

TROMBOSI VENOSA PROFONDA E EMBOLIA POLMONARE

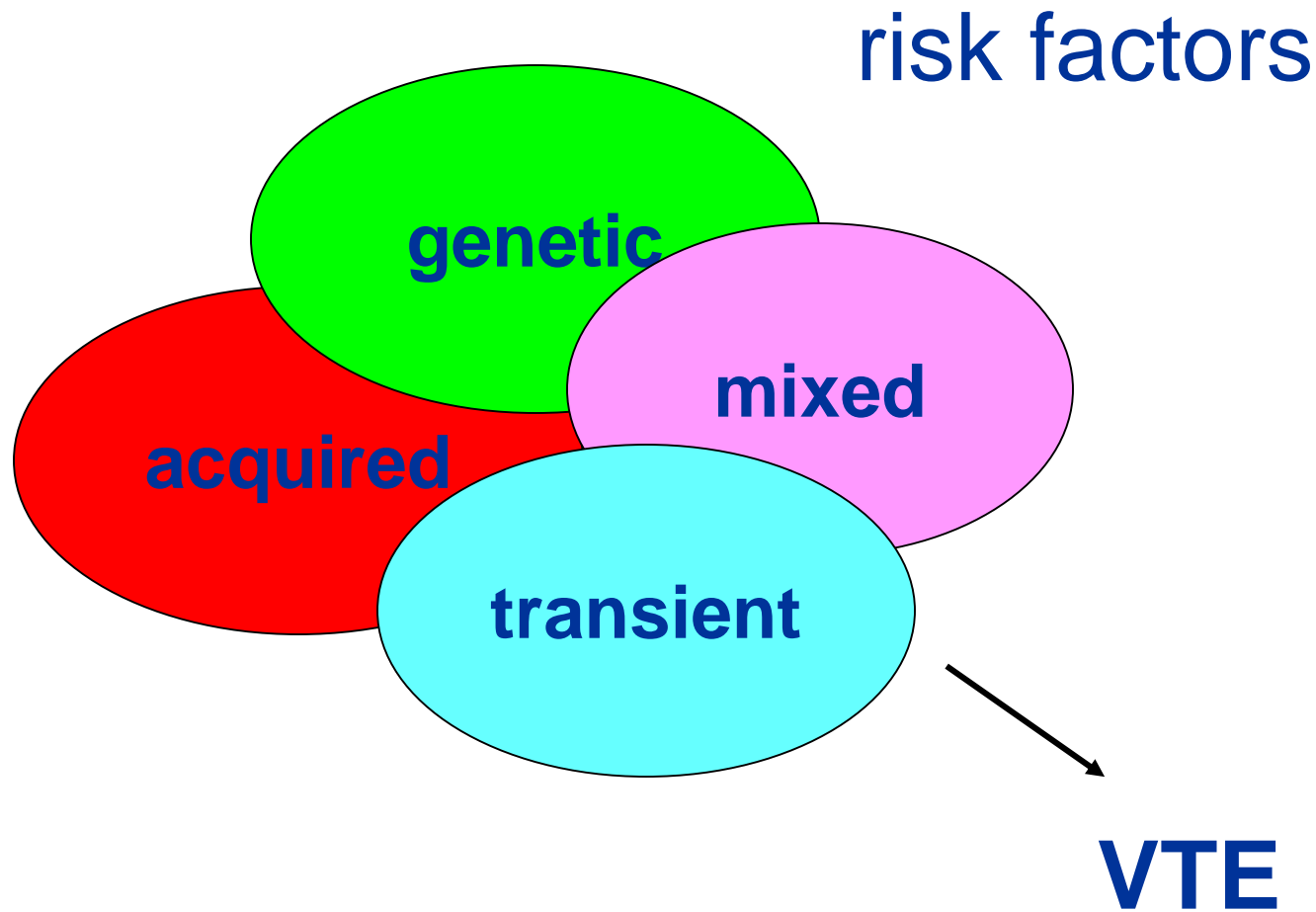
Fattori di rischio congeniti e acquisiti

Ida Martinelli

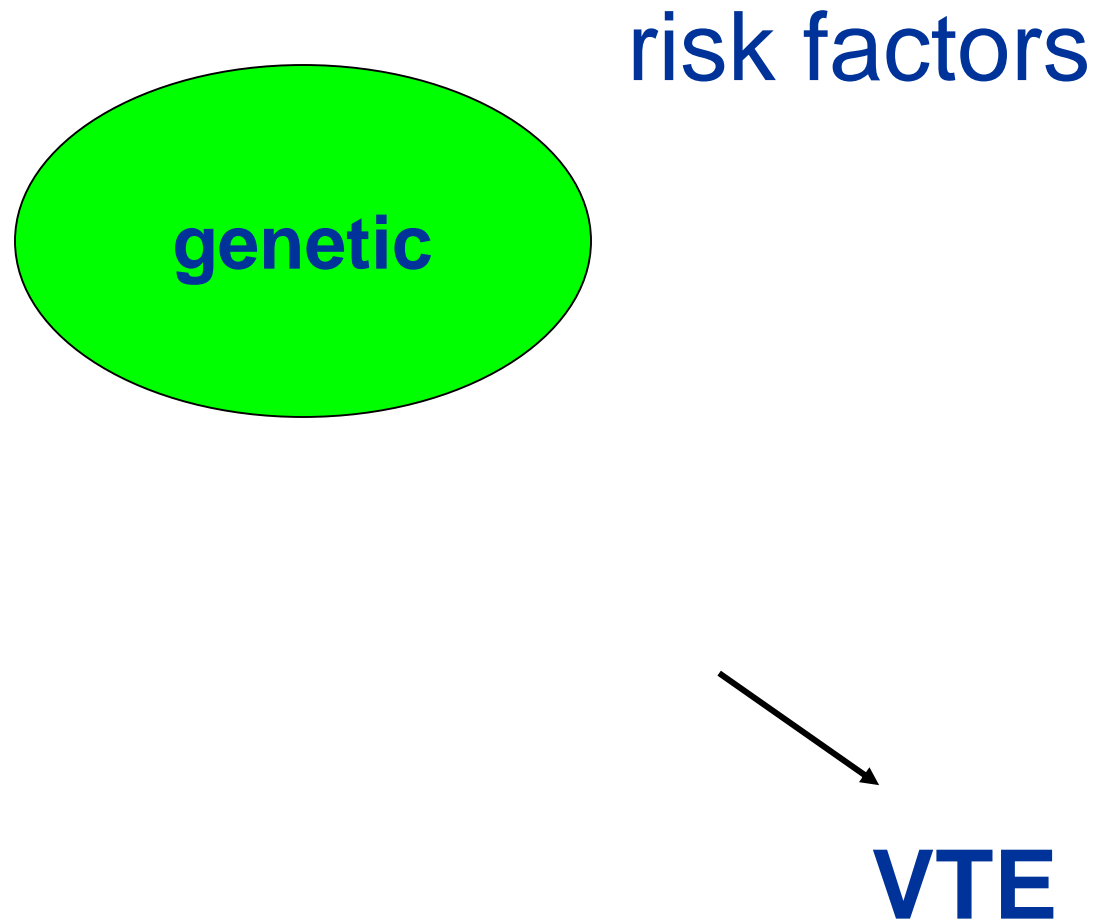
Centro Emofilia e Trombosi A.Bianchi Bonomi
IRCCS Fondazione ca' Granda -Ospedale Maggiore Policlinico
Milano

