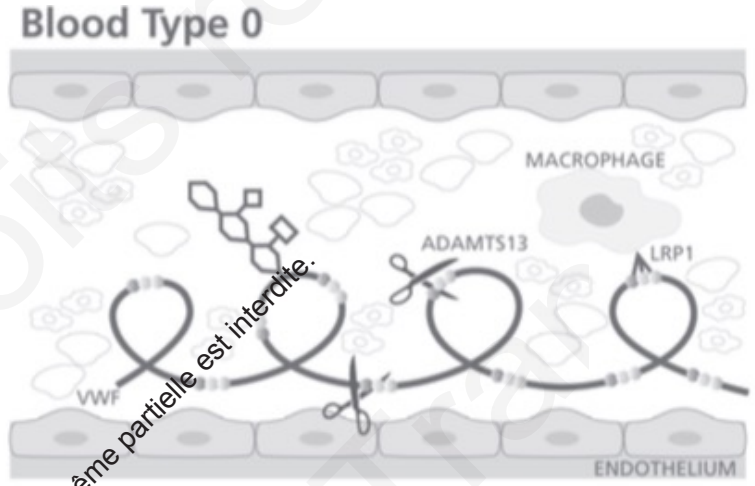
Augmentation du niveau de glycosylation du VWF

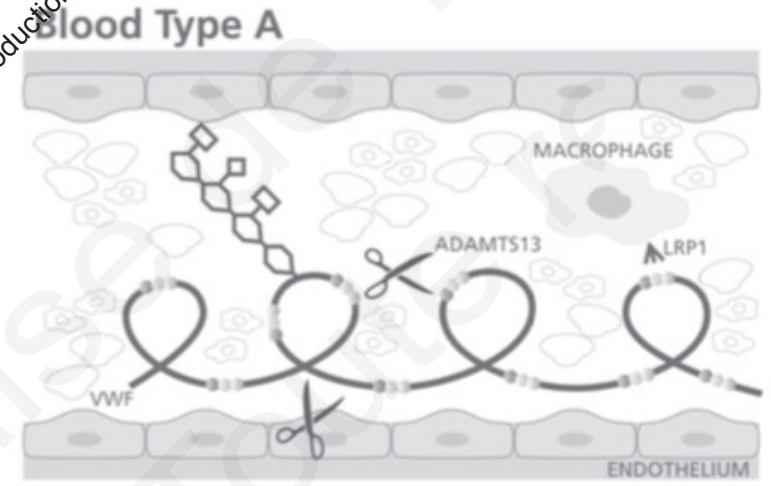


→ ↘ Protection du clivage par l'ADAMTS 13

→ ↘ Clairance par les macrophages via le récepteur LRP1 (protéine 1 liée aux récepteurs des lipoprotéines de basse densité)

→ Plus le VWF est glycosylé plus sa demi-vie et par conséquent ses taux plasmatiques sont élevés





Association between VWF and VT

	Mean (SD) value in patients		Mean (SD) value in controls	
	0 (n=82)	non-0 (n=219)	0 (n=128)	non-0 (n=173)
vWF antigen (IU/L)	1250 (377)	1410 (367)	1060 (359)	1330 (357)
FVIII coagulant activity (IU/L)	1200 (379)	1340 (318)	1000 (281)	1220 (276)

Pearson correlation coefficient (n=602) for blood group and vWF or factor VIII (FVIII)=0·19 for patients and 0·36 for controls (both p<0·001), and for vWF and factor VIII=0·62 for patients and 0·69 for controls (both p<0·001).

