Thrombophilie-Screening vor Kontrazeptiva

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OC and HRT and venous thromboembolism

Oral contraceptives

- Fatal VTE
- Thrombophilia and OC-related VTE
- OC, thrombophilia and stroke

Hormone replacement

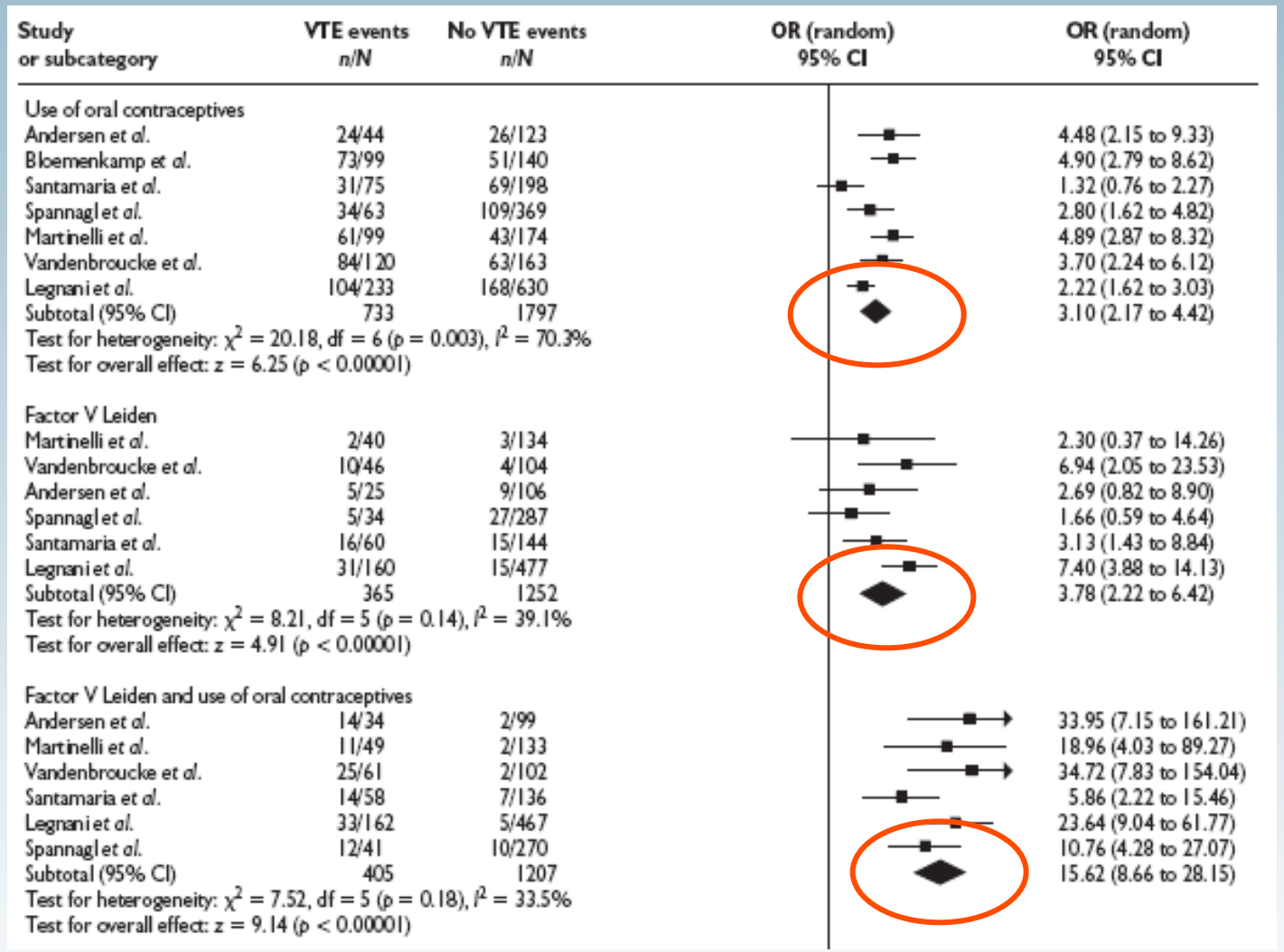
- Risk with different applications
- Thrombophilia and HRT-related VTE