***CORSO TROMBOSI - Siset Training Center
Cremona, 19-23 settembre 2016***

VTE: a multifactorial disease



VTE: a multifactorial disease



**Genetic
risk
factors**



**inherited
thrombophilia**

deficiency of
anticoagulant proteins

year of discovery

antithrombin

1965

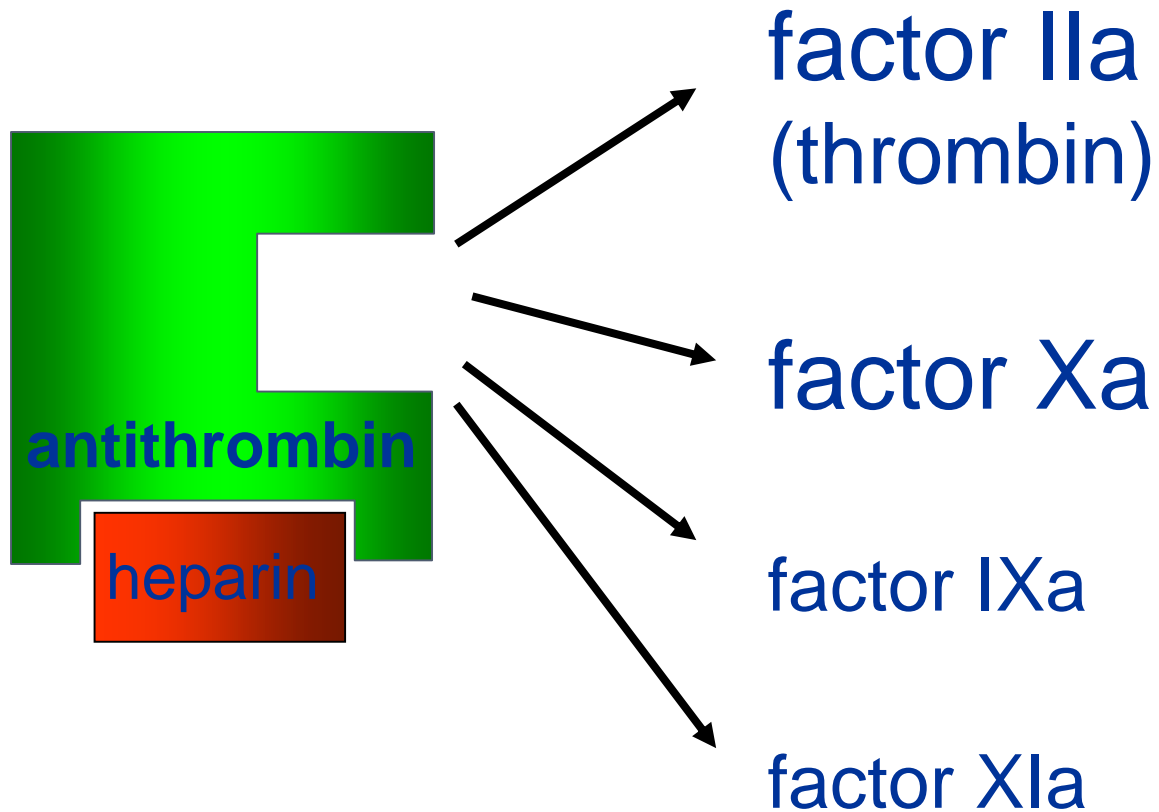
protein C

1981

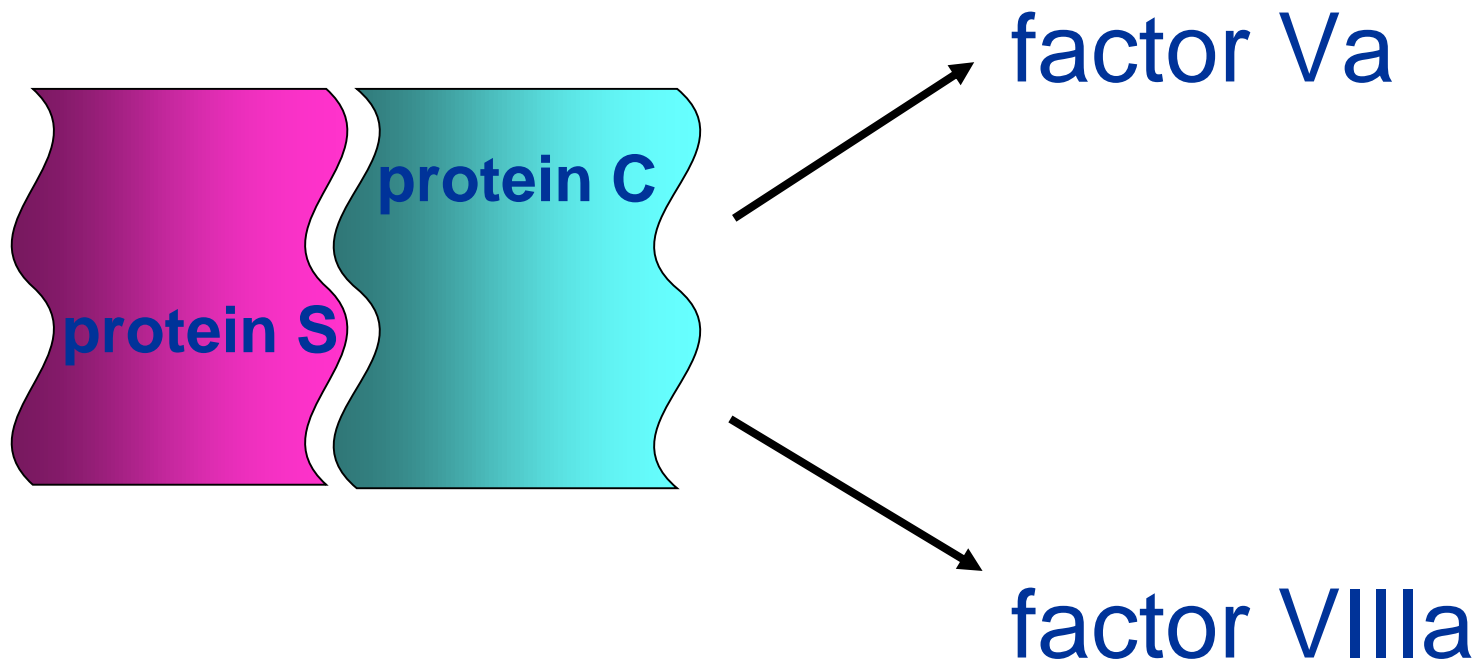
protein S