→ Taux de FVIII et VWF plus élevés chez les patients avec une TV

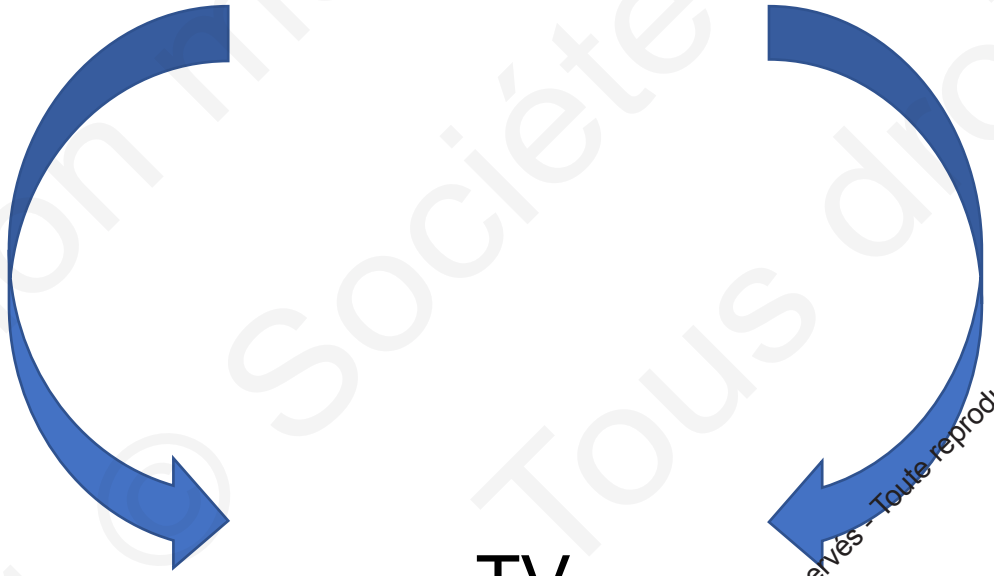
Koster, Lancet 1995

ABO - VT - VWF/FVIII

ABO

Groupes sanguins non-O

OR ~ 1,7

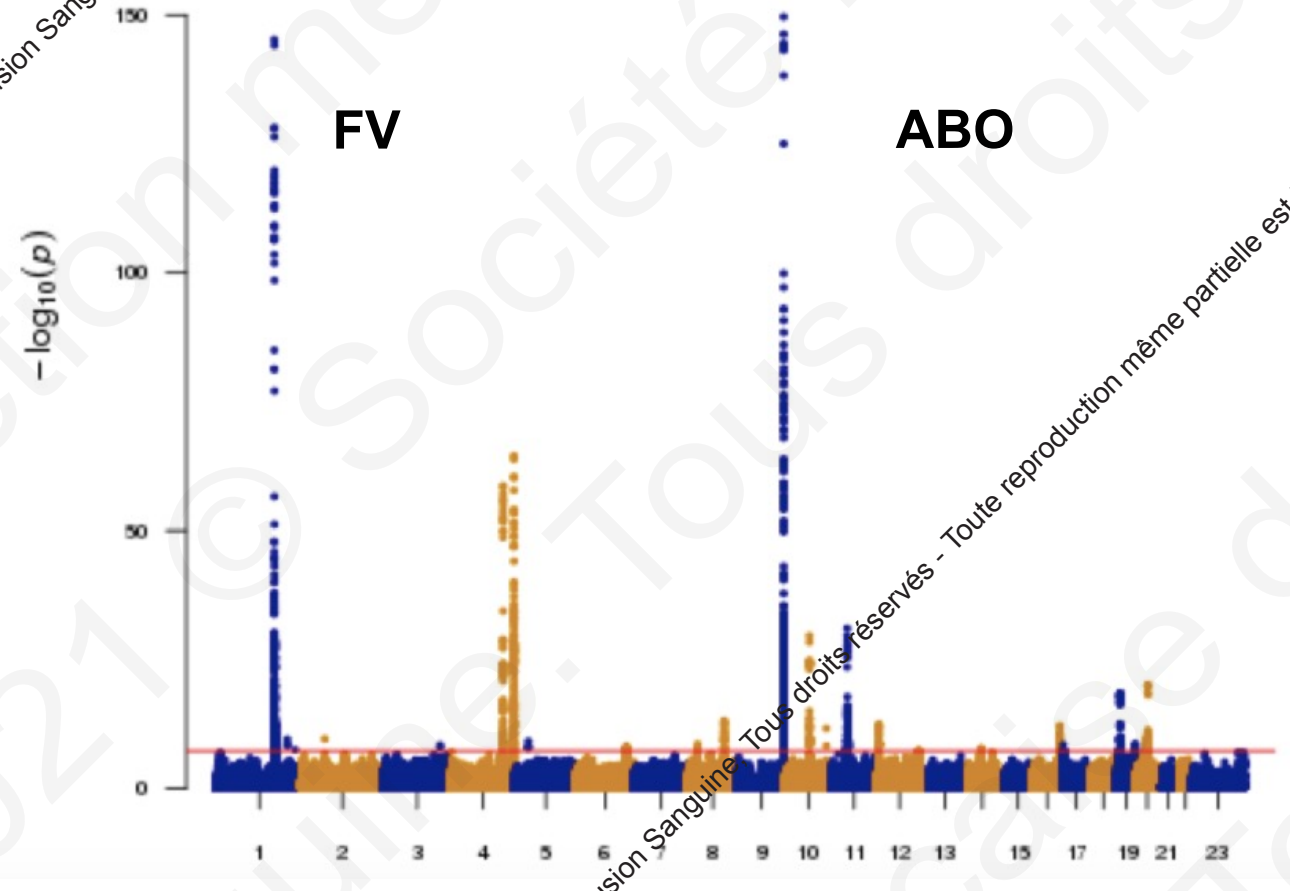


TV

Dentali, Semin Thromb Hemost 2012

Common variants
Extended meta-GWAS in INVENT

18 studies, 30,324 VT and 172,122 Controls
12,923,718 imputed SNPs were tested for association with VT



Lindstrom, Blood 2019

Genome – Wide significant loci 5 x 10^{-9}

Locus (location)	Status
ABO (exon)	Known
ABO (intron)	Known
ABO (intron)	Known
ABO (intron)	Known
C1orf198 (intron)	New locus–not replicated
C4BPA (intron)	New variant
F11 (intron)	Known
F11 (intron)	Known
F11 (intron)	New variant
F2 (intron)	Known
F5 (exon)	Known
F5 (exon)	Known
F8 (upstream)	Known
FGG (intron)	Known
GRK5 (intron)	New locus–replicated
Intergenic, EIF5A (upstream)	New locus–not replicated
Intragenic, ARID4A (downstream)	New locus–not replicated