Fatal PE and OC

	Time period	Absolute risk / million	Relative risk OR (95%CI)
Sweden	**1990-99**	**7.5 (4.7-10.3)**	**6.0 (3.1-10.5)**
New Zealand	**1990-98**	**10.5 (6.2-16.6)**	**OR 6.5 (2.6-16.1)**

Samulesson E et al. *Eur J Epidemiol* 2005;**20**:509-16
Parkin L et al. *Lancet* 2000,**355**:2133-4

Odds ratios for OC and Factor V Leiden



Study or subcategory	VTE events n/N	No VTE events n/N	OR (random) 95% CI	OR (random) 95% CI
Use of oral contraceptives				
Andersen et al.	24/44	26/123		4.48 (2.15 to 9.33)
Bloemenkamp et al.	73/99	51/140		4.90 (2.79 to 8.62)
Santamaria et al.	31/75	69/198		1.32 (0.76 to 2.27)
Spannagl et al.	34/63	109/369		2.80 (1.62 to 4.82)
Martinelli et al.	61/99	43/174		4.89 (2.87 to 8.32)
Vandenbroucke et al.	84/120	63/163		3.70 (2.24 to 6.12)
Legnani et al.	104/233	168/630		2.22 (1.62 to 3.03)
Subtotal (95% CI)	733	1797		3.10 (2.17 to 4.42)
Test for heterogeneity: $\chi^2 = 20.18$, df = 6 ($p = 0.003$), $I^2 = 70.3\%$				
Test for overall effect: $z = 6.25$ ($p < 0.00001$)				
Factor V Leiden				
Martinelli et al.	2/40	3/134		2.30 (0.37 to 14.26)
Vandenbroucke et al.	10/46	4/104		6.94 (2.05 to 23.53)
Andersen et al.	5/25	9/106		2.69 (0.82 to 8.90)
Spannagl et al.	5/34	27/287		1.66 (0.59 to 4.64)
Santamaria et al.	16/60	15/144		3.13 (1.43 to 8.84)
Legnani et al.	31/160	15/477		7.40 (3.88 to 14.13)
Subtotal (95% CI)	365	1252		3.78 (2.22 to 6.42)
Test for heterogeneity: $\chi^2 = 8.21$, df = 5 ($p = 0.14$), $I^2 = 39.1\%$				
Test for overall effect: $z = 4.91$ ($p < 0.00001$)				
Factor V Leiden and use of oral contraceptives				
Andersen et al.	14/34	2/99		33.95 (7.15 to 161.21)
Martinelli et al.	11/49	2/133		18.96 (4.03 to 89.27)
Vandenbroucke et al.	25/61	2/102		34.72 (7.83 to 154.04)
Santamaria et al.	14/58	7/136		5.86 (2.22 to 15.46)
Legnani et al.	33/162	5/467		23.64 (9.04 to 61.77)
Spannagl et al.	12/41	10/270		10.76 (4.28 to 27.07)
Subtotal (95% CI)	405	1207		15.62 (8.66 to 28.15)
Test for heterogeneity: $\chi^2 = 7.52$, df = 5 ($p = 0.18$), $I^2 = 33.5\%$				
Test for overall effect: $z = 9.14$ ($p < 0.00001$)				

Wu O et al. *Health Technol Assess* 2006;**10**:1-110

Thrombophilia and OC-related VTE: Homozygous Factor V Leiden

- Case-control study in 50 women with homozygous Factor V Leiden and 50 control women

OR for OC in homozygous women

4.0 (95%CI 1.6–10.4)

