

XXIV Congresso Nazionale Siset

Abano Terme 9-12 novembre 2016

**“Polimorfismi protrombotici: prospettive future
nella pratica clinica”**

Daniela Tormene

THROMBOPHILIA

A clinical condition characterised by increased tendency to venous thrombosis which may develop spontaneously and at young age and which cannot be satisfactorily explained by acquired risk factors.

MAIN CAUSES OF THROMBOPHILIA

INHERITED DISORDERS

AT III DEFECTS

PROTEIN C DEFECTS

PROTEIN S DEFECTS

FV LEIDEN MUTATION

PROTHROMBIN 20210A

DYSFIBRINOGENEMIA

ELEVATED FACTOR VIII

ELEVATED FACTOR IX

ELEVATED FACTOR XI

ACQUIRED DISORDERS

APLA (LAC, ACA)

CANCER

MYELOPROLIFERATIVE SDR

PNH

NEPHROTIC SYNDROME

MILD HYPERHOMOCYSTEINEMIA

TACT PROSPECTIVE STUDY

	Observed years	Spontaneous VTE	Incidence % / y (95 % CI)
ANTITHROMBIN (n = 45)	125.3	2	1.6 (0.2-5.8)
PROTEIN C (n = 93)	204.2	2	1.0 (0.1-3.5)
PROTEIN S (n = 70)	281.9	1	0.4 (0.0-2.0)
TOTAL (n = 208)	611.4	5	0.8 (0.3-1.9)

TOTAL INCIDENCE OF VTE

	ALL		AT		PC		PS	
	DEFECT	NO DEFECT	DEFECT	NO DEFECT	DEFECT	NO DEFECT	DEFECT	NO DEFECT
TOTAL NUMBER OF VTE (%)	68 (27%)	2 (0.8%)	19 (35.2)	1 (1.4)	24 (25.3)	0	25 (24.3)	1 (1.16)
ANNUAL INCIDENCE (P-Yrs)	2.1% (1.6-2.7)	0.05% (0.006-0.2)	2.6% (1.6-4.0)	0.008% (0.002-0.4)	2.05% (1.3-3.0)		1.9% (1.2-2.8)	0.08% (0.002-0.4)
RR	43.6 (95% CI, 10.7-178)		33.7 (95% CI, 4.5-252)		31.6 (95% CI, 4.3-234)		24.4 (95% CI, 3.3-181)	
Mean age at the time of the event (years)	47	49	47	59	51		44	38

INCIDENCE OF SPONTANEOUS VTE

	ALL		AT		PC		PS	
	DEFECT	NO DEFECT	DEFECT	NO DEFECT	DEFECT	NO DEFECT	DEFECT	NO DEFECT
TOTAL NUMBER OF VTE (%)	39 (15.5)	0	12 (22.2)	0	15 (15.8)	0	12 (11.6)	0
ANNUAL INCIDENCE (P-Yrs)	1.2% (0.9-1.7)		1.6% (0.8-2.9)		1.3% (0.7-2.1)		0.9% (0.5-1.0)	
RR	50.0 (95% CI, 6.9-364)		21.3 (95% CI, 2.7-164)		19.7 (95% CI, 2.6 -150)		11.7 (95% CI, 15-90.4)	
Mean age at the time of the event (years)	51.6		55		52		48	

RISK PERIOD-RELATED VTE*

	ALL		AT		PC		PS	
	Defect	No defect	Defect	No defect	Defect	No defect	Defect	No defect
ALL VTE	21 (8.3%)	2 (0.8%)	6 (11.1)	1(1.4)	5 (5.2)	0	10 (9.7)	1(1.2)
Incidence per % risk period	21.2% (13.1-32.4)	2.9% (0.37-10.8)	24 (8.8-52)	5.8 (0.14-32.8)	18.5 (6.0-43.2)		21.3 (10.2-39.1)	3.3 (0.008-18.6)
OR	7.1 (95% IC, 1.6-31.3)		4.0 (0.4-37)		3.7 (0.4-34.2)		6.4 (0.8-52.4)	
Mean age at the time of event (yrs)	47	48	47	59	51		44	38

*99 risk periods in 252 carriers: 37 surgery, 16 trauma, 6 immobilization, 4 plaster cast , 7 chemotherapy/cancer, 31 pregnancy

*67 risk periods in 249 non-carriers: 29 surgery, 3 trauma, 3 immobilization, 4 plaster cast , 12 chemotherapy/cancer, 16 pregnancy

-NUMBER OF VTE DURING RISK PERIOD IN THE PRESENCE OR ABSENCE OF PROPHYLAXIS.