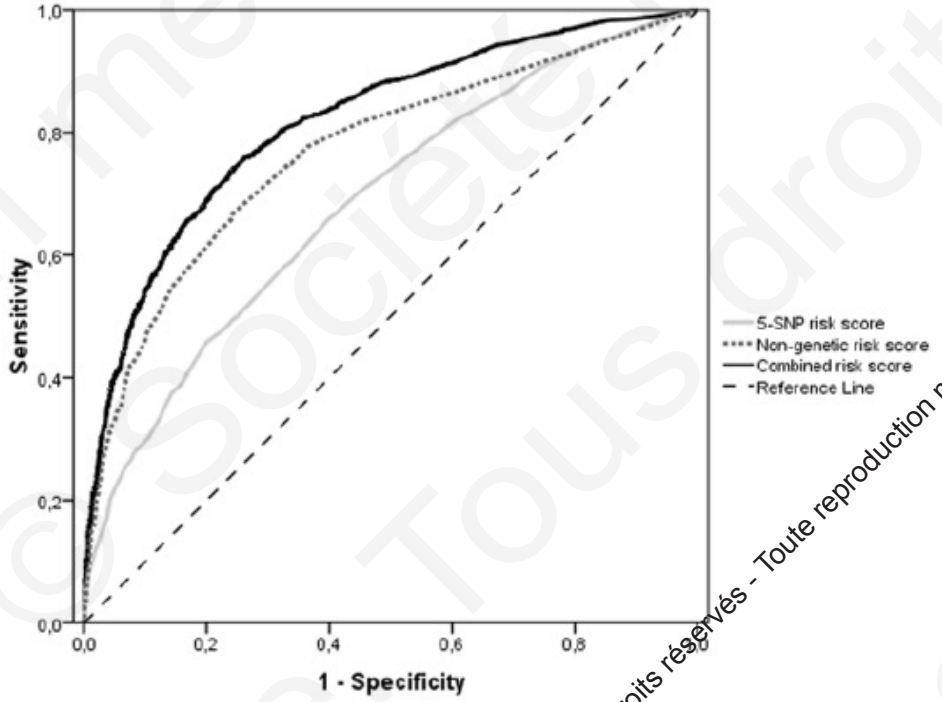
Locus (location)	Status
LRP4 (intron), F2 (downstream)	Known
MPHOSPH9 (intronic)	New locus–replicated
NLRP2 (intron), GP6 (downstream)	Known
NUGGC (intron), SCARA5 (upstream)	New locus–not replicated
OSMR-AS1 (intron)	New locus–replicated
PLCG2 (intron)	New locus–replicated
PLEK (intron)	New locus–replicated
PROCR (exon)	Known
PROCR (intron)	Known
SCL44A2 (intron)	Known
SMG6 (intron)	New locus–replicated
STX10 (intron)	New locus–not replicated
STXBP5 (intron)	Known
TSPAN15 (intron)	Known
VWF (exon)	New variant
VWF (intron)	Known
ZFPM2 (intron)	Known

Lindstrom, Blood 2019
Smith, ISTH 2020

Genetic score and the risk of VT

Table 2. Venous thrombosis prediction using genetic, nongenetic, and combined risk scores

	MEGA (N = 7092)		LETS (N = 881)	
	AUC (95% CI)	Nagelkerke pseudo r^2	AUC (95% CI)	Nagelkerke pseudo r^2
31-SNP risk score	0.71 (0.69-0.72)	0.161	0.69 (0.65-0.72)	0.149
5-SNP risk score	0.69 (0.67-0.70)	0.135	0.67 (0.64-0.71)	0.138
Nongenetic risk score	0.77 (0.76-0.78)	0.288	0.71 (0.68-0.74)	0.200
Combined risk score	0.82 (0.81-0.83)	0.378	0.77 (0.74-0.80)	0.292



The 5-SNP risk score (including FV Leiden, PT G20210A, ABO (rs8176719), FGG, F11) significantly improves the power of the nongenetic model

De Haan, Blood 2012

ABO and Venous Thrombosis

- No consensus how to analyze ABO blood group (incl. Serology)
- No consensus how to define ABO blood groups using ABO polymorphisms
- Comprehensive haplotype analyses of ABO blood group tagging SNPs in up to 5,425 cases and 8,445 controls from 6 studies (INVENT consortium)

ABO polymorphisms

	rs8176749	rs41302905	rs8176743	rs1053878	rs8176719	rs687621	rs55876802	rs2519093	rs514659	rs579459
Position on chr9	136131188	136131316	136131415	136131651	136132908	136137065	136137547	136141870	136142203	136154168
Location	coding	coding	coding	coding	coding	intronic	coding	intronic	intronic	5'
Reference sequence	C	C	C	G	G	A	C	C	T	T
Alternative sequence	T	**T**	**T**	**A**	**delG**	G	A	T	C	C
Reference Amino Acid	Leu310	Gly268	Gly235	Pro156			Arg18			
Alternative Amino Acid	Leu310	**Arg268**	**Ser235**	**Leu156**	**p.88fs118Stop**		Leu18			
ABO Blood groups		**O2**	**B**	**A2**	**O1**					

	Allele Frequencies									
rs8176749	C=0.915, T=0.085	1.0	0.003	1.0	0.01	0.142	0.157	0.003	0.21	0.157	0.025
rs41302905	C=0.971, T=0.029		1.0	0.003	0.003	0.046	0.017	1.0	0.007	0.017	0.109
rs8176743	C=0.915, T=0.085			1.0	0.010	0.142	0.157	0.003	0.021	0.157	0.025
rs1053878	G=0.901, A=0.099				1.0	0.148	0.187	0.003	0.020	0.187	0.022
rs8176719	delG=0.605, G=0.395					1.0	0.864	0.046	0.342	0.857	0.411
rs687621	A=0.629, G=0.371						1.0	0.017	0.387	0.991	0.285
rs55876802	C=0.971, A=0.029							1.0	0.007	0.017	0.109
rs2519093	C=0.815, T=0.185								1.0	0.385	0.823
rs514659	A=0.629, C=0.371									1.0	0.285
rs579459	T=0.786, C=0.214										1.0

Linkage Disequilibrium (r^2) matrix

Goumidi, Blood 2020

Association of ABO haplotypes with the risk of VT

ABO blood group	rs2519093	rs8176719	rs579459	rs1053878	rs8176743	rs41302905	Frequency[1]	OR for VT[2]
O1	C	delG	T	G	C	C	0.63	reference
O2	C	G	C	G	C	**T**	0.02	0.70[3] [0.57 – 0.86]
A1	**T**	G	C	G	C	C	0.20	1.78 [1.67 – 1.92]
A2	C	G	T	**A**	C	C	0.07	1.16 [1.03 – 1.31]
B	C	G	T	G	**T**	C	0.08	1.76 [1.58 – 1.96]

