2018

Progetto Ematologia Romagna

IL RUOLO DEL LABORATORIO

Giovanni Poletti

Patologia Clinica Ematologia Laboratorio AUSL Romagna

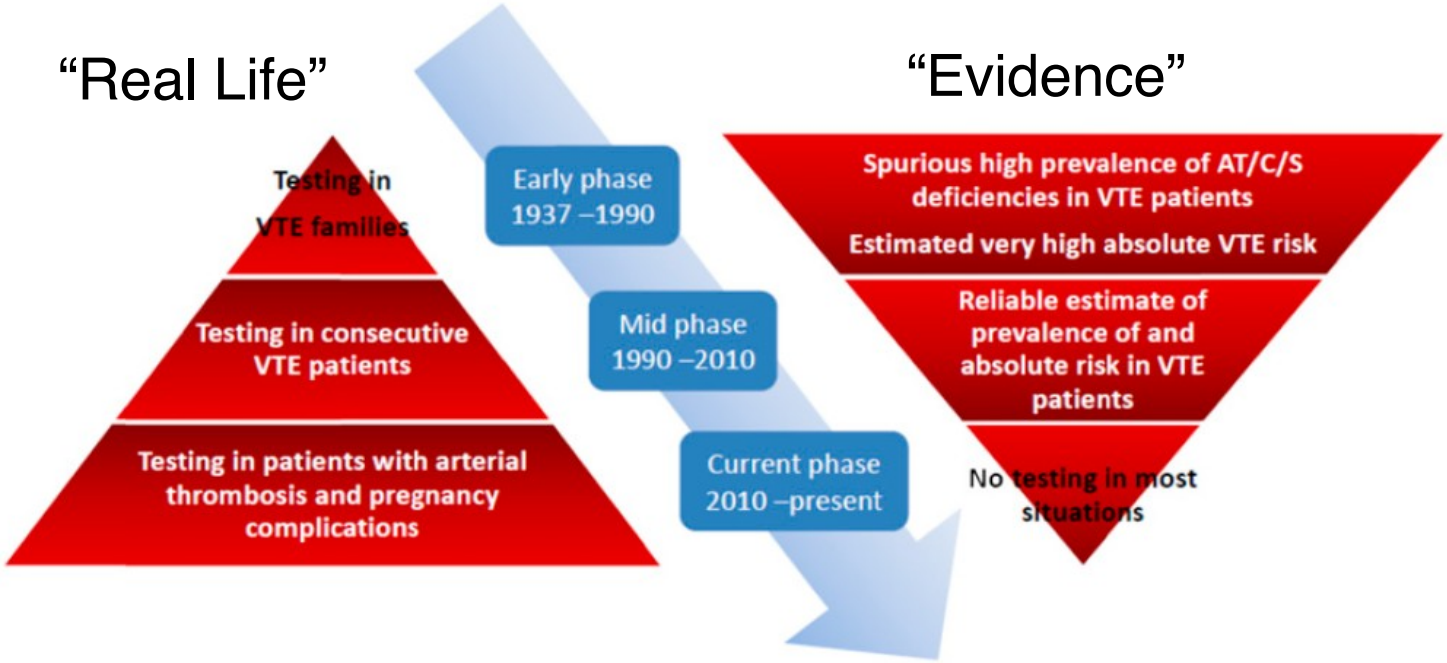
CONFLITTI DI INTERESSE: NESSUNO

Inherited thrombophilia: a double-edged sword

Saskia Middeldorp

Department of Vascular Medicine, Academic Medical Center, Amsterdam, The Netherlands

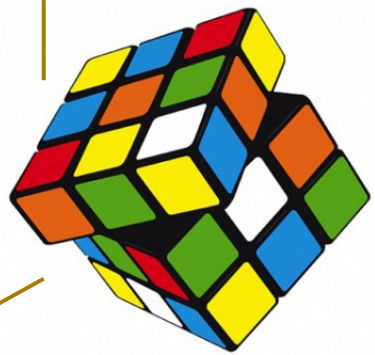
Hematology 2016



Trombofilia: difficoltà

- Molecole differenti, ciascuna con numerosi difetti molecolari
- Molecole con effetti biologici multipli:coagulazione/fibrinolisi/infiammazione
- Altri fattori di rischio “ambientali” e/o genetici

Biologia



Laboratorio

- Nessun test vede tutti i difetti
- Risultati patologici correlati a interferenze e cause acquisite
- Eterogeneità di metodi e kit commerciali

Clinica

- Variabile espressione clinica dei difetti anche nell’ambito della stessa famiglia
- Riscontro di difetti gravi con storia familiare assente
- Outcome clinico con dubbi ed evidenze contrastanti

..è molto facile creare danni

Confusione

Disinformazione

Ansia non motivata

Spreco di tempo e denaro

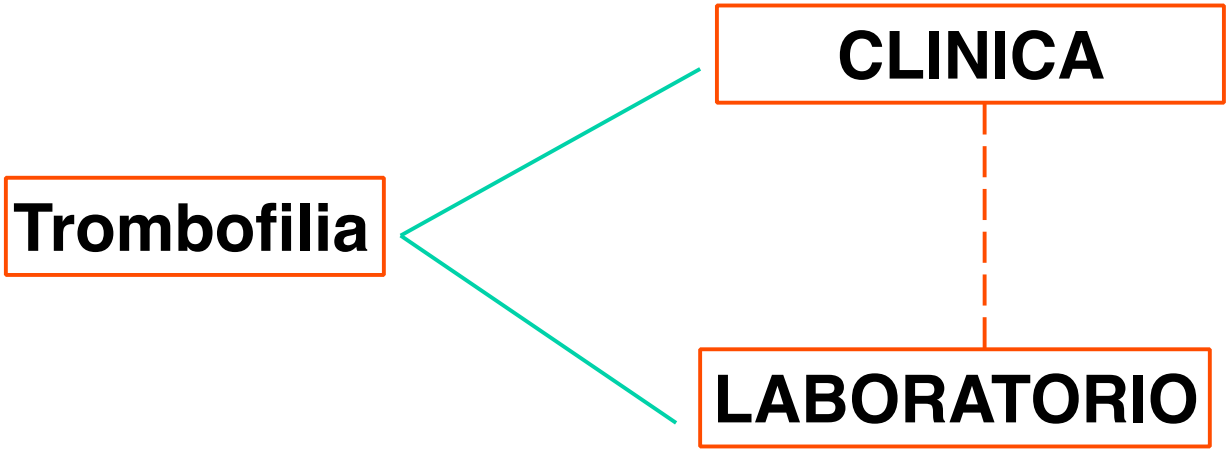
Decisione clinica inappropriata

Rassicurazione pericolosa

Anticoagulazione non indicata

1. *Atipie per: giovane età, recidive, "trigger" debole o assente, familiarità, sedi inusuali (splancnica, cerebrale)*
2. *APS*