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

**Genetic
risk
factors**

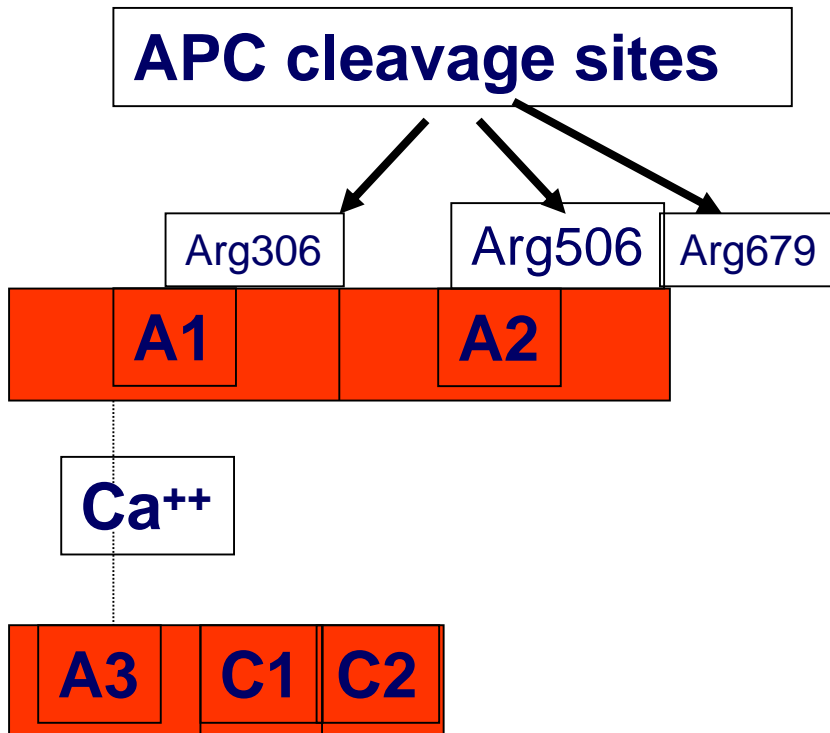


**inherited
thrombophilia**

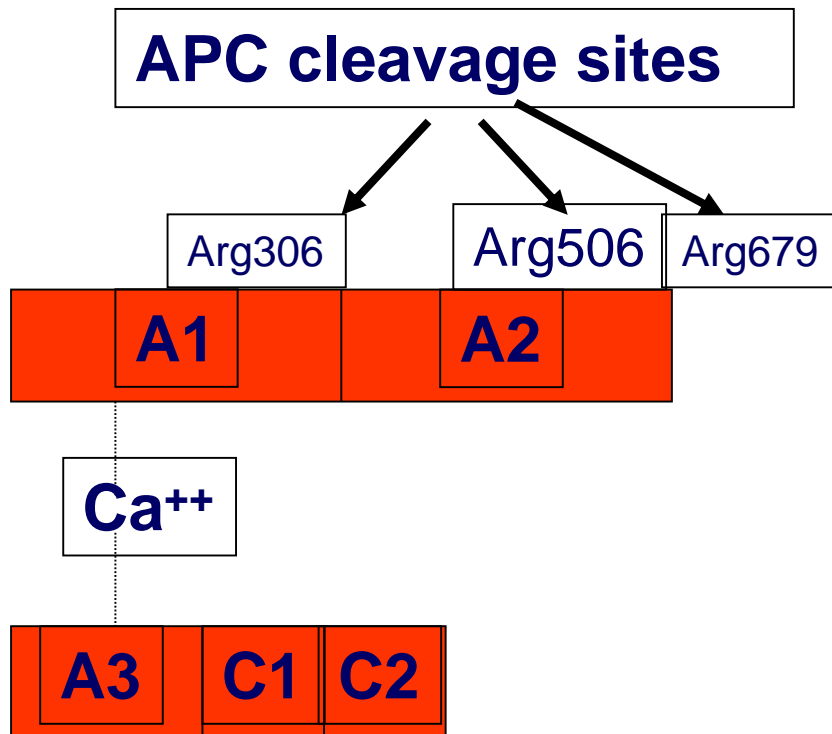
year of discovery

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

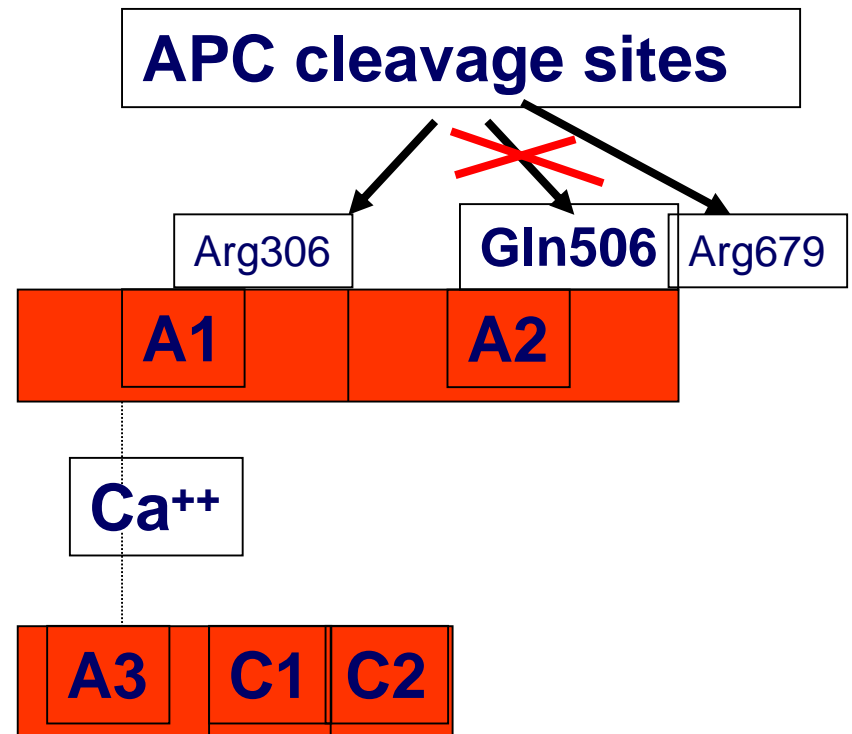
FACTOR V WILD TYPE



FACTOR V WILD TYPE

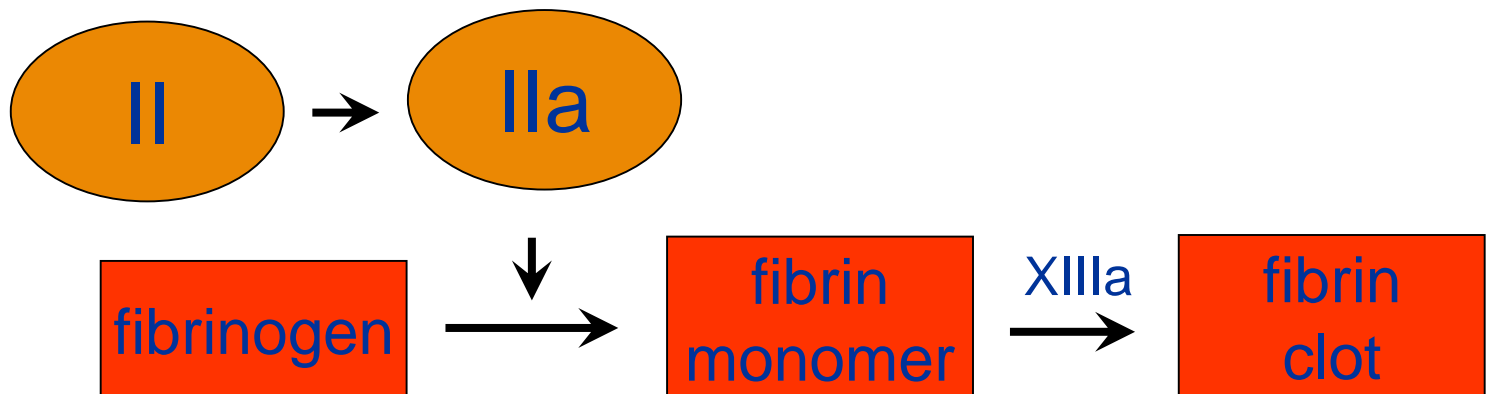


