

Contraception and Venous Thromboembolism



Elvira Grandone
Università di Foggia
&

*I.R.C.C.S. “Casa Sollievo della Sofferenza”
San Giovanni Rotondo (FG)*

FROM HEAD TO TOE,
TAKE CONTROL:
PREVENT THROMBOSIS,
PROTECT YOUR HEALTH

WORLD THROMBOSIS DAY

📍 13 OCTOBER



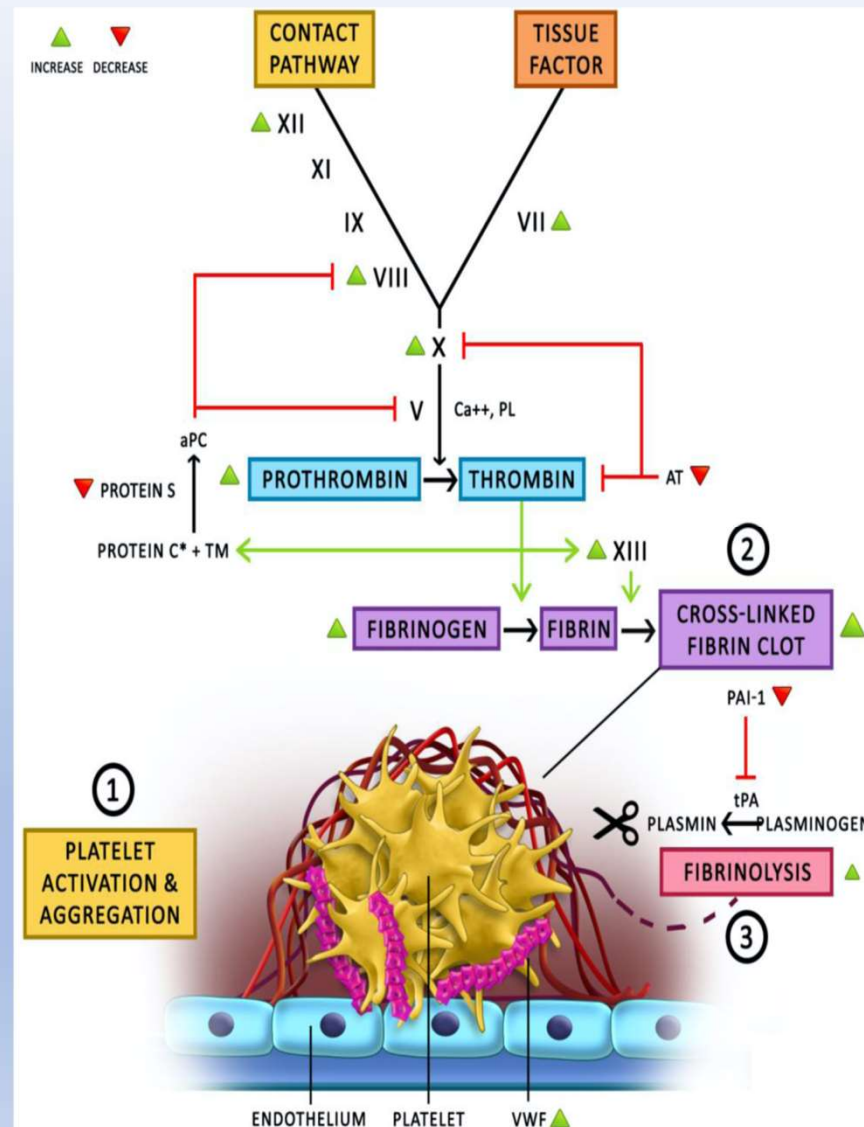
Agenda

- Physiopathological characteristics of Estrogen and Progestogen
- Risk profile by product type and route of administration
- Risk of recurrence

Agenda

- Physiopathological characteristics of Estrogen and Progestogen
- Risk profile by product type and route of administration
- Risk of recurrence

Current understanding of the effects of estrogen on hemostasis & thrombosis



Abou-Ismaïl MY, C et al.. Estrogen and thrombosis: A bench to bedside review. *Thromb Res.* 2020 ;192:40-51

Progestogens Impact on Haemostasis

Few clinical studies have focused on the effect of progestogen only therapy on the hemostatic system in vivo.