Evidente predisposizione alla trombosi(1)
….ed eventi gravidici avversi (2)



Presenza di uno o più difetti di laboratorio con documentato rischio trombotico

TROMBOFILIA: LABORATORIO

1. SCELTA DEI TEST
2. IDENTIFICAZIONE DEI SOGGETTI DA ESAMINARE
3. INTERPRETAZIONE DEI RISULTATI

1.SCELTA DEI TEST

TIPOLOGIA PRESCRIZIONE(S,H): SUGG ALTRO: PRIORITA' PRESCRIZIONE(U,B,D,P): D (Programmabile)

PRESCRIZIONE	QTA	
91.29.4 (4456.154) - FATTORE V (LEIDEN) ANALISI MUTAZIONE DNA CON PCR - SANGUE	1	---
91.29.4 (4457.154) - FATTORE MTHFR ANALISI MUTAZIONE DNA CON PCR - SANGUE	1	---
90.64.3 (4291.154) - FATTORE COAG.V - SANGUE	1	---
90.64.3 (1323.154) - FATTORE COAG.II - SANGUE	1	---
90.64.3 (4298.154) - FATTORE COAG.XIII - SANGUE	1	---
90.08.2 (2204.154) - CONVERTING ENZYME (ACE) - SANGUE	1	---
90.08.5 (1046.154) - APOLIPOPROTEINA B - SANGUE	1	---
90.65.1 (2230.154) - FIBRINOGENO - SANGUE	1	---

1.SCELTA DEI TEST

- Emogramma
- PT
- APTT
- Fibrinogeno

Emo-coagulazione di base

Difetti congeniti

- ANTITROMBINA
- PROTEINA C
- PROTEINA S LIBERA
- MUTAZIONE FV (G1691A)
- PGM (FII G20210A)

Difetto Acquisito (APS)

- LAC
- Ab anti-Cardiolipina IgG
- Ab anti-Cardiolipina IgM
- Ab anti-B2GP1 IgG
- Ab anti-B2GP1 IgM

rari

frequenti

Table 1. Prevalence of inherited thrombophilia and relative risk estimates for various clinical manifestations

	Antithrombin deficiency	Protein C deficiency	Protein S deficiency	Factor V Leiden	Prothrombin 20210A mutation
Prevalence in the general population*	0.02%	0.2%	0.03%-0.13%	3%-7%	0.7%-4%
Prevalence in consecutive patients with VTE*	1%	3%	2%	20%	5%
Relative risk for a first VTE†	5-10	4-6.5	1-10	3-5	2-3
Relative risk for recurrent VTE	1.9-2.6	1.4-1.8	1.0-1.4	1.4	1.4
Relative risk for arterial thrombosis	No association	No consistent association	No consistent association	1.3	0.9
Relative risk for pregnancy complications	1.3-3.6	1.3-3.6	1.3-3.6	1.0-2.6	0.9-1.3

Figures are derived from studies that are reviewed in detail elsewhere.[60]

*Population prevalences vary with geographic regions.

†Relative risks were derived, where possible, from family studies comparing the risk for a first VTE in thrombophilic relatives vs in nonthrombophilic relatives. Hence, the relative risk is not consistent with the ratio between the prevalence in consecutive VTE patients and in the general population.

Hematology 2016

I TEST

FVG1691A
FIIG20210A

- **Test genetici**

AT PC PS APS

- **Test immunologici**
- **Test funzionali (cromogenici-coagulativi)**

TEST immunologici e funzionali

Pitfalls:

- Acute Thrombosis
- Anticoagulation
- Pregnancy-puerperium
- Pills/Hormone Replacement Therapy
- Liver disease
- DIC
- Nephrotic syndrome
- Acute inflammatory processes

Stephan Moll. J Thromb Thrombolysis (2015) 39:367–378
Jean M Connors. N Engl J Med 377;12 (2017)

TROMBOFILIA: ALTRI TEST

- Ricerca cloni EPN
- Jak2
- D-Dimero
- Ab anti PF4-Eparina
- ADAMTS-13

Uncertain Hereditary Thrombophilic Markers

Weak evidence

- High TAFI plasma plasma levels • High coagulation factor levels (fibrinogen, FIX, FXI)
- EPCR polymorphisms