-DATA CONCERNING OCT

	ALL		WITH PROPHYLAXIS		NO PROPHYLAXIS		OCT	
	DEFECT (N=99)	NO DEFECT	DEFECT (N=66)	NO DEFECT	DEFECT (N=33)	NO DEFECT	DEFECT (N=15)	NO DEFECT
ALL VTE number (%)	21 (8.3)	2 (0.8)	8 (3.2)	0	13 (5.2)	2 (0.8)	8/15	0/12
Incidence per risk period per patient %	21.2% (13.1-32.4)	2.9% (0.37-10.8)	12.1 (5.2-23.9)		39.4 (21.0-67.4)	3.7 (0.5-13.6)	53.3 (23.0-105)	
OR	7.1 (95% IC, 1.6-31.3)		1.7 (0.2-14.7)		10.4 (2.2-49.2)		6.4 (0.7-58.5)	

Simioni et al, *NEJM* 1997

Simioni et al, *Blood* 2000

Prandoni et al *Ann Intern Med.* 2009

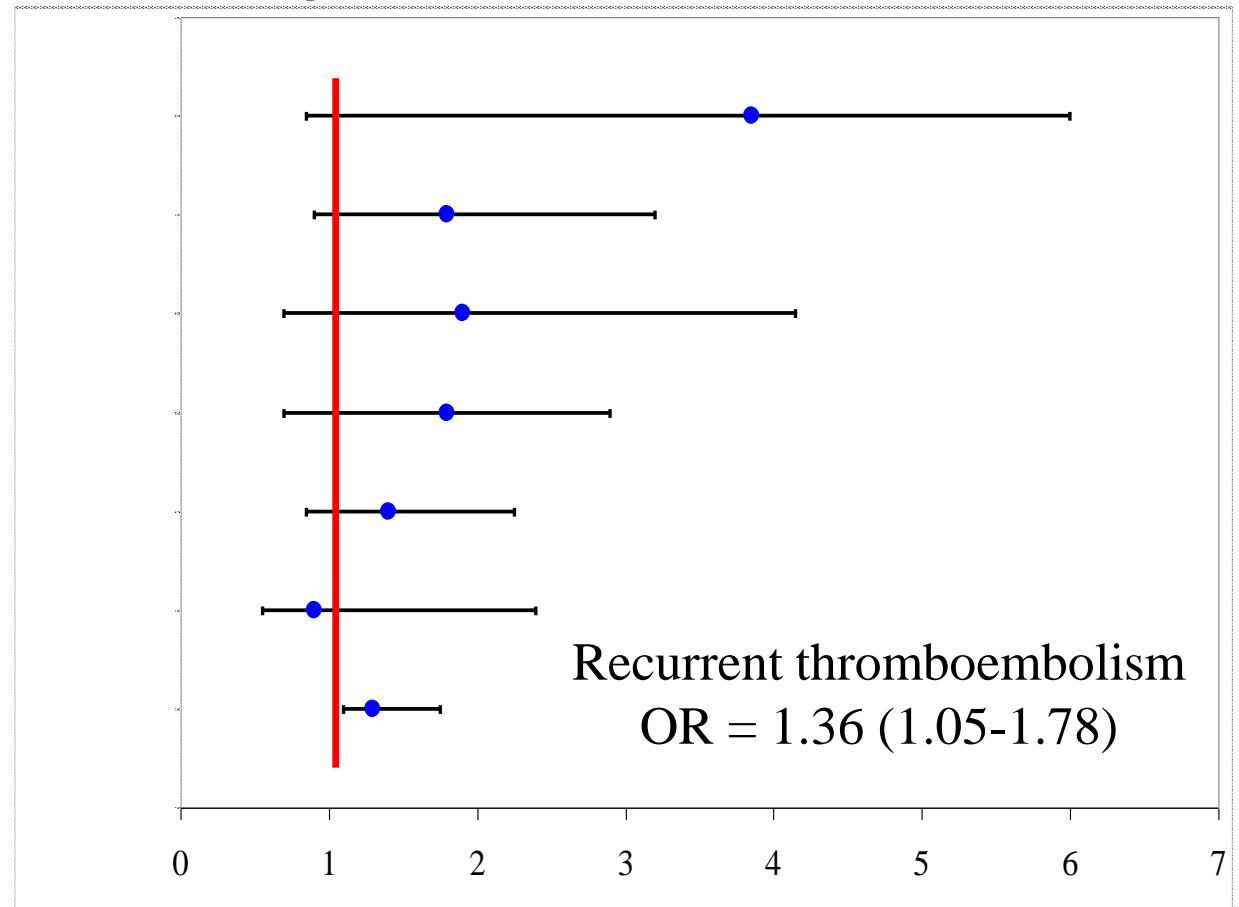
HR, 2.75 [CI, 1.71 to 4.43]

