Complicanze ostetriche e trombofilia

Valerio De Stefano

Istituto di Ematologia,
Università Cattolica,
Policlinico A. Gemelli , Roma

Complications of pregnancy and hemostasis

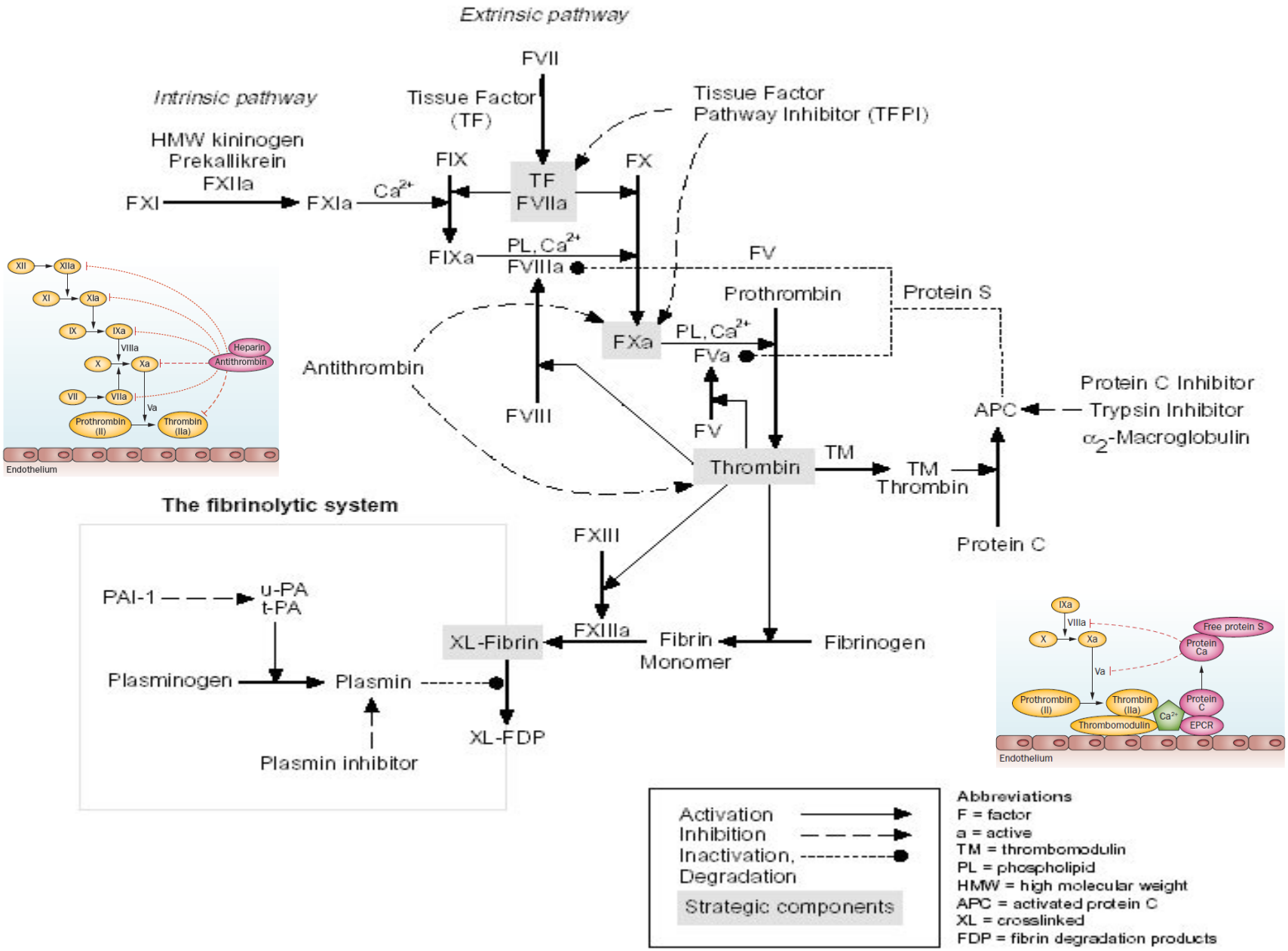
- Thrombophilic disorders
- Hemorrhagic disorders
- Confounding associated conditions

- Thrombosis
- Early and late fetal loss and other obstetric complications
- Postpartum hemorrhage

Outlines

- Inherited and acquired thrombophilia
- Thrombophilia and association with obstetric complications
- Heparin and prevention of obstetric complications

Which test ?


Extrinsic pathway
FVII
Intrinsic pathway
Tissue Factor (TF)
Tissue Factor Pathway Inhibitor (TFPI)
HMW kininogen
Prekallikrein
FXIIa
FXI
FXIa
Ca2+
FIX
TF FVIIa
FX
FIXa
PL, Ca2+
FVIIIa
FV
Prothrombin
Protein S
FXa
PL, Ca2+
FVa
Antithrombin
FVIII
FV
Thrombin
TM
TM Thrombin
Protein C Inhibitor
Trypsin Inhibitor
α2-Macroglobulin
APC
Protein C
FXIII
FXIIIa
XL-Fibrin
Fibrin Monomer
Fibrinogen
The fibrinolytic system
PAI-1
u-PA
t-PA
Plasminogen
Plasmin
Plasmin inhibitor
XL-FDP
XII
XIIa
XI
XIa
IX
IXa
VIIIa
X
Xa
Heparin
Antithrombin
VII
VIIa
Va
Prothrombin (II)
Thrombin (IIa)
Endothelium
IXa
VIIIa
X
Xa
Free protein S
Protein Ca
Va
Prothrombin (II)
Thrombin (IIa)
Protein C
Ca2+
Thrombomodulin
EPCR
Endothelium
Activation
Inhibition
Inactivation, Degradation
Strategic components
Abbreviations
F = factor
a = active
TM = thrombomodulin
PL = phospholipid
HMW = high molecular weight
APC = activated protein C
XL = crosslinked
FDP = fibrin degradation products

Inheritance: autosomal dominant, incomplete penetrance

Deficiency	antithrombin	protein C	protein S
Prevalence:	1:600[1] -5000[2]	1: 200[3]-600[4]	1: 800-4000[5]
VTE			
Prevalence: (unselected pts.)	1.9%	3.7%	2.3%
Prevalence: (selected pts.)	4.3%	4.8%	4.3%

[1] AT activity [2] AT antigen [3] PC antigen [4] PC activity [5] free PS and total PS

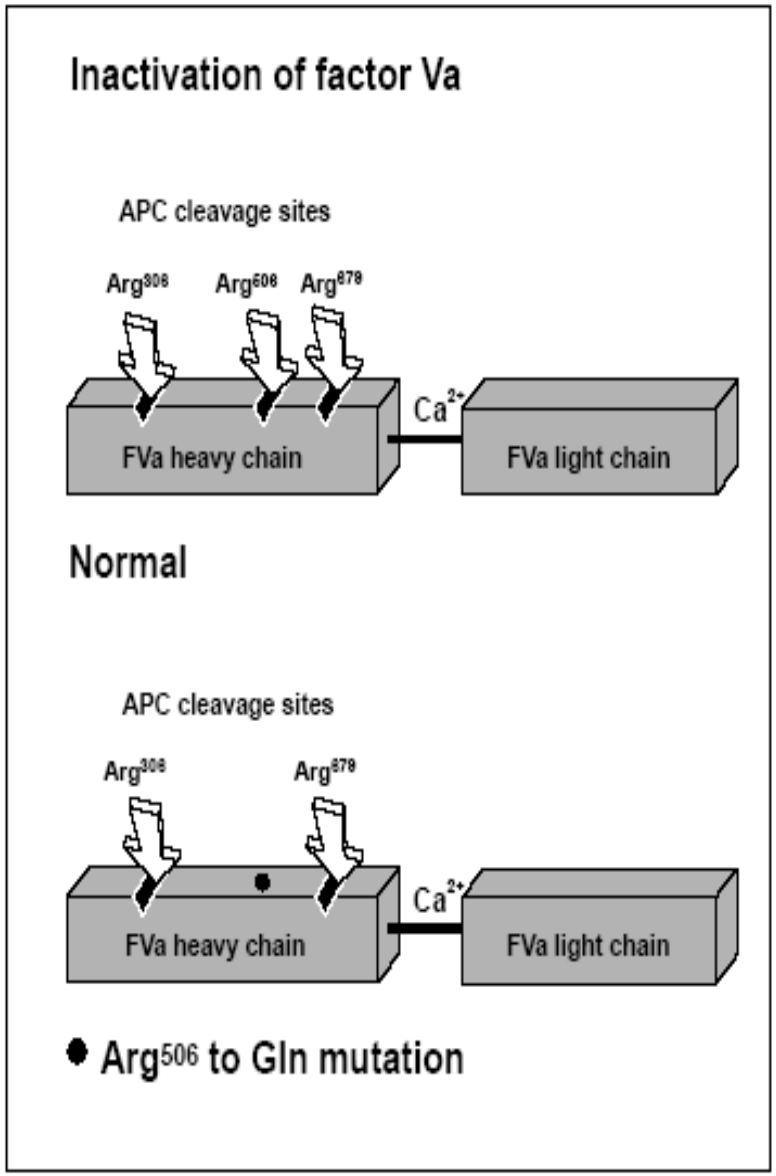
N Eng J Med 2001; 344: 1222 (modified)

Mutation in blood coagulation factor V associated with resistance to activated protein C

Rogier M. Bertina*, Bobby P. C. Koeleman*, Ted Koster†, Frits R. Rosendaal*†, Richard J. Dirven*, Hans de Ronde*, Pieter A. van der Velden* & Pieter H. Reitsma*

* Hemostasis and Thrombosis Research Center, and
† Department of Clinical Epidemiology, University Hospital, Bldg 1-C2R, PO Box 9600, 2300 RC Leiden, The Netherlands

NATURE · VOL 369 · 5 MAY 1994



PREVALENCE OF FACTOR V LEIDEN
De Stefano et al, Sem. Thromb. Hemostas. 24, 367,1998

Healthy individuals

European ancestry (n= 16.150)	4.8 %
Middle East (n= 2.366)	5.4 %
Africa (n= 717)	0
Asia (n= 2.274)	1.0 %
(India and Nepal n= 220)	2.7 %
Native Americans (n= 568)	0.3 %
African Americans (n= 957)	1.2 %

Caucasian patients with venous thrombosis

n= 2.456	18.4 %
n= 1.142 (consecutive)	18.8 %
n= 1.314 (selected)	18.1 %

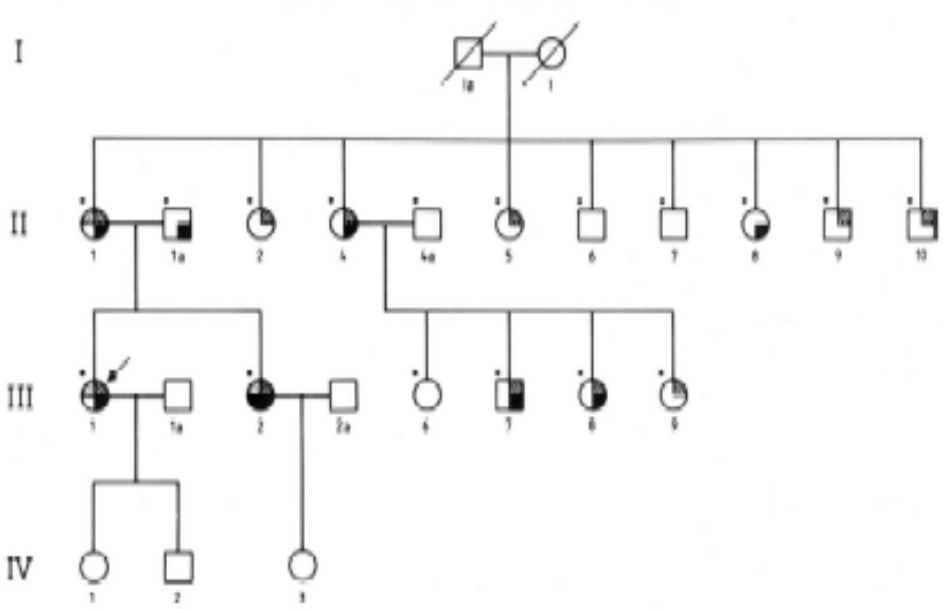
Caucasian patients with arterial thromboembolic disease.

n = 4.417	5.7 %

RAPID COMMUNICATION

A Common Genetic Variation in the 3′-Untranslated Region of the Prothrombin Gene Is Associated With Elevated Plasma Prothrombin Levels and an Increase in Venous Thrombosis

By Swibertus R. Poort, Frits R. Rosendaal, Pieter H. Reitsma, and Rogier M. Bertina



Blood, 1996; 88: 3698

Pooled analysis of 14 case-control studies:

7.3% heterozygotes among 3.356 patients with venous thromboembolism

3% heterozygotes among 6.267 controls

(pooled odds ratio 2.5)

De Stefano et al, Haematologica 2003

Eur J Epidemiol (2013) 28:621–647
DOI 10.1007/s10654-013-9825-8

META-ANALYSIS

Risk of venous thromboembolism associated with single and combined effects of Factor V Leiden, Prothrombin 20210A and Methylenetethraydrofolate reductase C677T: a meta-analysis involving over 11,000 cases and 21,000 controls