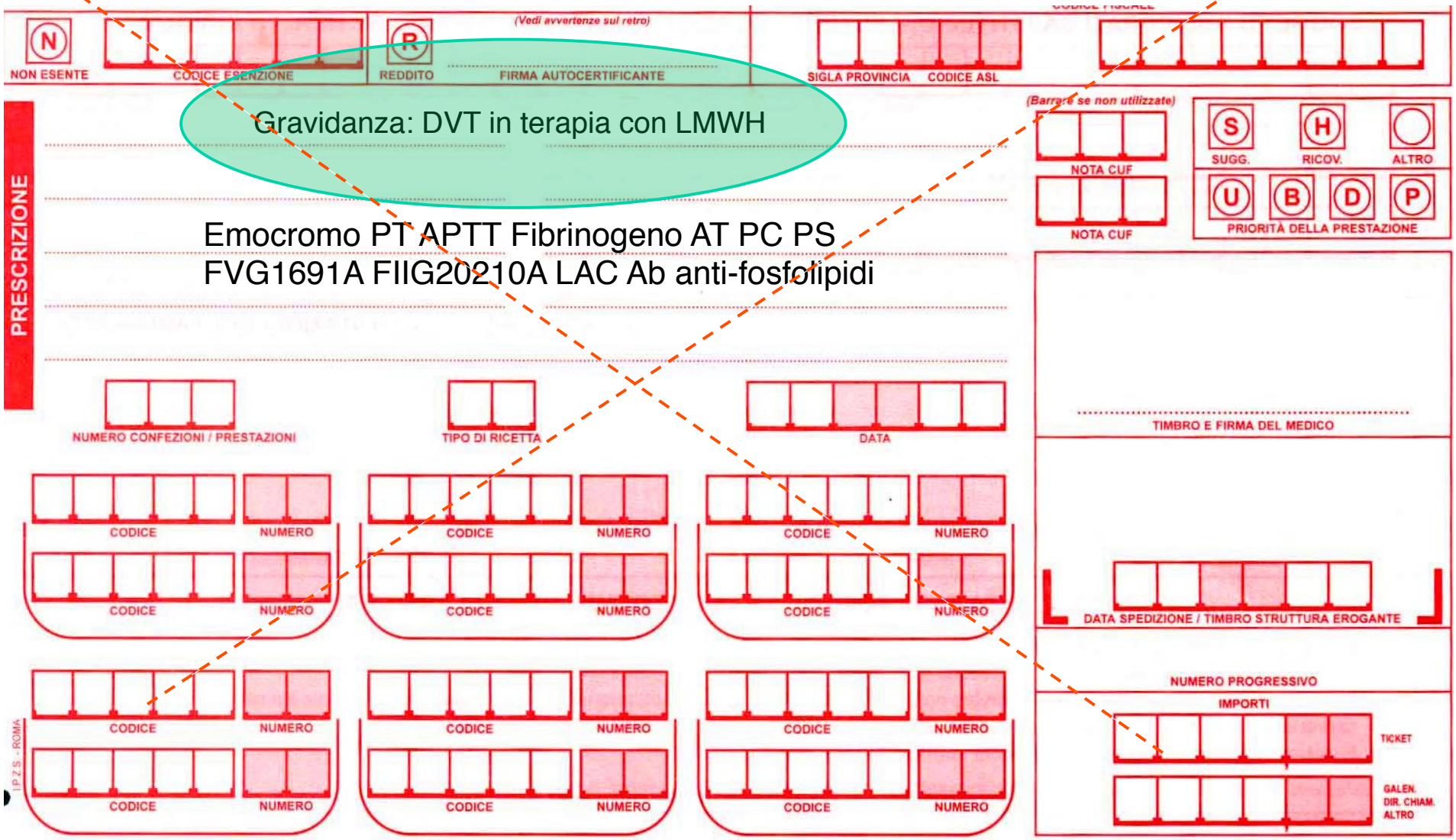
Lack of evidence

- Plasminogen deficiency
- High PAI-1 levels
- FXIII leu34val
- Lp(a)
- MTHFR C677T and A1298C polymorphisms • Low TFPI levels
- High coagulation factor levels (FV, FVII, FX) • Thrombomodulin polymorphisms
- ACE polymorphisms
- PZ/ZPI polymorphisms
- ADAMTS13 polymorphisms

Abbreviations: MTHFR, methylenetetrahydrofolate reductase; PAI-1, plasminogen activator inhibitor-1; TAFI, thrombin- activatable fibrinolysis inhibitor; TFPI, tissue factor pathway inhibitor; Lp(a), lipoprotein a; EPCR, endothelial protein C receptor; ACE, angiotensin-converting enzyme; ADAMTS, A Disintegrin And Metalloprotease with ThromboSpondin-1- like domains; PZ, protein Z; ZPI, protein Z-dependent protease inhibitor.

Thrombosis and Haemostasis 114.6/2015

2. IDENTIFICAZIONE DEI SOGGETTI DA ESAMINARE



"No full agreement exists between guidelines, societies and medical experts who should be tested for thrombophilia"

Stephan Moll. J Thromb Thrombolysis (2015) 39:367–378

2. IDENTIFICAZIONE DEI SOGGETTI DA ESAMINARE

Identify goals of testing

Strong Family History

Previous VTE
- **Unprovoked or "weak triggers"**
- **Recurrent**
- **Inusual locations**
- **Young age**

Consider testing

Pregnancy Complications (APS)

Patient's wish

Stephan Moll. J Thromb Thrombolysis (2015) 39:367–378
Jean M Connors. N Engl J Med 377;12 (2017)

2. IDENTIFICAZIONE DEI SOGGETTI DA ESAMINARE

- **Unselected patients**
- **VTE provoked by a major transient risk factor**
- **Inappropriate clinical setting (pitfalls)**

Do not Test

Stephan Moll. J Thromb Thrombolysis (2015) 39:367–378
Jean M Connors. N Engl J Med 377;12 (2017)

…the risk of vascular events should be weighted to tentatively assess the real clinical impact of thrombophilia

Defects with variable VTE Risk (RR-AR)

Combined defects/Homozygous state

Pregnancy and puerperium are thrombophilic

Strong Family History

Previous VTE/Features

- Recurrent
- Unprovoked
- Pregnancy/OC related
- Young age
- Unusual sites (splanchnic or cerebral veins)