FACTOR V LEIDEN



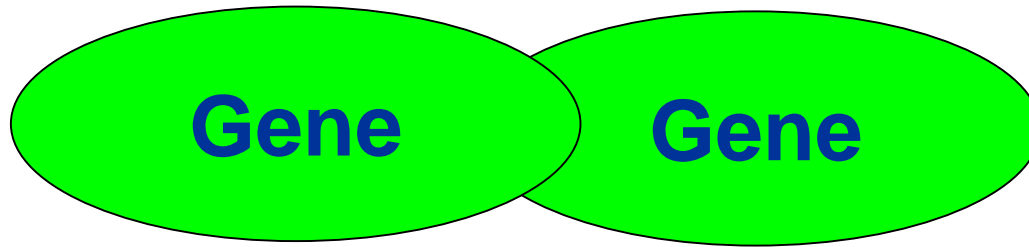
Prothrombin G20210A

- 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 +

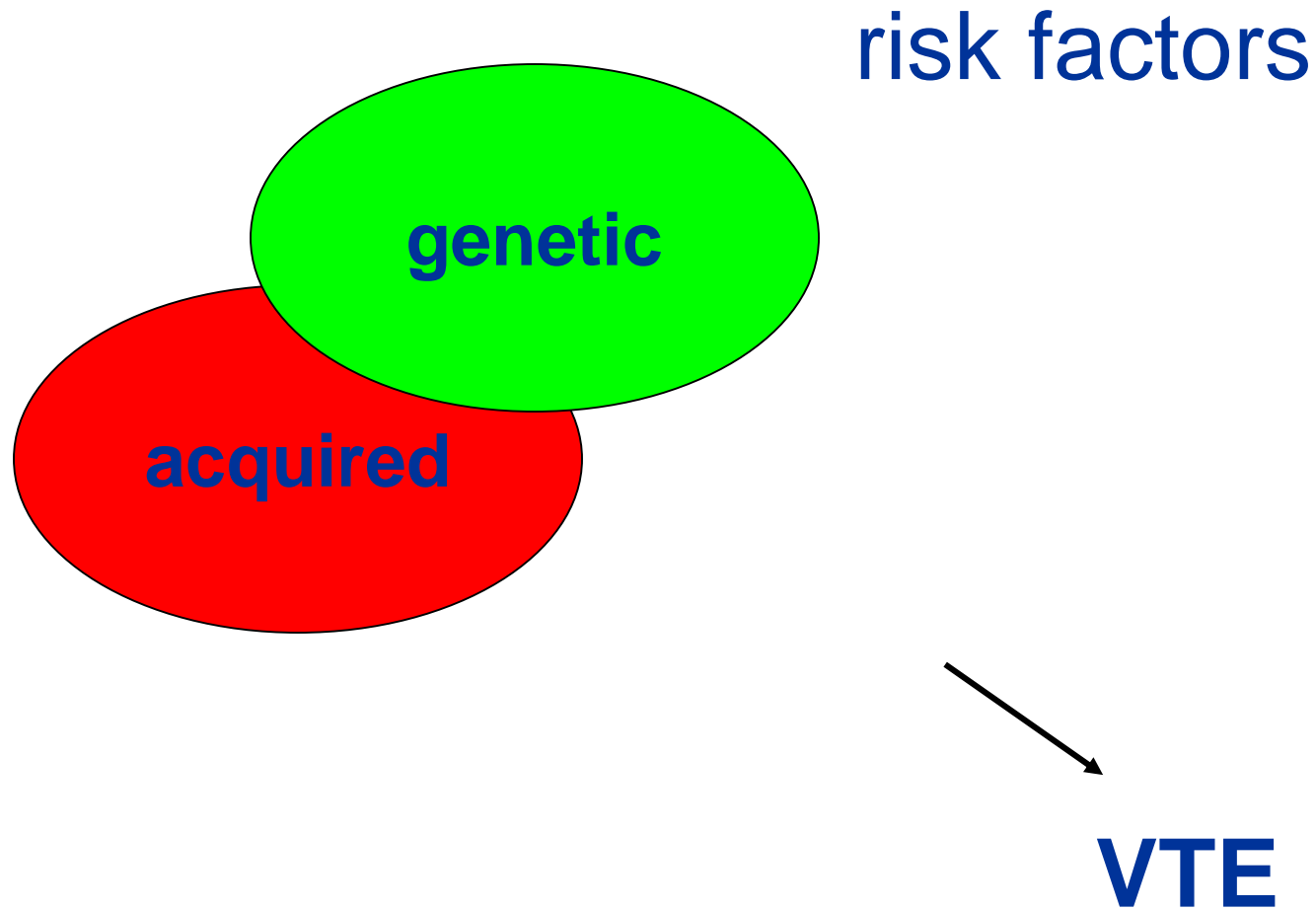
20-fold increased risk of VTE

G20210A prothrombin

Purpura Fulminans in a newborn with homozygous protein C deficiency



VTE: a multifactorial disease



**Acquired
risk factors**



often persistent
(unremovable)