Most of the current knowledge regarding the in vivo effect of progestogens on hemostasis is obtained from studies with combined contraceptives.

Progestogen-Only Pill: Impact on Haemostasis

- Very old studies showed no significant effect on the plasma levels of coagulation factors and inhibitors as well as fibrinolytic capacity.
- One study demonstrated increased rate of **platelet aggregation** in women treated with POP supporting the platelet activating capacity of progestogens previously reported in animal models and in cell studies.

Progestogens Impact on Haemostasis Studies in Human Cell Lines

- Human cell culture studies are inconclusive.
- The observed effects are dependent on the cell lines and the progestogen formulation used.
- The noted effect of progestogens on platelet activation supports the findings recorded in animal studies and may indicate that **platelet aggregation** is augmented by progestogens.

Progestogens Impact on Haemostasis Animal Studies

- The combined results of the animal studies imply that progestogens, in particular MPA, are without an effect on the plasma concentration of most coagulation factors and has a modest effect on fibrinolysis.
- The effects on platelet function and fibrinogen may be significant and were supported by studies in human cell lines.

Progestogen-Only Pill: Impact on Haemostasis

- Desogestrel (DSG) and LNG have been reported to be associated with a reduction in the activity of FVII and reduced plasma concentration of prothrombin fragment 1 + 2 (F1 + 2) indicating that both progestogens reduced the potency of the tissue factor induced pathway of coagulation and the turnover of prothrombin.
- The effect of progestogens on FVII was confirmed in a study of the effect of DRSP and DSG on the hemostatic system (*Regidor PA, et al. Gynecol Endocrinol 2016*).

Agenda

- Physiopathological characteristics
- Risk profile by product type and route of administration
- Risk of recurrence

COC & TEV

Features to be taken into account

- EE dose
- Type of Estrogen (*E2, 17 β -estradiol; E2V, estradiol valerate; E4, estetrol*)
- Type of Progestogen
- Administration Route

The venous thrombotic risk of oral contraceptives, effects of oestrogen dose and progestogen type: results of the MEGA case-control study

A van Hylckama Vlieg, research fellow,¹ F M Helmerhorst, professor of clinical epidemiology of fertility,^{1,2} J P Vandenbroucke, professor of clinical epidemiology,¹ C J M Doggen, research fellow,¹ F R Rosendaal, professor of clinical epidemiology, head of department^{1,3,4}

Table 4 | The risk of venous thrombosis associated with different doses of ethinylestradiol in monophasic oral contraceptives. Data are odds ratios adjusted for age (95% CI) unless stated otherwise

Ethinylestradiol dose (µg)	Percentage use among controls*	Levonorgestrel	Gestodene	Desogestrel
20	11.2	1.1 (0.4 to 3.1)	0.3 (0.2 to 0.7)	0.7 (0.4 to 1.2)
30†	84.4	1	1	1
50	4.4	2.2 (1.3 to 3.7)	—	—

*In total, 51 women used a monophasic preparation with 20 µg ethinylestradiol, 385 women used one with 30 µg, and 20 used one with 50 µg (total 456).

†Reference category is the most commonly used dose of oestrogen among controls.

(BMJ, 2009)

Table 2 VTE risk and combined contraception according to the types of hormonal contraceptives.

	Combined contraceptive OR (95% CI)					
	Gestodene (+30 µg EE)	Desogestrel (+30 µg EE)	Norgestimate (+35 µg EE)	Drospirenone (+30 µg EE)	Cyproterone acetate (+35 µg EE)	Vaginal ring
(19) ^a			1.2 (0.9–1.5) ^b	1.7 (1.4–2.2)	1.8 (1.4–2.3)	1.7 (1.3–2.3)
(17) ^c	1.5 (1.2–2.0)	1.8 (1.4–2.2)	1.0 (0.7–1.3)	1.6 (1.2–2.1)	1.6 (1.1–2.2)	1.5 (1.2–1.8) ^d

LNG, levonorgestrel; EE, ethinyl-estradiol; OR, odds ratio.

