LA VALUTAZIONE DEL RISCHIO

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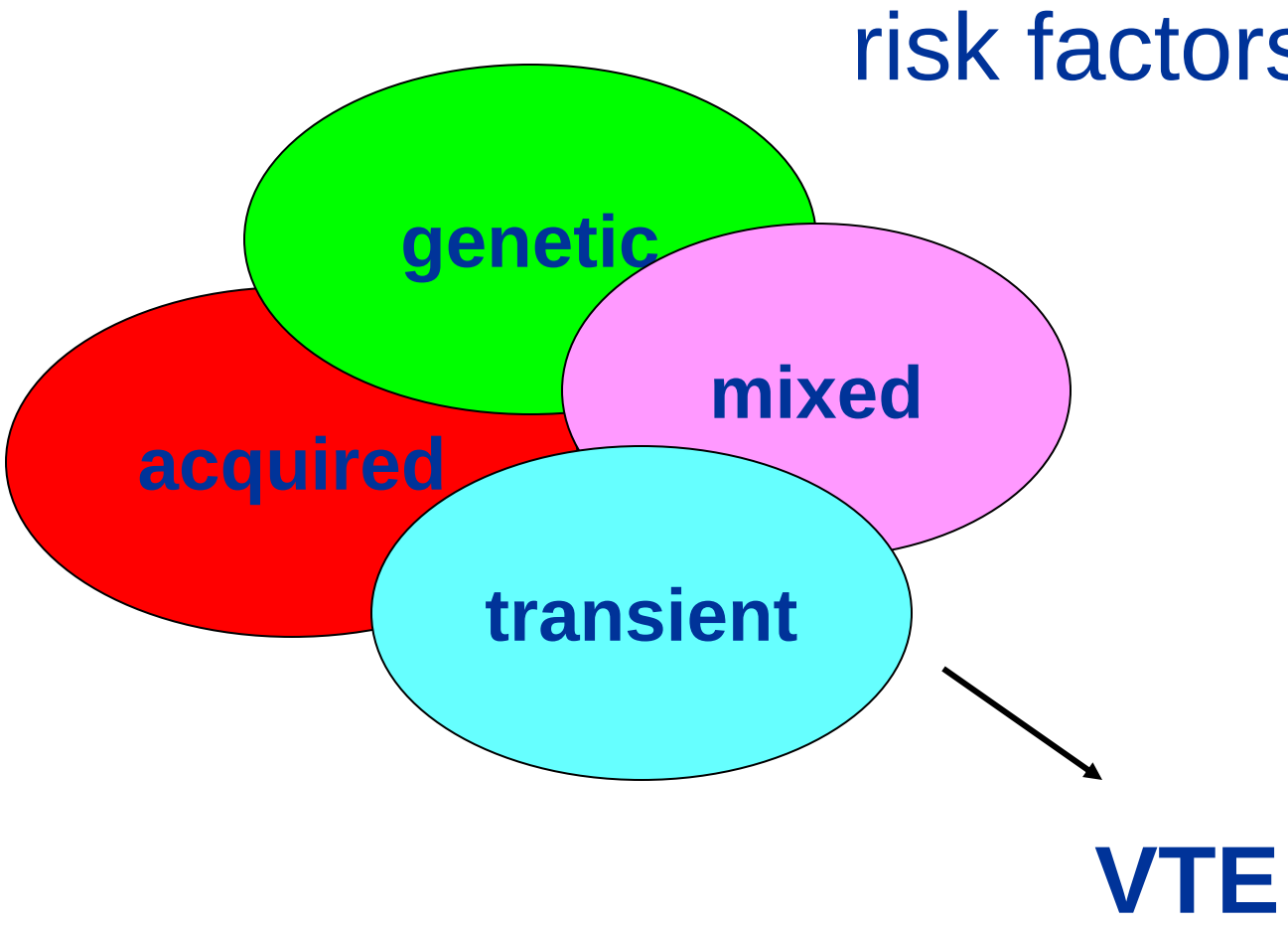
CENTRI EMOSTASI E TROMBOSI, SPECIALISTI OSPEDALIERI E MEDICINA DEL TERRITORIO NELLA GESTIONE DELLE MALATTIE EMORRAGICHE E TROMBOEMBOLICHE