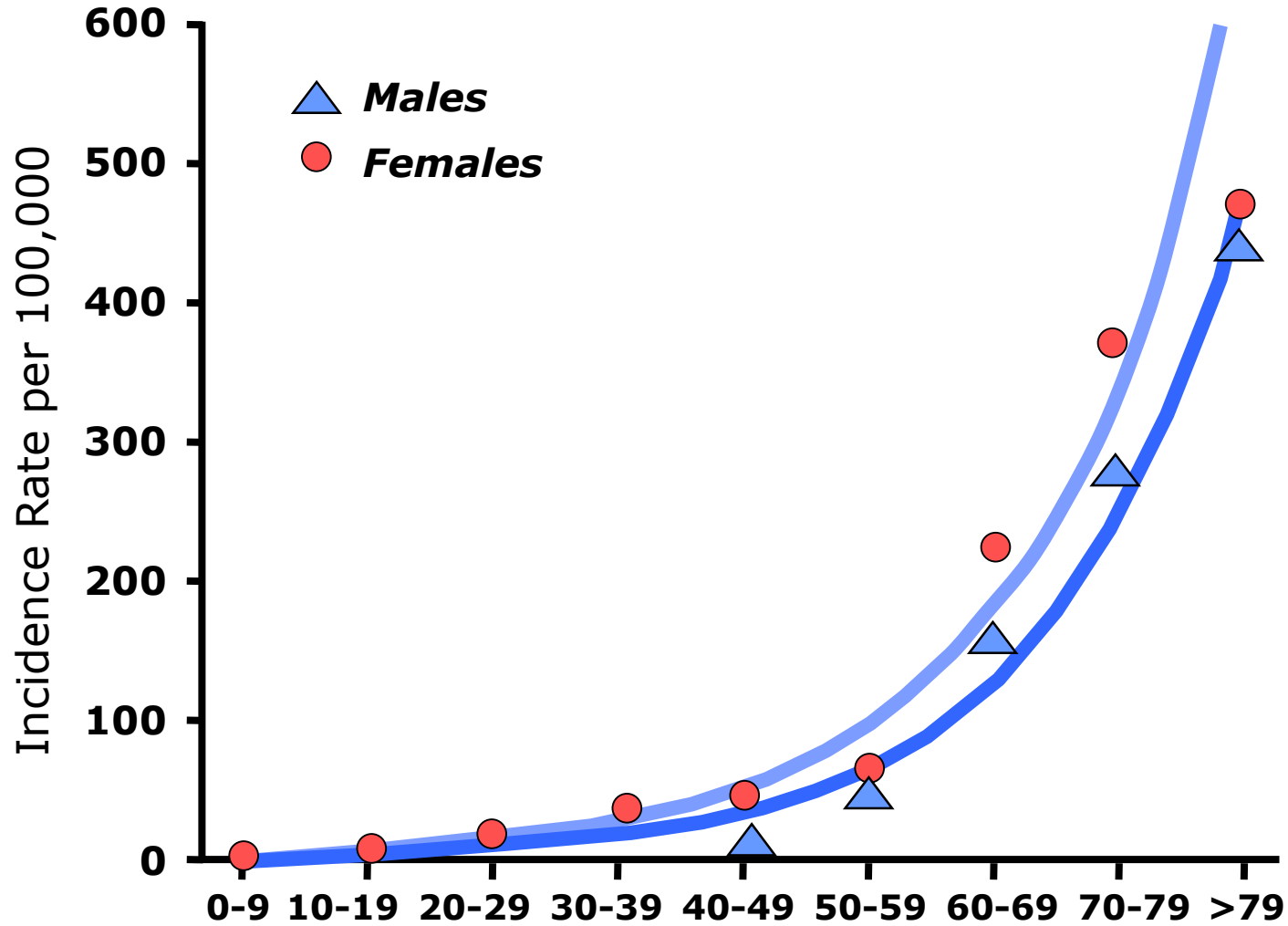
older age - sex

cancer

antiphospholipid antibodies

previous venous thromboembolism

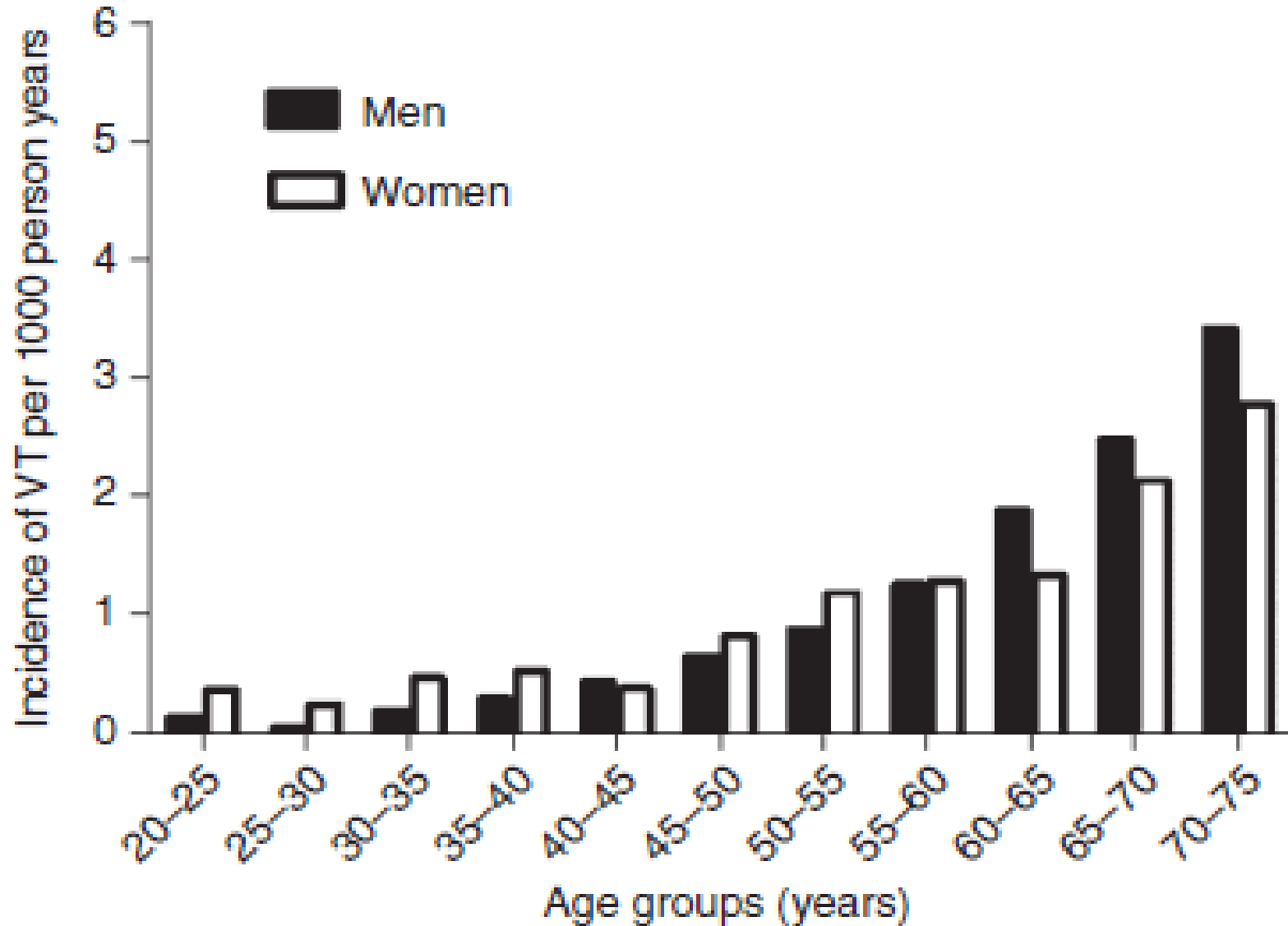