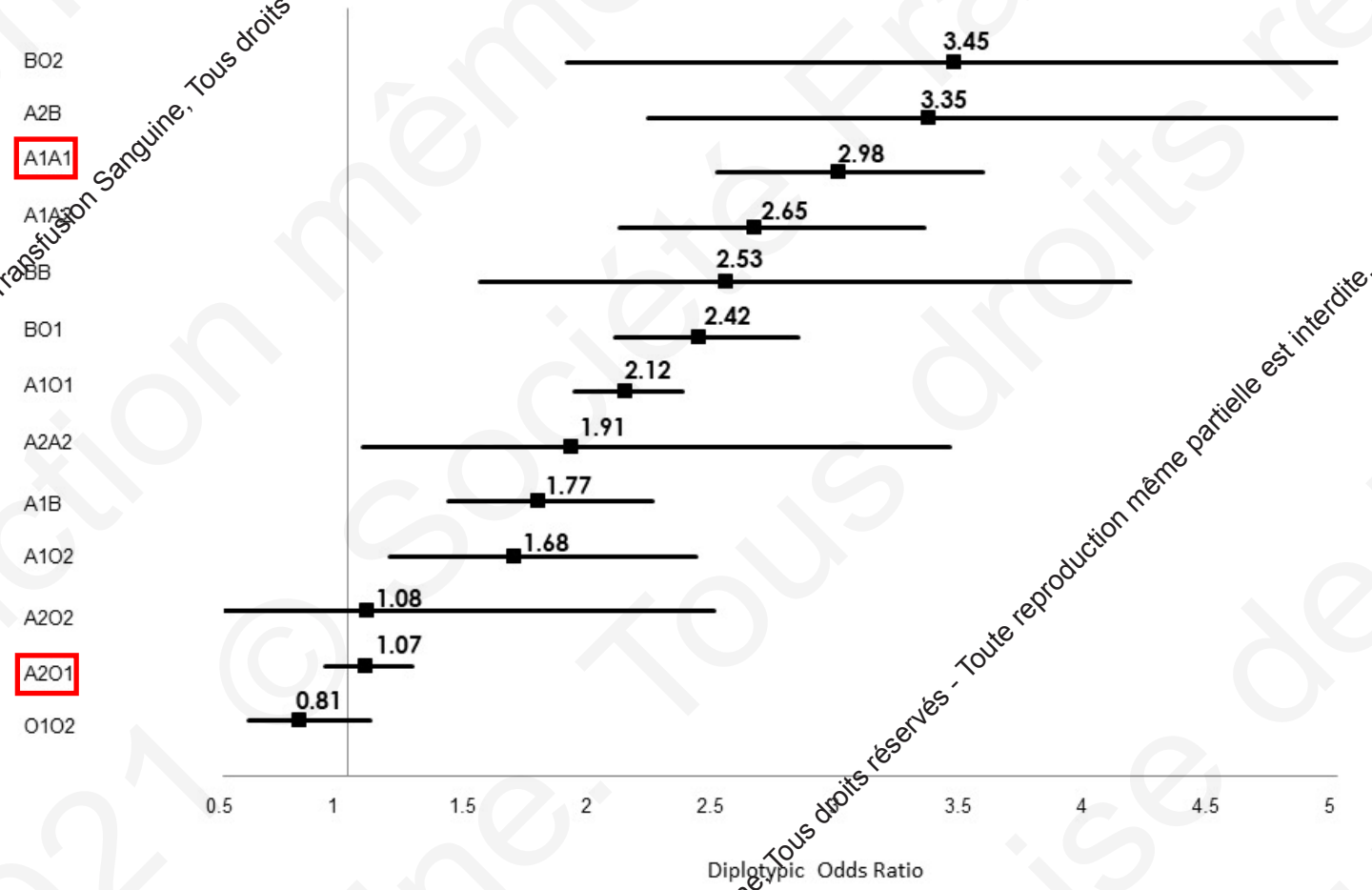
A1 & B ~same risk of VT

But using only O1 vs non O1 is suboptimal
as among non O1, O2 are protected and A2 are at a much lower risk than A1/B

Goumidi, Blood 2021

Forest plot showing the association of ABO diplotypes with VT risk

Phenotypic group A



Goumidi, Blood 2021

Summary information about the association of ABO haplotypes with studied traits

ABO blood group	rs2519093	rs8176719	rs579459	rs1053878	rs8176743	rs41302905	Frequency[1]	OR for VT[2]	Impact on VWF/FVIII levels[4]	Impact on ICAM1 levels[4]
O1	C	delG	T	G	C	C	0.63	reference	reference	reference
O2	C	G	C	G	C	**T**	0.02	0.70[3] [0.57 – 0.86]	-	-
A1	T	G	C	G	C	C	0.20	1.78 [1.67 – 1.92]	↑↑↑	↓↓↓
A2	C	G	T	**A**	C	C	0.07	1.16 [1.03 – 1.31]	↑	↓
B	C	G	T	G	**T**	C	0.08	1.76 [1.58 – 1.96]	↑↑↑	-

Goumidi, Blood 2021

The influence of age, gender and ABO blood group on soluble endothelial cell markers and adhesion molecules

Group	n	Mean ± SD
A	130	105 ± 33
B	27	99 ± 29
AB	10	104 ± 34
O	142	92 ± 35
A	93	46 ± 21
B	23	56 ± 20
AB	8	47 ± 17
O	102	58 ± 19
A	95	42 ± 13
B	26	54 ± 15
AB	10	45 ± 13
O	109	41 ± 13