Benedetto Simone · Valerio De Stefano · Emanuele Leoncini · Jeppe Zacho · Ida Martinelli · Joseph Emmerich · Elena Rossi · Aaron R. Folsom · Wassim Y. Almawi · Pierre Y. Scarabin · Martin den Heijer · Mary Cushman · Silvana Penco · Amparo Vaya · Pantep Angchaisuksiri · Gulfer Okumus · Donato Gemmati · Simona Cima · Nejat Akar · Kivilcim I. Oguzulgen · Véronique Ducros · Christoph Lichy · Consuelo Fernandez-Miranda · Andrzej Szczeklik · José A. Nieto · Jose Domingo Torres · Véronique Le Cam-Duchez · Petar Ivanov · Carlos Cantu-Brito · Veronika M. Shmeleva · Mojka Stegnar · Dotun Ogunyemi · Suhair S. Eid · Nicola Nicolotti · Emma De Feo · Walter Ricciardi · Stefania Boccia

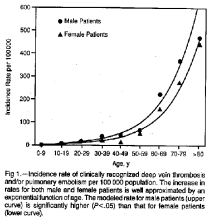
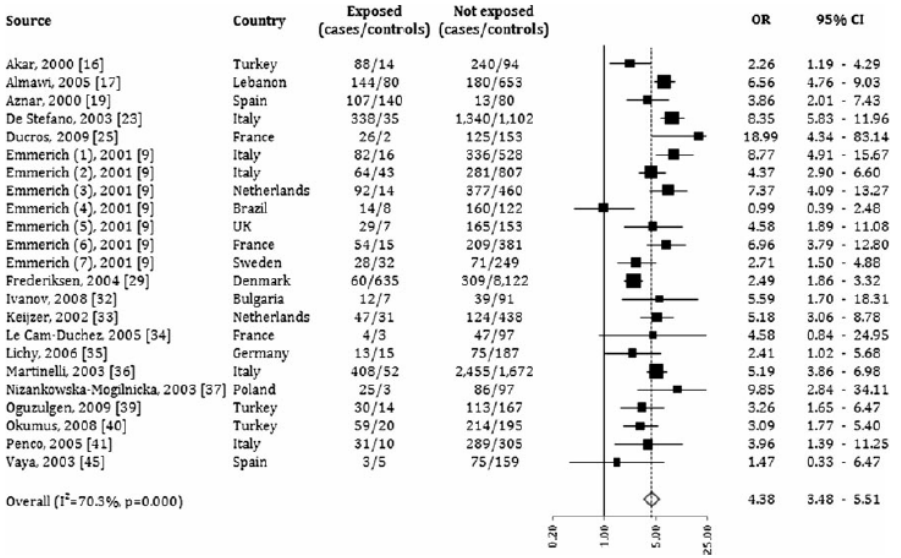


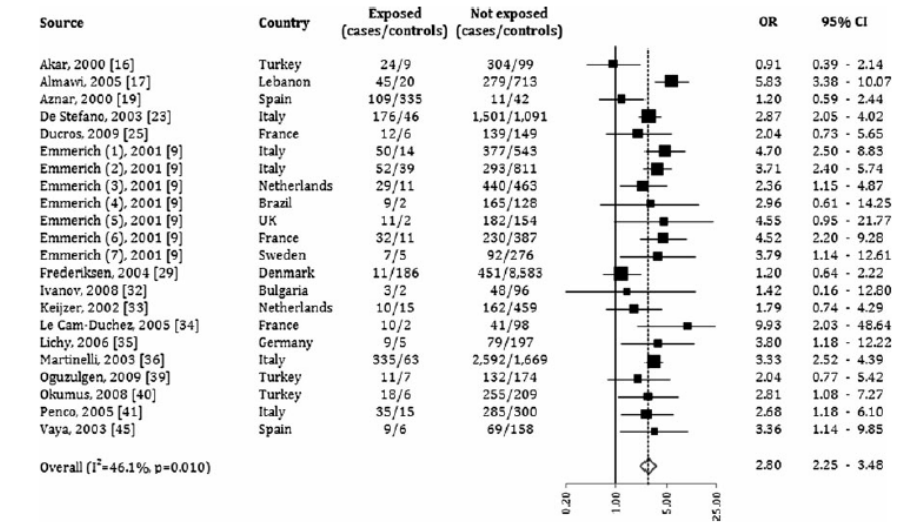
Fig 1.—Incidence rate of clinically recognized deep vein thrombosis and/or pulmonary embolism per 100 000 population. The increase in rates for both male and female patients is well approximated by an exponential function of age. The modeled rate for male patients (upper curve) is significantly higher ($P<.05$) than that for female patients (lower curve).

Odds ratio for VTE

Heterozygous FV Leiden	*4.22*
Heterozygous PT20210A	*2.79*
Double heterozygotes	*3.42*
Homozygous FV Leiden	*11.45*
Homozygous PT20210A	*6.74*



Source	Country	Exposed (cases/controls)	Not exposed (cases/controls)	OR	95% CI
Akar, 2000 [16]	Turkey	88/14	240/94	2.26	1.19 - 4.29
Almawi, 2005 [17]	Lebanon	144/80	180/653	6.56	4.76 - 9.03
Aznar, 2000 [19]	Spain	107/140	13/80	3.86	2.01 - 7.43
De Stefano, 2003 [23]	Italy	338/35	1,340/1,102	8.35	5.83 - 11.96
Ducros, 2009 [25]	France	26/2	125/153	18.99	4.34 - 83.14
Emmerich (1), 2001 [9]	Italy	82/16	336/528	8.77	4.91 - 15.67
Emmerich (2), 2001 [9]	Italy	64/43	281/807	4.37	2.90 - 6.60
Emmerich (3), 2001 [9]	Netherlands	92/14	377/460	7.37	4.09 - 13.27
Emmerich (4), 2001 [9]	Brazil	14/8	160/122	0.99	0.39 - 2.48
Emmerich (5), 2001 [9]	UK	29/7	165/153	4.58	1.89 - 11.08
Emmerich (6), 2001 [9]	France	54/15	209/381	6.96	3.79 - 12.80
Emmerich (7), 2001 [9]	Sweden	28/32	71/249	2.71	1.50 - 4.88
Frederiksen, 2004 [29]	Denmark	60/635	309/8,122	2.49	1.86 - 3.32
Ivanov, 2008 [32]	Bulgaria	12/7	39/91	5.59	1.70 - 18.31
Keijzer, 2002 [33]	Netherlands	47/31	124/438	5.18	3.06 - 8.78
Le Cam-Duchez, 2005 [34]	France	4/3	47/97	4.58	0.84 - 24.95
Lichy, 2006 [35]	Germany	13/15	75/187	2.41	1.02 - 5.68
Martinelli, 2003 [36]	Italy	408/52	2,455/1,672	5.19	3.86 - 6.98
Nizankowska-Mogilnicka, 2003 [37]	Poland	25/3	86/97	9.85	2.84 - 34.11
Oguzulgen, 2009 [39]	Turkey	30/14	113/167	3.26	1.65 - 6.47
Okumus, 2008 [40]	Turkey	59/20	214/195	3.09	1.77 - 5.40
Penco, 2005 [41]	Italy	31/10	289/305	3.96	1.39 - 11.25
Vaya, 2003 [45]	Spain	3/5	75/159	1.47	0.33 - 6.47
Overall (I^2=70.3%, p=0.000)				4.38	3.48 - 5.51



Source	Country	Exposed (cases/controls)	Not exposed (cases/controls)	OR	95% CI
Akar, 2000 [16]	Turkey	24/9	304/99	0.91	0.39 - 2.14
Almawi, 2005 [17]	Lebanon	45/20	279/713	5.83	3.38 - 10.07
Aznar, 2000 [19]	Spain	109/335	11/42	1.20	0.59 - 2.44
De Stefano, 2003 [23]	Italy	176/46	1,501/1,091	2.87	2.05 - 4.02
Ducros, 2009 [25]	France	12/6	139/149	2.04	0.73 - 5.65
Emmerich (1), 2001 [9]	Italy	50/14	377/543	4.70	2.50 - 8.83
Emmerich (2), 2001 [9]	Italy	52/39	293/811	3.71	2.40 - 5.74
Emmerich (3), 2001 [9]	Netherlands	29/11	440/463	2.36	1.15 - 4.87
Emmerich (4), 2001 [9]	Brazil	9/2	165/128	2.96	0.61 - 14.25
Emmerich (5), 2001 [9]	UK	11/2	182/154	4.55	0.95 - 21.77
Emmerich (6), 2001 [9]	France	32/11	230/387	4.52	2.20 - 9.28
Emmerich (7), 2001 [9]	Sweden	7/5	92/276	3.79	1.14 - 12.61
Frederiksen, 2004 [29]	Denmark	11/186	451/8,583	1.20	0.64 - 2.22
Ivanov, 2008 [32]	Bulgaria	3/2	48/96	1.42	0.16 - 12.80
Keijzer, 2002 [33]	Netherlands	10/15	162/459	1.79	0.74 - 4.29
Le Cam-Duchez, 2005 [34]	France	10/2	41/98	9.93	2.03 - 48.64
Lichy, 2006 [35]	Germany	9/5	79/197	3.80	1.18 - 12.22
Martinelli, 2003 [36]	Italy	335/63	2,592/1,669	3.33	2.52 - 4.39
Oguzulgen, 2009 [39]	Turkey	11/7	132/174	2.04	0.77 - 5.42
Okumus, 2008 [40]	Turkey	18/6	255/209	2.81	1.08 - 7.27
Penco, 2005 [41]	Italy	35/15	285/300	2.68	1.18 - 6.10
Vaya, 2003 [45]	Spain	9/6	69/158	3.36	1.14 - 9.85
Overall (I^2=46.1%, p=0.010)				2.80	2.25 - 3.48

Remethylation

Remethylation

THF

Methionine

Dimethylglycine

AdoMet

R

RCH_3

AdoHcy

Methylene-THF

B_{12}

MS

BHMT

MTHFR

B_2

Methyl-THF

Homocysteine

Betaine

B_6

CBS

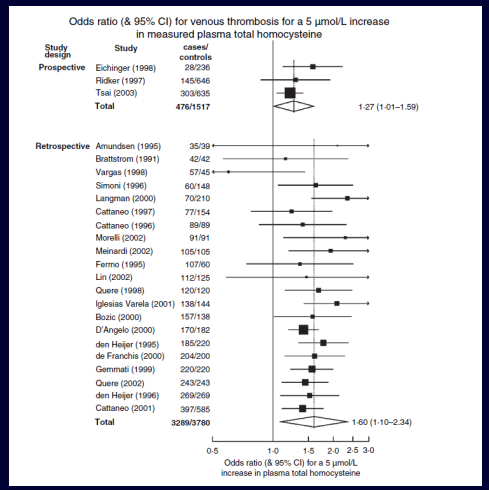
Cystathionine

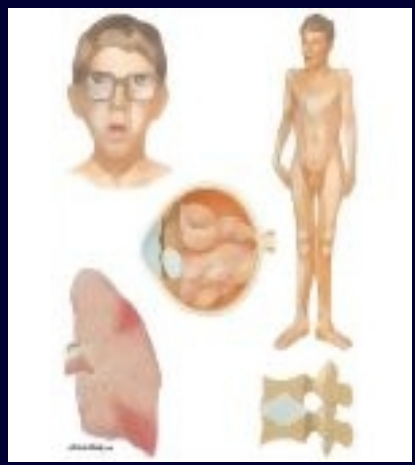
B_6

Cysteine

Trans-sulfuration

Severe HyO (homocystinuria)





Box 2 | Mechanisms associated with thrombophilia

Known mechanisms

Loss-of-function

- Antithrombin deficiency
- Protein C deficiency
- Protein S deficiency

Gain-of-function

- Factor V Leiden
- Prothrombin G20210A
- High factor VIII level
- Non-O blood group
- Dysfibrinogenaemia

Postulated mechanisms

- Low tissue factor pathway inhibitor level
- High fibrinogen level
- High factor IX level
- High factor X level
- High factor XI level
- Resistance to antithrombin
- Global hypofibrinolysis
- High thrombin activatable fibrinolysis inhibitor level
- Hyperhomocysteinaemia

Martinelli, De Stefano & Mannucci, Nature Rev Cardiology, 2014

Thrombophilic abnormality	Risk (Odds Ratio)
AT deficiency	10.2 - 18.3
PC deficiency	4.1 - 16.2
PS deficiency	7.6 - 16.2
FV Leiden	2.5 - 7.5
PT G20210A	1.7 - 5.2
Combined alterations	6.4 (FVL + PT)

Reviewed in Rossi et al, Thromb Haemost , 2011

Journal of Thrombosis and Haemostasis, 9 (Suppl. 1): 258–264 DOI: 10.1111/j.1538-7836.2011.04311.x

INVITED REVIEW

Lessons from genome-wide association studies in venous thrombosis

P. E. MORANGE*† and D. A. TREGOUET‡
*INSERM, UMR_S 626, Marseille; †Université de la Méditerranée, Marseille; and ‡INSERM UMR_S 937, Université Pierre et Marie Curie (UPMC, Paris 6), Paris, France

Table 1 Known susceptibility genes for VT before the GWAS era

Locus	SNP	Alleles*	Frequency†	OR/RR‡	Associated phenotype§	References¶
ABO	[O,A2] vs. [A1,B]		0.30	1.50	↑ FVIII, ↑ VWF	[13]
F2	rs1799963	G/A	0.02	2.50	↑ FII	[9]
F5	rs6025	G/A	0.05	3.00	Resistance to activated protein C	[9]
FGG	rs2066865	C/T	0.25	1.47	↓ Fibrinogen γ'	[15]
PROC	Multiple private			~ 10	Protein C deficiency	[6]
PROS1	mutations				Protein S deficiency	[7]
SERPINC1					Antithrombin deficiency	[5]

*Underlined are the at risk alleles. †Estimates of the risk allele frequency observed in references population. ‡Estimates of the odds ratio (OR) or relative risk (RR) associated the risk allele. §Phenotype associated with the at risk allele. ¶According to references numbering.