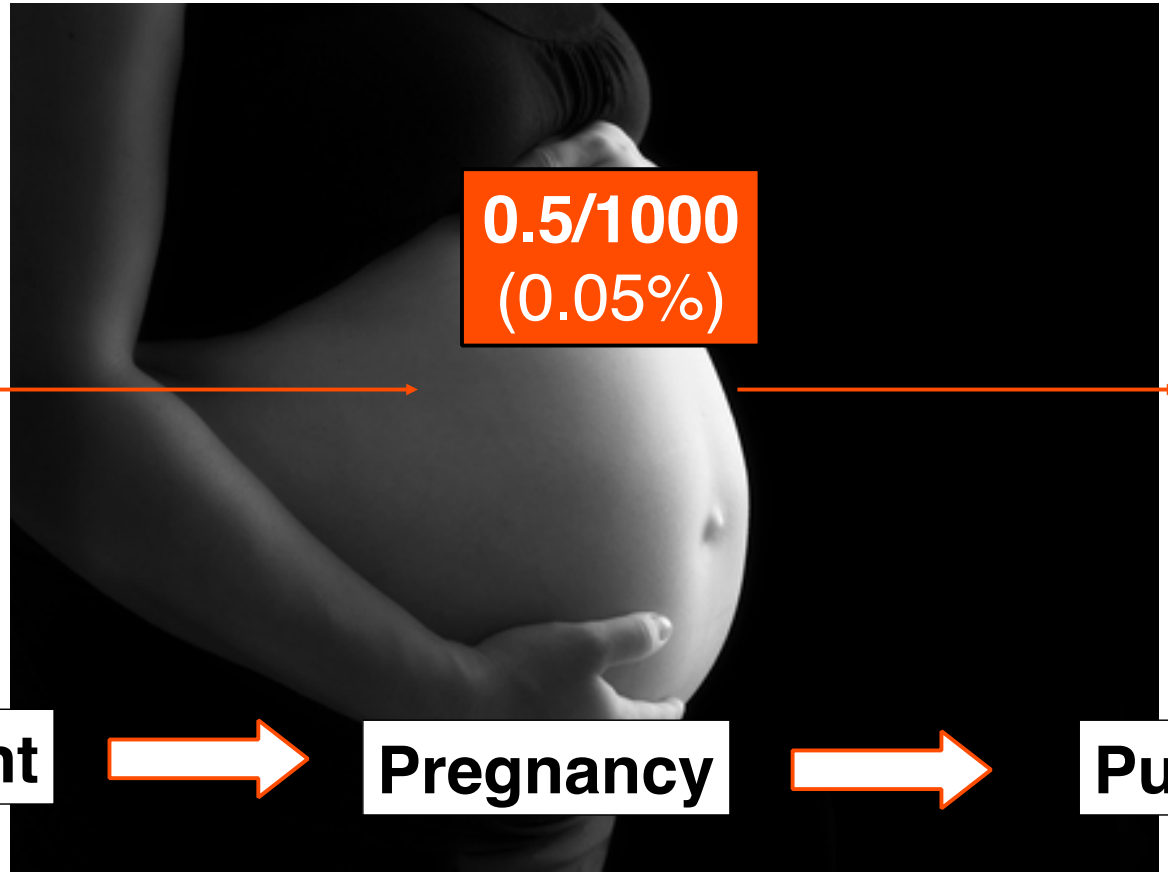
Provoked by transient major risks

Other Risk Factors

Age
BMI
Smoke
N° of pregnancies
Cesarean section
Comorbidities
…

- ACOG Practice Bulletin Vol 132 n. 1 July **2018**
- J Thromb Thrombolysis (**2016**) 41:154–164
- Green-top Guidelines 37a, April **2015**
- 9th Ed ACCP Guidelines **2012**
- NICE Guidelines [CG144] June **2012**
- British Journal of Haematology, **2010**;149: 209-220

VTE RISK



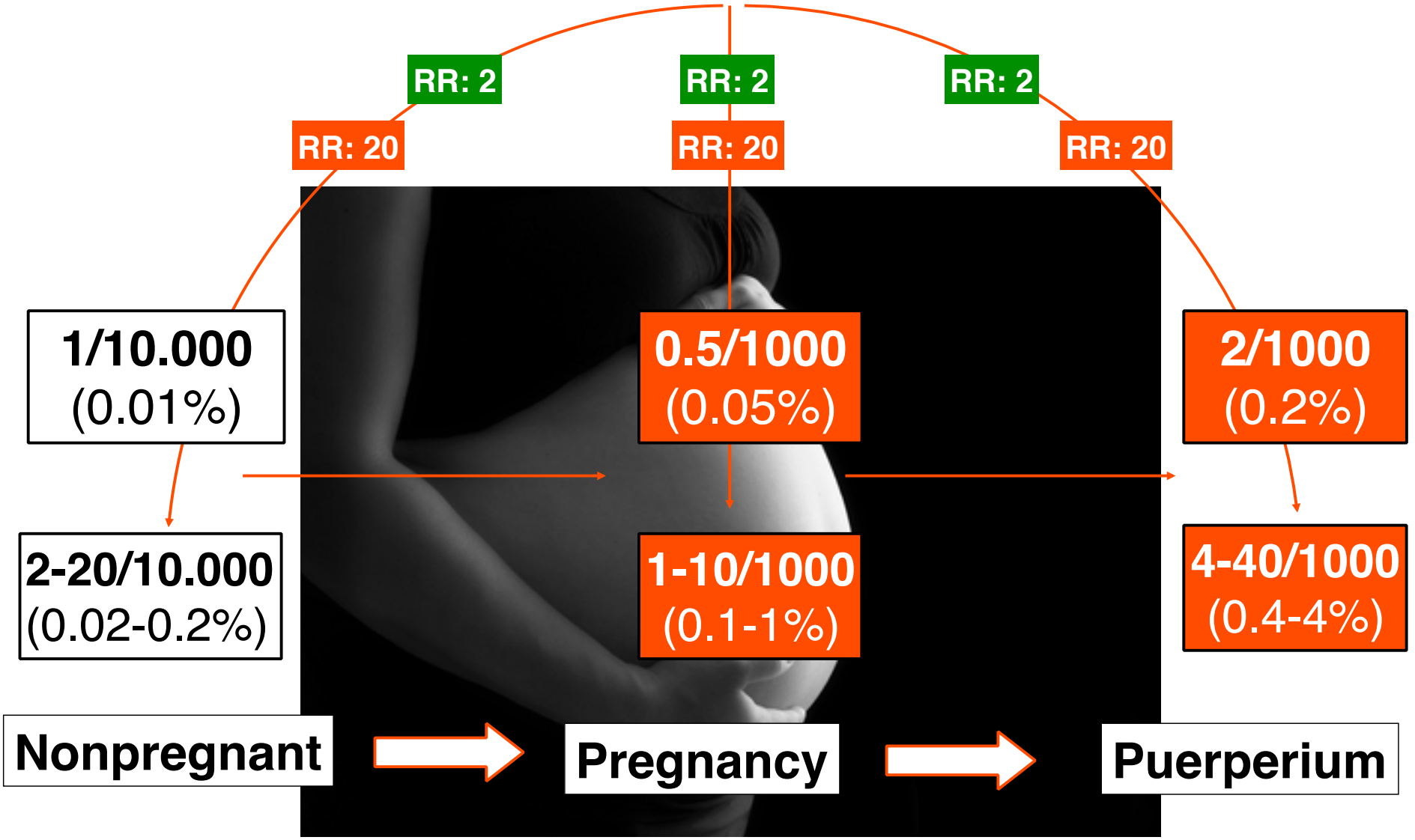
1/10.000
(0.01%)

0.5/1000
(0.05%)

2/1000
(0.2%)

Nonpregnant → **Pregnancy** → **Puerperium**

ANY VTE RISK FACTOR



Guidance for the evaluation and treatment of hereditary and acquired thrombophilia

Scott M. Stevens[1,2] · Scott C. Woller[1,2] · Kenneth A. Bauer[3] · Raj Kasthuri[4] · Mary Cushman[5] · Michael Streiff[6] · Wendy Lim[7] · James D. Douketis[7]