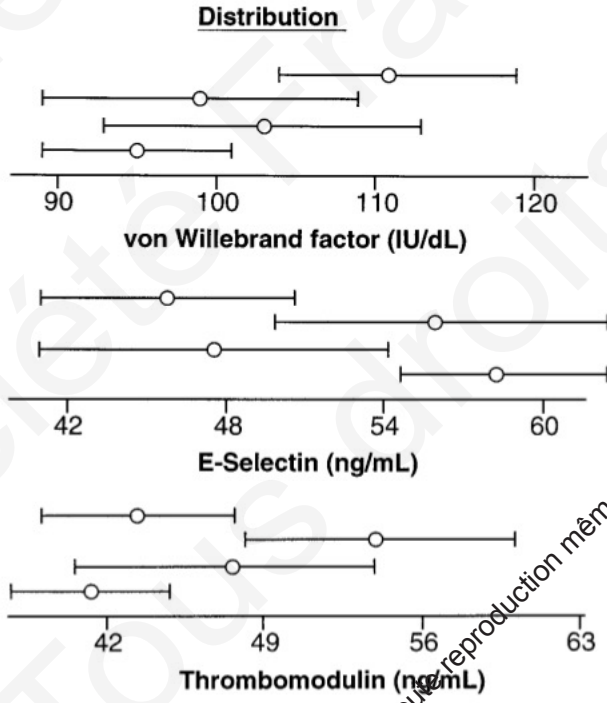


Fig 1. Details of von Willebrand factor, E-selectin and thrombomodulin analysed according to blood group. The circle is the mean value; bars are the 95% confidence intervals.

Blann, BJH 1995

ABO locus and plasma proteomics

4137 proteins covering most predicted extracellular proteins were measured in the serum of 5457 Icelanders over 65 years of age.

ABO	*Cis*	1.087	8e-244
SELE	*Trans*	-0.963	9e-193
EDGRF5	*Trans*	-0.815	8e-125
ROBO4	*Trans*	-0.730	1e-114
IL3RA	*Trans*	-0.613	5e-81
QSOX2	*Trans*	0.625	4e-73
INSR	*Trans*	-0.595	3e-70
ICAM2	*Trans*	-0.593	3e-67
FAM3D	*Trans*	0.581	8e-66
KDR	*Trans*	-0.508	5e-50
EPHA4	*Trans*	-0.492	2e-49
ICAM5	*Trans*	-0.457	5e-40
FLT4	*Trans*	-0.442	1e-36
F8	*Trans*	0.393	9e-32
ENG	*Trans*	-0.394	1e-30
ISLR2	*Trans*	-0.387	1e-28
KIN	*Trans*	-0.376	2e-28
GOLM1	*Trans*	0.379	2e-28
CD200	*Trans*	-0.357	2e-25
MET	*Trans*	-0.367	3e-25
GLCE	*Trans*	0.360	1e-24
LIFR	*Trans*	-0.337	1e-22
C1GALT1C1	*Trans*	0.326	2e-20
SHANK3	*Trans*	0.314	4e-20
ICAM4	*Trans*	-0.323	5e-20
ACE	*Trans*	-0.316	2e-19

CHST15	*Trans*	-0.292	1e-17
SELP	*Trans*	-0.248	7e-13
IGF1R	*Trans*	-0.237	1e-12
CDH5	*Trans*	-0.242	1e-12
VWF	*Trans*	0.244	2e-12
SEMA6A	*Trans*	-0.236	6e-12
L1CAM	*Trans*	-0.232	2e-11
CD109	*Trans*	-0.211	7e-10
CCL28	*Trans*	-0.217	8e-10
IL6ST	*Trans*	-0.202	3e-09
CHST12	*Trans*	0.199	1e-08
DPEP2	*Trans*	-0.196	2e-08
JAG1	*Trans*	-0.185	2e-08
MBL2	*Trans*	0.194	2e-08
B3GNT2	*Trans*	0.191	5e-08
GNS	*Trans*	-0.189	7e-08
PEAR1	*Trans*	-0.184	9e-08

Emilsson, Science 2018

ABO and VTE recurrence

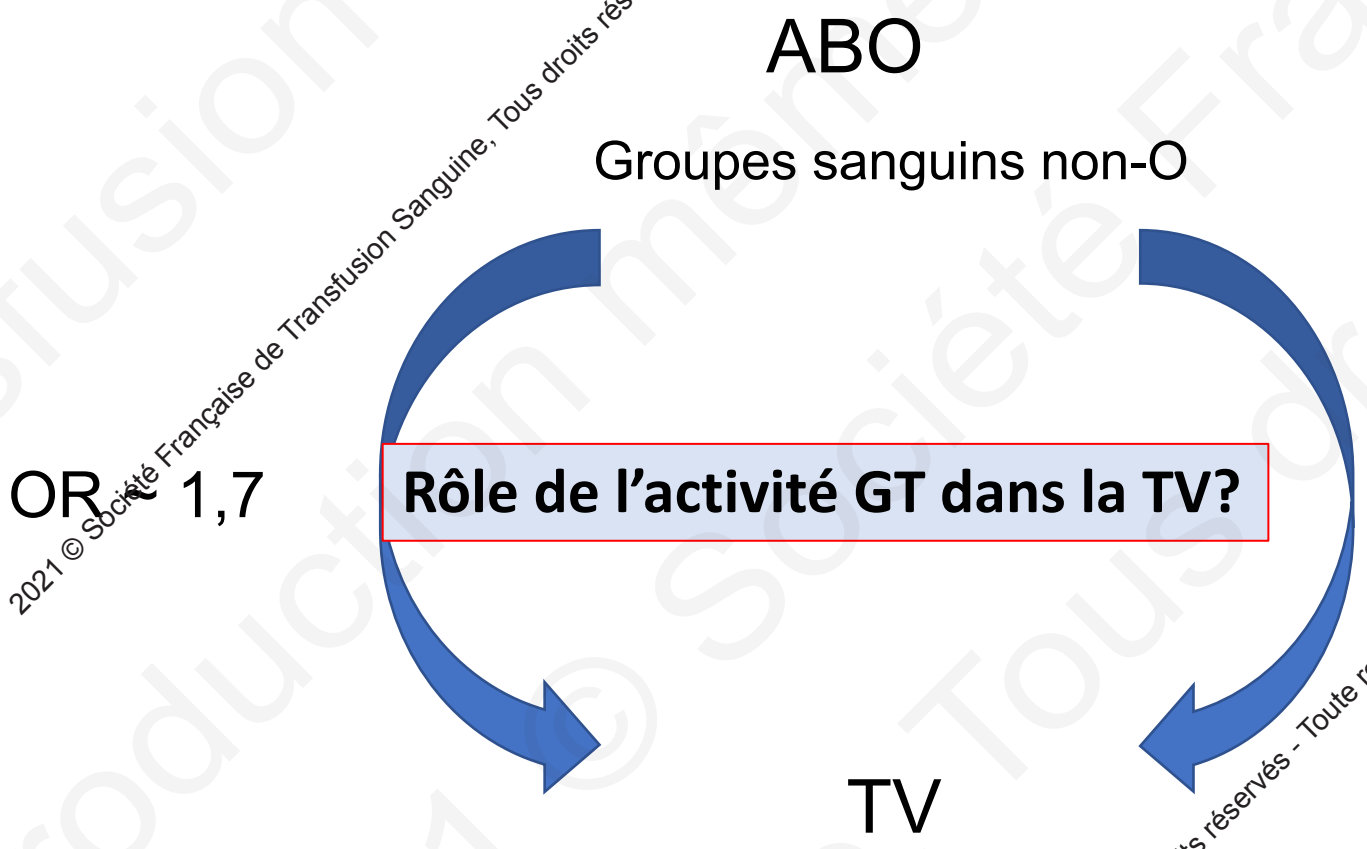
Table 3: Association of clinical variables and ABO haplotypes with VT recurrence in MARTHA (*prospective* and *ambispective*) and MEGA