Table 2 New variants associated with VT identified by GWAS approaches

Locus	SNP	Alleles*	Frequency†	OR‡	Associated phenotype§	References¶
C4BPB/C4BPA	rs3813948	T/C	0.08	1.18	↑ $\alpha_7\beta_0$ C4BP	[32]
F11	rs2036914	C/T	0.52	1.35	↑ FXI	[23]
	rs2289252	C/T	0.41	1.35	↑ FXI	
GP6	rs1613662	A/G	0.82	1.15	↑ Platelet activation and aggregation	[18]
KNG1	rs710446	T/C	0.45	1.20	↓ aPTT	[28]
HIVEP1	rs169713	T/C	0.21	1.20	Still unknown	[25]
SERPINC1	rs2227589	C/T	0.10	1.29	↓ Antithrombin	[18]
STXBP5	rs1039084	A/G	0.46	1.11	↑ VWF	[38]
TC2N	rs1884841	C/T	0.44	1.27	↑ VWF	[39]
VWF	rs1063856	A/G	0.37	1.15	↑ VWF	[38]

*Underlined are the at risk alleles. †Estimates of the risk allele frequency observed in references population. ‡Estimates of the odds ratio (OR) associated the risk allele. §Phenotype associated with the at risk allele. ¶According to references numbering.

LABORATORY SCREENING

Italian Cooperation on Inherited Thrombophilia
ICIT Working Group, October 2004

- **AT heparin cofactor**
- **PC (functional assay)**
- **PS (immunologic assay)**
- **APC-resistance (and/or FV Leiden)**
- **PT 20210A**
- **Fasting homocysteine**
- **LAC and aPL**

Routinary search for other polymorphisms in factor V, factor II, and MTHFR (as well as in other genes) is discouraged .

Diagnostic panel for thrombophilia of a Public Hospital in Rome (2017)

- Factor V Leiden
- Factor V H1299R
- Factor II G20210A
- Factor XIII V34L
- Beta Fbg -455GA
- Plt Ag HPA1 a/b
- MTHFR C677T
- MTHFR A1298C
- ApoLp B-100 R3500Q
- Beta-thromboglobulin
- PAI 4G/5G
- Homocysteine
- AT, PC, PS
- APC-resistance
- LAC / ACA

Unappropriate tests are written in red

677 TT MTHFR POLYMORPHISM AND RISK FOR DVT

- **Controls:**
  390 / 2.856 (13.6%)

- **Patients with DVT and inherited thrombophilia:**
  74 / 527 (14.0%)

- **Patients with DVT and no inherited thrombophilia:**
  224 / 1.564 (14.3%)

De Stefano et al, Sem Thromb Haemost 26,305,2000
(pooled analysis of 8 published series)

ORIGINAL INVESTIGATION

No Association Between the Common *MTHFR* 677C→T Polymorphism and Venous Thrombosis

Results From the MEGA Study

Irene D. Bezemer, MSc; Carine J. M. Doggen, PhD; Hans L. Vos, PhD; Frits R. Rosendaal, MD

Arch Intern Med. 2007;167:497-501

Table 1. *MTHFR* Genotype Distribution Among Patients With Venous Thrombosis and Control Subjects

MTHFR 677C→T	Cases, No. (%) (n = 4375)	Control Subjects No. (%) (n = 4856)	Odds Ratio (95% Confidence Interval)
CC	2044 (47)	2245 (46)	1 [Reference]
CT	1891 (43)	2094 (43)	0.99 (0.91-1.08)
TT	440 (10)	517 (11)	0.94 (0.81-1.08)

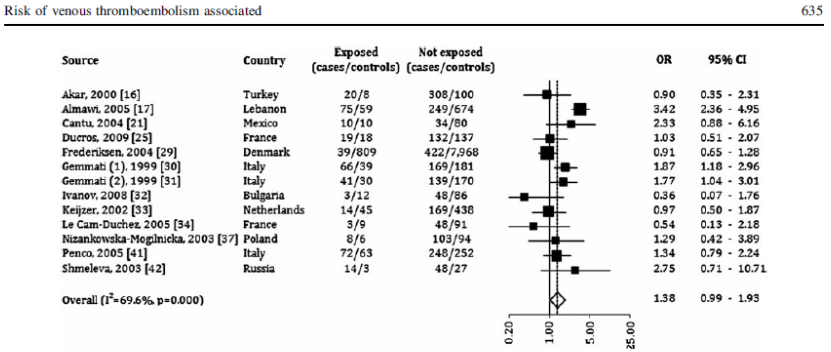
C677T polymorphism is associated with

Increased risk for

- Basal cell carcinoma
- Cerebral hemorrhage
- Chronic allograft nephropathy
- Essential hypertension
- Ischemic stroke
- Lung cancer
- Male infertility
- Migraine
- Pancreatic cancer
- Primary open-angle glaucoma
- Sqamous cell carcinoma of the head and neck
- Sudden hearing loss
- Schizophrenia
- Steatosis and fibrosis in chronic hepatitiS C
- Type 2 diabetes
- Venous thromboembolism

Decreased risk

- Acute lymphoblastic leukemia
- Colorectal cancer
- Multiple myeloma

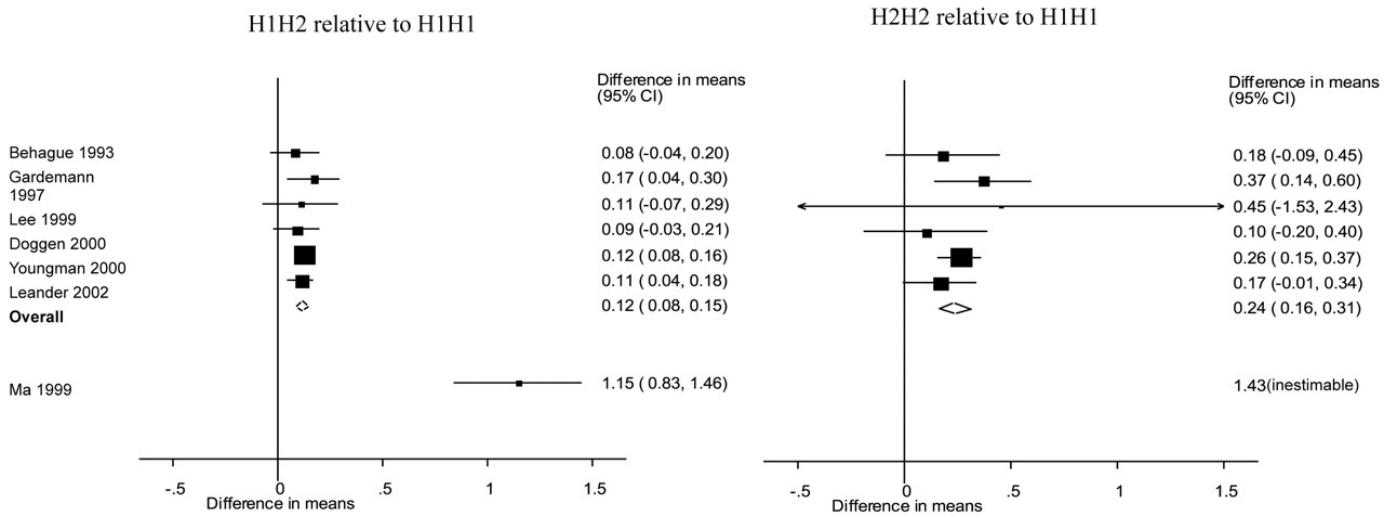


Source	Country	Exposed (cases/controls)	Not exposed (cases/controls)	OR	95% CI
Akar, 2000 [16]	Turkey	20/8	308/100	0.90	0.35 - 2.31
Almawi, 2005 [17]	Lebanon	75/59	249/674	3.42	2.36 - 4.95
Cantu, 2004 [21]	Mexico	10/10	34/80	2.33	0.88 - 6.16
Ducros, 2009 [25]	France	19/18	132/137	1.03	0.51 - 2.07
Frederiksen, 2004 [29]	Denmark	39/809	422/7,968	0.91	0.65 - 1.28
Gemmati (1), 1999 [30]	Italy	66/39	169/181	1.87	1.18 - 2.96
Gemmati (2), 1999 [31]	Italy	41/30	139/170	1.77	1.04 - 3.01
Ivanov, 2008 [32]	Bulgaria	3/12	48/86	0.36	0.07 - 1.76
Keijzer, 2002 [33]	Netherlands	14/45	169/438	0.97	0.50 - 1.87
Le Cam-Duchez, 2005 [34]	France	3/9	48/91	0.54	0.13 - 2.18
Nizankowska-Mogilnicka, 2003 [37]	Poland	8/6	103/94	1.29	0.42 - 3.89
Penco, 2005 [41]	Italy	72/63	248/252	1.34	0.79 - 2.24
Shmeleva, 2003 [42]	Russia	14/3	48/27	2.75	0.71 - 10.71
Overall (I^2=69.6%, p=0.000)				1.38	0.99 - 1.93

Fig. 4 Forrest plot: association between *Methylenetetrahydrofolate reductase C677T* and venous thromboembolism (odds ratios are represented on log scale)

Simone et al, Eur J Epidemiol, 2013

Differences in mean plasma fibrinogen between those in control groups with different genotypes



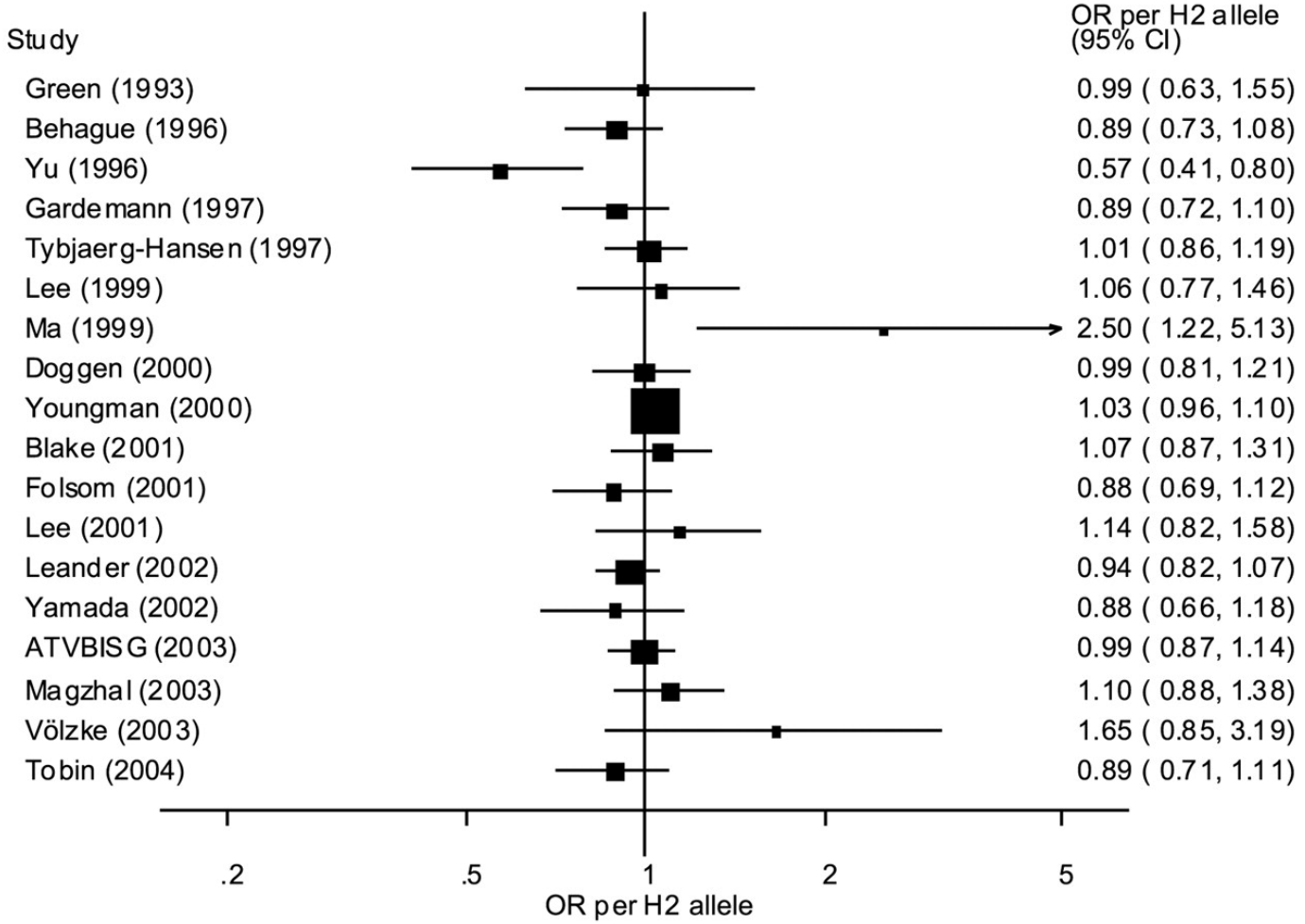
Smith, G. D. et al. Arterioscler Thromb Vasc Biol 2005;25:2228-2233