- This risk is superimposed on the 50-120-fold increased risk of homozygous patients

Ehrenforth S et al. *J Thromb Haemost* 2004;**2**:430-6

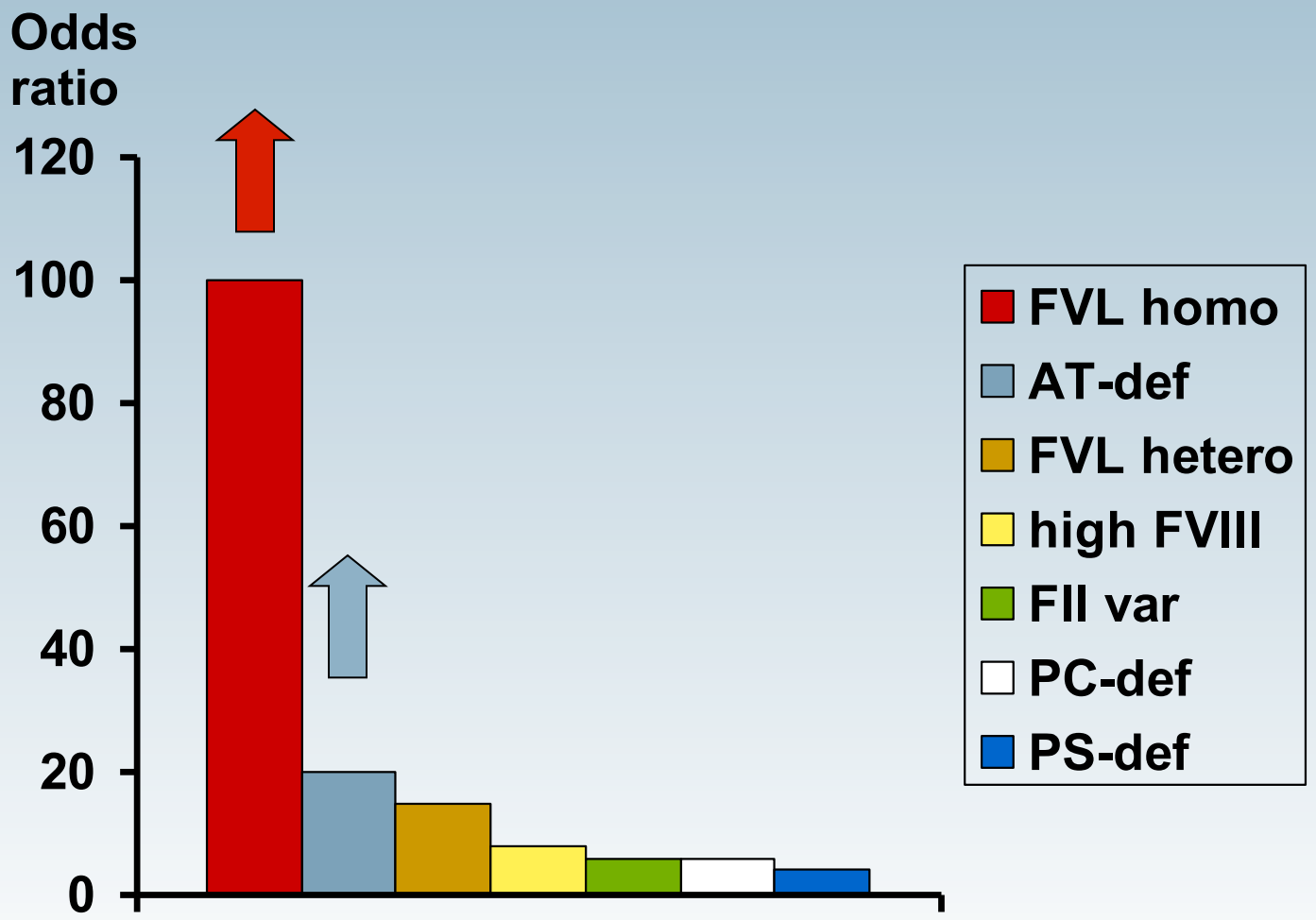
Thrombophilia and OC-related VTE
Increased Factor VIII