Variables	MARTHA *Prospective* N=839 Nb recurrences=159		MARTHA *Ambispective* N=1,504 Nb recurrences=565		MEGA N=1,248 Nb recurrences=428		Meta-analysis MARTHA Ambispective & MEGA	
	HR ± SE*	P	HR ± SE	P	HR ± SE	P	HR ± SE	P
Gender								
Men	1.47 ± 0.18	0.034	1.65 ± 0.10	$4.0x10^{-7}$	1.81 ± 0.11	$5.9x10^{-8}$	1.72 ± 0.08	$3.0x10^{-12}$
Age at the first VT (10 years increase)	0.91 ± 0.06	0.105	1.08 ± 0.03	0.020	0.99 ± 0.04	0.810	1.05 ± 0.03	0.107
Type of the first VT								
DVT	0.85 ± 0.18	0.368	1.17 ± 0.10	0.140	1.15 ± 0.10	0.168	1.16 ± 0.07	0.036
Characteristic of the first VT								
Provoked	0.69 ± 0.19	0.059	0.99 ± 0.11	0.920	0.61 ± 0.11	$6.7x10^{-6}$	0.78 ± 0.08	$1.2x10^{-3}$
ABO haplotypes								
A1	1.32 ± 0.13	0.035	1.15 ± 0.07	0.045	1.21 ± 0.08	0.018	1.18 ± 0.06	$4.2x10^{-3}$
A2	1.13 ± 0.26	0.644	1.27 ± 0.13	0.061	1.11 ± 0.13	0.409	1.19 ± 0.09	0.062
O1	Reference		Reference		Reference		Reference	
O2	1.05 ± 0.41	0.896	1.19 ± 0.25	0.476	0.86 ± 0.28	0.584	1.03 ± 0.20	0.880
B	1.00 ± 0.23	0.998	1.02 ± 0.11	0.874	1.00 ± 0.13	0.987	1.01 ± 0.09	0.900

** : Hazard Ratio ± Robust Standard Error*

Munsch, Submitted

Rôle des activités glycosyltransférases A et B dans la TV



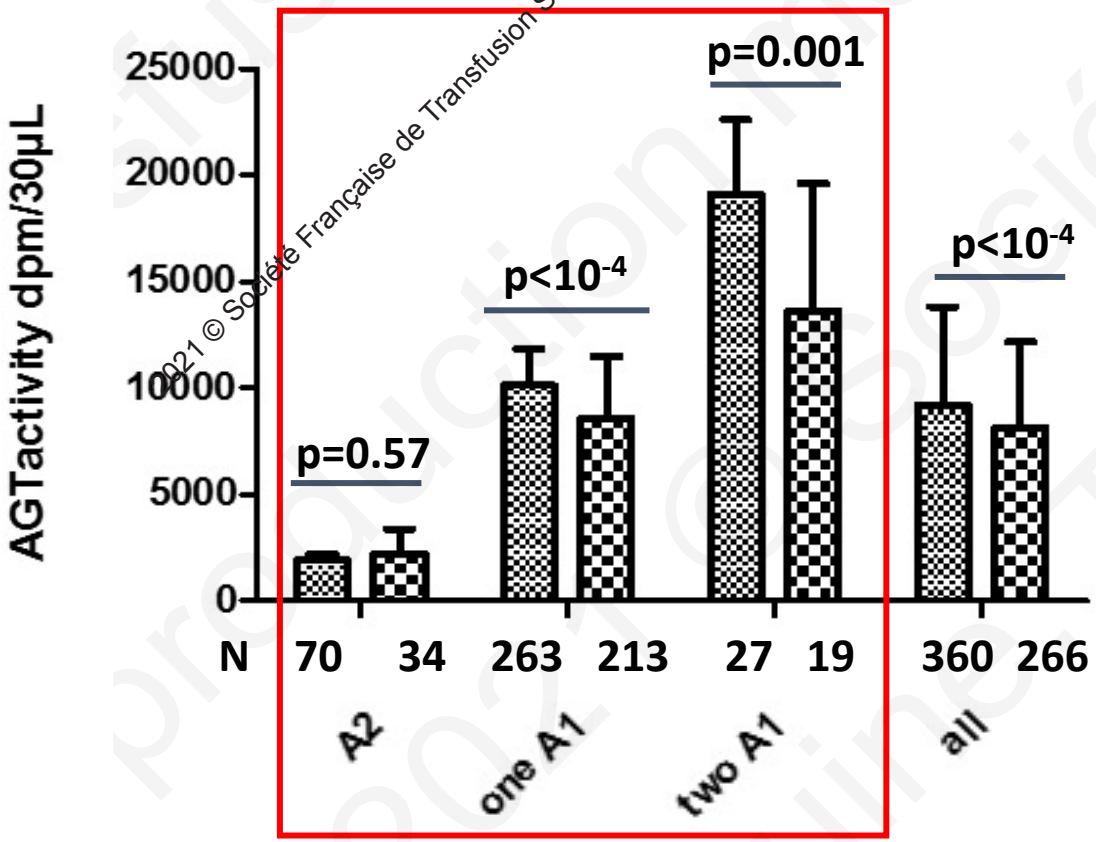
Autres protéines endothéliales et inflammatoires…..

