

Il Ruolo degli Estrogeni in Contraccezione. Tutti gli Estrogeni sono Uguali?

Angelo Cagnacci,
DINOEMI
University Hospital Policlinico San
Martino
Genoa, Italy

**CORSO
SIGO
YOUNG**
in collaborazione con:
AOGOI GIOVANI
SIC

Segui il Corso da qui

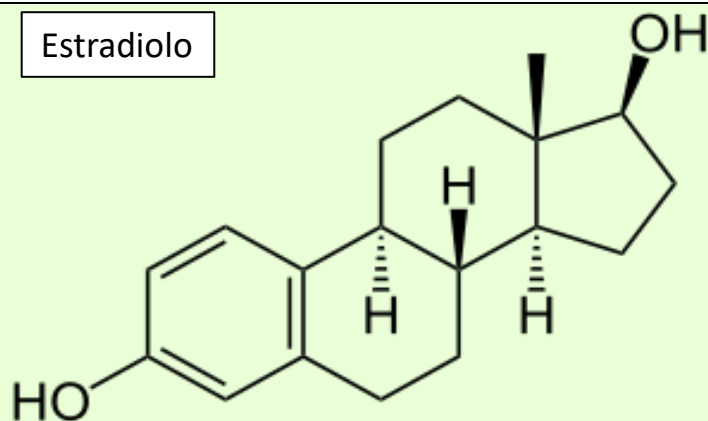
MILANO
1 Luglio 2024

HOTEL DEI CAVALIERI
Piazza Giuseppe Missori, 1

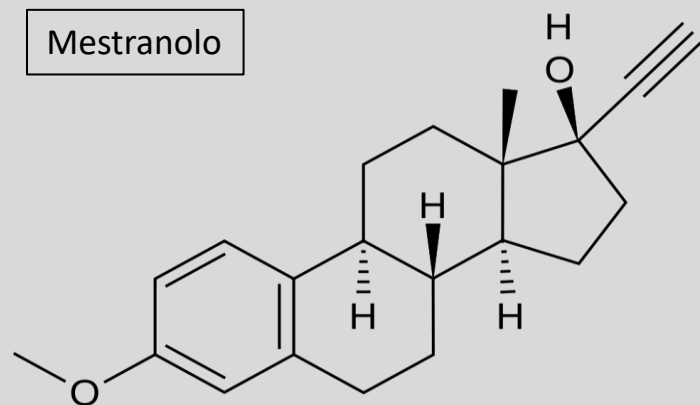
Coordinatori scientifici:
A. Cagnacci, N. Colacurci
Direttore del Corso
M. Vignali