Arteriosclerosis, Thrombosis, and Vascular Biology

Copyright ©2005 American Heart Association

American Heart Association®
Learn and Live℠

Studies reporting association between {beta}-fibrinogen genotype and CHD

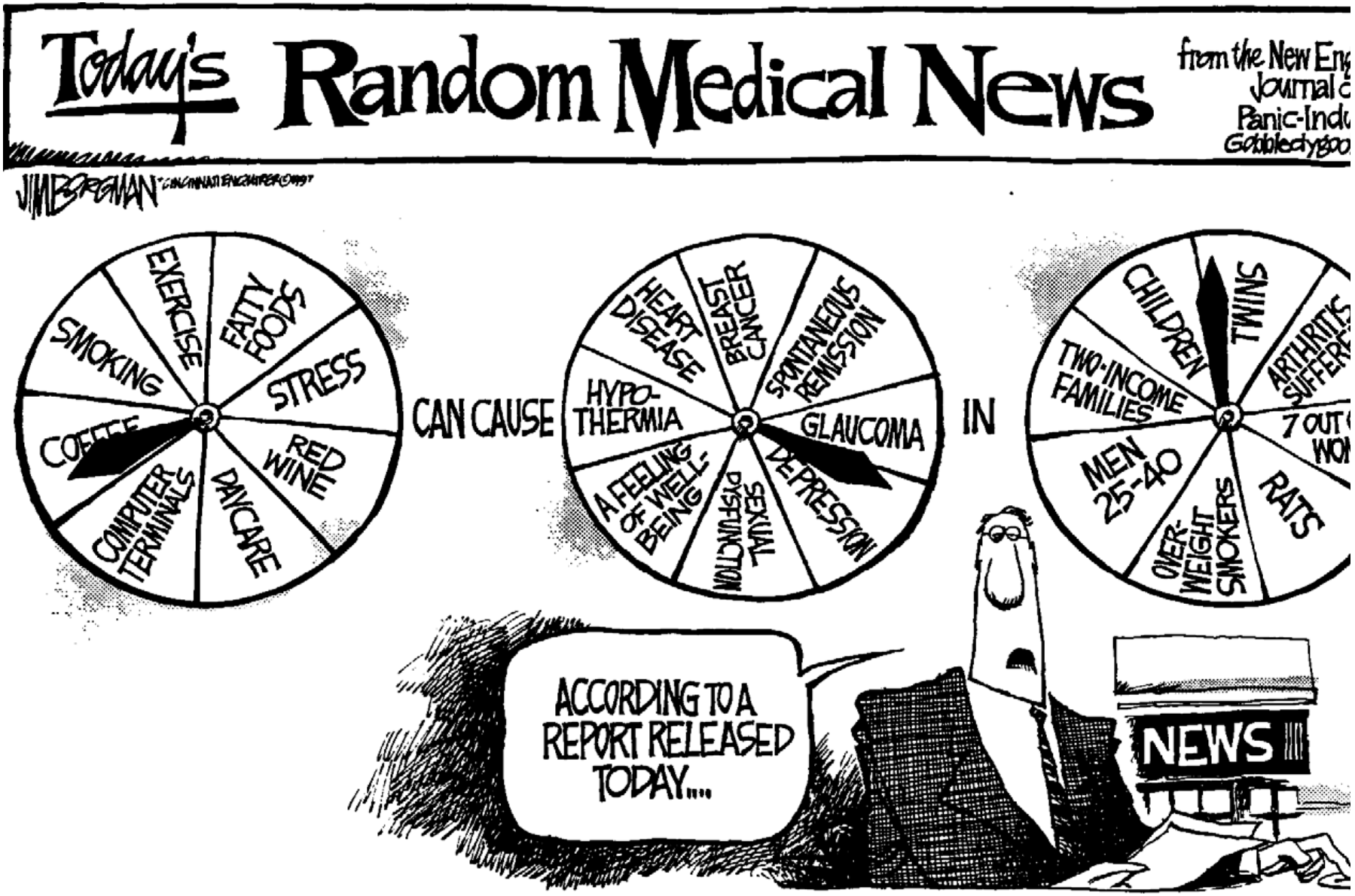


Smith, G. D. et al. Arterioscler Thromb Vasc Biol 2005;25:2228-2233

Arteriosclerosis, Thrombosis, and Vascular Biology

Copyright ©2005 American Heart Association

American Heart Association®
Learn and Live℠



Lancet, 22 May 2004

Unmatched Case/Control Studies

(To use this page, your browser must recognize JavaScript.)

Choose which calculation you desire, enter the relevant population values (as decimal fractions) for p0 (exposure in the controls) and RR (relative risk of disease associated with exposure) and, if calculating power, a sample size (assumed the same for each sample). You may also modify α (type I error rate) and the power, if relevant. After making your entries, hit the **calculate** button at the bottom.

- ◉ Calculate Sample Size (for specified Power)
- ○ Calculate Power (for specified Sample Size) **Enter a value for p0:** 0.60

Enter a value for RR: 2

- ○ 1 Sided Test
- ◉ 2 Sided Test **Enter a value for α (default is .05):** 0.05

Enter a value for desired power (default is .80): 0.80

The sample size (for cases and controls, separately) is: 152

CARRIER CASES	CARRIER CONTROLS	ODDS RATIO (95%CI)	P
100 / 152 (65.7%)	90 / 152 (59.2%)	1.32 (0.83-2.11)	0.28
105 / 152 (69.0%)	90 / 152 (59.2%)	1.53 (0.95-2.46)	0.09
110 / 152 (72.3%)	90 / 152 (59.2%)	1.80 (1.11-2.91)	0.02

+ 22% cases in respect to the baseline prevalence

Unmatched Case/Control Studies

(To use this page, your browser must recognize JavaScript.)

Choose which calculation you desire, enter the relevant population values (as decimal fractions) for p0 (exposure in the controls) and RR (relative risk of disease associated with exposure) and, if calculating power, a sample size (assumed the same for each sample). You may also modify α (type I error rate) and the power, if relevant. After making your entries, hit the **calculate** button at the bottom.

- ◉ Calculate Sample Size (for specified Power)
- ○ Calculate Power (for specified Sample Size) **Enter a value for p0:** 0.03

Enter a value for RR: 2

- ○ 1 Sided Test
- ◉ 2 Sided Test **Enter a value for α (default is .05):** 0.05

Enter a value for desired power (default is .80): 0.80

The sample size (for cases and controls, separately) is: 829

CARRIER CASES	CARRIER CONTROLS	ODDS RATIO (95%CI)	P
30 / 829 (3.6%)	25 / 829 (3.0%)	1.41 (0.84-2.39)	0.23
40 / 829 (4.8%)	25 / 829 (3.0%)	1.63 (0.97-2.71)	0.07
50 / 829 (6.0%)	25 / 829 (3.0%)	2.06 (1.26-3.37)	0.004

+ 100% cases in respect to the baseline prevalence

Table 5 | Laboratory assays for diagnosis of inherited thrombophilia[226]

Abnormality	Assay*	Disadvantages
Antithrombin deficiency	Heparin cofactor activity against factor IIa or Xa	Anti-factor Xa assays can miss some type II defects; heparin binding-site defects are missed (a heparin-free test is needed)
Protein C deficiency	Amidolytic assay with snake venoms as activators	Some rare type II variants are missed (a clot-based test is needed)
Protein S deficiency	Free antigen assay	Type II is missed (a clot-based test is needed)
Factor V Leiden	DNA assay	Activated protein C resistance not associated with factor V Leiden is missed
Prothrombin G20210A	DNA assay	Activated protein C resistance not associated with prothrombin G20210A is missed
High factor VIII level	One-stage clotting assay	Increased during acute-phase response
Dysfibrinogenaemia	Immunoassay combined with a clot-based test	Fibrinogen antigen and activity levels are method-dependent
Hyperhomocysteinaemia	Fasting plasma homocysteine assay	Evaluation of folate and vitamin B6 and B12 status is advised

*Acquired conditions that can cause of misleading test results: liver disease (decreased antithrombin, protein C, protein S, acquired dysfibrinogenaemia); proteinuria, inflammatory bowel disease, or prolonged heparin treatment (decreased antithrombin); vitamin K antagonist use (decreased protein C, protein S); pregnancy or oestrogen use (decreased protein S, increased factor VIII); acute phase reactions (decreased free protein S, increased factor VIII); kidney dysfunction or hypothyroidism (increased homocysteine); homocysteine levels are influenced by many drugs.[109]

Martinelli, De Stefano & Mannucci, Nature Rev Cardiology, 2014

Who ?

REASONS FOR TESTING FOR INHERITED THROMBOPHILIA

Venous thromboembolism	44%
Premature arterial thrombosis	23%
Obstetric complications	17%
Asymptomatic individuals	16%

Coppens et al. Blood 2007
Gartner et al. Contraception 2008
Laberge et al. Genet Med 2009
Suthers et al. Royal Coll Path Australasia 2009

Obstetric complications

- ***Recurrent miscarriage:***

  - three (two) or more
  - (consecutive) miscarriages
  - before 20 (24) weeks of gestation

Obstetric complications

- ***Recurrent miscarriage:***

- anatomic factors (uterine septum, cervical incompetence) 10-15%
- thrombophilia 3-15%
- chromosomal abnormalities 2-4%
- hormonal abnormalities (hypotiroidism, hyperprolactinemia, luteal phase defect) 25-40%
- unexplained 50%

Obstetric complications

- ***Abruptio placentae:***

  separation of the normally located placenta after the 20th week of pregnancy of gestation and prior to birth.

- Class 1 (48%) mild, no coagulopathy, no fetal distress
- Class 2 (27%) fetal distress, hyofibrinogenemia
- Class 3 (24%) severe, maternal shock, coagulopathy, fetal death

Obstetric complications

- ***Intrauterine growth retardation (IUGR):*** IUGR occurs when the unborn baby is at or below the 10th weight percentile for his or her age in weeks bruptio placentae

Obstetric complications

- ***Preeclampsia:***

  new onset hypertension (≥140 mm Hg systolic or ≥ 90 mm Hg diastolic) and proteinuria (≥ 300 mg in a 24 hour collection).

  ⇒ eclampsia, HELLP syndrome

- Heritable patterns
- Heterogeneity of the pathogenetic mechanisms (hemodynamic factors, oxidative stress, thrombophilia, genetic factors, angiogenic factors),

Inherited thrombophilia and obstetric complications

- In Western countries up to 18% of pregnancies ends in fetal loss (0.8% as stillbirth)
- 5% of women experienced 2 or more fetal losses (1% > 2 fetal losses)
- Abruptio placentae complicates 1% of births
- Preeclampsia complicates 5-7% of births and in 5-10% of cases HELLP can arise (0.5 per cent deliveries)