Age and VTE



Anderson et al, 1991

Absolute risk of 1st VTE

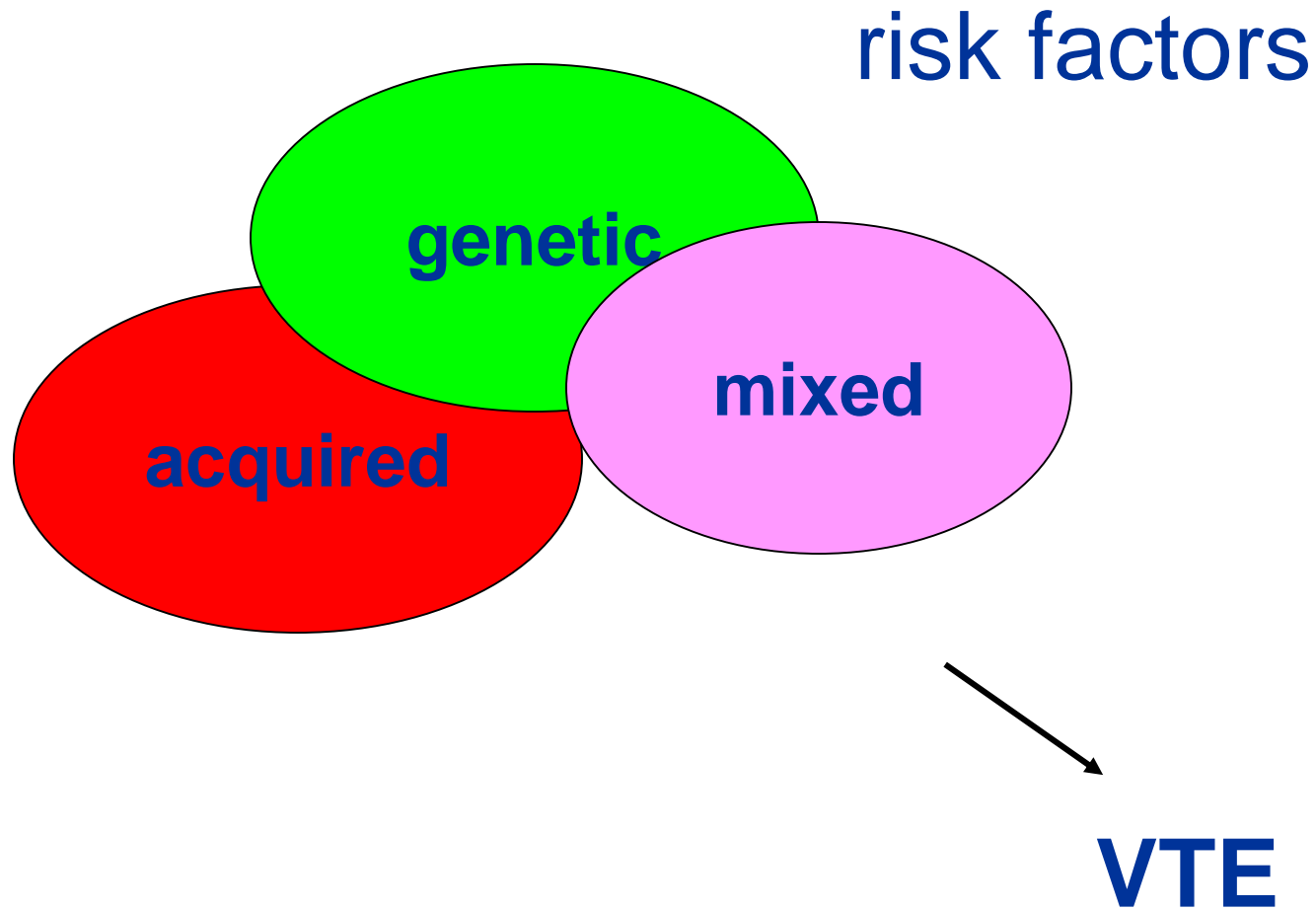
(adapted from Naess et al. 2007)