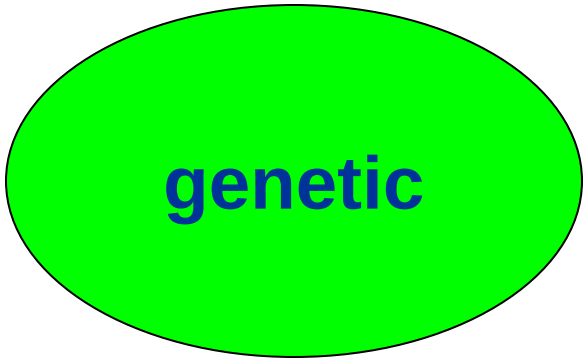
Cremona, 10 marzo 2017

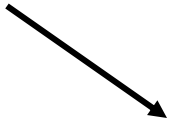
VTE: a multifactorial disease



VTE: a multifactorial disease

risk factors



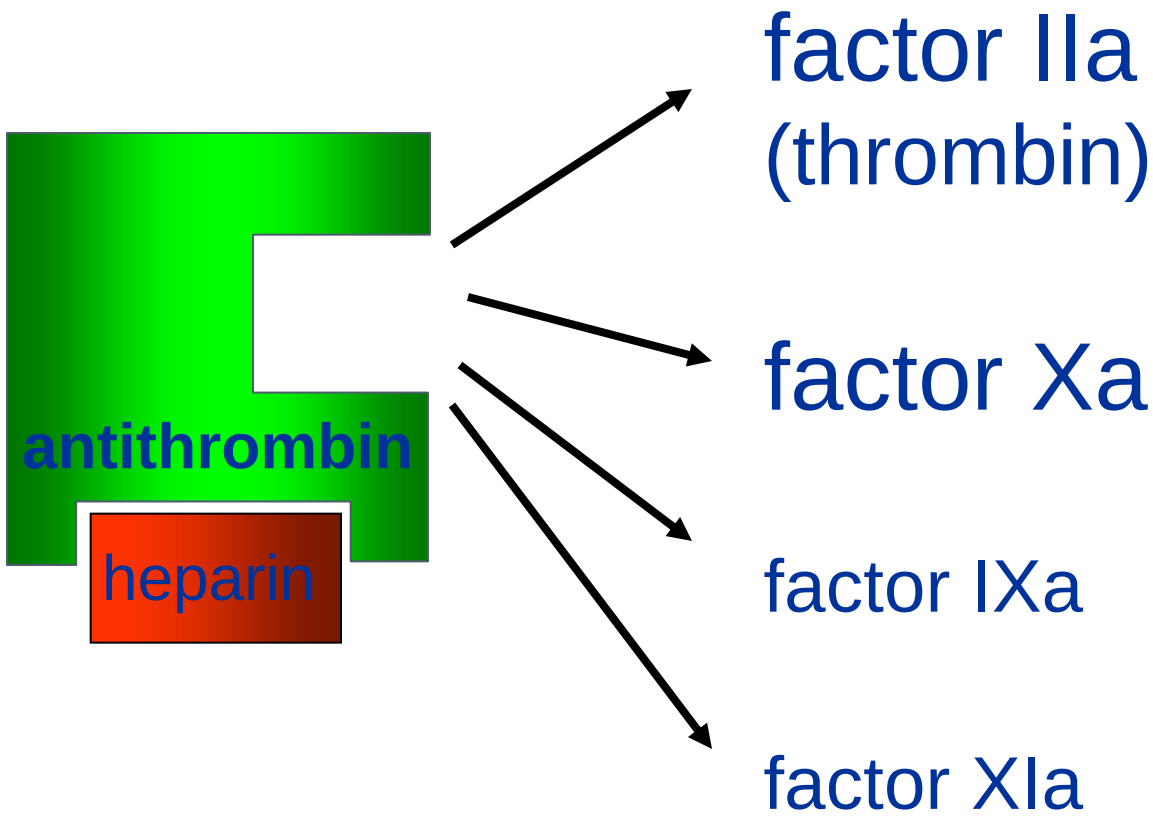


VTE

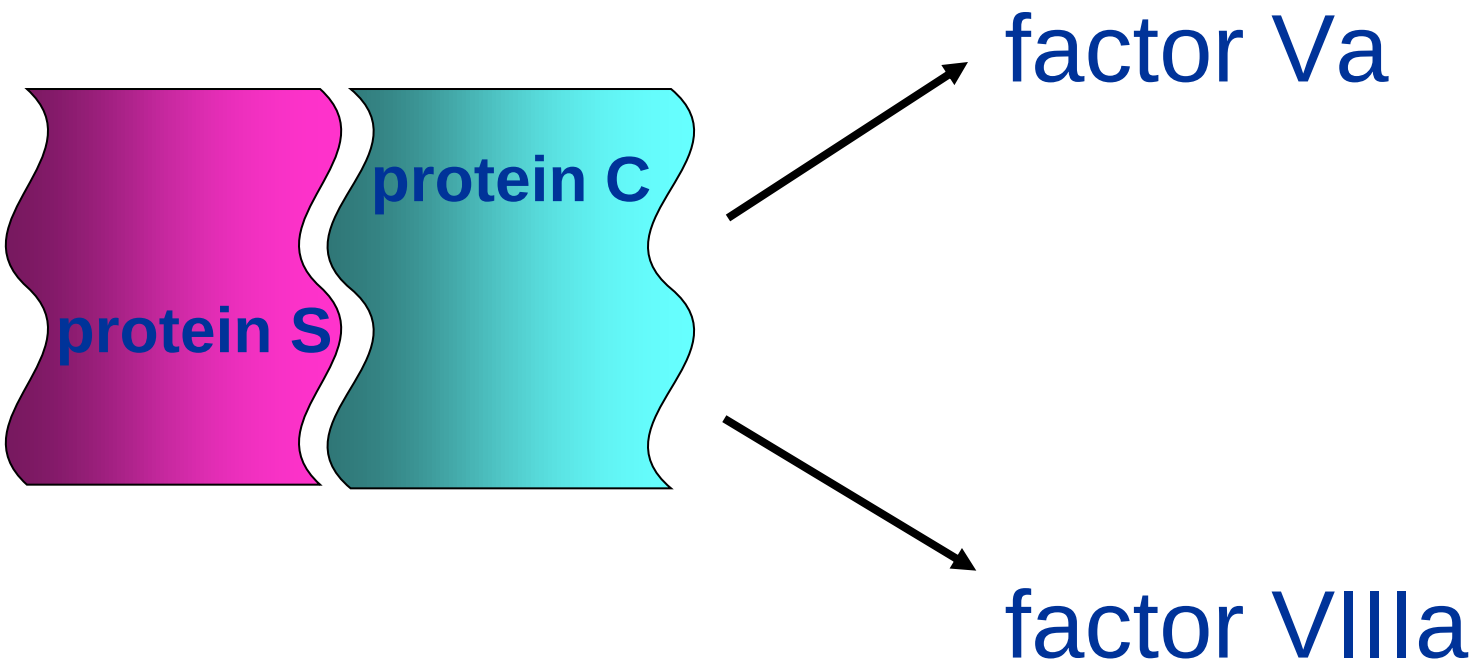
inherited
thrombophilia

deficiency of anticoagulant proteins	year of discovery
antithrombin	1965
protein C	1981
protein S	1984

Antithrombin inhibition



Protein C/S inhibition



Prevalence/risk of deficiencies

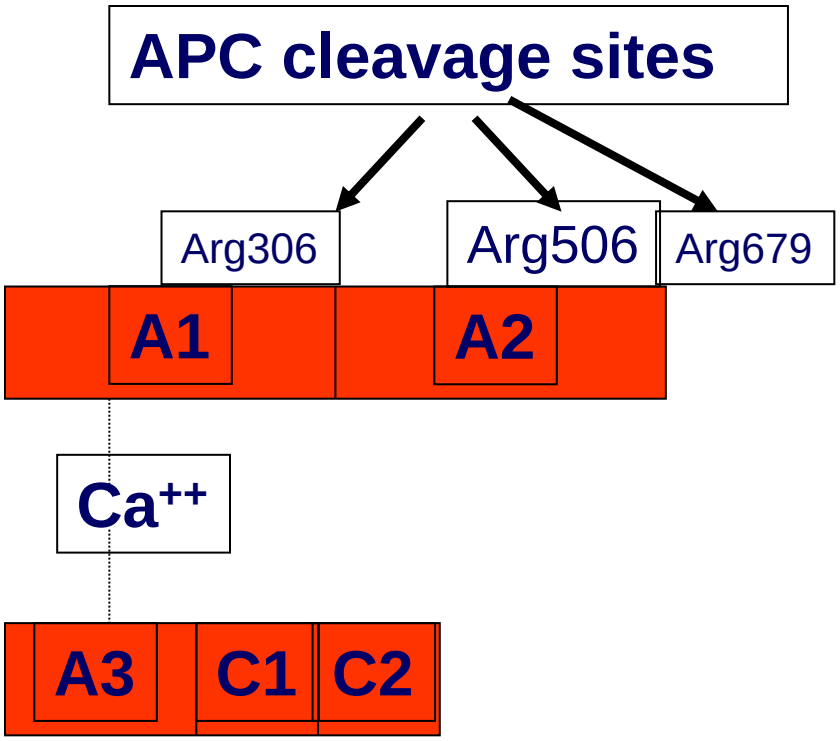
	general population	unselected VTE patients	↑RR
antithrombin	0.02 - 0.2 %	1 %	5 - 50
protein C	0.1 - 0.5 %	3 %	7 - 15
protein S	?	1 - 2 %	6 - 10

inherited
thrombophilia

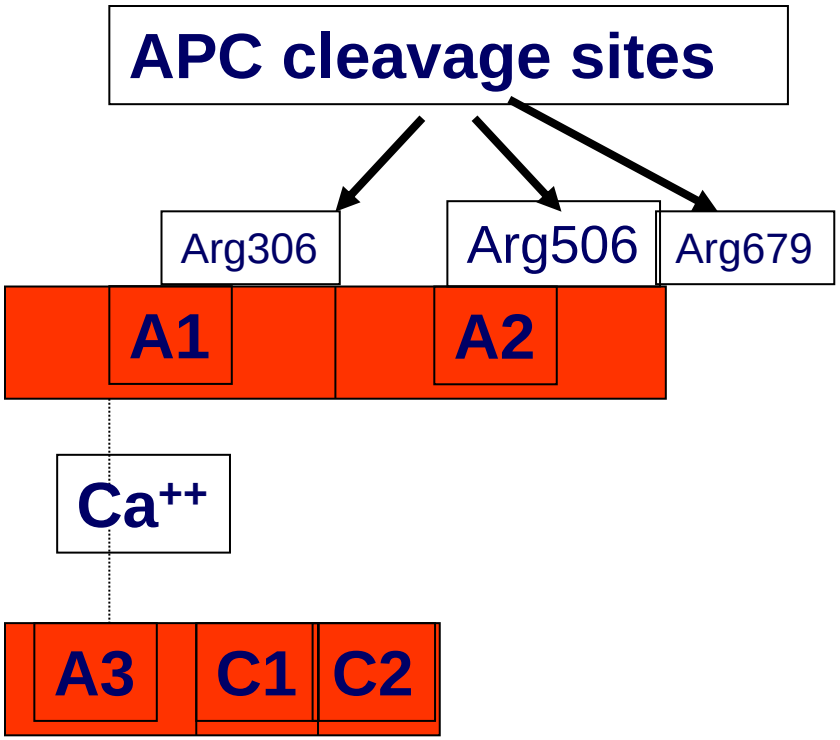
year of discovery

factor V Leiden (G1691A) (resistance to activated protein C)	1993/94
prothrombin mutation (G20210A)	1996