Meta analysis for recurrent VTE in F.V Leiden

(Marchetti M et al, *Thromb Haemost* 2000)

Lower Risk Higer Risk

- Ridker et al.
- Simioni et al.
- Margaglione et al.
- Lindmaker et al.
- De Stefano et al.
- Elchinger et al.
- SUMMARY OR



Predictive Value of D-Dimer Test for Recurrent Venous Thromboembolism After Anticoagulation Withdrawal in Subjects With a Previous Idiopathic Event and in Carriers of Congenital Thrombophilia

Gualtiero Palareti, Cristina Legnani, Benilde Cosmi, Lelia Valdré, Barbara Lunghi, Francesco Bernardi and Sergio Coccheri

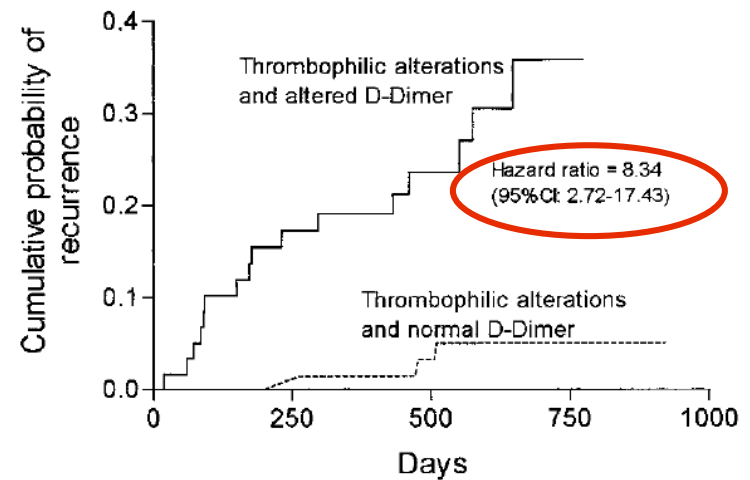
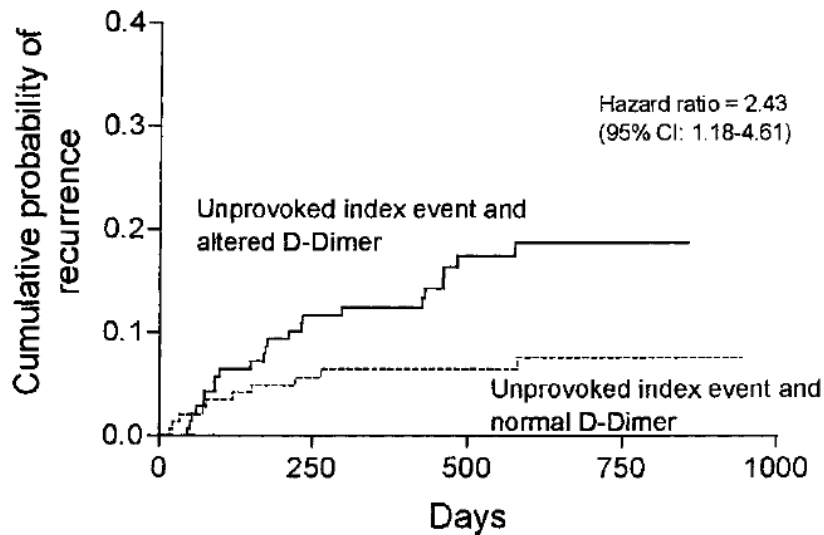


Figure 1. Cumulative probability of recurrence in subjects with an unprovoked qualifying venous thromboembolic event with normal (≤ 500 ng/mL) or altered (> 500 ng/mL) D-dimer results obtained 1 month after OAT interruption.

Figure 2. Cumulative probability of VTE recurrence in subjects with congenital thrombophilic alterations according to normal (≤ 500 ng/mL) or altered (> 500 ng/mL) D-dimer results obtained 1 month after anticoagulation was stopped.