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

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

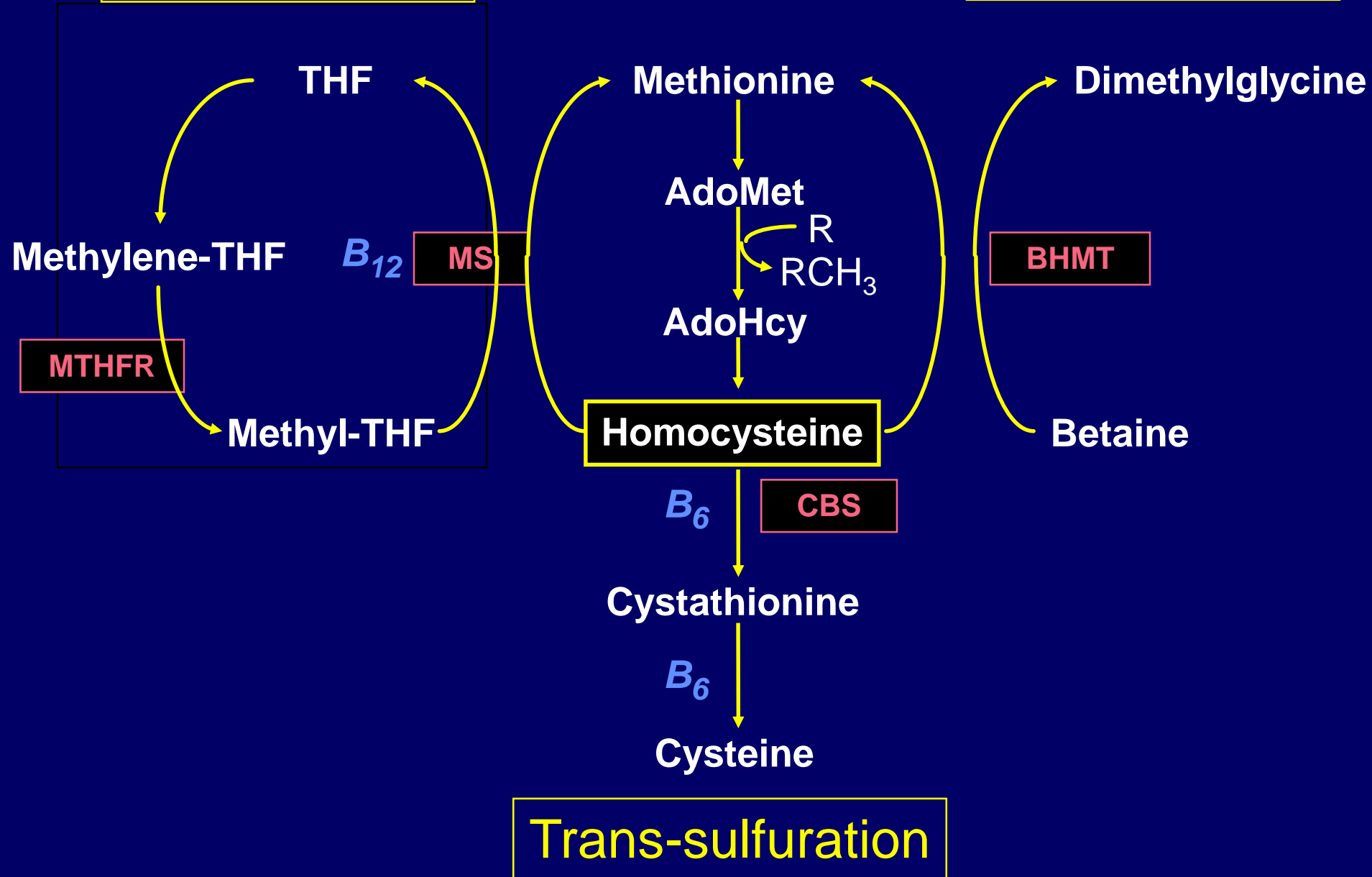
Prevalence/risk of mixed risk factors

	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

* 90th-95th percentile

Remethylation

Remethylation



~~C677T variant (or others)~~

~~MTHFR~~

Risk of thrombosis associated with thrombophilia

I N H E R I T	antithrombin deficiency	++++	} severe
	protein C deficiency	+++	
	protein S deficiency	++	
	homoz. factor V Leiden	+++	
	homoz. G20210A prothrombin	+++	
	ACQUIRED		
	antiphospholipid Ab	++++	
E D	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:

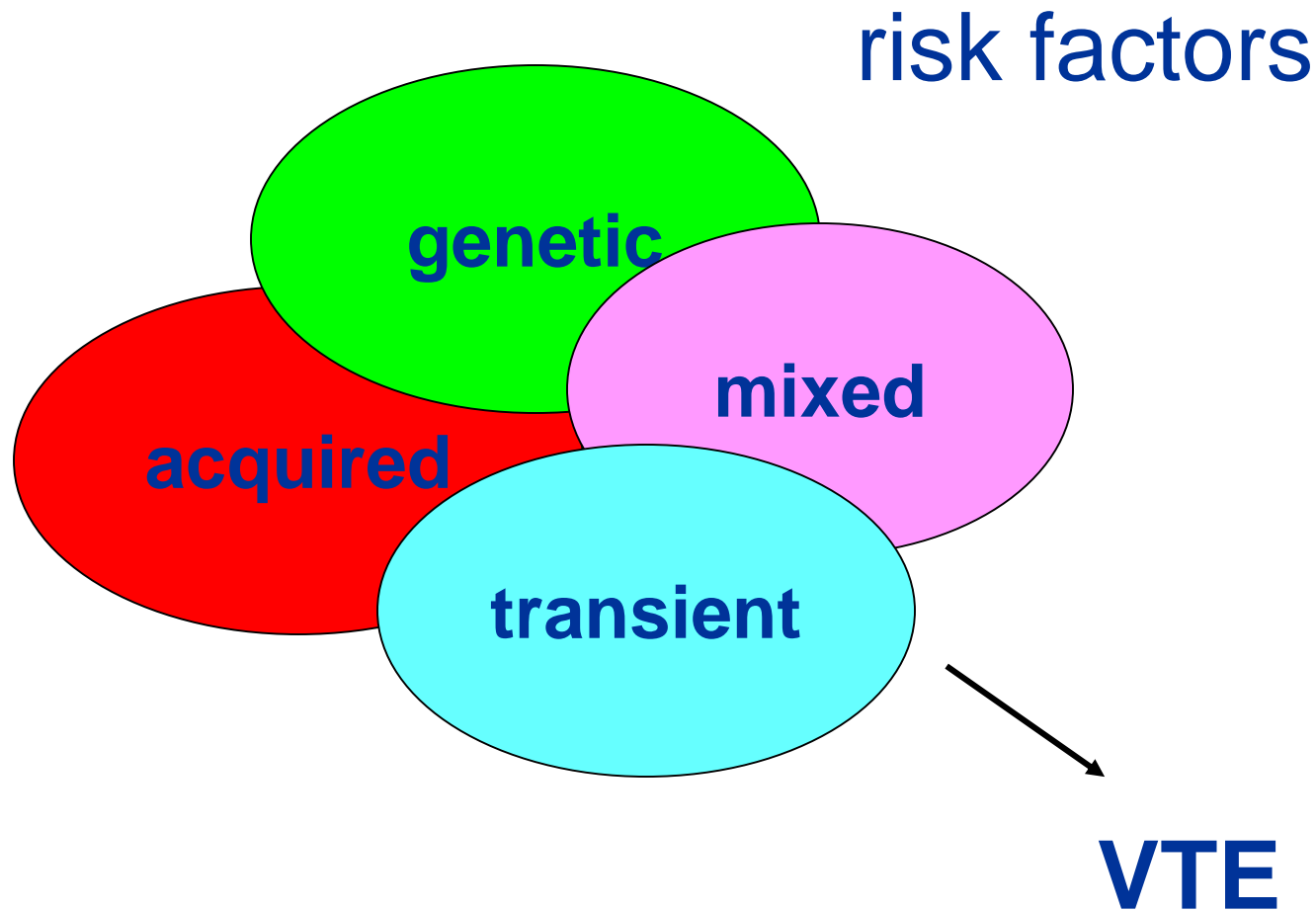
Gene	Mutazione	Destino	Fenotipo
FV Fattore V	G1691A (Leiden)	-/-	Normale
FV Fattore V	H1299R (R2)	+/-	Eterozigote
FII Protrombina	G20210A	-/-	Normale
FXIII Fattore XIII	V34L	+/-	Eterozigote
FBG β -Fibrinogeno	-455G>A	-/-	Normale
PAI-1 Inibitore dell'attivatore del plasminogeno	4G/5G	+/-	Eterozigote
HPA-1 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



**Transient
risk factors**



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

Thrombophilia and oral contraceptives in VTE

Martinelli et al, ATVB 1999

115 case women and 179 control women

<u>thrombophilia</u>	<u>oral contraceptives</u>	<u>OR (95% CI)</u>
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

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

ptrend=0.02

OC – progestin content

Divided into “generations” based on when progestins were first produced:

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

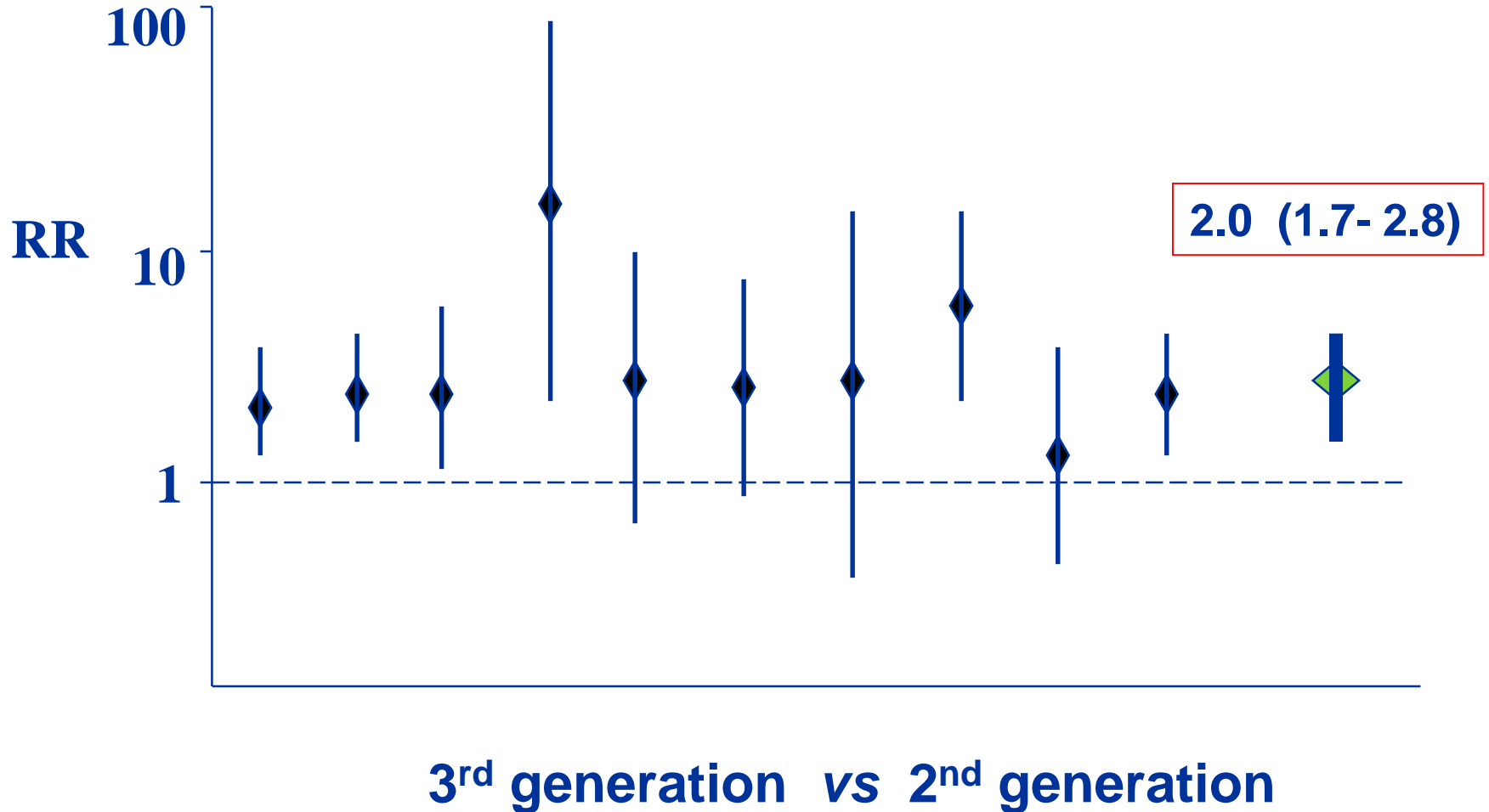
2nd generation (1970s): norgestrel, levonogestrel, norgestrone

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



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

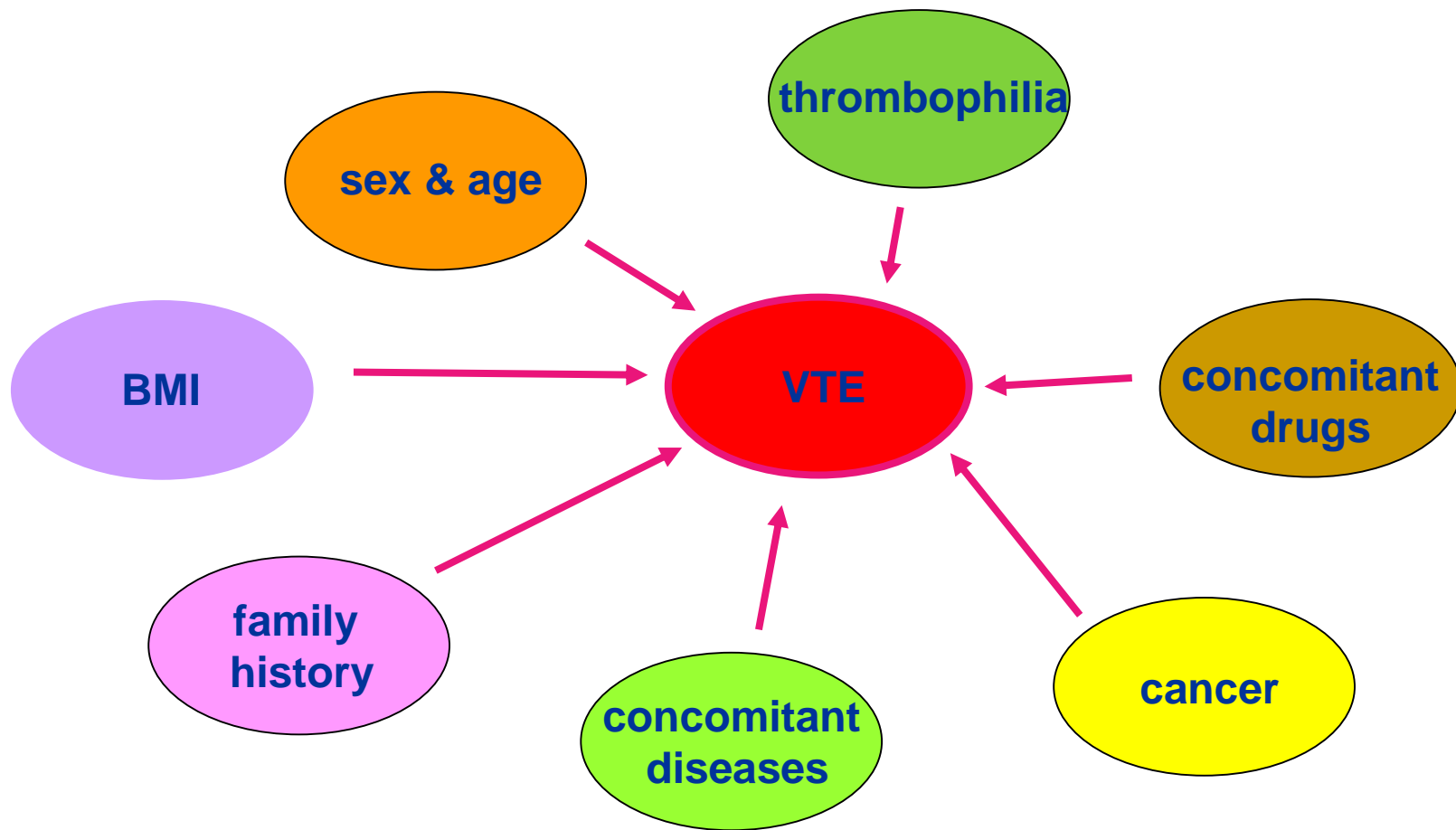
	cases	controls	
	n=196	n=746	OR (95%CI)
OC use n (%)			
Never	31 (16)	141 (19)	1 (Ref.)
Former	78 (40)	469 (63)	0.8 (0.5-1.2)
Current	86 (44)	134 (18)	3.0 (1.9-4.8)

Risk of VTE during early OC use

Lidegaard et al, Contraception 2002

	OR (95%CI)
<hr/>	
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