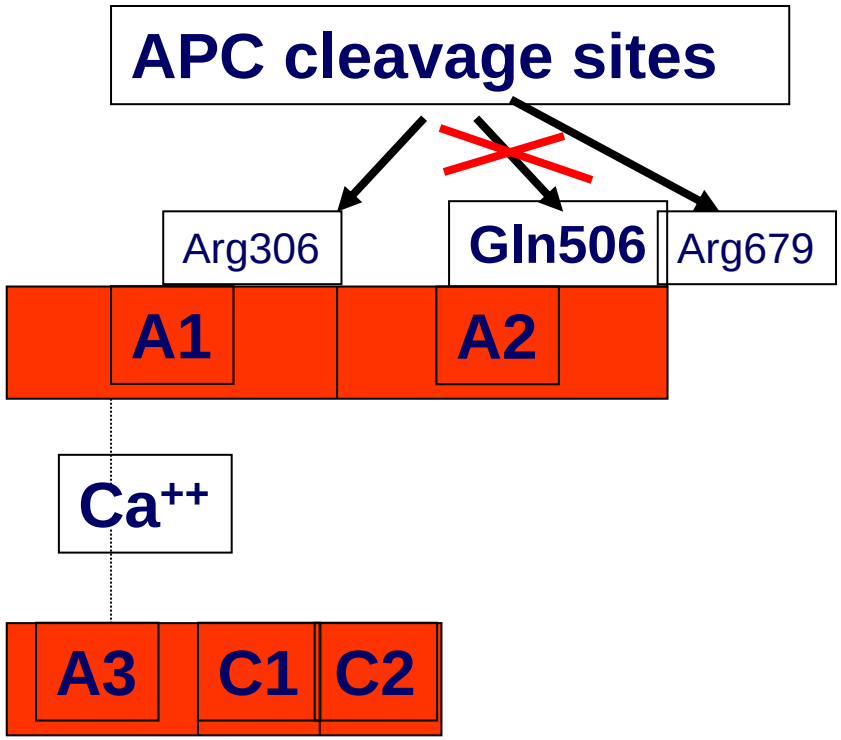
FACTOR V WILD TYPE



FACTOR V WILD TYPE



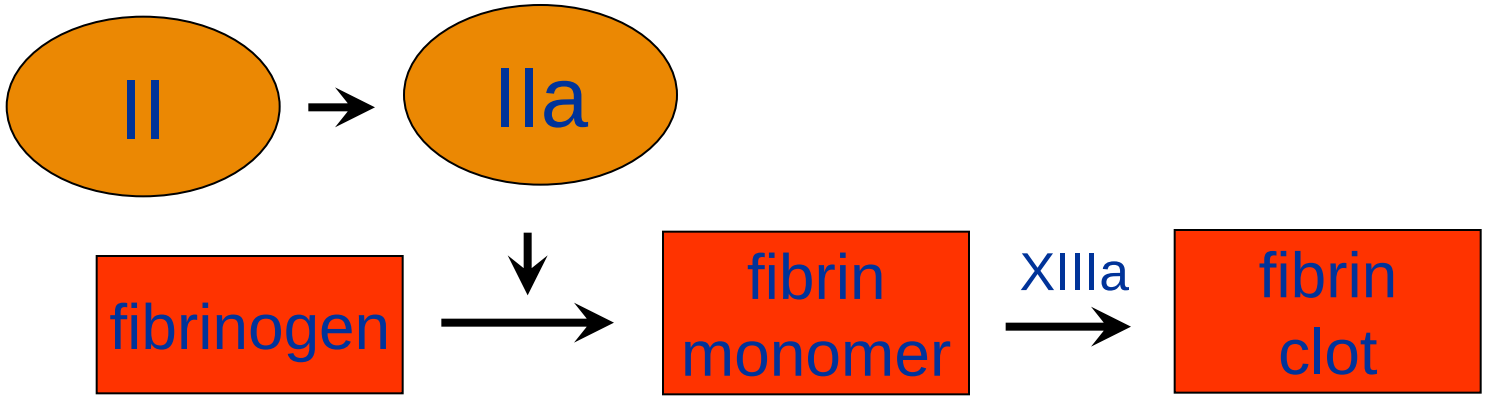
FACTOR V LEIDEN



Prothrombin G20210A

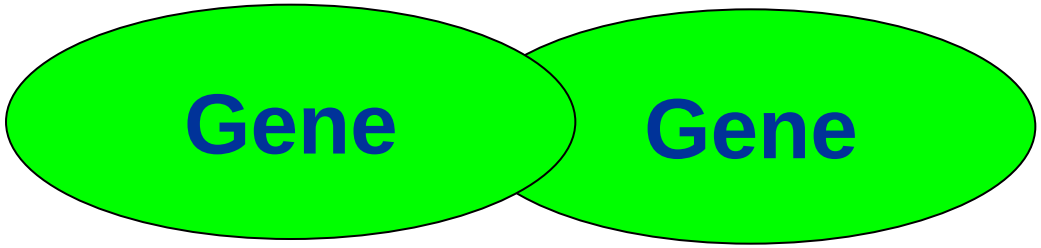
- mutation (G>A) at position 20210 in the 3'-untranslated region of the gene coding for prothrombin (factor II)

- ~ 30% increase plasma levels of prothrombin



Prevalence/risk of inherited thrombophilia

	general population	unselected VTE patients	↑RR
antithrombin	0.02 - 0.2 %	1 %	5 - 50
protein C	0.1 - 0.5 %	3 %	7 - 15
protein S	?	1 - 2 %	6 - 10
factor V Leiden	4 %	12 %	5 - 8
G20210A protrombin	4 %	8 %	2 - 4