- Case-control study in women of reproductive age
- 174 women with VTE and 484 controls
- Higher vs lower quartile of Factor VIII

- OR 13.0 (95% CI 4.9-34)

Legnani C et al. *Haematologica* 2004;**89**:1347-51

Different thrombosis risk factors and OC-related risk of VTE vs non-thrombophilic non-user



Risk with different progestogens

- 1995: Three studies describe a higher risk with third-generation progestogens:
  - WHO Collaborative Study. *Lancet* 1995;**346**:1572-82
  - Jick H et al. *Lancet* 1995;**346**:1589-93
  - Bloemenkamp KW et al. *Lancet* 1995;**346**:1593-6

- Progestogens:

  Second-generation: Levonorgestrel

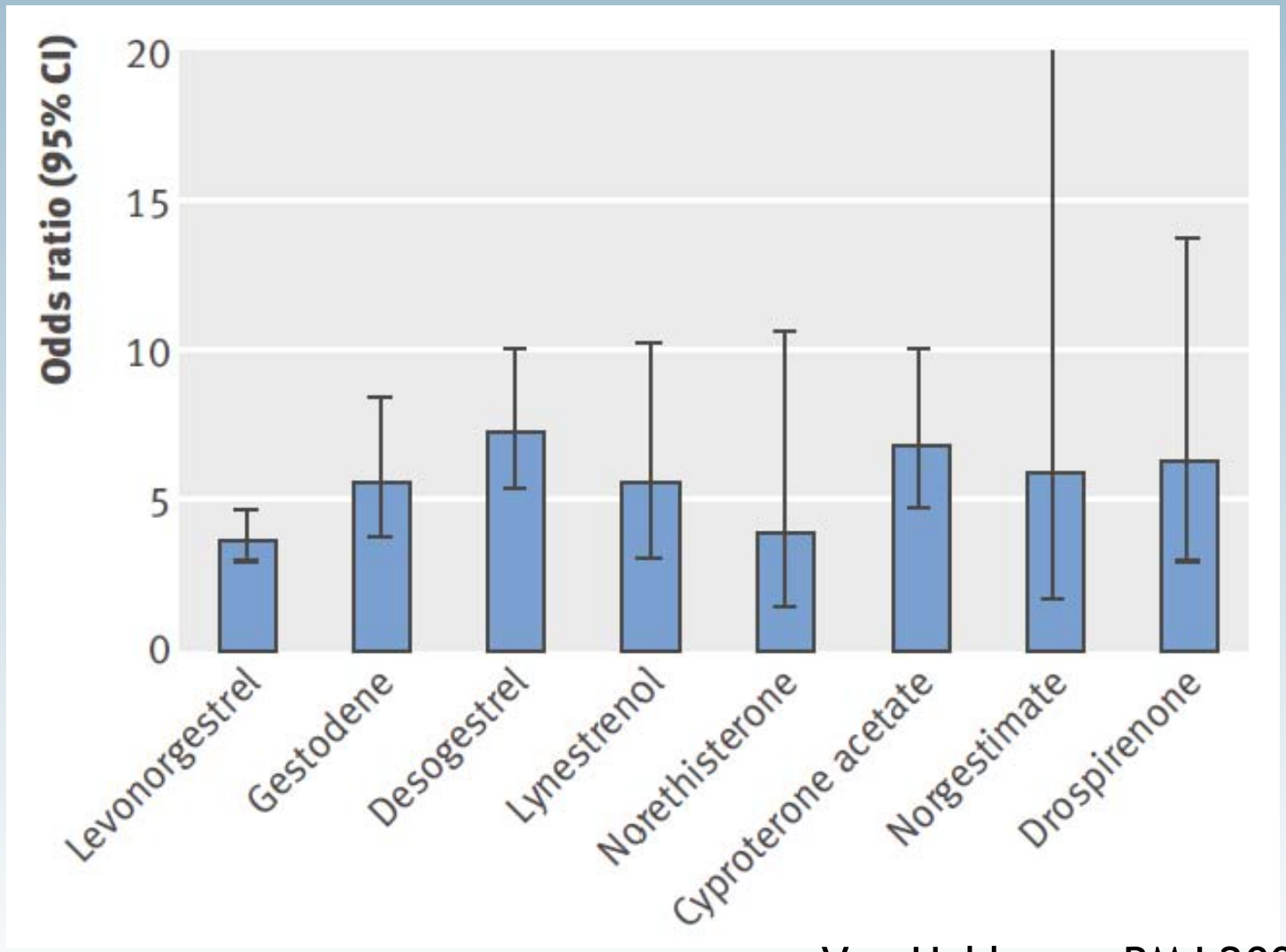
  Third-generation: Gestodene, desogestrel, norgestimate