Table 1. Baseline Characteristics of the 608 Study Patients.*

Characteristic	Normal D-Dimer Level (N=385)	Abnormal D-Dimer Level (N=223)	P Value [†]	Abnormal D-Dimer Level without Anticoagulation (N=120)	Abnormal D-Dimer Level with Anticoagulation (N=103)	P Value [‡]
Female sex — no. (%)	173 (44.9)	118 (52.9)	0.07	70 (58.3)	48 (46.6)	0.11
Age						
Mean — yr	59.3±16.2	69.7±13.0	<0.001 [‡]	68.2±12.5	70.1±13.7	0.07 [‡]
≥65 yr — no. (%)	171 (44.4)	165 (74.0)	<0.001	86 (71.7)	79 (76.7)	0.49
Type of venous thromboembolism — no. (%)						
Proximal deep-vein thrombosis with no pulmonary embolism	241 (62.6)	140 (62.8)	0.97	73 (60.8)	67 (65.0)	0.61
Deep-vein thrombosis plus symptomatic pulmonary embolism	68 (17.7)	41 (18.4)	0.92	25 (20.8)	16 (15.5)	0.41
Isolated pulmonary embolism [§]	76 (19.7)	42 (18.8)	0.88	22 (18.3)	20 (19.4)	0.99
Congenital thrombophilic alteration — no. (%)						
Total no. evaluated	366	217		118	99	
Factor V Leiden mutation	35 (9.6)	26 (12.0)	0.44	10 (8.5)	16 (16.2)	0.13
Prothrombin mutation	23 (6.3)	16 (7.4)	0.74	10 (8.5)	6 (6.1)	0.68
Combined alterations or homozygous mutation	8 (2.2)	3 (1.4)	0.71	1 (0.8)	2 (2.0)	0.87
Duration of previous anticoagulation — no. (%)						
≤6 mo	65 (16.9)	35 (15.7)	0.79	16 (13.3)	19 (18.4)	0.39
7–12 mo	187 (48.6)	123 (55.2)	0.15	71 (59.2)	52 (50.5)	0.25
>12 mo	133 (34.5)	65 (29.1)	0.20	33 (27.5)	32 (31.1)	0.66
Time from enrollment to assignment to groups — days	32.0±9.4	33.5±7.2	0.008 [‡]	33.5±7.3	33.4±7.2	0.95 [‡]
Total duration of follow-up for all patients — yr	550.2	314.6		165.5	149.1	
Follow-up — yr	1.39±0.35	1.38±0.38		1.31±0.42	1.45±0.32	

D-Dimer as a Risk Factor for Deep Vein Thrombosis: The Leiden Thrombophilia Study

Astrid C. M. Andreescu¹, Mary Cushman^{1,2}, Frits R. Rosendaal³

D-dimer $\geq 70^{\text{th}}$ Percentile *	Hemostatic Defect *	OR (95% CI)**				
		Factor V Leiden	Prothrombin 20210A	High Factor VIIIc	High Factor IX	Any Defect
-	-	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
-	+	7.3 (3.2-16.8)	2.0 (0.8-5.1)	2.7 (1.5-4.8)	1.8 (1.0-3.2)	2.8 (1.9-4.2)
+	-	1.8 (1.3-2.4)	2.0 (1.5-2.6)	1.9 (1.4-2.5)	1.9 (1.4-2.5)	1.5 (1.0-2.1)
+	+	12.4 (5.6-27.7)	7.2 (2.1-25.1)	3.9 (2.4-6.3)	3.6 (2.2-6.0)	4.9 (3.4-7.2)

* presence of (+) or absence of (-) the listed risk factor

** unadjusted

Table 4 Odds ratio of DVT for D-dimer greater than the 70th percentile, with or without hemostatic defects

Factor V Leiden pseudo-homozygotes have a more pronounced hypercoagulable state than factor V Leiden homozygotes

J Thromb Haemost 2011

C. DUCKERS,* P. SIMIONI,† D. TORMENE,† S. CARRARO,† J. ROSING* and E. CASTOLDI*

Journal of Thrombosis and Haemostasis, 10: 73–80

J Thromb Haemost 2012

DOI: 10.1111/j.1538-7836.2011.04546.x

ORIGINAL ARTICLE

Genetic modulation of the FV_{Leiden}/normal FV ratio and risk of venous thrombosis in factor V Leiden heterozygotes

O. SEGERS,* P. SIMIONI,† D. TORMENE,† C. BULATO,† S. GAVASSO,† J. ROSING* and E. CASTOLDI*

**Thrombosis
and
Haemostasis**

CIRCULATING MICROPARTICLES IN CARRIERS OF FACTOR V LEIDEN WITH AND WITHOUT A HISTORY OF VENOUS THROMBOSIS

Running Title: Microparticles and Factor V Leiden

Elena Campello¹, Luca Spiezia¹, Claudia M. Radu¹, Maria Bon¹, Sabrina Gavasso¹, Patrizia Zerbinati¹, Barry Woodhams², Daniela Tormene¹, Paolo Prandoni¹ and Paolo Simioni¹

New Prothrombin Mutation (Arg596Trp, Prothrombin Padua 2) Associated With Venous Thromboembolism

Cristiana Bulato, Claudia Maria Radu, Elena Campello, Sabrina Gavasso, Luca Spiezia, Daniela Tormene, Paolo Simioni

Arterioscler Thromb Vasc Biol. 2016

X-Linked Thrombophilia with a Mutant Factor IX (Factor IX Padua)

Paolo Simioni, M.D., Ph.D., Daniela Tormene, M.D., Ph.D., Giulio Tognin, M.D., Sabrina Gavasso, Ph.D., Cristiana Bulato, Ph.D., Nicholas P. Iacobelli, B.A., Jonathan D. Finn, Ph.D., Luca Spiezia, M.D., Ph.D., Claudia Radu, Ph.D., and Valder R. Arruda, M.D., Ph.D.