^aCompared with COC containing LNG.

^bResult from Table 3.

^cCompared with COC containing 30 µg EE + LNG.

^dCompared with norgestimate pill.

COC & VTE

Hormone preparations	Progesterone	Estrogen (mcg) (multiple numbers indicate multiphasic/extended formulations)	Effectiveness*	VTE risk
Progestin only pills	Norethindrone	None	93.0%	No increased risk
	Drospirenone	None		
LNG IUD	Levonorgestrel	None	99.7%	No increased risk
Implant†	Etonogestrel	None	99.9%	No increased risk
Injectable ("Depo")	Medroxyprogesterone	None	96.0%	OR 2.2 (1.3-4.0) [‡]
Vaginal ring	Segesterone	Ethinyl estradiol (13 mcg/day)	93.0%	6.5-fold (4.7-8.9) increased risk compared to non hormone users (mixed data compared to oral preparations) [§]
	Etonogestrel	Ethinyl estradiol (15 mcg/day)		
Transdermal patch¶	Levonorgestrel	Ethinyl estradiol (30 mcg/day)	93.0%	7.9-fold (3.5-17.7) increased risk compared to non hormone users (mixed data compared to oral preparations) [§]
	Norelgestromin	Ethinyl estradiol (30 mcg/day)		
4 th Generation Progesterone COC	Dienogest	Estradiol valerate (3,2,2,1 mg)	93.0%	Similar/improved risk as 2 nd generation progesterone COC
2 nd Generation Progesterone COC	Levonorgestrel	Ethinyl estradiol (20, 10)	93.0%	OR 2.38 (2.18-2.59)**
		Ethinyl estradiol (20)		
		Ethinyl estradiol (30)		
		Ethinyl estradiol (20, 25, 30,10)		
1 st Generation Progesterone COC	Norethindrone acetate	Ethinyl estradiol (30, 10)	93.0%	No data comparing 1st and 2nd generation, recommend lowest dose of estrogen for lowest risk of VTE
		Ethinyl estradiol (10,10)		
		Ethinyl estradiol (20)		
		Ethinyl estradiol (30)		
	Norethisterone ^{††}	Ethinyl estradiol (20,30,35)		
		-		
		-		
	Norethindrone	Ethinyl estradiol (35)		
	Ethinodiol diacetate	Ethinyl estradiol (35)		
		Ethinyl estradiol (50) ^{††}		
	Norgestrel	Ethinyl estradiol (30)		
		Ethinyl estradiol (50) ^{††}		
	Medroxyprogesterone ^{††}	-		
3 rd Generation Progesterone COC	Norgestimate	Ethinyl estradiol (35)	93.0%	OR 2.53 (2.17-2.96)**
	Desogestrel	Ethinyl estradiol (20,0,10)	93.0%	OR 3.64 (3.00-4.43)**
		Ethinyl estradiol (30)		
	Gestodene ^{††}	-		OR 4.28 (3.66-5.01)**
4 th Generation Progesterone COC	Drospirenone	Ethinyl estradiol (20)	93.0%	Similar risk as 3 rd generation progesterone COC
		Estetrol (14.2 mg)		

Lowest risk

Highest risk

Setting	Estimated Risk	Reference
Non-pregnant non-user	2/10 000 WY	EMA/739865/2013
Pregnancy / post-partum	20/10 000 WY	Population- based study (30years lasting)
COC - EE+LNG - EE+NETA - EE+NGM	5-7/10 000 WY	EMA/739865/2013
COC - EE+GSD - EE+DSG - EE+DRP	9-12/10 000 WY	EMA/739865/2013
COC - EE+CMA	NA	N/A
COC - EE+DNG	8-11/10 000 WY ('EMA)	EMA
E2V+DNG	7,0/10 000 WY vs 3,5 in non users and 9,9 in users of LNG/EE	INAS-SCORE
E2+NOMAC	2,0/10 000 WY vs 8 in non users and 3,0 in users of LNG/EE	PRO-E2
E4+DRSP	NA	Didembourg M, Lower reporting of venous thromboembolisms events ...: A disproportionality analysis of the Eudravigilance database. Contraception. 2024 Oct 17:110727.