Risk in combined OCs: Ethinylestradiol with different progestogens

Study	OR 2nd	OR 3rd
Jick, 1995	2.2	9.2
Bloemenkamp, 1995	3.8	8.7
WHO, 1995	3.6	7.4
Spitzer, 1996	3.0	4.4

Spitzer WO et al. *BMJ* 1996;**312**:83-8

Risk of venous thrombosis associated with different types of progestogens in combined oral preparations



Van Hyklama, BMJ 2009

Risk of different types of venous thrombosis associated with oral contraceptive use by different type of progestogen.

Type of progestogen	No of controls	Deep venous thrombosis of leg		Pulmonary embolism*	
		No of patients	Odds ratio (95% CI)†	No of patients	Odds ratio (95% CI)†
All	654	661	6.6 (5.4 to 8.0)	407	3.9 (3.2 to 4.8)
Levonorgestrel‡	373	300	5.0 (3.8 to 6.5)	171	2.8 (2.1 to 3.8)
Gestodene‡	67	74	8.1 (5.2 to 12.7)	43	3.8 2.2 to 6.3)
Desogestrel‡	108	159	8.7 (6.1 to 12.4)	122	7.1 (4.9 to 10.4)
Lynestrenol‡	19	27	7.3 (3.7 to 14.2)	15	4.5 (2.1 to 9.6)
Norethisterone	7	7	5.4 (1.8 to 16.6)	4	3.1 (0.8 to 11.5)
Cyproterone acetate	62	77	9.4 (6.1 to 14.3)	41	5.6 (3.4 to 9.2)
Norgestimate	4	5	8.7 (2.1 to 35.5)	4	5.2 (1.1 to 23.7)
Drospirenone	14	12	9.1 (3.9 to 21.5)	7	6.2 (2.2 to 17.6)
No oral contraceptive (reference)	1102	197	1	198	1

*With or without deep venous thrombosis.
†Odds ratio per type of progestogen adjusted for age and period of inclusion (categorical; divided per 6 calendar months).
‡Analysis restricted to preparation with most commonly used dose of oestrogen. For levonorgestrel, gestodene, and desogestrel, this was 30 µg (388 patients with deep venous thrombosis of the leg, 242 patients with pulmonary embolism, and 385 controls). For lynestrenol, this was 37.5 µg (25 patients with deep venous thrombosis of the leg, 15 with pulmonary embolism, and 19 controls).