N Engl J Med 2009

?

Influence of proband's characteristics on the risk for venous thromboembolism in relatives with factor V Leiden or prothrombin G20210A polymorphisms

Paolo Bucciarelli, Valerio De Stefano, Serena M. Passamonti, Daniela Tormene, Cristina Legnani, Elena Rossi, Giancarlo Castaman, Paolo Simioni, Michela Cini, and Ida Martinelli. *Blood*. 2013

**Age- and Gender-Specific Familial Risks for Venous Thromboembolism
A Nationwide Epidemiological Study Based on Hospitalizations in Sweden**

Bengt Zoëller, MD, PhD; Xinjun Li, MD, PhD; Jan Sundquist, MD, PhD; Kristina Sundquist, MD, PhD *Circulation*. 2011

A lower risk of recurrent venous thrombosis in women compared with men is explained by sex-specific risk factors at time of first venous thrombosis in thrombophilic families

Willem M. Lijfering,¹ Nic J. G. M. Veeger,¹ Saskia Middeldorp,^{2,3} Karly Hamulyák,⁴ Martin H. Prins,⁵ Harry R. Büller,² and Jan van der Meer¹

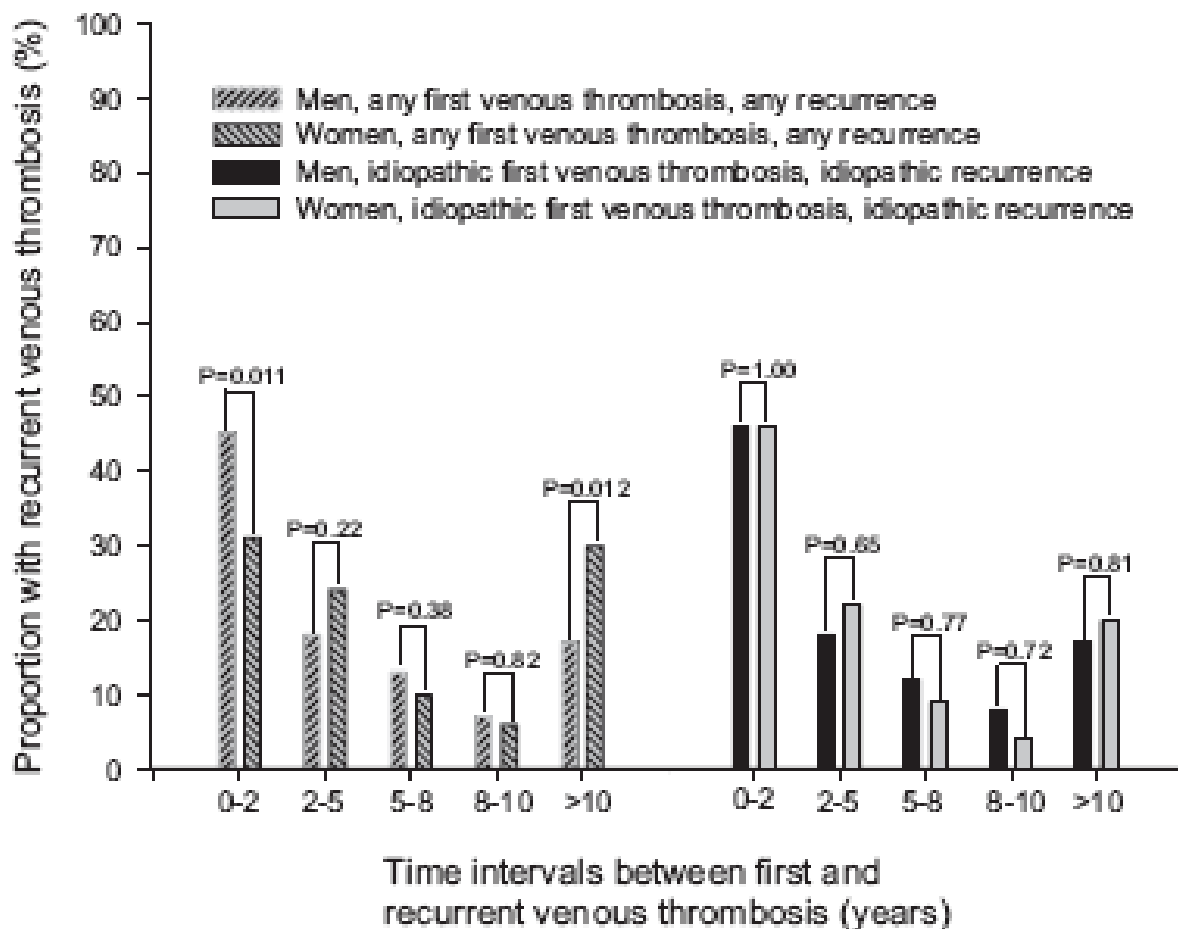


Figure 2. Time intervals between end of anticoagulant treatment for first venous thrombosis and recurrence.

ORIGINAL ARTICLE

Aspirin plus Heparin or Aspirin Alone in Women with Recurrent Miscarriage

Stef P. Kaandorp, M.D., Mariëtte Goddijn, M.D., Ph.D.,
Joris A.M. van der Post, M.D., Ph.D., Barbara A. Hutten, Ph.D.,
Harold R. Verhoeve, M.D., Karly Hamulyák, M.D., Ph.D.,