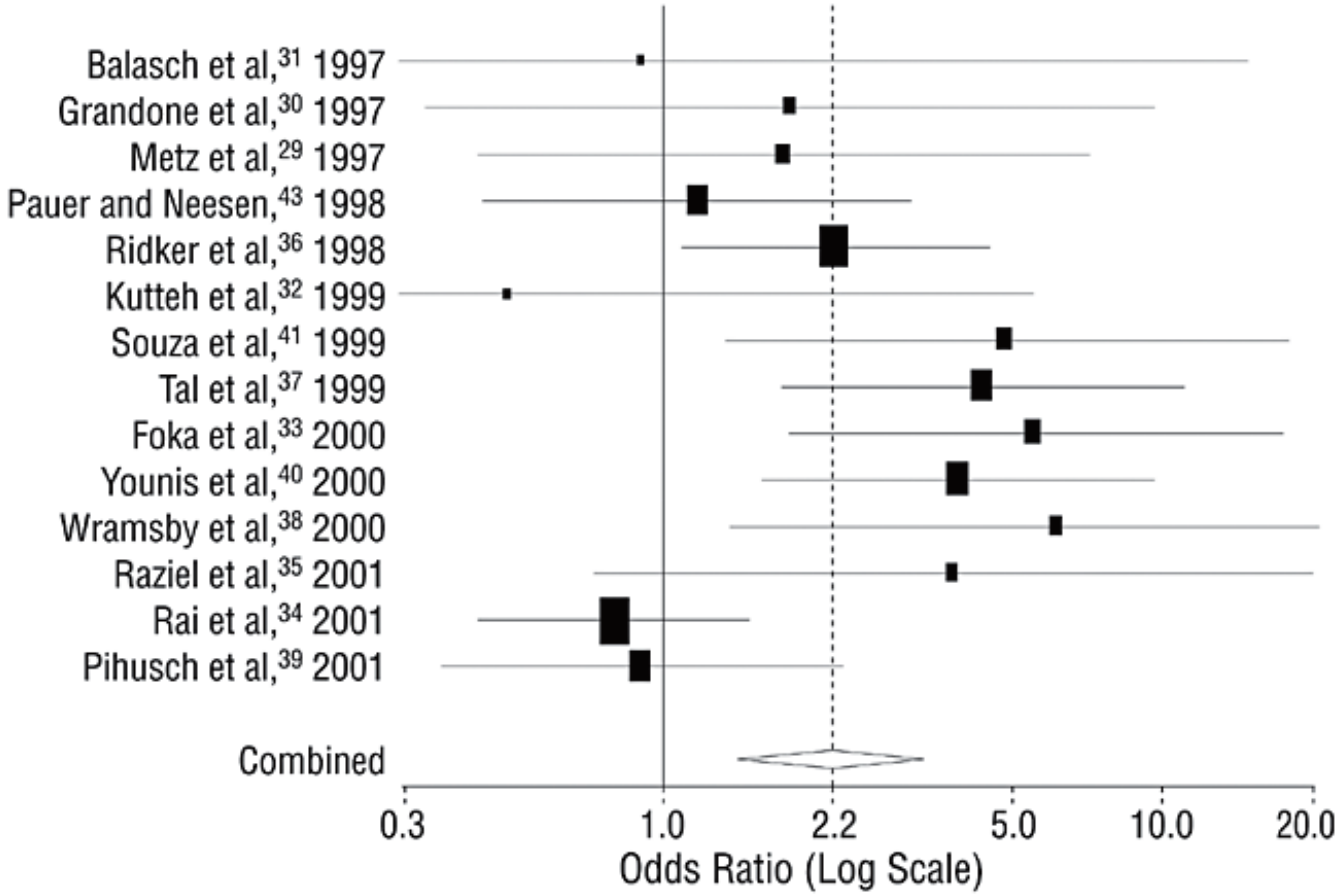
Inherited thrombophilia and obstetric complications

- Women with AT, PC or PS deficiency were first recognized at higher risk of fetal loss in 1996

  (Preston et al, Lancet 1996, Sanson et al, Thromb Haemost 1996)
- Overall, inherited thrombophilia was diagnosed in 38% of 110 women with obstetrical complications

  (Kupferminc et al, New Engl J Med 1999)

Association of factor V Leiden mutation and recurrent pregnancy loss

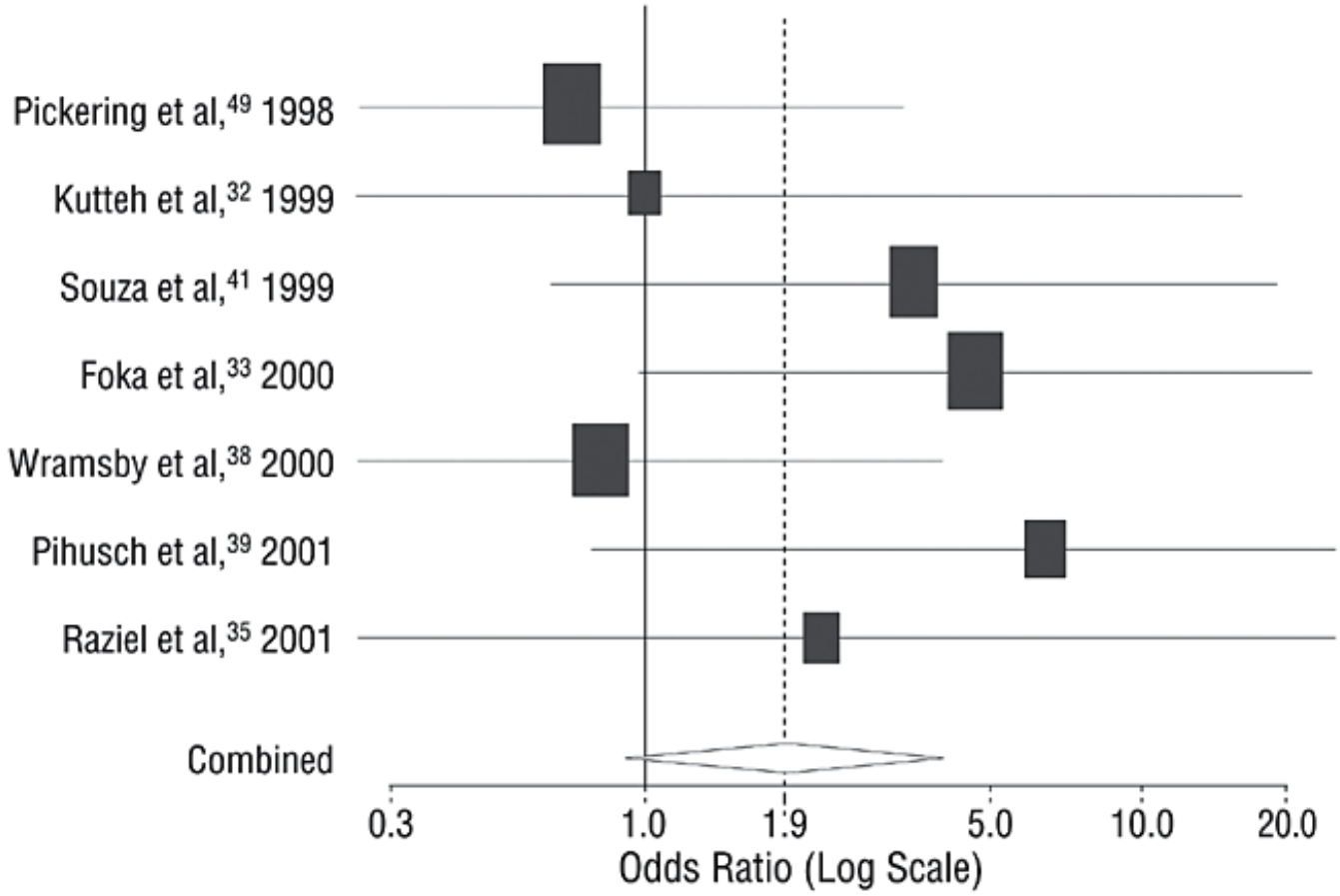


Kovalevsky, G. et al. Arch Intern Med 2004;164:558-563.

Copyright restrictions may apply.

ARCHIVES OF INTERNAL MEDICINE

Association of prothrombin mutation and recurrent pregnancy loss



Kovalevsky, G. et al. Arch Intern Med 2004;164:558-563.

Copyright restrictions may apply.

ARCHIVES OF INTERNAL MEDICINE

Table 2. Combined Odds Ratios for Association Between Factor V Leiden and Prothrombin Mutations and Recurrent Pregnancy Loss

	Factor V Leiden		Prothrombin Gene (G20210A)	
	OR	95% CI	OR	95% CI
Crude bivariate analysis	2.1	1.6-2.7	2.5	1.3-4.7
Adjusted stratified analysis*	2.0	1.5-2.7	2.0	1.0-4.0
Logistic regression*	2.2	1.6-2.9	2.2	1.1-4.3
Fixed-effects meta-analysis	2.0	1.5-2.6	1.9	0.96-3.9
Random-effects meta-analysis	2.2	1.4-3.3	1.9	0.96-3.9

Abbreviations: CI, confidence interval; OR, odds ratio.
*Analysis performed while adjusted for among-study heterogeneity.

Kovalevsky, G. et al. Arch Intern Med 2004;164:558-563

Table 3. Associations Between Factor V Leiden and Prothrombin Mutations With RPL When Examined Within Subgroups

	Factor V Leiden		Prothrombin Gene (G20210A)	
	OR	95% CI	OR	95% CI
No. of miscarriages				
≥3	2.1	1.5-3.0	1.6	0.7-3.7
≥2	2.5	1.7-3.6	4.5	1.5-13.3
Time of miscarriages				
First trimester only	1.6	1.2-2.2	3.4	1.5-8.0
First and second trimesters	2.7	2.0-3.7	2.2	1.1-4.4
Race				
White only	1.5	1.1-2.2	3.4	1.3-9.1
Other races included	3.4	2.2-5.1	1.8	0.7-4.4
Other causes				
Unexplained only	2.1	1.5-3.0	1.9	0.7-5.2
Other causes not excluded	2.3	1.5-3.5	3.0	1.3-6.8

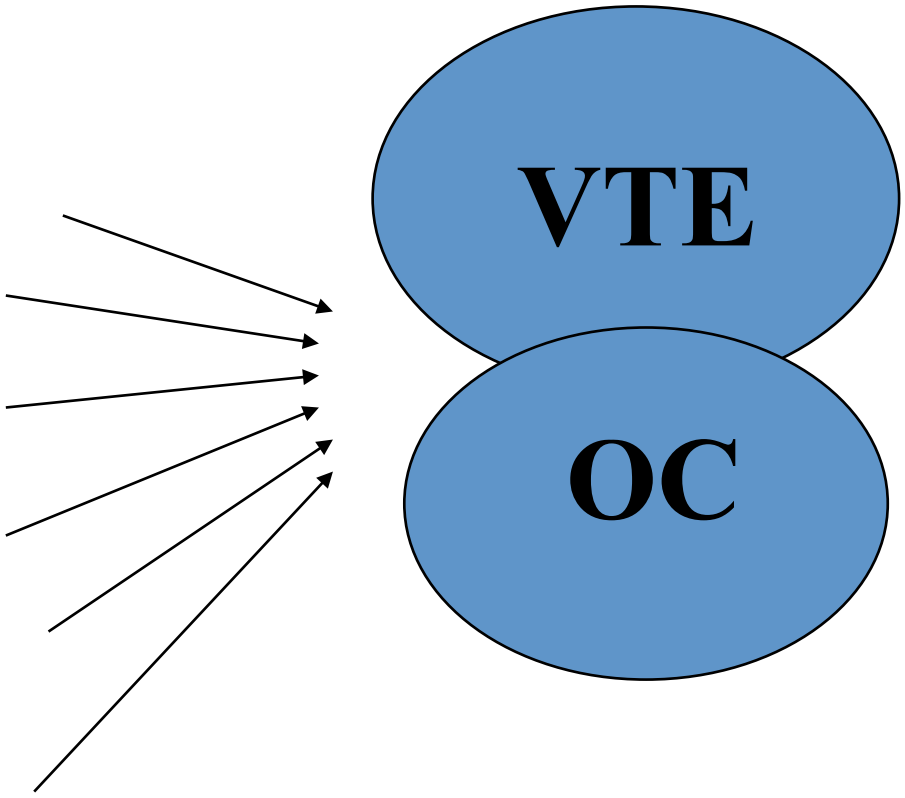
Abbreviations: CI, confidence interval; OR, odds ratio; RPL, recurrent pregnancy loss.

Kovalevsky, G. et al. Arch Intern Med 2004;164:558-563

VENOUS THROMBOEMBOLIC DISEASE (VTE) AND OBSTETRIC COMPLICATIONS (OC)

MULTICAUSAL MODEL

Gene defect(s)
Gene defect(s)
Age
Dietary habit
Triggering event
Acquired factors



PARTICIPANTS TO THE STUDY

Clinical phenotype of the proband	Kindreds	Relatives	Carriers
Venous thromboembolism	344	1,088	625
Premature arterial thrombosis	30	113	51
Obstetric complication	86	257	146
Asymptomatic	106	262	145
Total	566	1,720	967

Rossi et al, Thromb Haemost 2011

Analysis according to Cox proportional hazards model

Clinical phenoype of the proband	Hazard ratio for DVT in carriers vs. non-carriers	Log-rank test
Venous thromboembolism	**3.11 (95% CI 1.40-4.67)**	**0.002**
Premature arterial thrombosis	**0.55 (95% CI 0.05-5.46)**	**0.62**
Obstetric complication	**not applicable**	**0.07**
Asymptomatic	**not applicable**	**0.17**

Rossi et al, Thromb Haemost 2011

Inherited thrombophilia and obstetric complications

- **The relative risk for recurrent fetal losses (> 2) is double among the carriers of AT, PC, and PS or factor V Leiden .**
- **The risk for stillbirth was 2 to 7 fold increased among carriers of factor V Leiden**
- **The risk associated with PT 20210A is more uncertain**

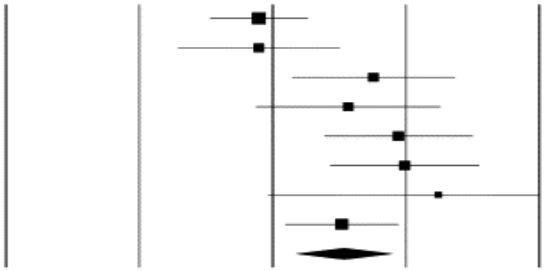
Rey et al, Lancet 2003

Kovalevsky et al, Arch Intern Med 2004

IUGR
Howley et al,
AJOG 2005

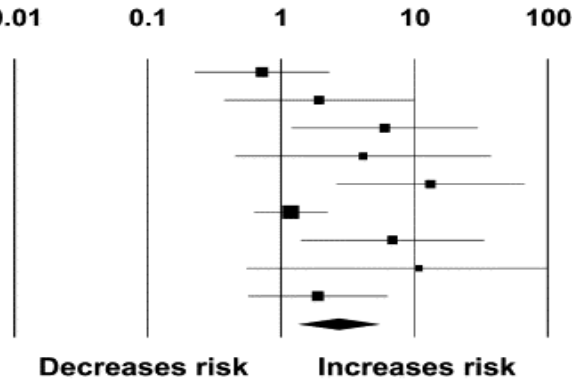
A *FVL and/or PGV*

Citation	Effect	Lower	Upper
McCowan 2003	.79	.34	1.84
Franchi 2003	.79	.19	3.20
Agostaros 2003	5.70	1.39	23.36
Verspyck 2002	3.69	.75	18.26
Kupferminc 2002	8.80	2.44	31.74
Martinelli 2001	9.78	2.69	35.52
Lee 2001	17.46	.92	330.96
Kupferminc 1999	3.30	1.24	8.80
Random Combined (8)	**3.44**	**1.48**	**7.98**