J Thromb Thrombolysis (2016) 41:154–164

Table 2 Prevalence and thrombosis risk for selected thrombophilias

Thrombophilia	Prevalence	Relative (*absolute annualized*) risk of Initial VTE[a]	Relative risk of recurrent VTE	Relative (*absolute annualized*) risk of initial VTE, OCP users[a,b]	Relative (*absolute annualized*) risk of initial VTE, HRT users[a,b,c]	Relative (*absolute*) risk of initial VTE, pregnancy[a]
FVL Heterozygous	2–7 %	3.48–5.51 (0.05-0.2 %)	1.1–1.8	2.47–15.04 (0.1–0.6 %)	1.4–13.16 (1.6–5.97 %)	8.3 (0.8–4.6 %)
FVL Homozygous	0.06–0.25 %	6.79–19.29 (0.8 %)	1.8	Uncertain	Uncertain	34.4 (1.4–25.8 %)
PGM Heterozygous	1–2 %	2.25–3.48 (0.13 %)	0.7–2.3	3.60–8.63	(2.85 %)	6.8 (0.3–5.6 %)
PGM Homozygous	Rare	2.19–20.72	Uncertain	Uncertain	Uncertain	26 (0.2–78.3 %)
Compound FVL & PGM Heterozygosity	0.1 %	1.13–5.04 (0.42 %)	2.7	3.79–76.47 (0.17 %)	Uncertain	(4 %)
PC deficiency	0.2–0.5 %	10 (0.4–2.3 %)	1.8	1.7–23.9 (1.7–7.1 %)	(2.96 %)	4.8 (0.4–8.9 %)
PS deficiency	0.1–0.7 %	9.6 (0.7–3.2 %)	1.0	1.4–17.1 (1.3–2.4 %)	(2.3 %)	3.2 (0.2–14.7 %)
AT deficiency	0.02 %	10–30 (1.2–4.4 %)	2.6	1.4–115.8 (2.5–5.1 %)	(5.73 %)	4.7 (0.08–15.8 %)
APS	2 %	7	1.5–6.8	0.3–3.1	(1.05–2.63 %)	15.8

OCP oral contraceptive pill (containing estrogen), *HRT* hormone replacement therapy (containing estrogen), *VTE* venous thromboembolism, *FVL* factor V Leiden, *PGM* prothrombin Gene G20210A, *PC* protein C, *PS* protein S, *AT* antithrombin, *APS* antiphospholipid syndrome

[a] Data for are taken from several sources; absolute differences may therefore differ from calculations based on prevalence and relative risk [16, 17, 23, 32, 38, 50, 56, 62, 75–79]

[b] Relative risks are compared to non-users without thrombophilia

[c] With the exception of heterozygous FVL, estimates are based on modeling rather than epidemiologic studies

STRONG RISK FACTORS

- Antithrombin
- FVG1691A Homozygous
- FVG1691A Homozygous
- FVG1691A-FIIG20210A Compound Hetrerozygsity
- APS

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- British Journal of Haematology, **2010**;149: 209-220

The American College of Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS

ACOG PRACTICE BULLETIN

Clinical Management Guidelines for Obstetrician–Gynecologists

NUMBER 197 (Replaces Practice Bulletin Number 138, September 2013)

Table 1. Risk of Venous Thromboembolism With Different Inherited Thrombophilias

	Prevalence in General Population (%)	VTE Risk Per Pregnancy (No History) (%)	VTE Risk Per Pregnancy (Previous VTE) (%)	Percentage of All VTE	References
Factor V Leiden heterozygote	1–15	0.5–3.1	10	40	1–4, 11, 12
Factor V Leiden homozygote	<1	2.2–14.0	17	2	1–4, 11, 12
Prothrombin gene heterozygote	2–5	0.4–2.6	>10	17	1–4, 11, 12
Prothrombin gene homozygote	<1	2–4	>17	0.5	1–4, 11, 12
Factor V Leiden/ prothrombin double heterozygote	0.01	4–8.2	>20	1–3	1–4, 12
Antithrombin deficiency	0.02	0.2–11.6	40	1	1, 5, 6, 11, 12
Protein C deficiency	0.2–0.4	0.1–1.7	4–17	14	1, 5, 7, 11, 12
Protein S deficiency	0.03–0.13	0.3–6.6	0–22	3	1, 8–12

Abbreviation: VTE, venous thromboembolism.

Risultati negativi

- Attenzione la storia familiare e/o personale positive sono fattori di rischio indipendentemente dai test

ACOG Practice Bulletin Vol 132 n. 1 July **2018**
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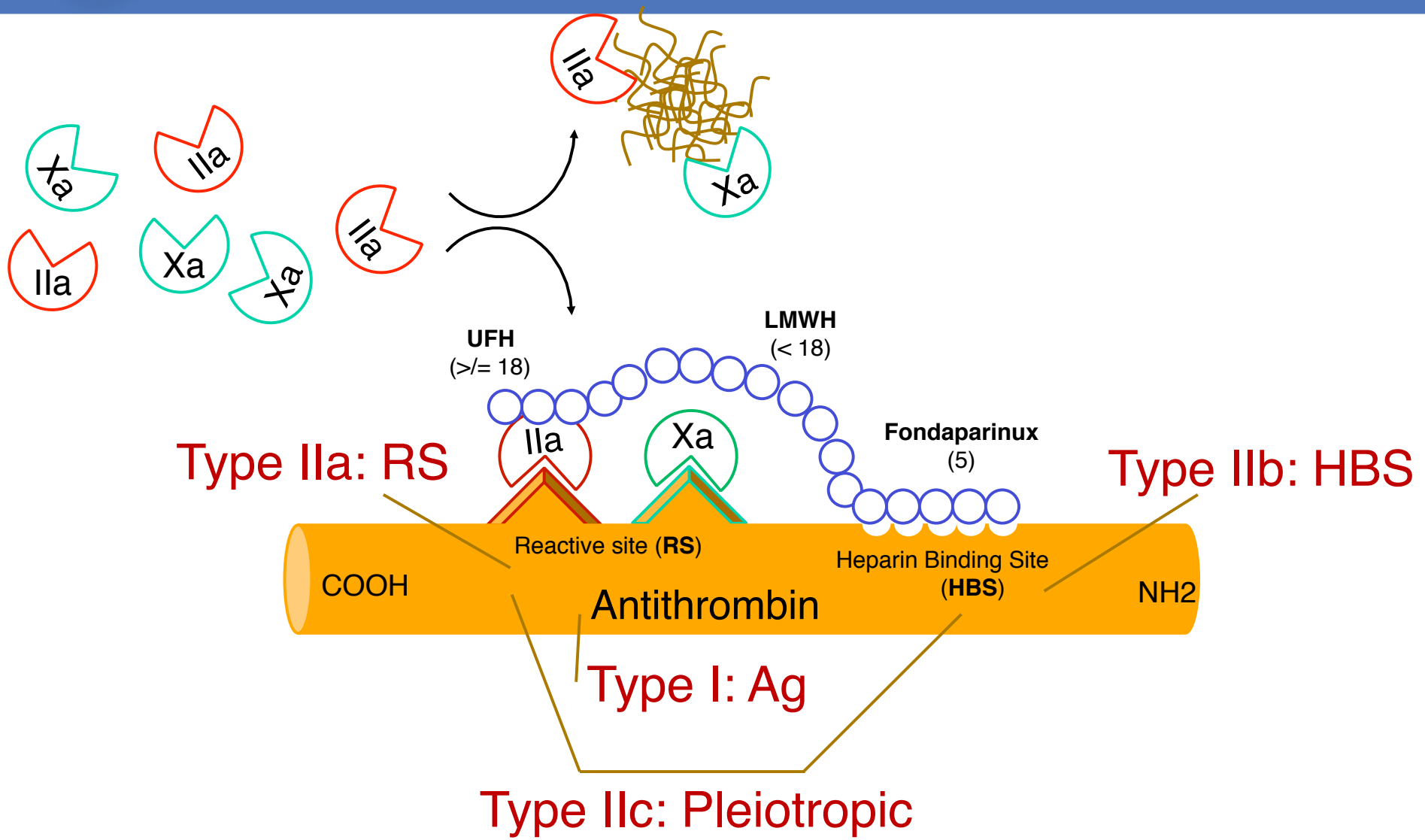
Risultati positivi: implicazioni di laboratorio