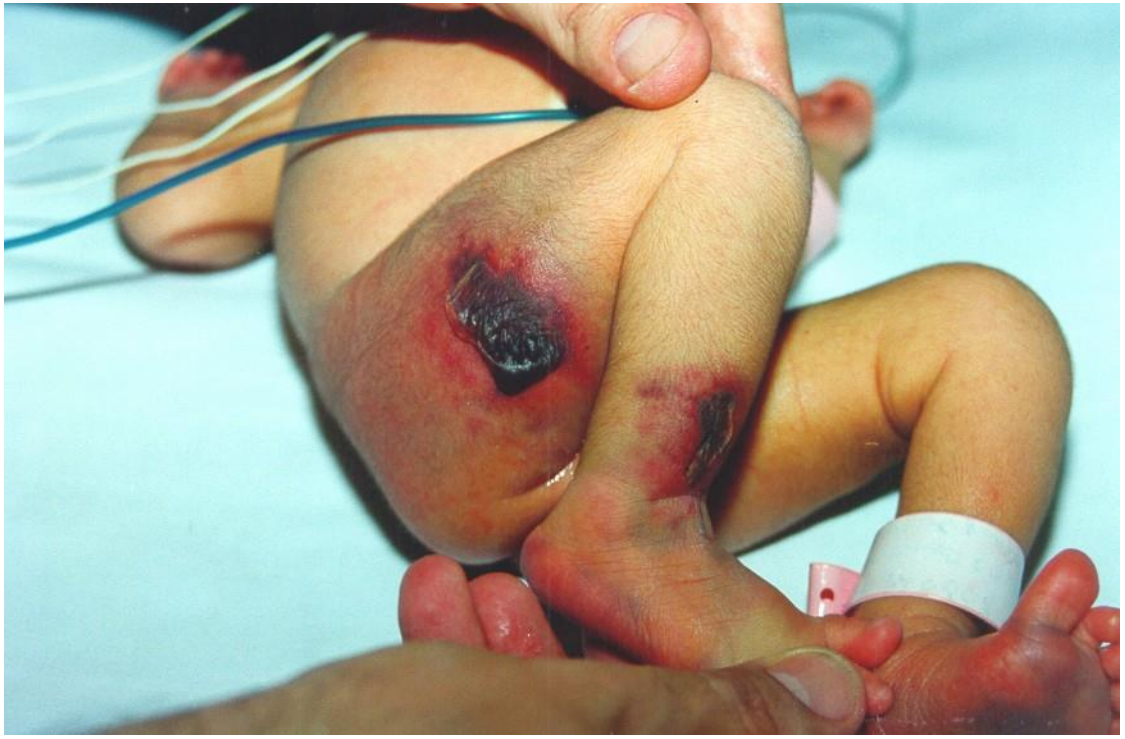
homozygous

AT deficiency	death in utero
PC, PS deficiency	neonatal purpura fulminans
factor V Leiden	80-fold increased risk of VTE
G20210A prothrombin	?

double heterozygous

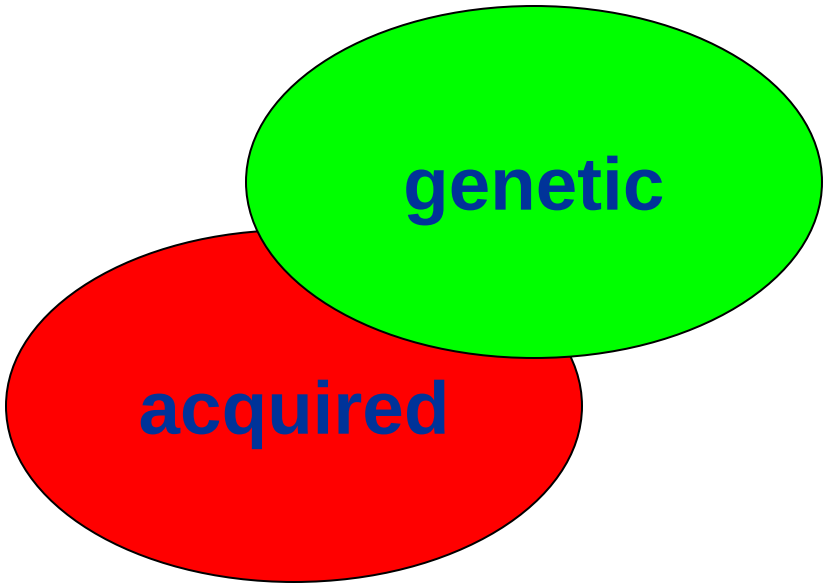
factor V Leiden + G20210A prothrombin	20-fold increased risk of VTE

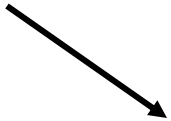
Purpura Fulminans in a newborn with homozygous protein C deficiency



VTE: a multifactorial disease

risk factors





VTE

often persistent
(unremovable)