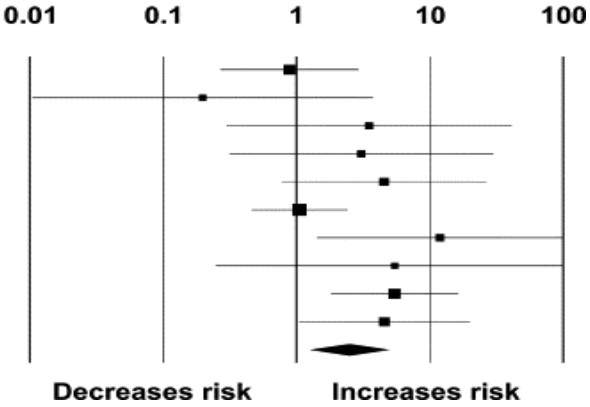
B *FVL only*

Citation	Effect	Lower	Upper
McCowan 2003	.72	.23	2.30
Franchi 2003	1.93	.37	9.97
Agostaros 2003	6.00	1.20	30.10
Verspyck 2002	4.13	.45	37.63
Kupferminc 2002	13.24	2.60	67.42
Infante-Rivard 2002	1.19	.63	2.24
Martinelli 2001	6.87	1.41	33.55
Lee 2001	10.85	.55	214.13
Kupferminc 1999	1.89	.57	6.30
Random Combined (9)	**2.72**	**1.35**	**5.49**



C *PGV only*

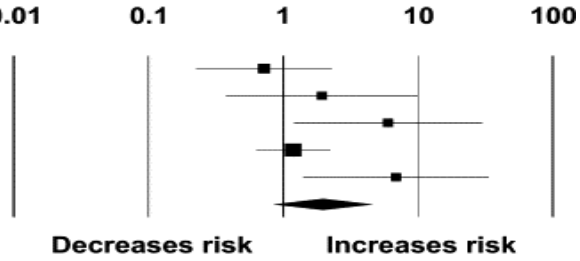
Citation	Effect	Lower	Upper
McCowan 2003	.89	.27	2.93
Franchi 2003	.20	.01	3.75
Agostaros 2003	3.50	.30	41.17
Verspyck 2002	3.06	.31	29.98
Kupferminc 2002	4.55	.77	26.68
Infante-Rivard 2002	1.05	.46	2.41
Martinelli 2001	11.93	1.43	99.56
Lee 2001	5.47	.25	120.37
Kupferminc 2000	5.45	1.82	16.33
Kupferminc 1999	4.57	1.04	20.04
Random Combined (10)	**2.51**	**1.26**	**4.98**



IUGR
Howley et al,
AJOG 2005

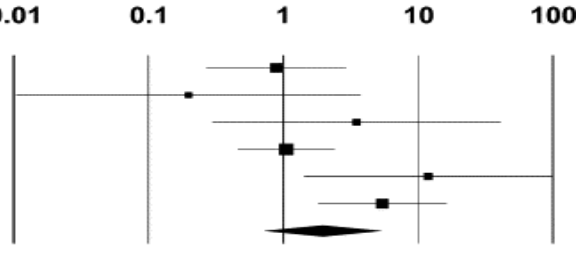
A *Birth weight <10th centile, for FVL*

Citation	Effect	Lower	Upper
McCowan 2003	.72	.23	2.30
Franchi 2003	1.93	.37	9.97
Agostaros 2003	6.00	1.20	30.10
Infante-Rivard 2002	1.19	.63	2.24
Martinelli 2001	6.87	1.41	33.55
Random Combined (5)	**1.97**	**.84**	**4.62**



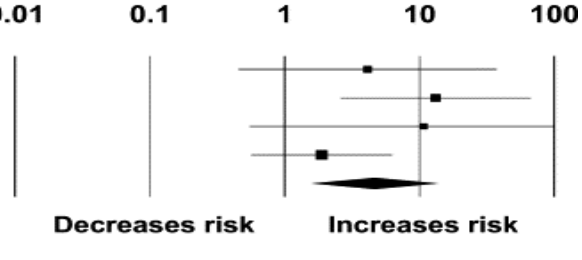
B *Birth weight <10th centile, for PGV*

Citation	Effect	Lower	Upper
McCowan 2003	.89	.27	2.93
Franchi 2003	.20	.01	3.75
Agostaros 2003	3.50	.30	41.17
Infante-Rivard 2002	1.05	.46	2.41
Martinelli 2001	11.93	1.43	99.56
Kupferminc 2000	5.45	1.82	16.33
Random Combined (6)	**1.97**	**.72**	**5.40**



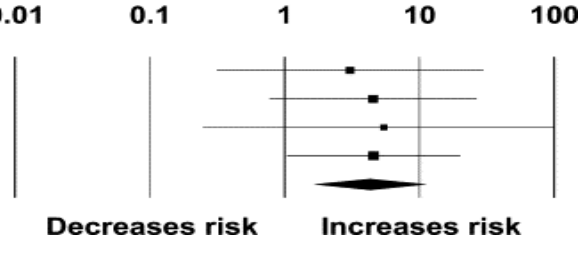
C *Birth weight <5th centile, for FVL*

Citation	Effect	Lower	Upper
Verspyck 2002	4.13	.45	37.63
Kupferminc 2002	13.24	2.60	67.42
Lee 2001	10.85	.55	214.13
Kupferminc 1999	1.89	.57	6.30
Random Combined (4)	**4.68**	**1.59**	**13.78**



D *Birth weight <5th centile, for PGV*

Citation	Effect	Lower	Upper
Verspyck 2002	3.06	.31	29.98
Kupferminc 2002	4.55	.77	26.68
Lee 2001	5.47	.25	120.37
Kupferminc 1999	4.57	1.04	20.04
Random Combined (4)	**4.32**	**1.65**	**11.35**



Inherited thrombophilia and obstetric complications – uncertain associations

- **Severe preeclampsia**

  Morrison et al, Thromb Haemost 2002

  kosmas et al, J Hypetens 2003

  Lin et al, Obstetr Gynecol 2005

- **Intrauterine growth restriction**

  Howley et al, AJOG 2005

Inherited thrombophilia and obstetric complications – uncertain associations

- **Abruptio placentae**

  Only 3 studies available (on 20, 27, and 50 cases) reporting inherited thrombophilia present in ***30 to 50%*** of cases)

CANDIDATES FOR SCREENING

- All women with recurrent unexplained fetal losses and non recurrent late unexplained fetal loss are candidates for screening.

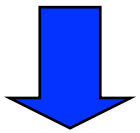
- **The population study "NOHA first" found a 2 to 3-fold increase in risk for miscarriage after 10 weeks of gestation among carriers of factor V Leiden or PT 20210A (JTH 2005)**

IS LMWH TREATMENT JUSTIFIED FOR PREGNANT WOMEN WITH PREVIOUS (RECURRENT) FETAL LOSS ?

- It has been estimated that after one miscarriage the risk of another is 20%;

- after two miscarriages it is 25%,

- and after three miscarriages 30%.



i.e.: the probability of deliver a viable newborn after three miscarriages is 70% without any pharmacological intervention

Journal of Thrombosis and Haemostasis, 1: 433–438

IN FOCUS

2003

Thromboprophylaxis improves the live birth rate in women with consecutive recurrent miscarriages and hereditary thrombophilia

H. CARP,*‡ M. DOLITZKY* and A. INBAL†

*Department of Obstetrics and Gynecology, †Institute of Thrombosis and Hemostasis, Sheba Med
Faculty of Medicine; and ‡Department of Embryology, Sackler Faculty of Medicine, Tel Aviv Univ

Summary. The effect of thromboprophylaxis with low molecular weight heparin (LMWH), on the subsequent live birth rate, in thrombophilic women with recurrent miscarriage has not been sufficiently assessed. The present study is a cohort study undertaken to assess the effect of enoxaparin on the subsequent live birth rate in women with hereditary thrombophila. Eighty-five patients with three or more consecutive pregnancy losses and a hereditary thrombophilia subsequently conceived. Thirty-seven were treated with daily subcutaneous injections of enoxaparin 40 mg and 48 were not treated. The outcome of the subsequent pregnancy was assessed in both groups of patients in terms of live births or repeat miscarriage. Forty-seven of the 85 patients were subsequently delivered, 38 have miscarried. Twenty-six of the 37 pregnancies in treated patients (70.2%) resulted in live births, compared with 21 of 48 (43.8%) in untreated patients ($P < 0.02$, OR 3.03, 95% CI 1.12–8.36). The beneficial effect was seen mainly in primary aborters, i.e. women with no previous live births ($P < 0.008$, OR 9.75, 95% CI 1.59–52.48). This benefit was also found in patients with a poor prognosis for a live birth (five or more miscarriages), where the live birth rate was increased from 18.2% to 61.6%. However, the benefit was not statistically significant, probably due to the small number of patients. If the beneficial effects of enoxaparin are confirmed by additional studies, thromboprophylaxis can be recommended for patients with hereditary thrombophilia and recurrent pregnancy loss.

2004

Low-molecular-weight heparin versus low-dose aspirin in women with one fetal loss and a constitutional thrombophilic disorder

Jean-Christophe Gris, Eric Mercier, Isabelle Quéré, Géraldine Lavigne-Lissalde, Eva Cochery-Nouvellon, Médéric Hoffet, Sylvie Ripart-Neveu, Marie-Laure Tailland, Michel Dauzat, and Pierre Marès

Table 3. Effect of the two treatments on pregnancy outcome

	N	Live births	*P* *	OR	95% CI	*P*
All women			< .0001			
Aspirin	80	23 (29%)				
Enoxaparin	80	69 (86%)		15.5	7-34	< .0001
AIIFVL			< .0001			
Aspirin	36	12 (33%)				
Enoxaparin	36	34 (94%)		34	7-166	< .0001
AIIFIIL			.0007			
Aspirin	30	10 (33%)				
Enoxaparin	30	24 (80%)		8	2.5-26	.0005
AIIPS			.0006			
Aspirin	14	01 (07%)				
Enoxaparin	14	11 (79%)		48	4-526	.0016

Reduction of high fetal loss rate by anticoagulant treatment during pregnancy in antithrombin, protein C or protein S deficient women

2007

Nienke Folkeringa,[1] Jan Leendert P. Brouwer,[1] Fleurisca J. Korteweg,[2] Nic J. G. M. Veeger,[3] Jan Jaap H. M. Erwich,[2] Jozien P. Holm[2] and Jan van der Meer[1]

[1]*Division of Haemostasis, Thrombosis and Rheology, Department of Haematology,* [2]*Department of Obstetrics and Gynaecology, and* [3]*Trial Coordination Centre, University Medical Centre Groningen, Groningen, the Netherlands*

Table III. Fetal loss in deficient and non-deficient women, who did or did not receive thromboprophylaxis during pregnancy.

	Deficient		Non-deficient	
Thromboprophylaxis	Yes	No	Yes	No
Pregnancies, *n*	45	19	4	20
Fetal loss, *n* (%)	1 (2)	11 (58)	1 (25)	1 (5)
Women, *n*	26	11	3	15
Fetal loss, *n* (%)*	0 (0)	5 (45)	1 (33)	1 (7)
	$P = 0{\cdot}001$†		$P = 0{\cdot}37$†	

*Only first pregnancy analysed.

†Compared with deficient women on thromboprophylaxis.

2008

Antithrombotic prophylaxis during pregnancy in women with deficiency of natural anticoagulants

Elvira Grandone[a], Valerio De Stefano[b], Elena Rossi[b], Filomena Cappucci[a], Donatella Colaizzo[a] and Maurizio Margaglione[a,c]

Blood Coagulation and Fibrinolysis 2008, 19:226–230

Seven of eight treated pregnancies [88.9%, 95% confidence interval (CI) 52.9–97.7] and 27 of 95 not treated pregnancies (28.4%, 95% CI 20.3–38.1) resulted in the delivery of a live newborn ($P = 0.001$), with a risk of foetal loss in untreated pregnancies 3.1 times (95% CI 1.7–3.5)

- Heparin and aspirin may be effective in preventing miscarriages in women with antiphopsholipid antibodies, but not in those without, as shown in two recent randomized controlled trials in women with at least two consecutive unexplained miscarriages (*Clark et al, Blood 2010; Kaandorp et al, NEJM 2010*)

- Efficacy of heparin has been demonstrated in two randomized pilot studies on women with a history of previous obstetric complications *(Rey et al, J Thromb Haemost 2009; Gris et al, Thromb and Haemost 2010)*

- Large studies on women with inherited thrombophilia and previous obstetric complications are urgently needed

The NEW ENGLAND JOURNAL of MEDICINE

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.