Adapted from Morimont L, et alk. Front Endocrinol (Lausanne). 2021 Dec 9;12:769187.

OC & VTE

Hormone preparations	Progesterone	Estrogen (mcg) (multiple numbers indicate multiphasic/extended formulations)	Effectiveness*	VTE risk
Progestin only pills	Norethindrone	None	93.0%	No increased risk
	Drospirenone	None		
LNG IUD	Levonorgestrel	None	99.7%	No increased risk
Implant†	Etonogestrel	None	99.9%	No increased risk
Injectable ("Depo")	Medroxyprogesterone	None	96.0%	OR 2.2 (1.3-4.0) [‡]
Vaginal ring	Segesterone	Ethinyl estradiol (13 mcg/day)	93.0%	6.5-fold (4.7-8.9) increased risk compared to non hormone users (mixed data compared to oral preparations) [§]
	Etonogestrel	Ethinyl estradiol (15 mcg/day)		
Transdermal patch¶	Levonorgestrel	Ethinyl estradiol (30 mcg/day)	93.0%	7.9-fold (3.5-17.7) increased risk compared to non hormone users (mixed data compared to oral preparations) [§]
	Norelgestromin	Ethinyl estradiol (30 mcg/day)		
4 th Generation Progesterone COC	Dienogest	Estradiol valerate (3,2,2,1 mg)	93.0%	Similar/improved risk as 2 nd generation progesterone COC
2 nd Generation Progesterone COC	Levonorgestrel	Ethinyl estradiol (20, 10)	93.0%	OR 2.38 (2.18-2.59)**
		Ethinyl estradiol (20)		
		Ethinyl estradiol (30)		
		Ethinyl estradiol (20, 25, 30,10)		
1 st Generation Progesterone COC	Norethindrone acetate	Ethinyl estradiol (30, 10)	93.0%	No data comparing 1st and 2nd generation, recommend lowest dose of estrogen for lowest risk of VTE
		Ethinyl estradiol (10,10)		
		Ethinyl estradiol (20)		
		Ethinyl estradiol (30)		
	Norethisterone ^{††}	Ethinyl estradiol (20,30,35)		
		-		
		-		
	Norethindrone	Ethinyl estradiol (35)		
		Ethinyl estradiol (35)		
	Ethinodiol diacetate	Ethinyl estradiol (50) ^{††}		
		Ethinyl estradiol (30)		
3 rd Generation Progesterone COC	Norgestrel	Ethinyl estradiol (50) ^{††}	93.0%	OR 2.53 (2.17-2.96)**
		-		
		-		
3 rd Generation Progesterone COC	Norgestimate	Ethinyl estradiol (35)	93.0%	OR 3.64 (3.00-4.43)**
		Ethinyl estradiol (20,0,10)		
		Ethinyl estradiol (30)		
4 th Generation Progesterone COC	Drospirenone	-	93.0%	OR 4.28 (3.66-5.01)**
		-		
		-		
4 th Generation Progesterone COC	Drospirenone	Ethinyl estradiol (20)	93.0%	Similar risk as 3 rd generation progesterone COC
		Ethinyl estradiol (30)		
		Estetrol (14.2 mg)		

Lowest risk

Highest risk

The importance of family history to weigh the risk

	Controls (%) n = 1288	Cases (%) n = 1327	OR * (95% CI)	OR _a † (95% CI)
Family History				
Negative family history	1099 (85)	982 (74)	Reference	Reference
Positive family history in 1 parent/sibling	177 (14)	296 (22)	2.0 (1.6-2.4)	2.0 (1.6-2.5)
Positive family history in > 1 parent/sibling	12 (1)	49 (4)	5.0 (2.6-9.4)	5.2 (2.6-10.6)