Dentali, Semin Thromb Hemost 2012

Rôle des activités glycosyltransférases A et B dans la TV

✓ Population cas-témoins N=420 - **Témoins**: donneurs **EFS:** âge moyen 43 ± 12 ans, 42% de femmes
- **Cas**: population **MARTHA:** âge moyen 43 ± 13 ans, 53% de femmes
- Appariement âge, groupe sanguin

✓ Comparaison des activités GTA entre les témoins et les cas en fonction du nombre d'allèles A1

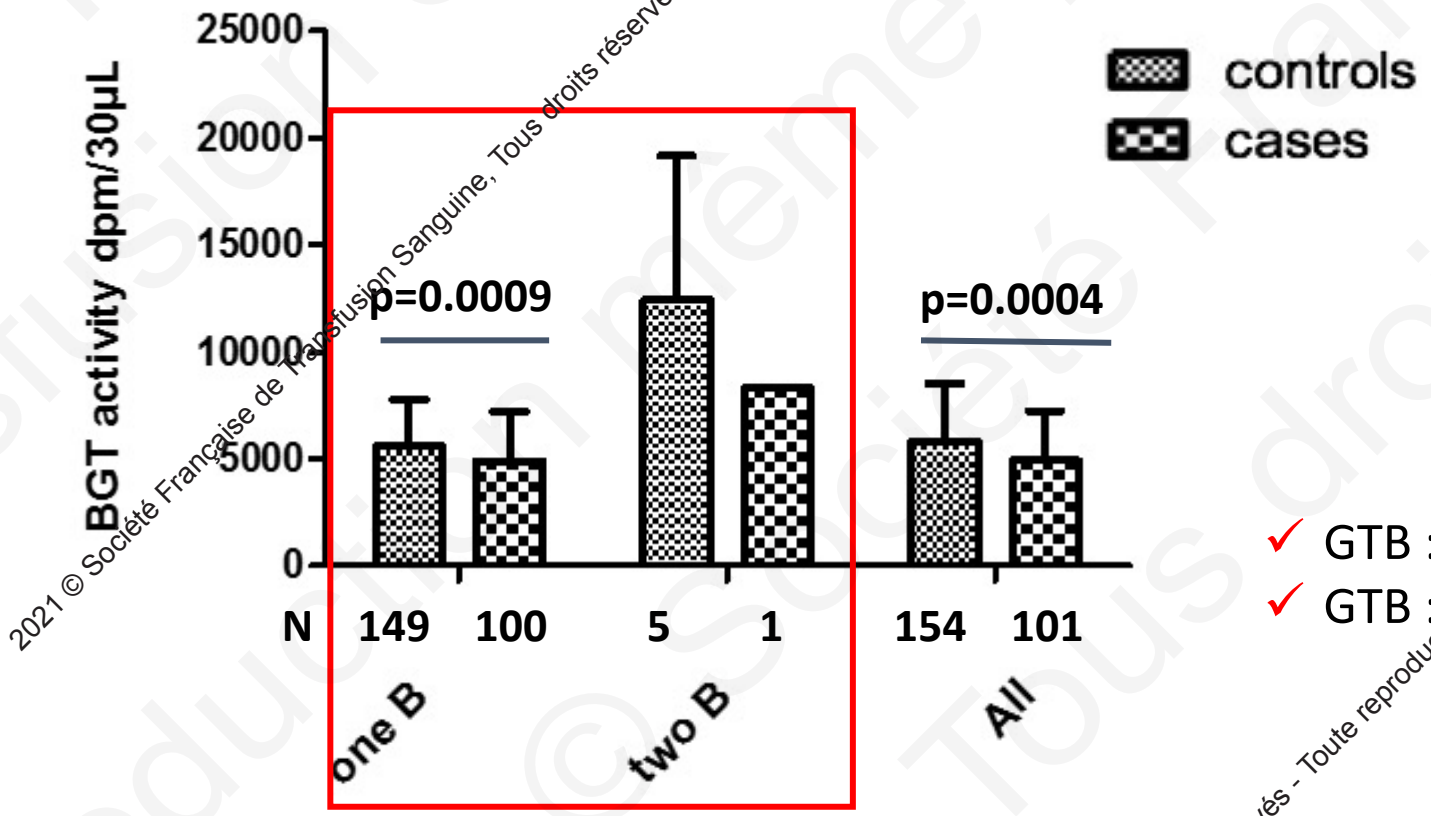


✓ GTA : ↗ en fonction du nombre d'allèles A1
✓ GTA : cas < témoins

Ibrahim-Kosta, Thromb Res 2020

Rôle des activités glycosyltransférases A et B dans la MTEV

✓ Comparaison des activités GTB entre les témoins et les cas en fonction du nombre d'allèles B