Ben Willem Mol, M.D., Ph.D., Nienke Folkeringa, M.D., Ph.D.,
Marleen Nahuis, M.D., Dimitri N.M. Papatsonis, M.D., Ph.D.,
Harry R. Büller, M.D., Ph.D., Fulco van der Veen, M.D., Ph.D.,
and Saskia Middeldorp, M.D., Ph.D.

blood

2010 115: 4162-4167
Prepublished online March 17, 2010;
doi:10.1182/blood-2010-01-267252

SPIN (Scottish Pregnancy Intervention) study: a multicenter, randomized controlled trial of low-molecular-weight heparin and low-dose aspirin in women with recurrent miscarriage

Peter Clark, Isobel D. Walker, Peter Langhorne, Lena Crichton, Andrew Thomson, Mike Greaves, Sonia Whyte and Ian A. Greer

Heparin in pregnant women with previous placenta-mediated pregnancy complications: a prospective, randomized, multicenter, controlled clinical trial

Ida Martinelli, Piero Ruggerenti, Irene Cetin, Giorgio Pardi, Annalisa Perna, Patrizia Vergani, Barbara Acaia, Fabio Facchinetti, Giovanni Battista La Sala, Maddalena Bozzo, Stefania Rampello, Luca Marozio, Olimpia Diadei, Giulia Gherardi, Sergio Carminati, Giuseppe Remuzzi and Pier Mannuccio Mannucci

Journal of Thrombosis and Haemostasis, 10: 64–72

J Thromb Haemost 2012

DOI: 10.1111/j.1538-7836.2011.04553.x

ORIGINAL ARTICLE

Low-molecular-weight heparin added to aspirin in the prevention of recurrent early-onset pre-eclampsia in women with inheritable thrombophilia: the FRUIT-RCT