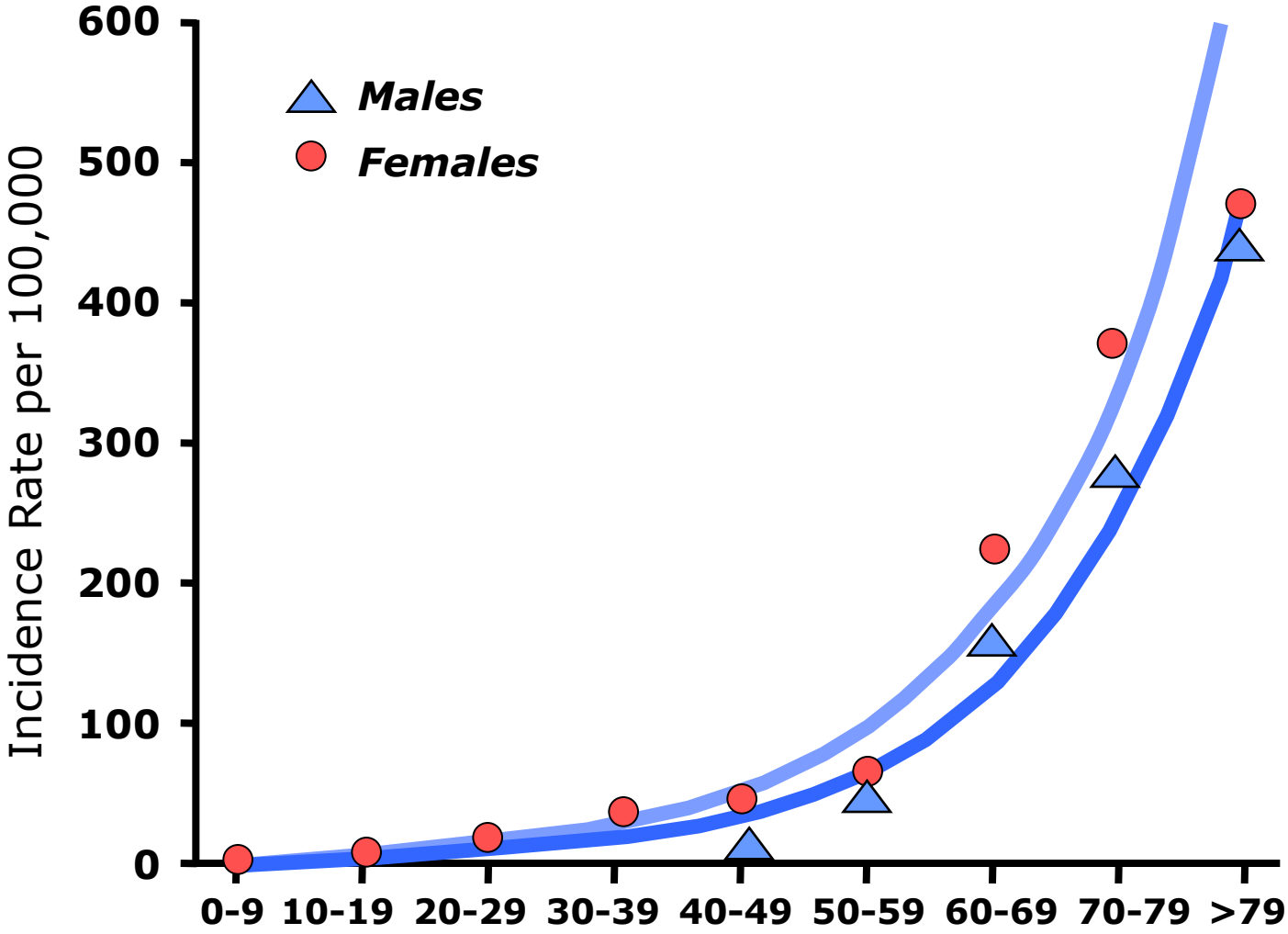
older age - sex

cancer

antiphospholipid antibodies

previous venous thromboembolism

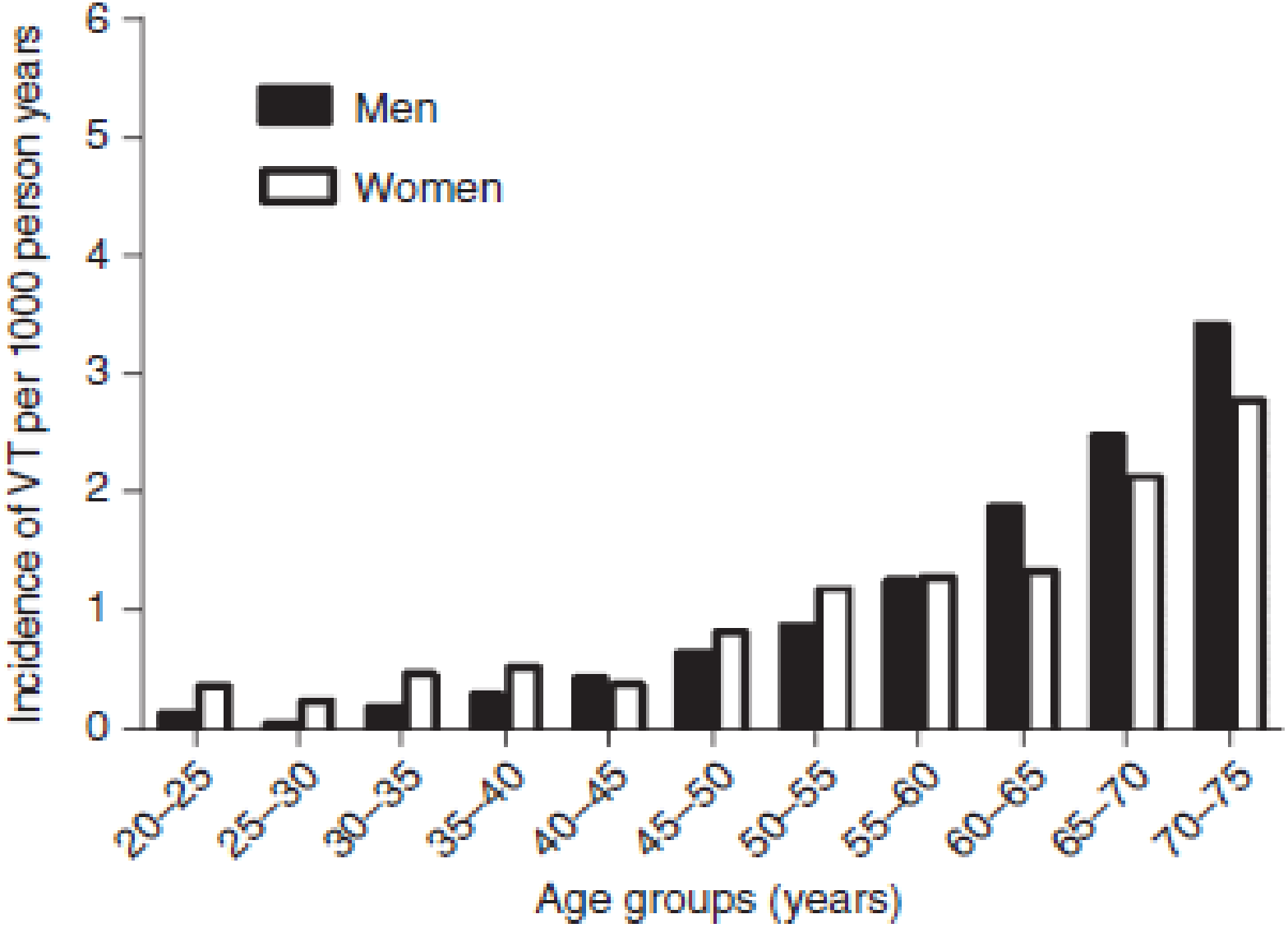
Age and VTE



Anderson et al, 1991

Absolute risk of 1st VTE

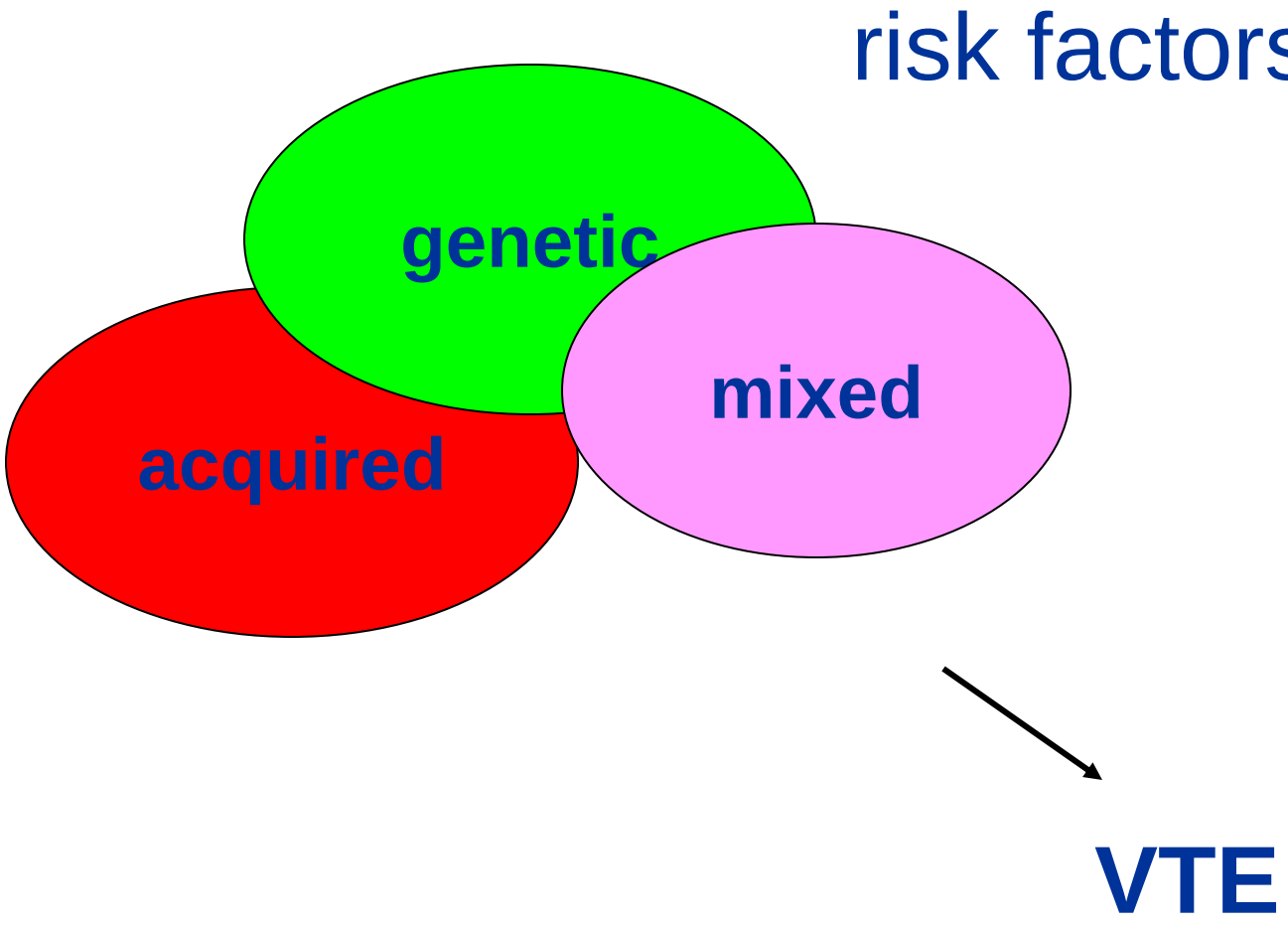
(adapted from Naess et al. 2007)



Prevalence/risk of acquired risk factors

	general population	unselected VTE patients	↑RR
cancer	2 - 3 %	3 - 20 %	7
antiphospholipid antibodies	1 - 2 %	5 - 15 %	9
previous VTE	-	6 - 10 %	8