	Controls n=1288	Cases n=1327	OR (95% CI)
Family history and hormones			
Negative FH, no CHC or HT	911 (71%)	582 (44%)	reference
Positive FH, no CHC or HT	165 (13%)	250 (19%~~%~~)	2.2 (1.7-2.8)
Positive FH, treatment with HT	18 (1.4%)	55 (4.1%)	5.9 (3.3-11)
Positive FH, treatment with CHC	6 (0.5%)	40 (3.0%)	15.3 (6.1-38)
<i>Sonnevi K et al. Thromb Res 2013; 132: 164</i>			

The importance of family history to weigh the risk

TOTAL N= 532 N (%)	PREGNANCY-ASSOCIATED VTE (GROUP A) N= 200	COC-ASSOCIATED VTE (GROUP B) N=157	OTHER VTE (GROUP C) N=175	P
AGE AT ENROLLMENT, MEDIAN (IQR)	32.5 (9)	33 (16)	39 (10)	<0.001
BMI, MEDIAN (IQR)	25 (6.7)	23.7 (7)	24.6 (5.8)	NS
SMOKE, YES	28 (14.3)	31 (20.8)	23 (13.9)	<0.001
THROMBOPHILIA ^ YES /TESTED	76/186 (40.9)	68/112 (60.7)	92/131 (70.2)	<0.001
ACTIVE CANCER	0	1	4	0.015
HISTORY OF CANCER	7	2	13	<0.001
FAMILY HISTORY VTE	4 (2)	23 (14.6)	15 (8.6)	<0.001
ISCHEMIC HEART DISEASE	3 (1)	8 (5.1)	3 (1.7)	
ISCHEMIC STROKE	2 (1)	4 (2.5)	2 (1.1)	
HEMOGLOBIN G/DL	12.1 (1.8)	13.2 (1.5)	12.9 (1.8)	0.03
RBC, MEDIAN (IQR)	4.3 (0.8)	4.5 (0.5)	4.6 (0.6)	NS
PLATELET, MEDIAN (IQR)	195.5 (237)	241.5(129)	245 (125)	NS
ALT, MEDIAN (IQR)	17.5 (15)	16.5 (10)	16 (15)	NS
AST, MEDIAN (IQR)	18.5 (12)	17(10)	17 (11)	NS
GFR MEDIAN (IQR)	132 (66)	110 (43)	113.5 (35)	<0.001