- Escludere inappropriatezza (pitfalls)
- Ripetere i/il test informando il laboratorio
- Valutare storia familiare e personale
- Valutare altri fattori di rischio
- Decidere l'utilità di estendere l'indagine ai parenti

Deficit di AT



AT: i test

Dosaggi Funzionali Cromogenici:

- **Cofattore Eparinico** (con Eparina + FXa o Trombina)
- **Attività Progressiva** (senza addizione di Eparina + FXa o Trombina)

Dosaggi Quantitativi Immunologici:

- **AT Antigene (Nefelometria,** Immunodiffusione Radiale, Elettroimmunodiffusione)

Haemophilia (2008), **14**, 1229–1239 DOI: 10.1111/j.1365-2516.2008.01830.x

ORIGINAL ARTICLE

Inherited antithrombin deficiency: a review

M. M. PATNAIK* and S. MOLL†
**Department of Internal Medicine, University of Minnesota School of Medicine, Minneapolis, MN; and †Division of Hematology-Oncology, Department of Medicine, University of North Carolina School of Medicine, Chapel Hill, NC, USA*

Table 1. Types of antithrombin (AT) deficiency.

Type of defect		Defect where?	Results of laboratory assays: AT activity: Heparin co-factor assay*	AT activity: Progressive AT assay†	AT antigen	Prevalence in general population	Prevalence in patients with thrombosis	Prevalence of VTE in persons with this subtype of deficiency (%)
Type I	Quantitative		Low	Low	Low	12% of all ATD	60% of all ATD	53
Type II	Qualitative					88% of all ATD	40% of all ATD	6–66
	IIa	Thrombin-binding domain	Low	Low	Often normal			58
	IIb	Heparin-binding domain	Low	Normal	Often normal			6
	IIc	Pleiotropic	Low	Varied	Low			66

*Inactivation of thrombin or factor Xa in the presence of heparin.
†In the absence of heparin or with low concentration of heparin.

Patient	Genotype	AT antigen (%)	AT activity (%)					
			BIO	BIO 30	LIQ	COA	COA110	INN
1	p.Pro73Leu	92	118	104	108	91	86	51
2	p.Pro73Leu	115	100	88	118	84	74	57
3	p.Pro73Leu	95	92	87	99	83	65	58
4	p.Pro73Leu	122	126	106	126	93	81	60
5	p.Pro73Leu	100	107	94	106	89	72	47
6	p.Pro73Leu	92	104	98	99	79	65	49
7	p.Pro73Leu	150	132	113	126	108	96	74
8	p.Asn77His	95	108	93	95	67	43	47
9	p.Arg79Cys	97	66	59	51	48	25	49
10	p.Arg79Cys	90	68	63	50	42	24	54
11	p.Arg79Cys	110	76	70	61	54	47	56
12	p.Arg79Cys	88	72	69	63	51	34	59
13	p.Arg79Cys	98	76	69	63	53	42	57
14	p.Arg79Cys	96	nd	nd	53	53	34	45
15	p.Arg79Cys	105	75	71	57	50	30	65
16	p.Arg79Cys	137	71	73	68	45	53	63
17	p.Arg79Cys	81	67	64	49	47	36	44
18	p.Arg79Cys	147	74	75	67	52	51	66
19	p.Arg79Cys	110	nd	nd	56	44	47	51
20	p.Arg79Cys	128	72	68	58	58	51	61
21	p.Arg79Cys	100	65	63	59	55	49	54
22	p.Arg79Cys	103	83	73	60	57	58	56
23	p.Arg79His	112	102	91	117	78	87	55
24	p.Arg79His	105	110	96	113	80	68	58
25	p.Arg79His	81	112	100	97	70	66	66
26	p.Arg79His	89	nd	nd	111	85	85	60
27*	p.Leu131Phe	72	77	69	73	39	45	22
28	p.Leu131Phe	91	96	87	65	68	51	51
29	p.Leu131Phe	84	92	86	80	66	72	50
30	p.Leu131Phe	72	91	93	78	71	74	50
31	p.Leu131Phe	80	93	89	77	72	68	46
32	p.Leu131Phe	68	90	87	82	86	65	62
33	p.Leu131Phe	95	93	85	77	74	74	64
34	p.Gln150Pro	91	81	70	64	43	43	46
35	p.Gln150Pro	87	nd	nd	53	35	35	48

Thrombosis Research 135 (2015) 1179–1185

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Regular Article

Antithrombin heparin binding site deficiency: A challenging diagnosis of a not so benign thrombophilia

Christelle Orlando [a,*], Olivier Heylen [a], Willy Lissens [b], Kristin Jochmans [a]

[a] Department of Haematology, Universitair Ziekenhuis Brussel, Vrije Universiteit Brussel (VUB), Laarbeeklaan 101, 1090 Brussels, Belgium
[b] Centre for Medical Genetics, Universitair Ziekenhuis Brussel, Vrije Universiteit Brussel (VUB), Laarbeeklaan 101, 1090 Brussels, Belgium

Table 3
Diagnostic performance of different commercial assays/assay conditions for the diagnosis of type II HBS deficiency.