✓ GTB : ↗ en fonction du nombre d'allèles B

✓ GTB : cas < témoins

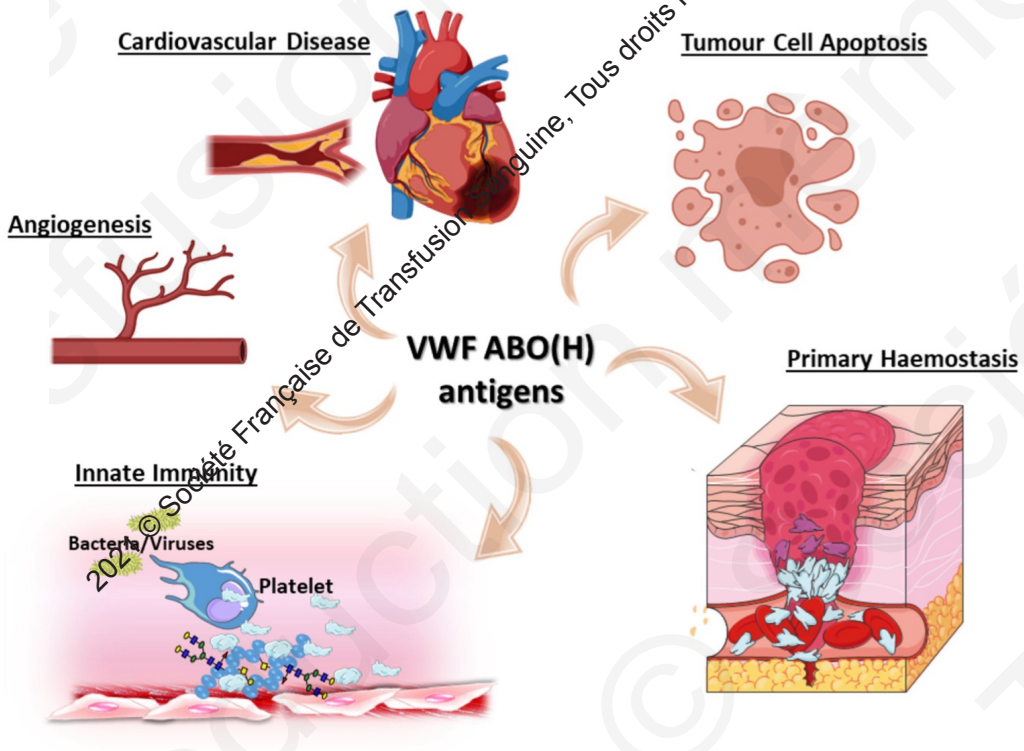
Implication d'autres voies physiopathologiques ?

Hypothèse: Diminution de l'activité GT → baisse de la glycosylation → baisse des taux d'un facteur protecteur de la TV : ex: molécules de l'inflammation (L-sélectine soluble, ICAM soluble?)

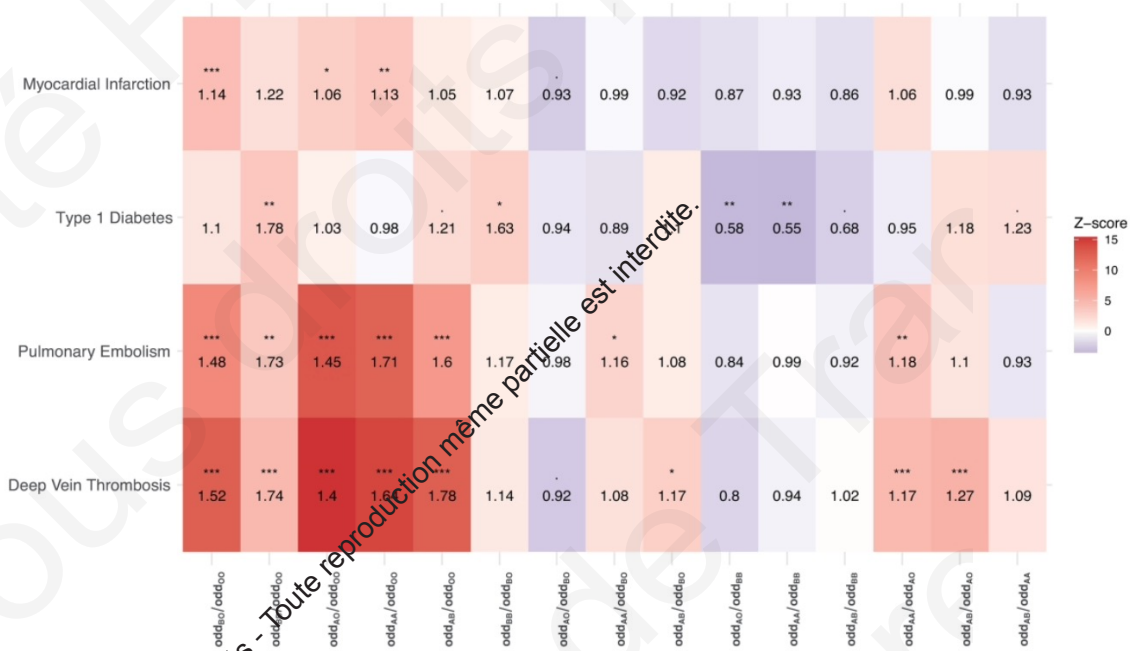
Ibrahim-Kosta, Thromb Res 2020

Conclusions perspectives

O' Donnell, Blood 2020



Hoglund, Am J Hematol 2021



Identification of molecular mechanisms associating endothelium/platelets/red cells and risk of thrombosis

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