ABSTRACT

BACKGROUND

Aspirin and low-molecular-weight heparin are prescribed for women with unexplained recurrent miscarriage, with the goal of improving the rate of live births, but limited data from randomized, controlled trials are available to support the use of these drugs.

METHODS

In this randomized trial, we enrolled 364 women between the ages of 18 and 42 years who had a history of unexplained recurrent miscarriage and were attempting to conceive or were less than 6 weeks pregnant. We then randomly assigned them to receive daily 80 mg of aspirin plus open-label subcutaneous nadroparin (at a dose of 2850 IU, starting as soon as a viable pregnancy was demonstrated), 80 mg of aspirin alone, or placebo. The primary outcome measure was the live-birth rate. Secondary outcomes included rates of miscarriage, obstetrical complications, and maternal and fetal adverse events.

Table 4. Live-Birth Rate in Prespecified Subgroups.*

Subgroup	Aspirin plus Nadroparin				Aspirin Only				Placebo
	Patients per Subgroup	Absolute Difference in Live-Birth Rate (95% CI)	Relative Risk (95% CI)	P Value for Interaction	Patients per Subgroup	Absolute Difference in Live-Birth Rate (95% CI)	Relative Risk (95% CI)	P Value for Interaction	Patients per Subgroup
	no./total no.				*no./total no.*				*no./total no.*
Inherited thrombophilia†									
Yes	9/13	16.3 (−18.2 to 50.8)	1.31 (0.74 to 2.33)	0.18	11/17	11.8 (−21.1 to 44.6)	1.22 (0.69 to 2.16)	0.32	9/17
No	45/92	−9.1 (−23.9 to 5.7)	0.84 (0.64 to 1.11)		42/82	−6.8 (−22.1 to 8.4)	0.88 (0.67 to 1.17)		47/81
Previous live birth									
Yes	27/53	−7.8 (−27.3 to 11.8)	0.87 (0.61 to 1.24)	0.49	23/45	−7.6 (−28.0 to 12.8)	0.87 (0.60 to 1.27)	0.89	27/46
No	40/70	1.1 (−15.0 to 17.3)	1.02 (0.77 to 1.36)		38/75	−5.3 (−21.3 to 10.6)	0.91 (0.67 to 1.22)		42/75
Age									
<36 yr	45/76	−3.1 (−18.6 to 12.3)	0.95 (0.74 to 1.23)	0.90	41/79	−10.4 (−25.9 to 5.0)	0.83 (0.63 to 1.10)	0.44	48/77
≥36 yr	22/47	−0.9 (−21.4 to 19.6)	0.98 (0.64 to 1.51)		20/41	1.1 (−20.2 to 22.3)	1.02 (0.66 to 1.59)		21/44
No. of miscarriages									
≥3	35/73	−3.4 (−19.6 to 12.8)	0.93 (0.67 to 1.29)	0.85	32/71	−6.3 (−22.5 to 10.0)	0.88 (0.63 to 1.23)	0.92	38/74
2	32/50	−2.0 (−20.9 to 17.0)	0.97 (0.72 to 1.30)		29/49	−6.8 (−26.1 to 12.5)	0.90 (0.66 to 1.22)		31/47

* Absolute differences in live-birth rate and relative risks were calculated for the comparison between patients receiving aspirin plus nadroparin (combination-therapy group) and the placebo group and between the aspirin-only group and the placebo group.
† A total of 302 of 364 women (83.0%) underwent a complete evaluation for inherited thrombophilia.

blood

2014 123: 822-828
Prepublished online December 19, 2013;
doi:10.1182/blood-2013-01-478958

Meta-analysis of low-molecular-weight heparin to prevent recurrent placenta-mediated pregnancy complications

Marc A. Rodger, Marc Carrier, Grégoire Le Gal, Ida Martinelli, Annalisa Perna, Évelyne Rey, J. I. P. de Vries and Jean-Christophe Gris

Table 1. Characteristics of studies included in the meta-analysis

Reference	Year	Country	Center	No. of participants	Previous outcome	Intervention/control	Primary outcome
12	2012	Multi-national		139	Prior early onset PE (n = 107) and/or SGA <10th percentile (n = 94)	Dalteparin 5000 IU + ASA vs ASA	PE prior to 34 wk GA
13	2012	Italy	Multi-center	135	Prior PE (n = 52), prior loss >15 weeks (n = 49), prior SGA <10th percentile (n = 28), or prior abruption (n = 5)	Nadroparin 3800 IU vs no nadroparin	PE, loss >15 wk GA, SGA <10th percentile, and/or abruption
9	2011	France	Single center	224	Prior severe PE (n = 224)	Enoxaparin 4000 IU + ASA vs ASA	PE, SB, abruption, SGA <5th percentile
11	2010	France	Single center	160	Prior abruption (n = 160; 70 with PE)	Enoxaparin 4000 IU ± ASA vs ± ASA	PE, SB, abruption, SGA <5th percentile
10	2009	Canada	Multi-center	116	Prior early PE (n = 60) Prior abruption (n = 16) Prior SGA <5th percentile (n = 21) Loss >12 wk (n = 17)	Dalteparin 5000 IU ± ASA vs ± ASA	PE, SB, abruption, SGA <5th percentile
14	2005	Italy	Single center	80	Prior PE with ACE DD (n = 80)	Dalteparin 5000 IU vs no dalteparin	PE, SGA <10th percentile

ACE DD, angiotensin converting enzyme deletion/deletion genotype; GA, gestational age; SB, stillbirth.

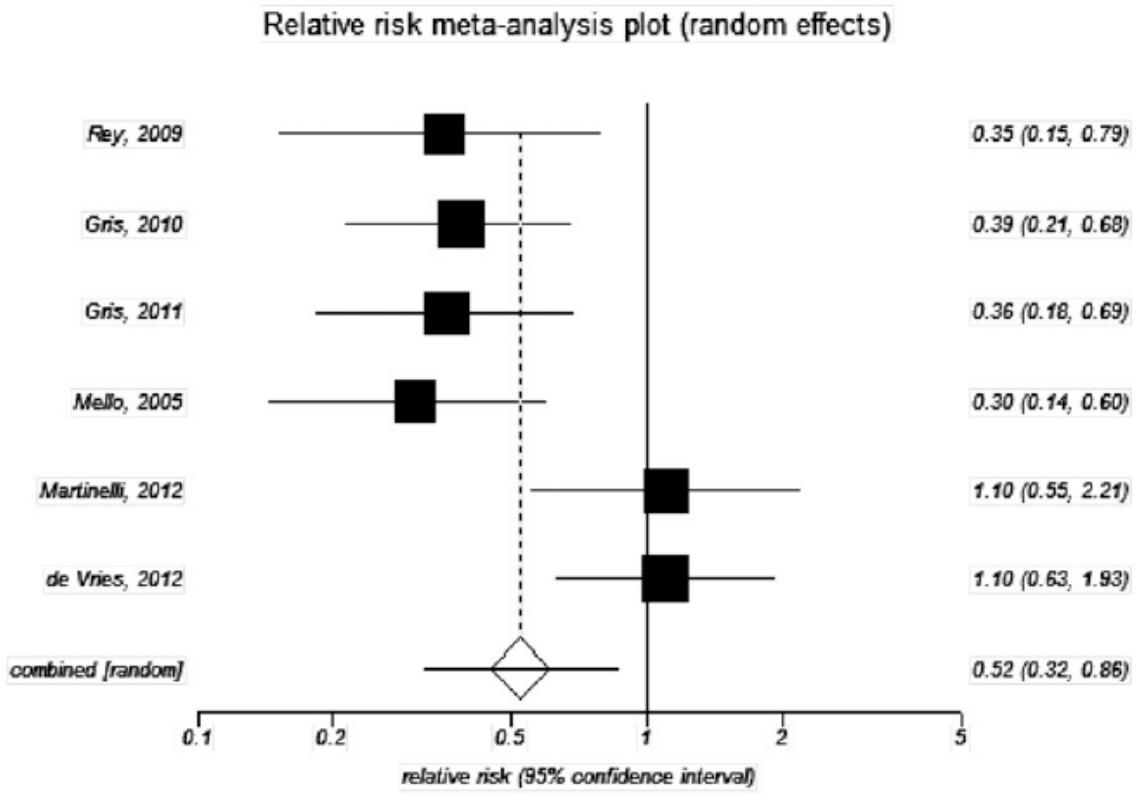


Figure 2. Primary outcome analysis. RR reduction of recurrent placenta-mediated pregnancy complications (any PE, placental abruption, SGA child [<10th percentile] or pregnancy loss >20 weeks) with LMWH in women with prior placenta-mediated pregnancy complications (PE, SGA child [<10th percentile], late pregnancy loss [>12weeks] or placental abruption).

Low-molecular-weight heparin and recurrent placenta-mediated pregnancy complications: a meta-analysis of individual patient data from randomised controlled trials *(Rodger et al, Lancet 2016)*

- Data from 963 eligible women in eight trials: 480 randomly assigned to LMWH and 483 randomly assigned to no LMWH; 403/963 (42%) had thrombophilia.
- In the primary analysis, LMWH did not significantly reduce the risk of recurrent placenta-mediated pregnancy complications (LMWH 62/444 [14%] versus no LMWH 95/443 (22%), p=0·09; relative risk 0·64, 95% CI 0·36–1·11, p=0·11).
- In subgroup analyses, lLMWH in multicentre trials reduced the primary outcome in women with previous abruption (p=0·006) but not in any of the other subgroups of previous complications.

9 th ACCP Conference, Chest 2012

Recommendations

10.2.1. For women with recurrent early pregnancy loss (three or more miscarriages before 10 weeks of gestation), we recommend screening for APLAs (Grade 1B).

10.2.2. For women with a history of pregnancy complications, we suggest not to screen for inherited thrombophilia (Grade 2C).

10.2.3. For women who fulfill the laboratory criteria for APLA syndrome and meet the clinical APLA criteria based on a history of three or more pregnancy losses, we recommend antepartum administration of prophylactic- or intermediate-dose UFH or prophylactic LMWH combined with low-dose aspirin, 75 to 100 mg/d, over no treatment (Grade 1B).

10.2.4. For women with inherited thrombophilia and a history of pregnancy complications, we suggest not to use antithrombotic prophylaxis (Grade 2C).

Royal College of Obstetricians & Gynaecologists

The Investigation and Treatment of Couples with Recurrent First-trimester and Second-trimester Miscarriage

Green–top Guideline No. 17

April 2011

5.4 Thrombophilias

Women with second-trimester miscarriage should be screened for inherited thrombophilias including factor V Leiden, factor II (prothrombin) gene mutation and protein S. D

A meta-analysis[68] of retrospective studies has reported a strong association between second-trimester miscarriage and inherited thrombophilias: factor V Leiden, factor II (prothrombin) gene mutation and protein S deficiency. Evidence level 2++

6.6 Inherited thrombophilias

There is insufficient evidence to evaluate the effect of heparin in pregnancy to prevent a miscarriage in women with recurrent first-trimester miscarriage associated with inherited thrombophilia. C

Heparin therapy during pregnancy may improve the live birth rate of women with second-trimester miscarriage associated with inherited thrombophilias. A

Women with known heritable thrombophilia are at an increased risk of venous thromboembolism. See RCOG Green-top Guideline No. 37a: ***Reducing the risk of thrombosis and embolism during pregnancy and the puerperium***.116

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

Daniela Tormene[1]; Elvira Grandone[2]; Valerio De Stefano[3]; Alberto Tosetto[4]; Gualtiero Palareti[5]; Maurizio Margaglione[6]; Giancarlo Castaman[4]; Elena Rossi[3] ; Angela Ciminello[3]; Leila Valdrè[5]; Cristina Legnani[5]; Giovanni Luca Tiscia[2]; Valeria Bafunno[6]; Sara Carraro[1]; Francesco Rodeghiero[4]; Paolo Simioni[1]