J. I. P. DE VRIES,* M. G. VAN PAMPUS,† W. M. HAGUE,‡ P. D. BEZEMER,§ J. H. JOOSTEN*
and ON BEHALF OF FRUIT INVESTIGATORS

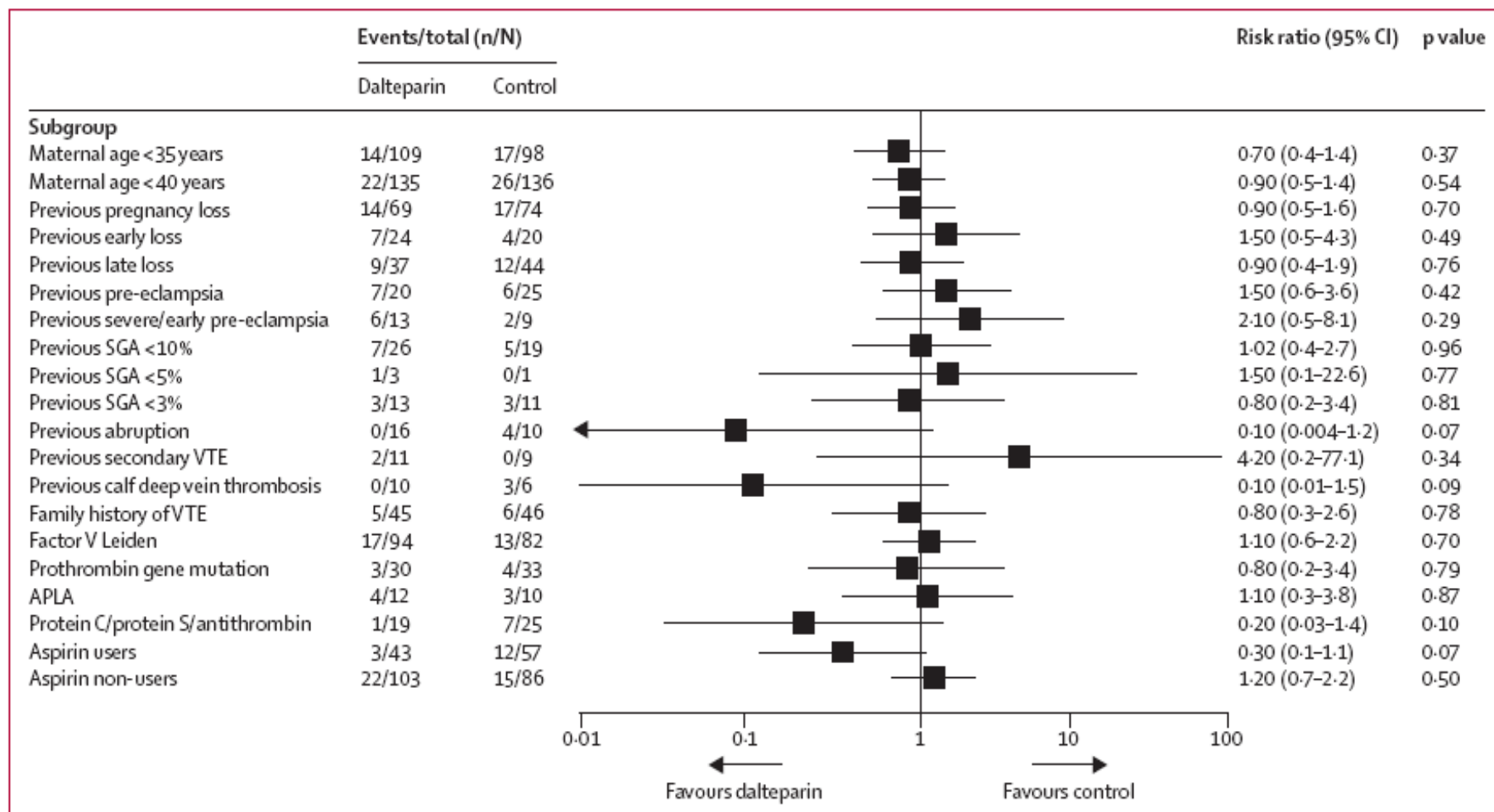


Figure 2: Subgroup analysis forest plot with risk ratio (95% CI) for the primary composite outcome

The primary composite outcome was major VTE or severe/early-onset pre-eclampsia, SGA infant (<10th percentile), or pregnancy loss. SGA=small for gestational age. VTE=venous thromboembolism. APLA=anti-phospholipid antibodies.

Obstetric complications and pregnancy-related venous thrombo-embolism: The effect of low-molecular-weight heparin on their prevention in carriers of factor V Leiden or prothrombin G20210A mutation

Thrombosis and Haemostasis 107.3/2012

- Daniela Tormene¹; Elvira Grandone²; Valerio De Stefano³; Alberto Tosetto⁴; Gualtiero Palareti⁵; Maurizio Margaglione⁶; Giancarlo Castaman⁴; Elena Rossi³; Angela Ciminello³; Leila Valdrè⁵; Cristina Legnani⁵; Giovanni Luca Tiscia²; Valeria Bafunno⁶; Sara Carraro¹; Francesco Rodeghiero⁴; Paolo Simioni¹