^ Test performed in 429 patients

Grandone E, et al. *Thromb Haemost.* 2023;123(11):1060-1068

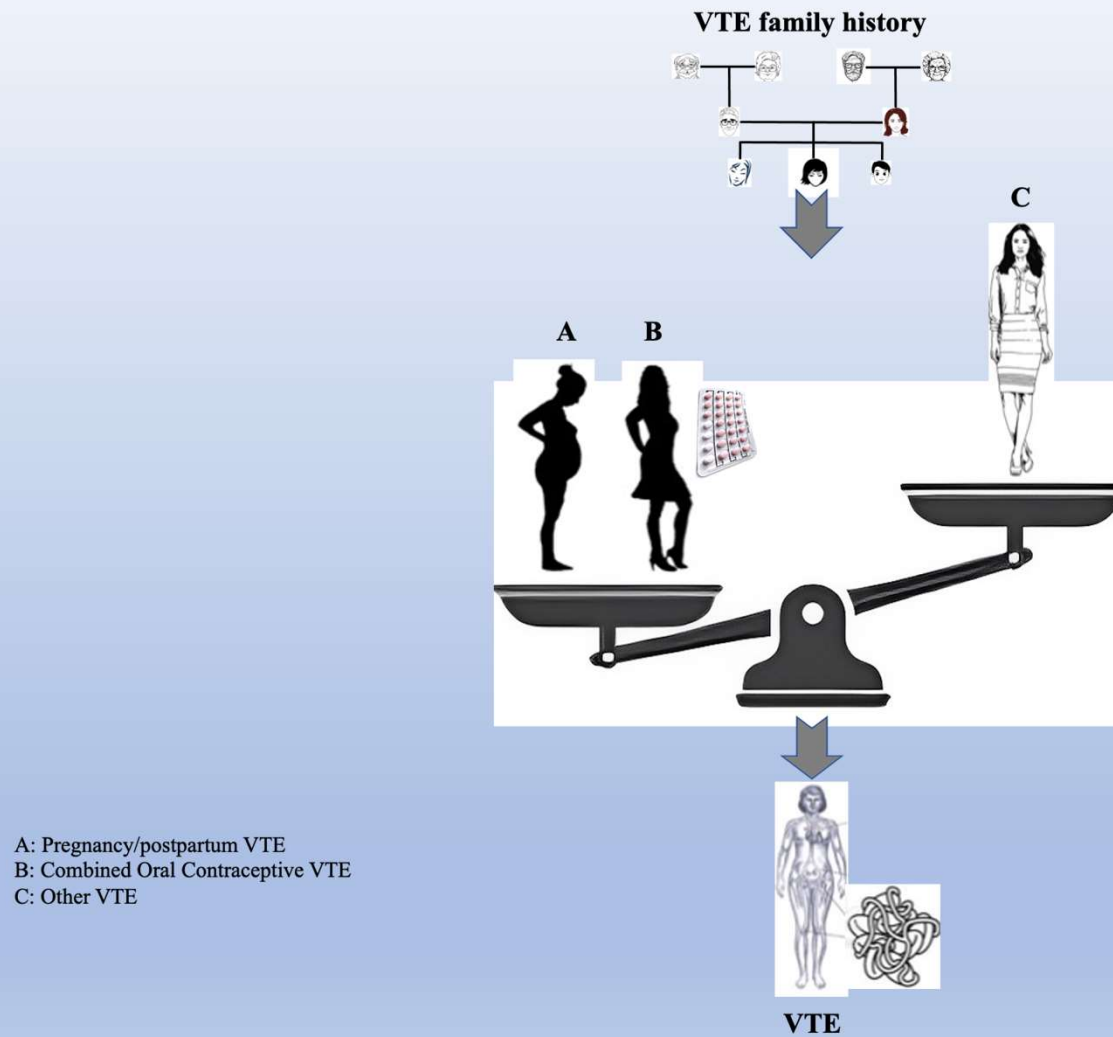
The importance of family history to weigh the risk

RISK FACTORS	OR	95%CI	P
PANEL A: FACTORS AFFECTING COC- ASSOCIATED VTE (GROUP B) IN COMPARISON WITH OTHER VTE (GROUP C)			
FAMILY HISTORY OF VTE	3.20	1.36- 7.54	0.008
AGE	0.97	0.93-0.99	0.04
THROMBOPHILIA	0.31	0.15- 0.64	0.002
PREVIOUS DIAGNOSIS OF CANCER	0.097	0.012- 0.81	0.03
PANEL B: FACTORS AFFECTING PREGNANCY- ASSOCIATED VTE (GROUP A) IN COMPARISON WITH COC- RELATED VTE (GROUP B)			
SMOKE	5.2	1.64- 16.53	0.005
THROMBOPHILIA	0.39	0.20 -0.80	0.008
PANEL C: FACTORS AFFECTING PREGNANCY- ASSOCIATED VTE (GROUP A) IN COMPARISON WITH OTHER VTE (GROUP C)			
FAMILY HISTORY OF VTE	3.09	1.41- 6.78	0.008
AGE	0.92	0.88-0.96	<0.001

COC: Combined Oral Contraceptives
VTE: Venous Thromboembolism

Grandone E, et al. Thromb Haemost. 2023;123(11):1060-1068

OR:3



VTE: Venous Thromboembolism

Visual summary: in women of childbearing age, family history of VTE has a relevant role in predicting Combined Oral Contraceptives- and pregnancy/ postpartum- VTE