	BIO	BIO30	LIQ	COA	COA110	INN
Sensitivity (%)	38.7	45.2	60.0	74.3	85.7	100.0
Specificity (%)	100.0	100.0	100.0	100.0	95.0	100.0

BIO = Biophen® AT, BIO 30 = Biophen ® AT with shortened incubation time of 30s, LIQ = HemosIL ®Liquid AT, COA = Coamatic® AT, COA 110 = Coamatic AT with fixed incubation time of 110 s, INN = Innovance®.

Table 2
Antithrombin antigen (Laurell rocket immunoelectrophoresis) and activity levels (four different commercial assays and two variant assay conditions) in 35 patients with genetically proven AT HBS deficiency.

Values outside reference interval (80-120%) are shaded grey. nd = not determinded due to short sample, BIO = Biophen® AT, BIO 30 = Biophen ® AT with shortened incubation time of 30s, LIQ = HemosIL ®Liquid AT, COA = Coamatic® AT, COA 110 = Coamatic AT with fixed incubation time of 110 s, INN = Innovance®. The patient indicated with * is homozygously affected.

Thrombosis Research 135 (2015) 1179–1185

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Regular Article

Antithrombin heparin binding site deficiency: A challenging diagnosis of a not so benign thrombophilia

Christelle Orlando [a,*], Olivier Heylen [a], Willy Lissens [b], Kristin Jochmans [a]

[a] Department of Haematology, Universitair Zie
[b] Centre for Medical Genetics, Universitair Ziek

Table 5
Prevalence of thrombotic events per specific AT Heparin Binding Site mutation.

Mutation	Affected individuals n	Index cases n	Thrombotic events		PT G20210A or FV Leiden
			Venous n (%)	Arterial n (%)	
All HBS deficiencies	82	51	29 (35)	16 (20)	10
p.Pro73Leu	13	12	1 (8)	6 (46)	-
p.Asn77His	1	1	1 (100)	-	-
p.Arg79Cys	25	15	7 (28)	6 (24)	5
p.Arg79His	5	3	2 (40)	2 (40)	1
p.Leu131Phe	28	14	14 (50)	-	3
Heterozygous	18	7	5 (28)	-	3
Homozygous	10	7	9 (90)	-	-
p.Gln150Pro	10	6	4 (40)	2 (20)	1

Table 4. Diagnostic Criteria for the Antiphospholipid Syndrome.

The antiphospholipid syndrome is present if at least one of the two clinical criteria and at least one of the three laboratory criteria are met:

Clinical criteria

Vascular thrombosis: one or more documented clinical episodes of arterial or venous thrombosis in any organ or tissue (documented by means of imaging or histopathological assessment) in the absence of vasculitis

Pregnancy complication

Unexplained death of a morphologically normal fetus at or beyond wk 10 of gestation

Premature birth of a morphologically normal neonate before wk 34 of gestation as a result of eclampsia, severe preeclampsia, or placental insufficiency

Three or more unexplained, consecutive, spontaneous abortions before wk 10 of gestation, not related to chromosomal or anatomical abnormalities in the parents