Van Hyklama, BMJ 2009

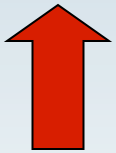
Risk with different progestogens

- Haemostatic changes:

  Third generation vs levonorgestrel:

APC-r Rosing J et al. *Lancet* 1999;**354**:2036-40

Protein S Tans G et al. *Thromb Haemost* 2000;**84**:15-21



F 1+2 Collaborative study; unpublished

Mean change in APC-r, SHBG, and protein S before (pre), and after (post) switch to a contaceptive ring or patch

Women switched from OC to ring (n=65) or patch (n=55)

Mean change in APC-r, SHBG, and protein S before (pre), and after (post) treatment with a CR or CP, all subjects

		APC-r ratio (95% CI)[a]	SHBG (nmol/L) (95% CI)[b]	Protein S % (95% CI)[c]
Contraceptive ring	Pre	3.07 (2.93 to 3.20)	147.6 (128.5 to 166.7)	88.3 (83.3 to 93.3)
	Post	3.09 (2.96 to 3.22)	146.0 (132.6 to 159.4)	93.6 (89.1 to 98.1)
	Mean change	0.02 (−0.10 to 0.14)	−1.6 (−16.6 to 13.5)	5.3 (1.1 to 9.6)
	p value	.698	.834	.014
Contraceptive patch	Pre	2.93 (2.79 to 3.08)	157.6 (136.5 to 178.8)	88.9 (82.9 to 94.9)
	Post	2.99 (2.85 to 3.14)	187.5 (167.0 to 208.0)	81.8 (76.8 to 86.8)
	Mean change	0.06 (−0.06 to 0.18)	29.9 (9.6 to 50.1)	−7.1 (−12.1 to −2.1)
	p value	.296	.005	.006
p value between groups	Mean change	0.647	0.012	<0.001

[a] APC-r ratio normal range >2.19.
[b] SHBG normal range 20–175 ng/mL.
[c] Protein S % of normal activity, normal range 73–149%.

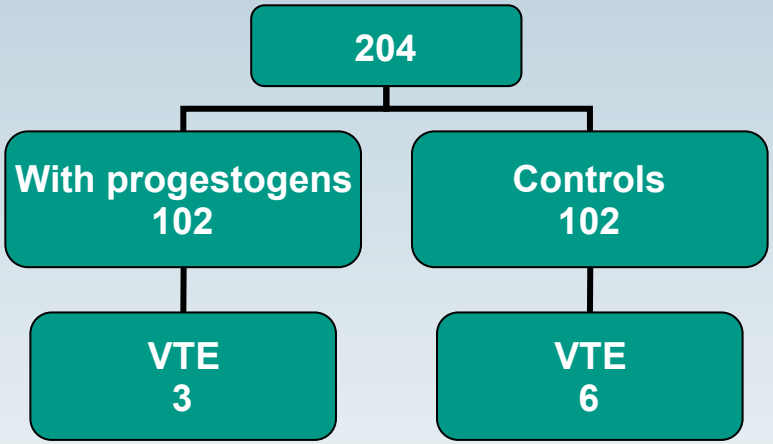
Risk of VTE in progestogen-only preparations

Route	Pts/Ctr	OR	95% CI
Oral	21/64	1.74	0.76-3.99
Intradermal	21/63	1.82	0.79-4.22
Bolus injection	11/34	2.19	0.66-7.26

WHO study. *Contraception* 1998;**57**:315-24

Risk of VTE in a cohort of women with progestogen-only contraception

Retrospective analysis of 204 women with high risk for VTE



OR 0.8 (0.2-3.9)

Conard J et al. *Contraception* 2004;**70**:437-41

Thrombophilia and OC in young women with stroke

119 women of fertile age with a history of ischaemic stroke

Factor V Leiden	OC	OR (95% CI)
No	No	1
No	Yes	2.1 (1.3-3.6)
Yes	No	1.4 (0.3-7.3)
Yes	Yes	12.9 (1.3-134)