ASH guidelines 2023

Table 4. Estimates used to calculate effect of thrombophilia testing in individuals with a family history of VTE

Thrombophilia defect in the family	RR for first VTE, positive vs negative (95% CI)	Treatment effect for VTE occurrence, RR (95% CI)*	Treatment effect major bleeding, RR (95% CI)*
FVL (FVL)	2.71 (2.06-3.56)	0.54 (0.32-0.91)	2.09 (1.33-3.27)
Prothrombin (PT) mutation	2.35 (1.46-3.78)		
Antithrombin (AT) deficiency	12.17 (5.45-27.17)		
Protein C (PC) deficiency	7.47 (2.81-19.81)		
Protein S (PS) deficiency	5.98 (2.45-14.57)		

*Estimates taken from ASH Medical Prophylaxis guideline-medical outpatients with minor provoking risk factors for VTE.

Middeldorp S. et al, Blood Adv 2023

NON-CONTRACEPTIVE BENEFITS OF HORMONAL CONTRACEPTION

Effects on menstrual symptoms

Dysmenorrhea
Heavy menstrual bleeding
Premenstrual syndrome
Menstrual headache
**Hyperandrogenic
symptoms**

Improvement of medical conditions

Endometriosis



Preventive effects on pathological conditions

**Pelvic inflammatory
disease**
Ectopic pregnancy
Ovarian cancer
Endometrial cancer
Colorectal cancer

Agenda

- Physiopathological characteristics
- Risk profile by product type and route of administration
- Risk of recurrence

Rate of VTE recurrence during anticoagulation in relation to hormones exposure

No hormone exposure during AC n=1413	All hormones exposure during AC N=475	COC exposure during AC N=306	Gestagen exposure only during AC N=317
4.7% per year (95%CI 3.3- 6.4)	3.7% per year (95%CI 1.5 - 7.7)	3.7 % per year (95%CI 1.0 - 9.4)	3.8% per year (95%CI 0.8 - 11.2)

Beyer-Westendorf J, et al.Vasa. 2018 ;47:441-450

APRICOT: Adapt hePaRin In pregnanCy- assOciated vTe



Invito a partecipare allo studio APRICOT

Adapt hePaRin In pregnanCy- assOciated vTe



Summary of information for clinical practice

Preparation	Type of study, Reference No. (year)	Main message
COC	Review, ¹⁰ (2001)	COC users: 3–6 times higher risk of VTE than non-users
	Historical cohort study, ³⁶ (2012)	COC with 20 µg EE/desogestrel/gestodene vs non-users: 1.5–2 times higher risk of MI
Progestogenonly pill	Systematic review, ³¹ (2018)	Adjusted RR for VTE, MI and stroke not statistically significant vs non-users
LNG-IUD	Large, retrospective study, ⁴³ (2012)	No increased risk of VTE vs non-users
Estradiol valerate/dienogest	Prospective, controlled, non-interventional, ⁴² (2016)	VTE and serious cardiovascular events not significantly different vs EE/LNG users
Non-oral preparations	Retrospective study, ⁴³ (2012)	Transdermal patches and vaginal ring vs non-users or users of COC containing LNG: ~7–8 fold higher VTE risk
	Historical cohort study, ³⁶ (2012)	Vaginal ring vs non-users: 2.5 higher risk of MI
Hormone replacement therapy	Randomized controlled trial, ⁵¹ (2002)	VTE, coronary heart disease and stroke 7–8 fold higher in CEE/MPA
	Case-control, ⁵⁴ (2019)	Estradiol confers a lower VTE risk than CEE w/o progestins or combined preparations
		CEE/MPA users show 2-fold higher VTE risk than non-users; estradiol/dydrogesterone users had the lowest risk
		Transdermal preparations did not increase VTE risk

Donatella Colaizzo

Giovanni Tiscia

Patrizia De Bonis

Filomena Cappucci

Lucia Fischetti

Paola Palumbo

Elena Chinni

Leonardo Latino

Mario Mastroianno

Silvana Santoro

Raffaella Palumbo