Laboratory criteria*

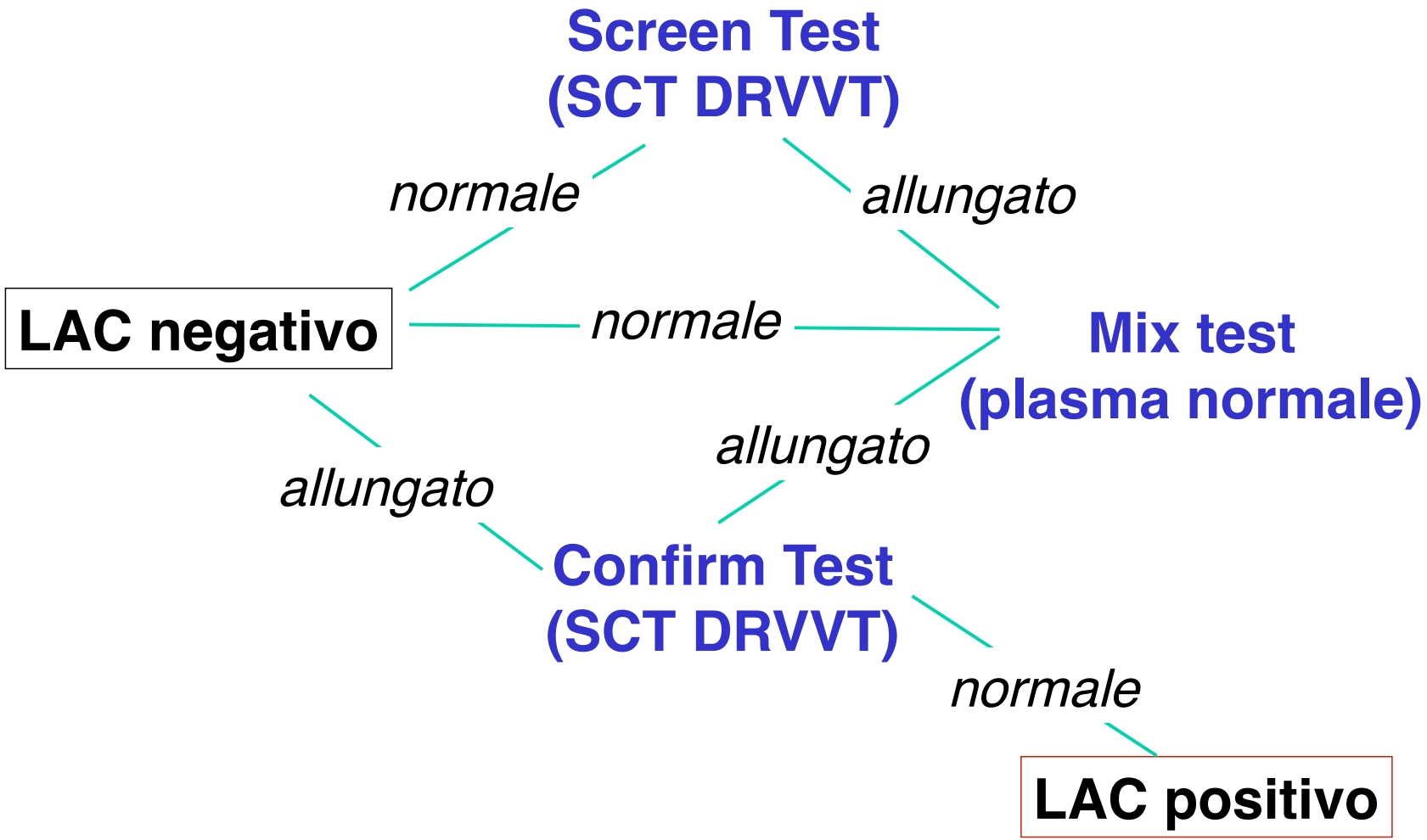
Lupus anticoagulant assay

IgG or IgM anticardiolipin antibody test

IgG or IgM anti–beta-2 glycoprotein 1 antibody test

- Persistenza (> 3 mesi)
- Ab titolo medio-alto
- Gravità proporzionata al numero di test positivi
- Il LAC ha una maggior implicazione clinica

* Approved assays for each of the three laboratory tests should be performed. Initial testing should include at least one but ideally two in vitro clot-based assays and the ELISA-based tests for anticardiolipin and anti–beta-2 glycoprotein 1 IgG and IgM antibodies. The diagnosis of the antiphospholipid syndrome requires the presence of both clinical events and positive laboratory test findings, according to the revised Sapporo criteria.[26] Patients with the diagnosis should have a documented vascular thrombotic event or pregnancy complication as described in the revised criteria and at least one laboratory test result that is positive on two occasions at least 12 weeks apart. For ELISA-based tests, results should be at least 40 units or in the 99th percentile. Ideally, in addition to ELISA-based tests, two in vitro clot-based assays should be performed to determine the presence of a lupus anticoagulant.


Screen Test
(SCT DRVVT)
normale
allungato
LAC negativo
normale
Mix test
(plasma normale)
allungato
allungato
Confirm Test
(SCT DRVVT)
normale
LAC positivo

LAC:
TEST COAGULATIVI CON RISCHIO DI INTERFERENZE DA ANTICOAGULANTI, PROTEINE DELLA FASE ACUTA, PARAPROTEINE, FARMACI…

[51] P-Anticoagulante lupus-like (LAC)				
SCT screen (miscela povera di fosfolipidi)	**3.97**	*	ratio	< 1.23
SCT mix (miscela con plasma normale)	**1.80**	*	ratio	< 1.17
SCT confirm (miscela ricca di fosfolipidi)	**2.59**	*	ratio	< 1.38
SCT screen/confirm	**1.54**	*	ratio	< 1.20
DVVT screen (miscela povera di fosfolipidi)	**1.13**		ratio	< 1.26
Conclusione				*(IL-TOP Coagulativo)*

[43] P-Tempo di Protrombina (PT-INR)	**1.00**			0.80 - 1.20
Dasit-Sysmex CA				
[43] P-T.di tromboplastina parziale attivata (aPTT)				
Secondi	**74**			
Ratio	**2.71**	*		0.80 - 1.20
Dasit-Sysmex CA				

[51] P-Fattore VIII	**3**	*	%	59 - 143
IL-TOP Coagulativo				

Esame	*Esito*		*U.M.*	*Intervalli Riferimento*
[51] P-Inibitore specifico Fattore VIII	**36**	*	U Beth.	< 0.5
Bethesda - modificato Nijmegen				

Eby C.
Novel anticoagulants and laboratory testing.
Int J Lab Hematol 2013;35:262–8.

Table 1. Interference patterns of direct oral anticoagulants on screening and diagnostic coagulation tests (↑- potential positive bias, ↓ - potential negative bias, ↔ -no or minimal bias, empty-no information available, numbers refer to references)

Test	Dabigatran	Rivaroxaban	Apixaban
PT	↑[8, 11, 30]	↑[9, 22, 33]	↑[13]
dPT	↑[11]	↑[16]	↑[16]
PiCT	↑[11]	↑[9, 22]	
aPTT	↑[8, 11, 26]	↑[9, 10]	↑
TT	↑	↔	
Fibrinogen -Clauss	↓/↔[8, 30]	↔[10, 33]	
PT/aPTT 1 : 1 mixing studies	↑[32]		
Extrinsic pathway factor activities -clot based	↓[30, 32]	↓[31, 33]	
Intrinsic pathway factor activities-clot based	↓[30, 32]	↓[31, 33]	
Chromogenic factor VIII activity	↔[32]	↓[31]	
Chromogenic heparin activity		↑[9, 13]	↑[13, 25]
Clot-based heparin activity-Heptest	↑[16; Unpub -lished]	↑[16]	↑[16]
Lupus anticoagulant -aPTT		↔[23]	
Lupus anticoagulant -DRVVT	↑(false positive) [30]	↑(false positive) [23]	
Antithrombin chromogenic -FXa	↔[26]	↑[10]	
Antithrombin chromogenic -FIIa	↑[11, 26, 32]	↔[10]	
Protein C activity -clot based	↑[32]		
Protein S activity -clot based	↑[32]	↑[33]	
APC resistance -aPTT based	↑[11, 26]	↑[10]	

Trombofilia quali test?

1. AT PC PS
2. Emogramma, PT, APTT, Fibrinogeno, AT, PC, PS, LAC, Ab anti fosfolipidi/proteine, Mutazione FV G1691A, Mutazione Fattore II G20210A
3. AT, PC, PS, LAC, Ab anti fosfolipidi/proteine, Mutazione FV G1691A, Mutazione Fattore II G20210A, MTHFR C677T
4. AT, PC, PS, MTHFR C677T

Trombofilia: è corretto affermare che

1. I test non vanno richiesti in modo indiscriminato e in caso di patologie acute, gravidanza, puerperio, uso di estroprogestinici o anticoagulanti
2. I test vanno richiesti solo se i risultati possono modificare la scelta clinica
3. Negli ultimi anni è evidente dalla letteratura che nella maggior parte dei casi i test hanno una dubbia utilità clinica
4. Tutte e tre le affermazioni sono corrette

Antitrombina

1. è caratterizzata da difetti tutti a elevato rischio trombofilico
2. nell'ambito dei difetti Tipo IIb (HBS) molti hanno un basso rischio rischio trombotico
3. il test cromogenico è in grado di evidenziare tutti i difetti
4. il test immunologico (Ag) è in grado di evidenziare tutti i difetti