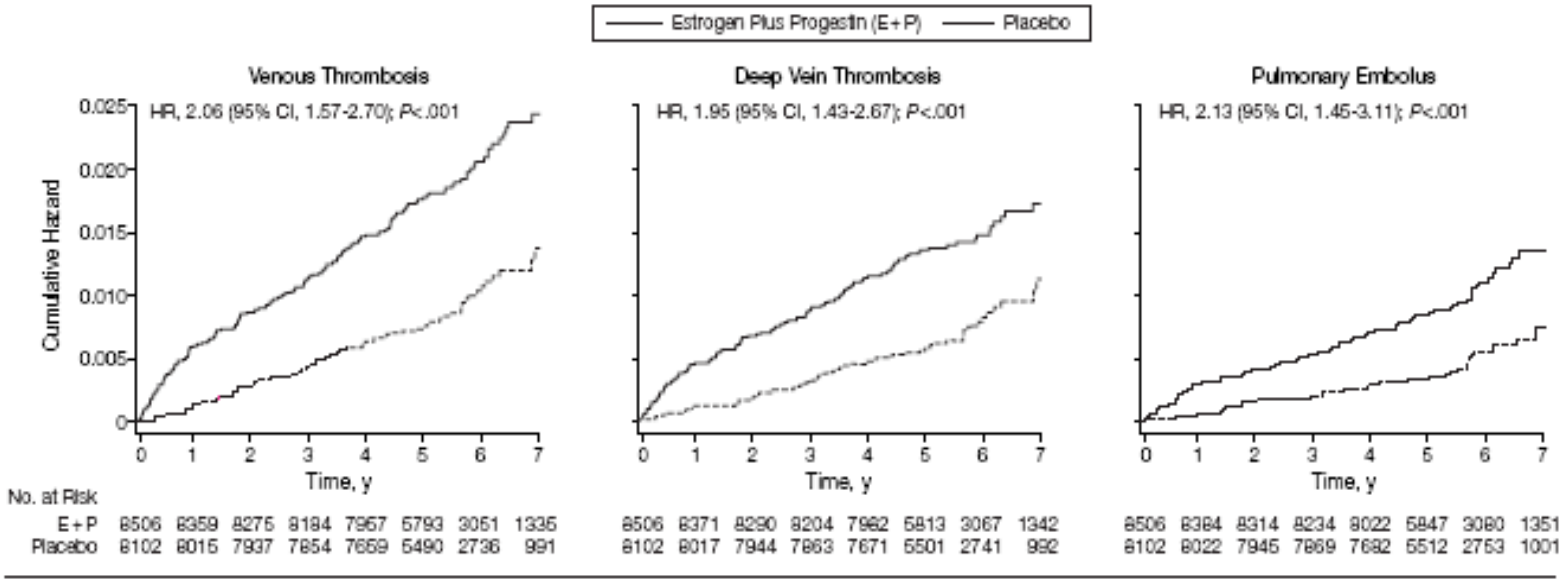
Martinelli I et al. *Haematologica* 2006;**91**:844-7

Hormone replacement therapy and venous thromboembolism

- First reports on a 2-4-fold increased risk
  - Daly E et al. *Lancet* 1996;**348**:977-81
  - Jick H et al, *Lancet* 1996;**348**:981-3
  - Grodstein F et al. *Lancet* 1996;**348**:983-7