VTE: a multifactorial disease



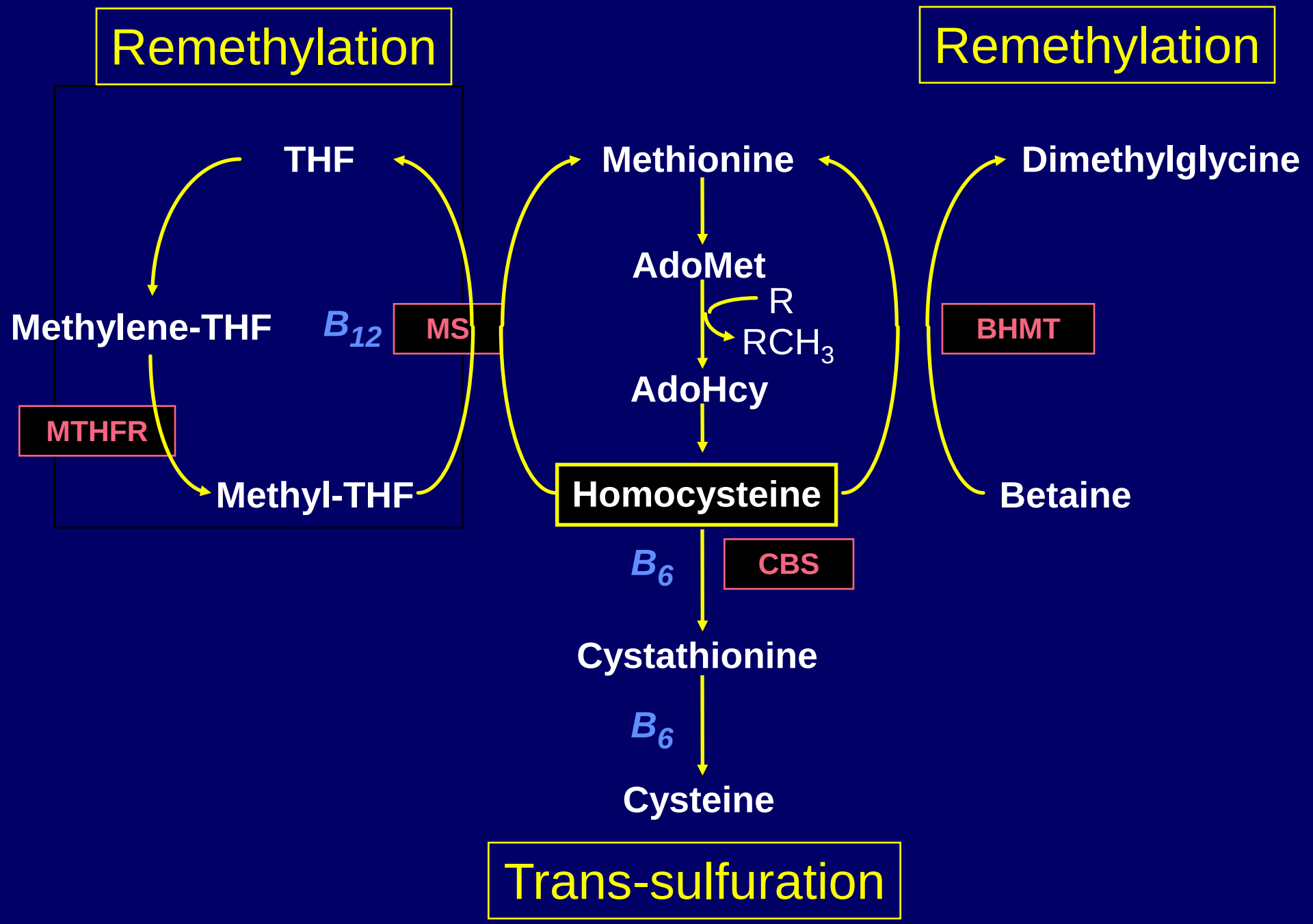
→ genetic or/and acquired

	year of discovery
hyperhomocysteinemia	1994
APC resistance (no F V Leiden)	1995
high factor VIII	1995

Prevalence/risk of mixed risk factors

	general population*	unselected VTE patients	↑RR
hyperhomocysteinemia	5 - 10 %	15 - 20 %	2
APC resistance (no FVL)	10 %	24 %	2 - 4
high factor VIII	10 %	19 - 25 %	3

* 90^{th}-95^{th} percentile


Remethylation
Remethylation
THF
Methionine
Dimethylglycine
AdoMet
R
RCH3
Methylene-THF
B12
MS
BHMT
AdoHcy
MTHFR
Methyl-THF
Homocysteine
Betaine
B6
CBS
Cystathionine
B6
Cysteine
Trans-sulfuration


C677T variant (or others)
MTHFR

Risk of thrombosis associated with thrombophilia

INHERITED	antithrombin deficiency	++++	severe
	protein C deficiency	+++	
	protein S deficiency	++	
	homoz. factor V Leiden	+++	
	homoz. G20210A prothrombin	+++	
ACQUIRED	antiphospholipid Ab	++++	
INHERITED	heteroz. factor V Leiden	+	mild
	heteroz. G20210A prothrombin	+	
MIXED	hyperhomocysteinemia	+	
	high factor VIII	+	

TEST PREDITTIVO PER RISCHIO TROMBOTICO E CARDIOVASCOLARE

Indicazione: Familiarità per coagulopatia
Id.: TR-04-A64
Cognome: [redacted]
Nome: [redacted]
Data di nascita: 29.06.2000
Medico richiedente: [redacted]
Data del referto: [redacted]

Metodiche applicate:

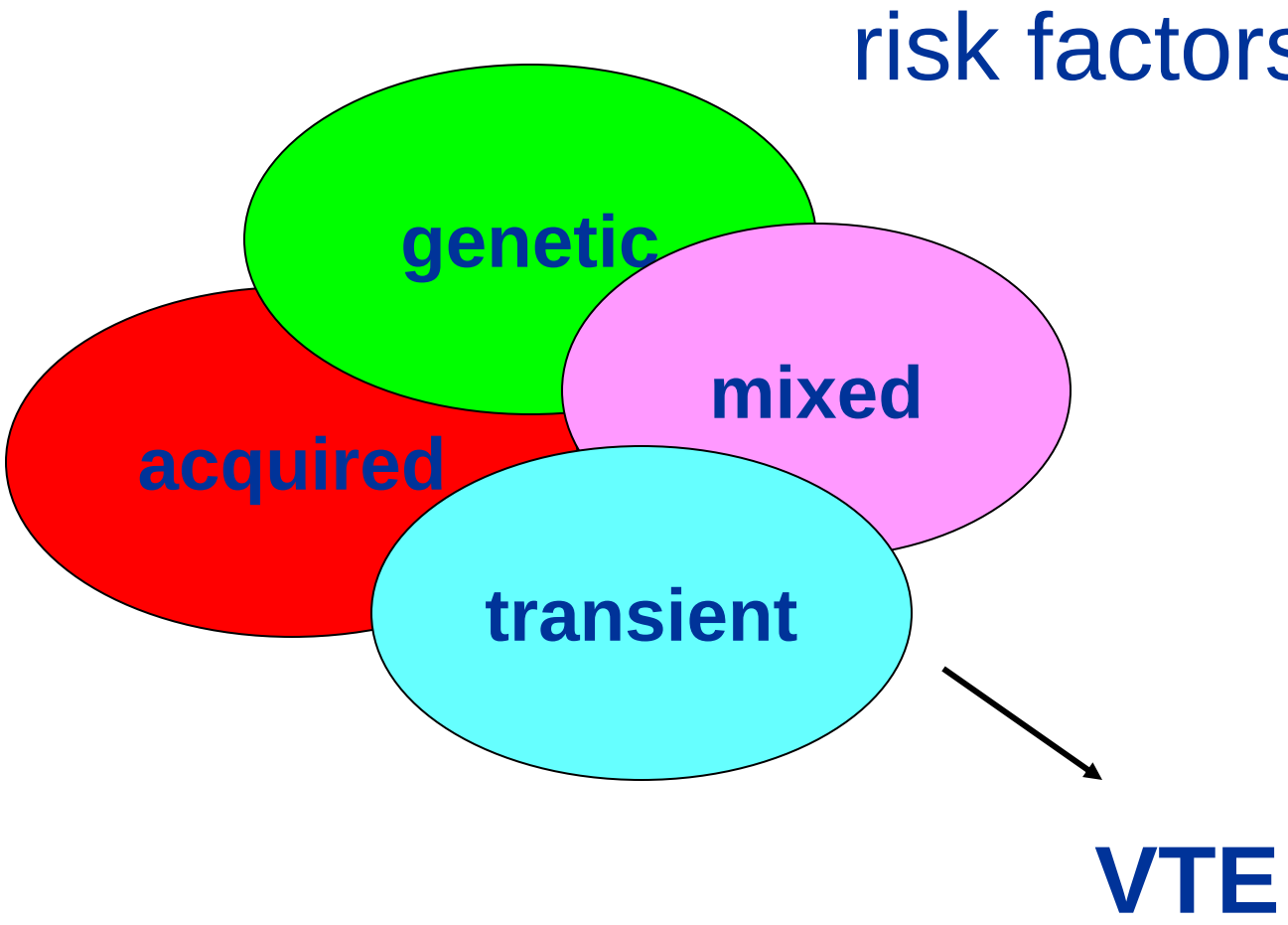
1. Isolamento del DNA da sangue intero.
2. Amplificazione simultanea delle regioni geniche interessate mediante la tecnica della PCR multiplex utilizzando oligonucleotidi biotinilati.
3. Ibridazione su strip dei frammenti amplificati biotinilati con sonde oligonucleotidiche allele-specifiche.
4. Rivelazione degli ibridi biotinilati utilizzando la streptavidina coniugata con fosfatasi alcalina e un substrato colorato.