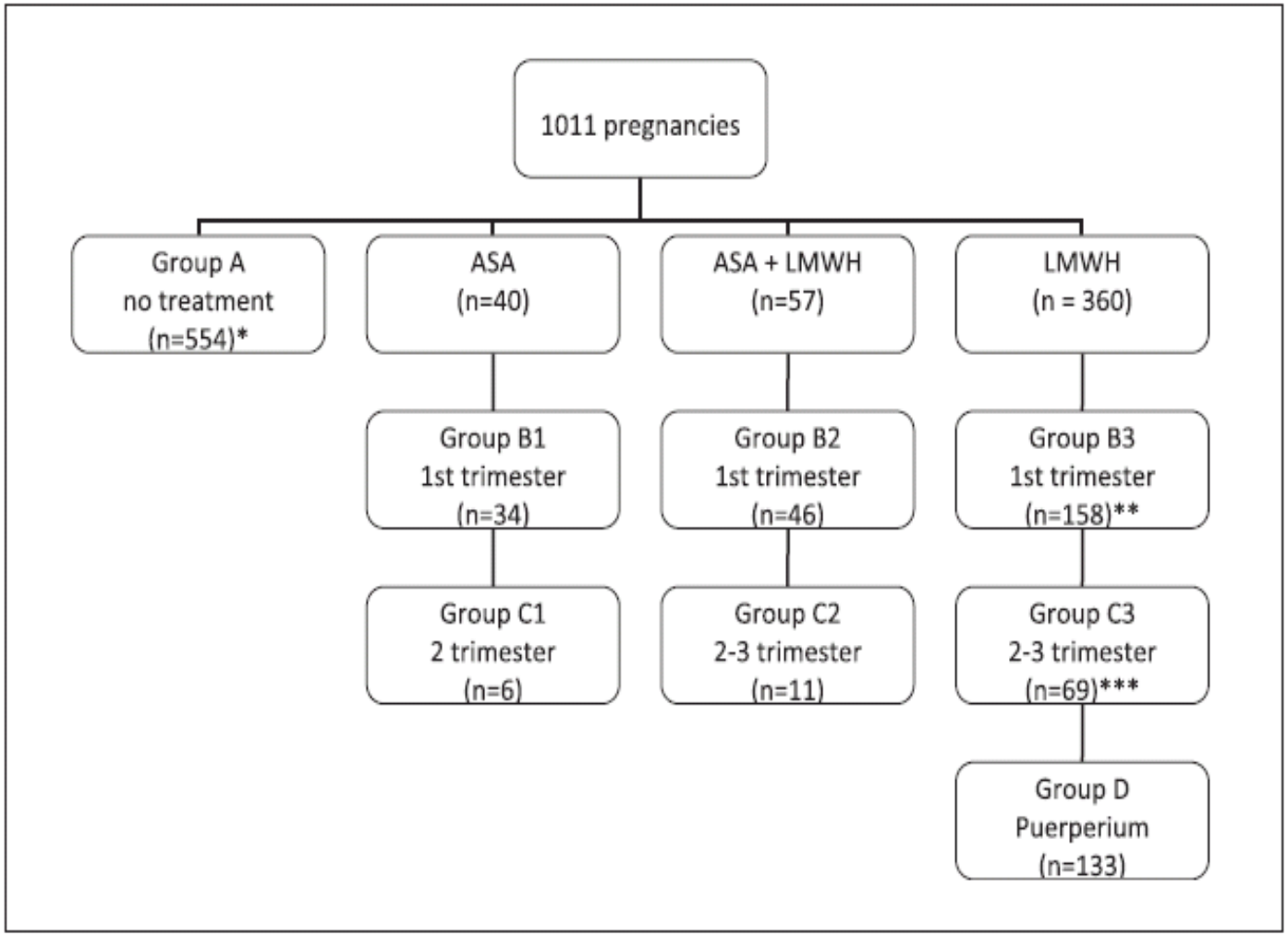
[1]Department of Cardiologic, Thoracic and Vascular Sciences, 2nd Chair of Internal Medicine, University of Padua, Padua, Italy; [2]Thrombosis & Haemostasis Unit, IRCCS "Casa Sollievo della Sofferenza", S. Giovanni Rotondo, Foggia, Italy; [3]Department of Hematology, Catholic University, Rome, Italy; [4]Department of Hematology, San Bortolo Hospital, Vicenza, Italy; [5]Department of Angiology and Coagulation Disorders, University of Bologna, Italy; [6]Medical Genetics, University of Foggia, Foggia, Italy

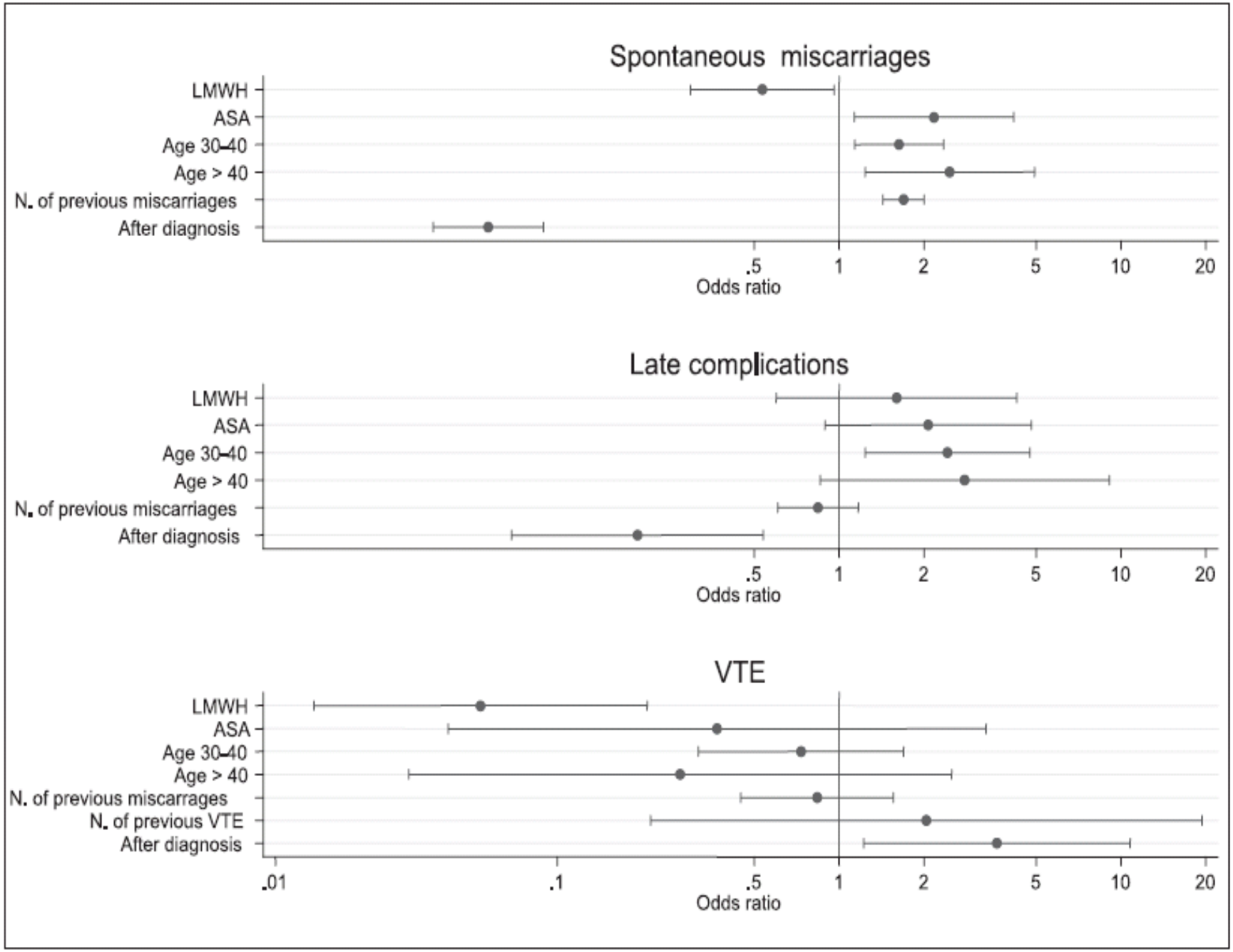
Thrombosis and Haemostasis, 2012; 107: 477

Table 1: Characteristics of investigated subjects.

	FV Leiden		Prothrombin G20210A		Double heterozygous (n=16)	P
	Heterozygous (n=255)	Homozygous (n=10)	Heterozygous (n=133)	Homozygous (n=2)		
Total number of pregnancies	617	22	332	3	37	-
Mean number of pregnancies (per subject)	2.4	2.2	2.5	1.5	2.4	0.85
Median age at first pregnancy (range)	30 (18–46)	27 (18–33)	30.0 (18–42)	32 (31–32)	30 (22–40)	0.23
Number of pregnancies after diagnosis of thrombophilia	318	12	160	2	19	0.84*
Median age at first pregnancy followed after diagnosis of thrombophilia (range)	34 (22–46)	31 (25–34)	34 (20–46)	32.5 (32–33)	37 (22–44)	0.01
Reason for screening (%)						
Fortuitous	19.8	11.2	18.4	0	14.3	0.02
VTE history	16.4	44.4	17.2	0	14.3	
Family history of VTE	30.4	44.4	20.2	100	50.0	
Obstetrical complications	33.4	0	44.2	0	21.4	

* vs. number of pregnancies before diagnosis


1011 pregnancies
Group A
no treatment
(n=554)*
ASA
(n=40)
ASA + LMWH
(n=57)
LMWH
(n = 360)
Group B1
1st trimester
(n=34)
Group B2
1st trimester
(n=46)
Group B3
1st trimester
(n=158)**
Group C1
2 trimester
(n=6)
Group C2
2-3 trimester
(n=11)
Group C3
2-3 trimester
(n=69)***
Group D
Puerperium
(n=133)


Spontaneous miscarriages
LMWH
ASA
Age 30–40
Age > 40
N. of previous miscarriages
After diagnosis
.5
1
2
5
10
20
Odds ratio
Late complications
LMWH
ASA
Age 30–40
Age > 40
N. of previous miscarriages
After diagnosis
.5
1
2
5
10
20
Odds ratio
VTE
LMWH
ASA
Age 30–40
Age > 40
N. of previous miscarrages
N. of previous VTE
After diagnosis
.01
.1
.5
1
2
5
10
20
Odds ratio

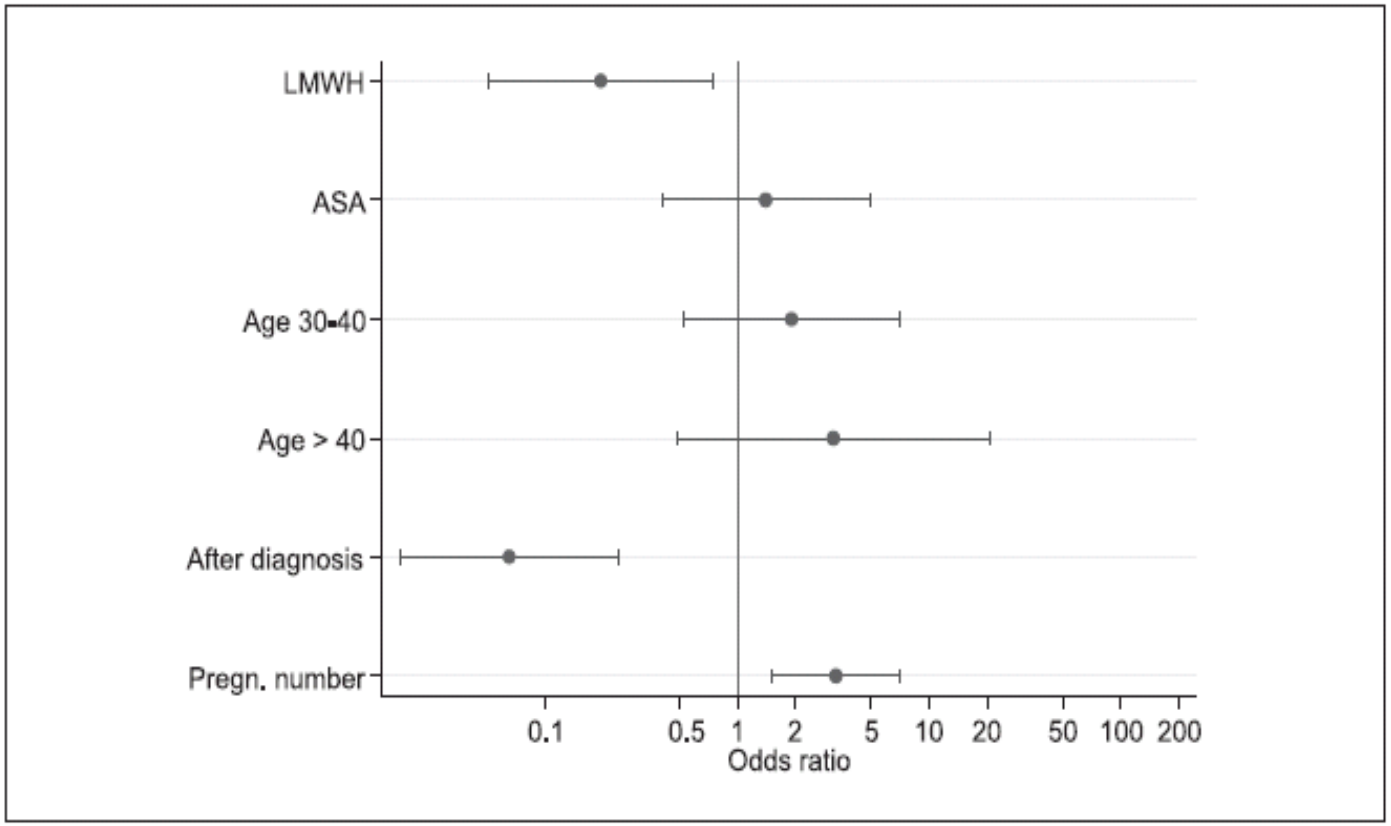


Figure 3: Live birth probability: nested analysis. Exclusion of pregnancies treated from 2nd and 3rd trimester.

CONCLUSIONS

- The pregnancy-related thrombotic risk of thrombophilic women is dependent on history but also on type of thrombophilia.
- Extreme caution should be adopted for women with rare thrombophilic abnormalities, in whom reports offer controversial data.
- LMWH is not justified for prevention of recurrent fetal loss in women without thrombophilia. But results of RCT cannot applied to thrombophilic women, in whom there is evidence of benefit.