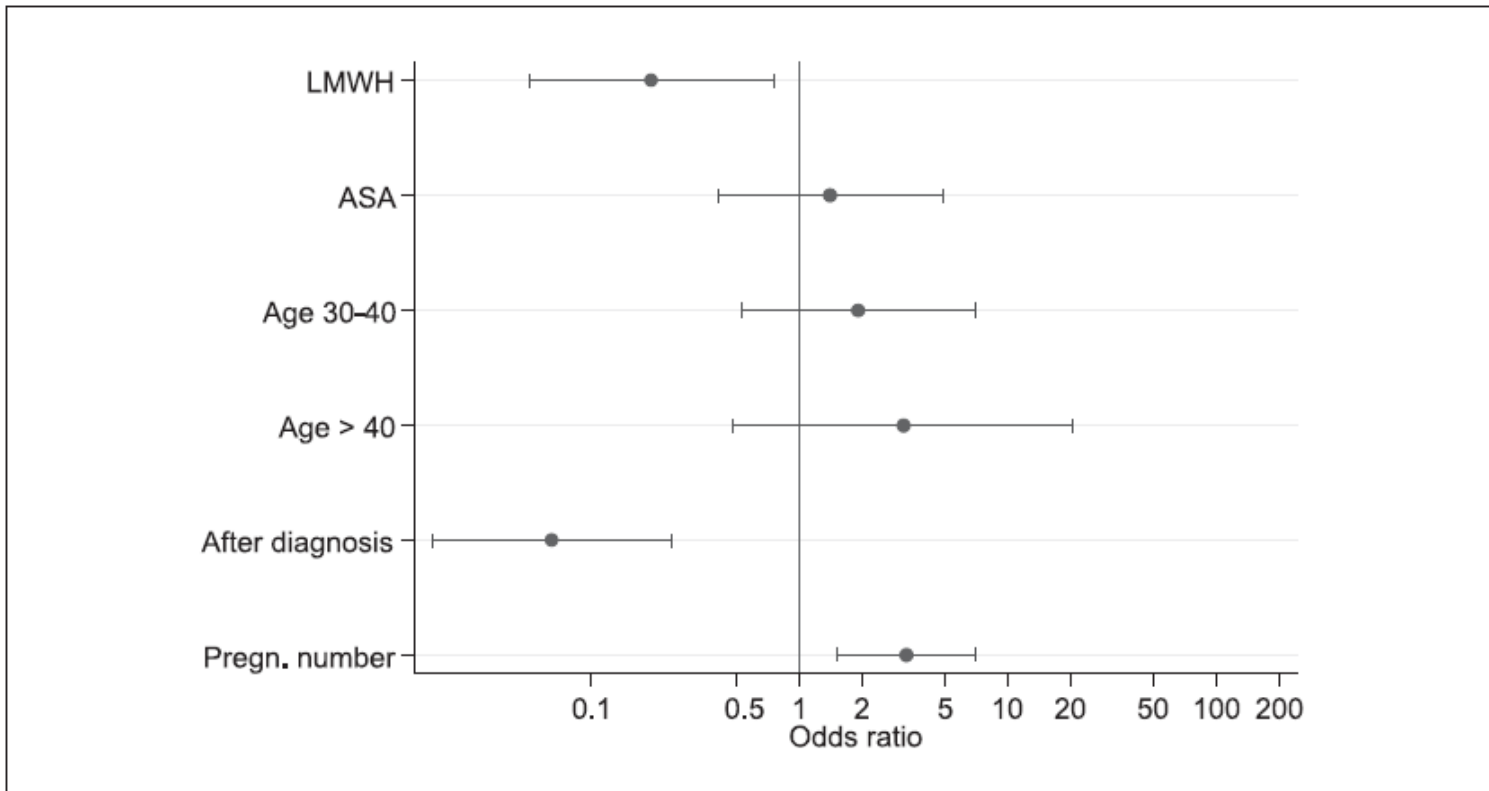


Figure 3: Live birth probability: nested analysis. Exclusion of pregnancies treated from 2nd and 3rd trimester.

Prophylaxis with low-dose low-molecular-weight heparin during pregnancy and postpartum: is it effective?

Roeters van Lennep JE, Meijer E, Klumper FJ, Middeldorp JM, Bloemenkamp KW, Middeldorp S. *J Thromb Haemost.* 2011 Mar

Although prophylaxis with low-dose LMWH during pregnancy and postpartum proved to be safe, the risk of pregnancy-related VTE is considerable in women with a high risk of VTE. VTE prophylaxis with low-dose LMWH may not be sufficiently effective in these women.

Hereditary Risk Factors of Thrombophilia and Probability of Venous Thromboembolism during Pregnancy and the puerperium

Andrea Gerhardt , Rüdiger E. Scharf , Ian A. Greer, Rainer B. Zotz **Blood 2016**

In women ≥ 35 years [< 35 years], the individual probability of gestational VTE was: 0.7% [0.5%] for heterozygous FVL; 3.4% [2.2%], for homozygous FVL; 0.6% [0.4%], for heterozygous prothrombin G20210A; 8.2% [5.5%] for compound heterozygotes for FVL and prothrombin G20210A; 9.0% [6.1%] for antithrombin deficiency; 1.1% [0.7%] for protein C deficiency; and 1.0% [0.7%] for protein S deficiency. These results were independent of a positive family history of VTE.

In contrast to current guidelines, these data suggest that women with high-risk thrombophilia should be considered for antenatal thromboprophylaxis regardless of family history of VTE.

- VTE at young ages or without clear risk factors
- The advice to be screened might be firmer if more than one first degree family members are found to have had deep vein thrombosis at young ages or without clear risk factors
- Typification of thrombophilia in highly qualified centers
- The clinical situation of the patient and the other family members will continue to direct the doctor's advice