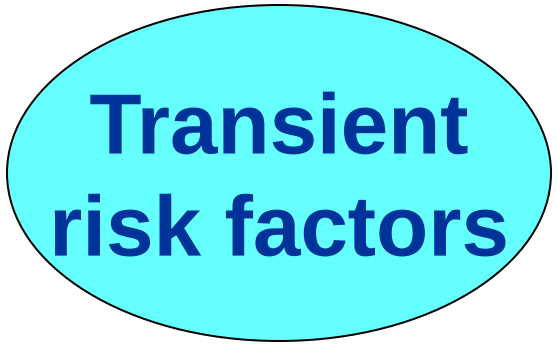
Risultati:

Gene		Mutazione	Lettura	Genotipo
FV	Fattore V	G1691A (Leiden)	-/-	Normale
FV	Fattore V	H1299R (R2)	+/-	**Eterozigote**
FII	Protrombina	G20210A	-/-	Normale
FXIII	Fattore XIII	V34L	+/-	**Eterozigote**
FBG	β-Fibrinogeno	–455G>A	-/-	Normale
PAI-1	Inibitore dell'attivatore del plasminogeno	4G/5G	+/-	**Eterozigote**
HPA-1	Glicoproteina IIIa	a/b	+/+	**Omozigote mutato**
MTHFR	Metilen-tetraidrofolato reduttasi	C677T	+/-	**Eterozigote**
MTHFR	Metilen-tetraidrofolato reduttasi	A1298C	+/-	**Eterozigote**
HFE	Emocromatosi	C282Y	-/-	Normale
APOB	Apolipoproteina B	R3500Q	-/-	Normale
APOE	Apolipoproteina E	codone 112: TGC	+	E3/3
APOE	Apolipoproteina E	codone 112: CGC	-	
APOE	Apolipoproteina E	codone 158: TGC	-	
APOE	Apolipoproteina E	codone 158: CGC	+	

Conclusioni: L'esame ha evidenziato la presenza di alcune mutazioni ritenute responsabili di un aumento del rischio per patologie cardio-vascolari: la mutazione H1299R (R2) nel gene per il fattore V (in eterozigosi); la mutazione a/b nel gene per la Glicoproteina IIIa (in omozigosi); la mutazione C677T nel gene per la Metilen-tetraidrofolato reduttasi (in eterozigosi); la mutazione A1298C nel gene per la Metilen-tetraidrofolato reduttasi (in eterozigosi).
Per quanto riguarda invece la mutazione V34L nel gene per il Fattore XIII (presente in eterozigosi) e la mutazione 4G/5G nel gene per l'Inibitore dell'attivatore del plasminogeno (presente in eterozigosi), si ritiene che possano avere un effetto protettivo.
Questo test va interpretato dal Medico richiedente tenendo conto anche degli altri risultati di laboratorio, del quadro clinico e dei dati anamnestici. Utile una consulenza genetica.

VTE: a multifactorial disease





temporary,
removable

surgery and major trauma

prolonged immobilization

pregnancy/puerperium (6 weeks postpartum)

oral contraceptives/hormone replacement therapy

Prevalence/risk of transient risk factors

	general population	unselected VTE patients	↑RR
surgery and trauma	4 %	12 - 70 %	6
immobilization	0.5 %	16 %	11
pregnancy	1 %	5 %	4
puerperium	1 %	8 %	14
oral contraceptives	30 %	60 %	5
HRT	14 - 26 %	15 - 43 %	2 - 4

LETS, 1995

Thrombophilia and oral contraceptives in VTE

Martinelli et al, ATVB 1999

115 case women and 179 control women

thrombophilia	oral contraceptives	OR (95% CI)
NO	NO	1 (Ref.)
YES	NO	2.6 (0.8 - 8.7)
NO	YES	4.6 (2.6 - 8.0)
YES	YES	18.2 (5.8 - 56.6)

The risk of venous thrombosis is associated with both

Estrogen → *dose*

Progestin → *type*

Effect of estrogen dose on VTE risk

Lidegaard et al, Contraception 2002

dose EE	OR (95%CI)
30-40 µg	1.0 (Ref.)
20 µg	0.6 (0.4-0.9)
50 µg	1.6 (0.9-2.8)

$p_{trend}=0.02$

OC – progestin content

Divided into "generations" based on when progestins were first produced:

***1st generation (1960s)*: norethisterone, norethinodrel, lynestrenol, ethynodialacetate**

***2nd generation (1970s)*: norgestrel, levonogestrel, norgestrone**

***3rd generation (1980s)*: desogestrel, gestodene**

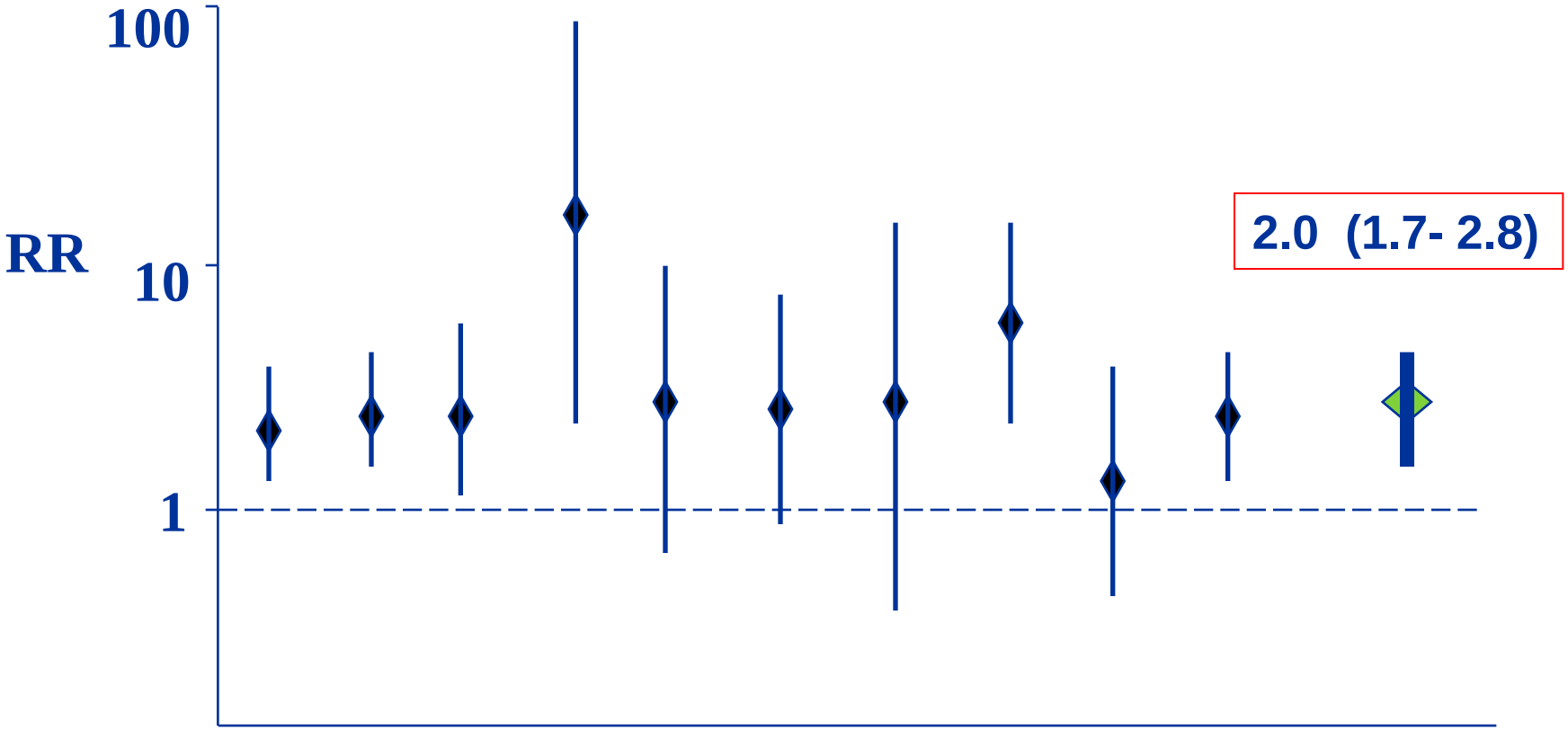
- widely used at the beginning of 1990s -

***4th generation (2000):* drospirenone**

- widely used at the beginning of 2000 -

Effect of progestin type

Helmerhorst et al, T&H 1997



3rd generation *vs* 2nd generation

Progestin type and VTE

MEGA Study, 1524 patients and 1760 controls
van Hylckama Vlieg et al, BMJ 2009

	OR (95%CI)
Use *vs* non use	5.0 (4.2-5.8)
Levonorgestrel	3.6 (2.9-4.6)
Gestodene	5.6 (3.7-8.4)
Desogestrel	7.3 (5.3-10.0)
Cyproterone acetate	6.8 (4.7-10.0)
Drospirenone	6.3 (2.9-13.7)

Case-control study, incident VTE

Sidney et al, Contraception 2004

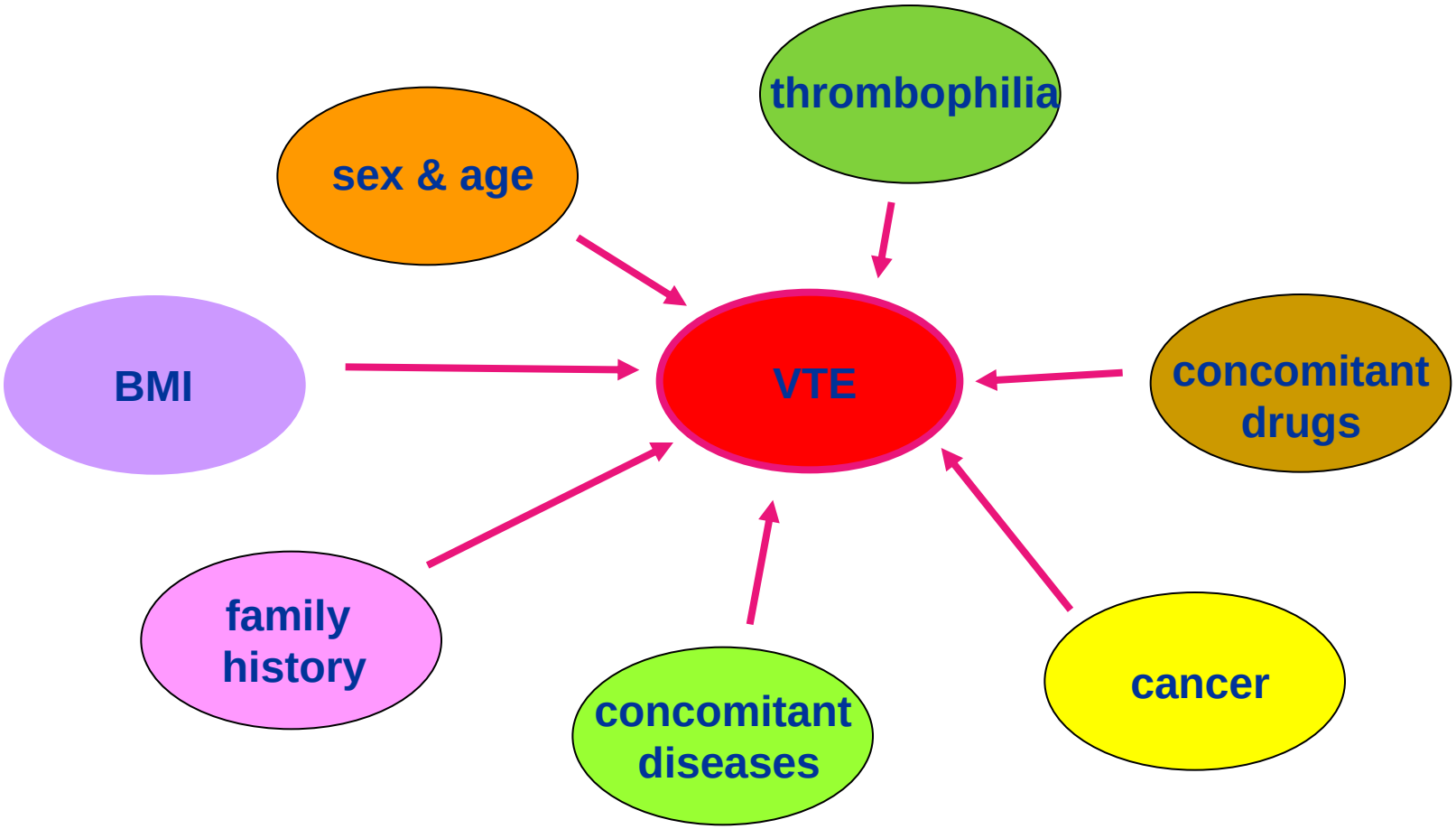
	cases n=196	controls n=746	OR (95%CI)
OC use n (%)			
Never	**31 (16)**	**141 (19)**	**1 (Ref.)**
Former	**78 (40)**	**469 (63)**	**0.8 (0.5-1.2)**
Current	**86 (44)**	**134 (18)**	**3.0 (1.9-4.8)**

Risk of VTE during early OC use

Lidegaard et al, Contraception 2002

	OR (95%CI)
Non users	**1.0 (Ref.)**
< 1 year	**7.0 (5.1-9.6)**
1-5 years	**3.6 (2.7-4.8)**
> 5 years	**3.1 (2.5-3.8)**

Evaluation of the risk of FIRST VTE



Evaluation of the risk of RECURRENT VTE