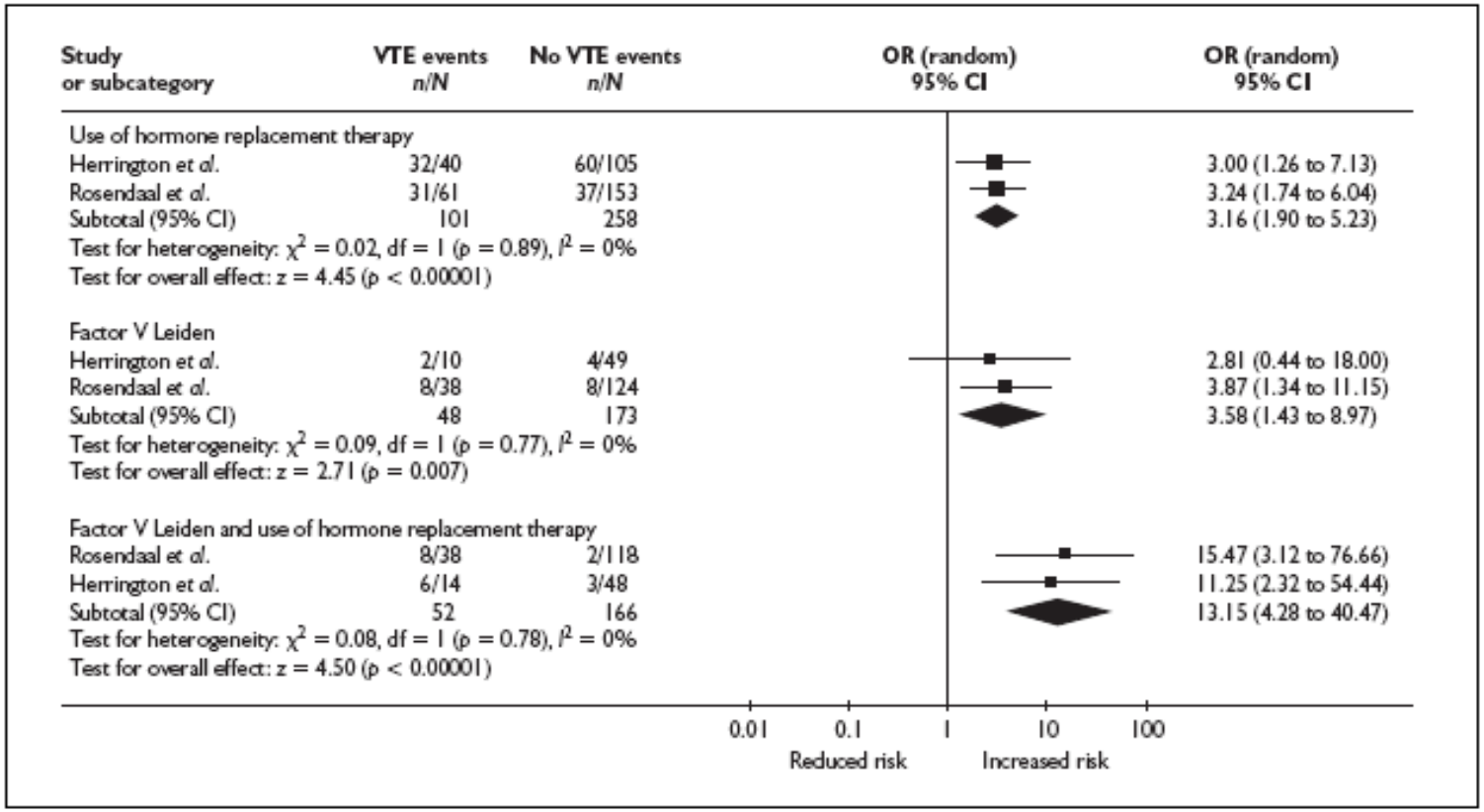
HRT and subsequent VTE: Data from the Women‘s Health Initiative

Observational nested case-control study in 16,608 women
Cases took oestrogen and medroxyprogesterone acetate



Cushman M et al. *JAMA* 2004;**292**:1573-80

Risk of VTE in women with HRT and thrombophilia



Wu O et al. *Health Technol Assess* 2006;**10**:1-110

Concluding remarks

- OC and HRT are relevant risk factors for the increase of VTE in the population
- Thrombophilia enhances the risk considerably, specifically the Factor V Leiden mutation and antithrombin-deficiency
- A general thrombophilia screening is not recommended
- Screening seems presently to be justified in women at high risk for VTE (family members of individuals with homozygous or heterozygous Factor V Leiden or antithrombin deficiency)
- Specific decisions on an individual basis may influence the risk of VTE in high-risk patients
  - Progestogen-only or levonorgestrel-containing OCs
  - Oestrogen-only or transdermal HRTs