5 crediti ECM

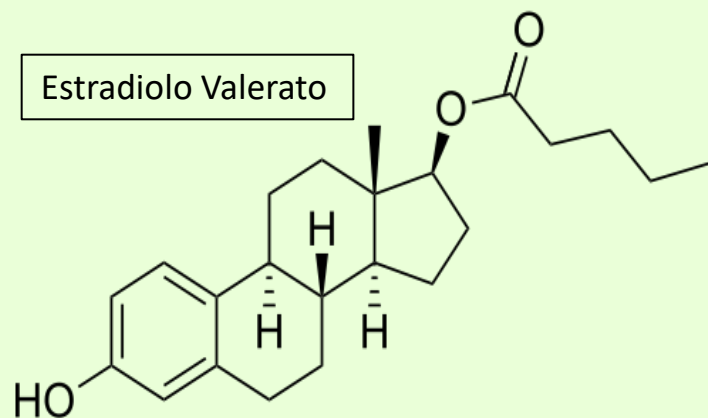
Estradiolo



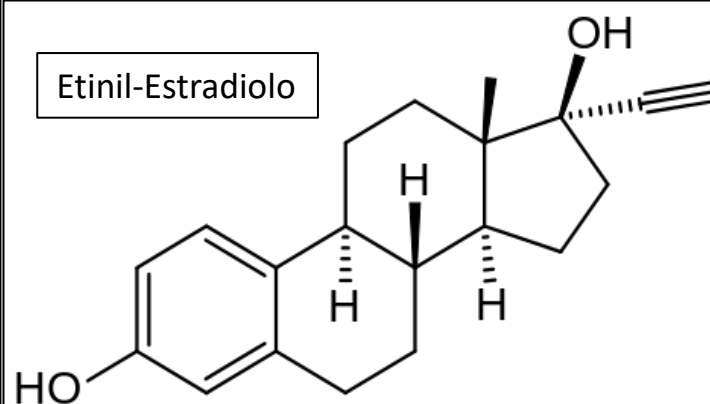
Mestranolo



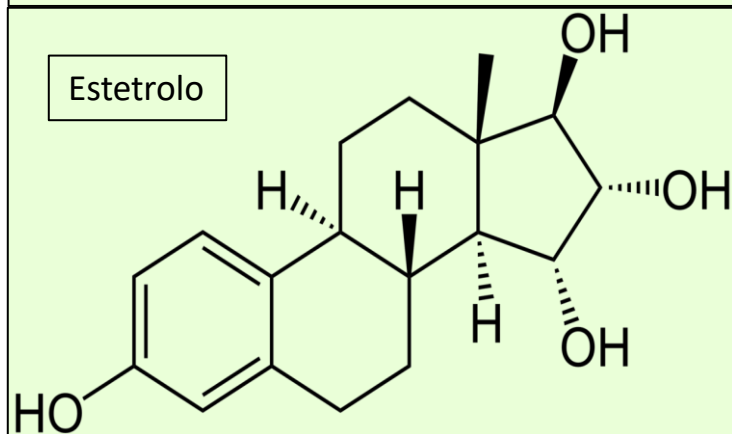
Estradiolo Valerato



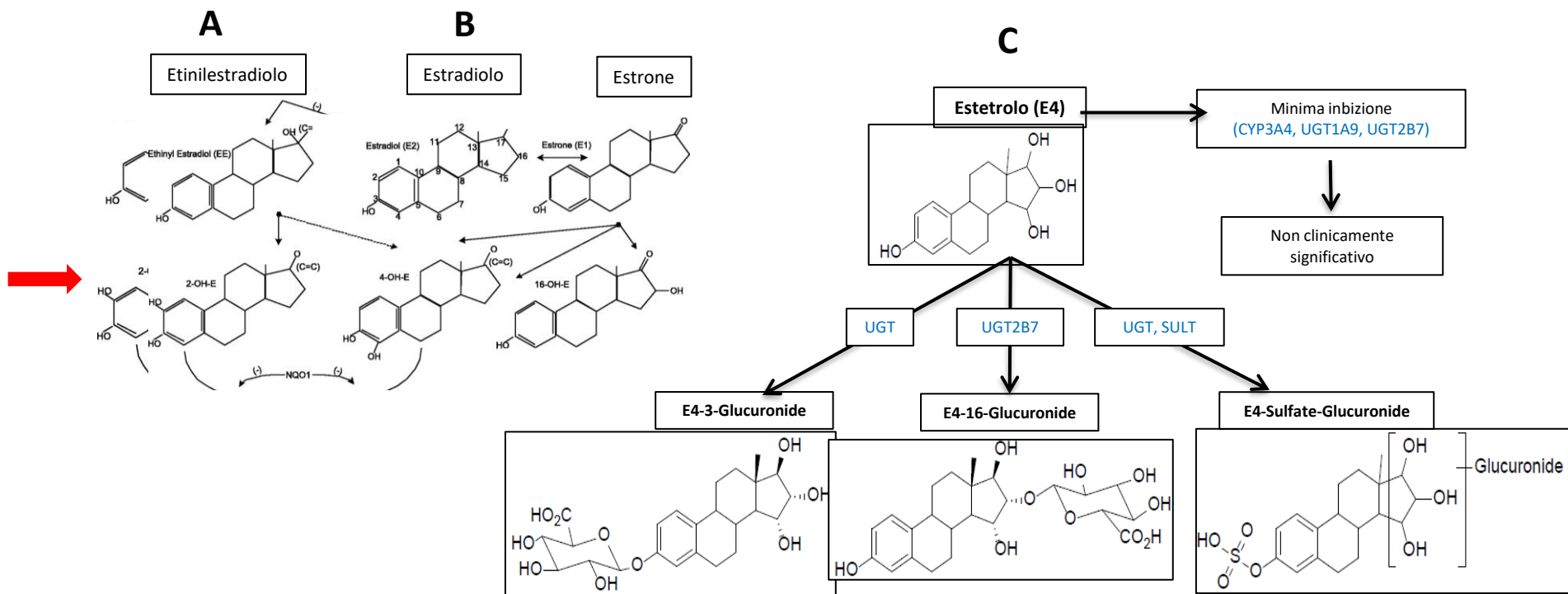
Etinil-Estradiolo



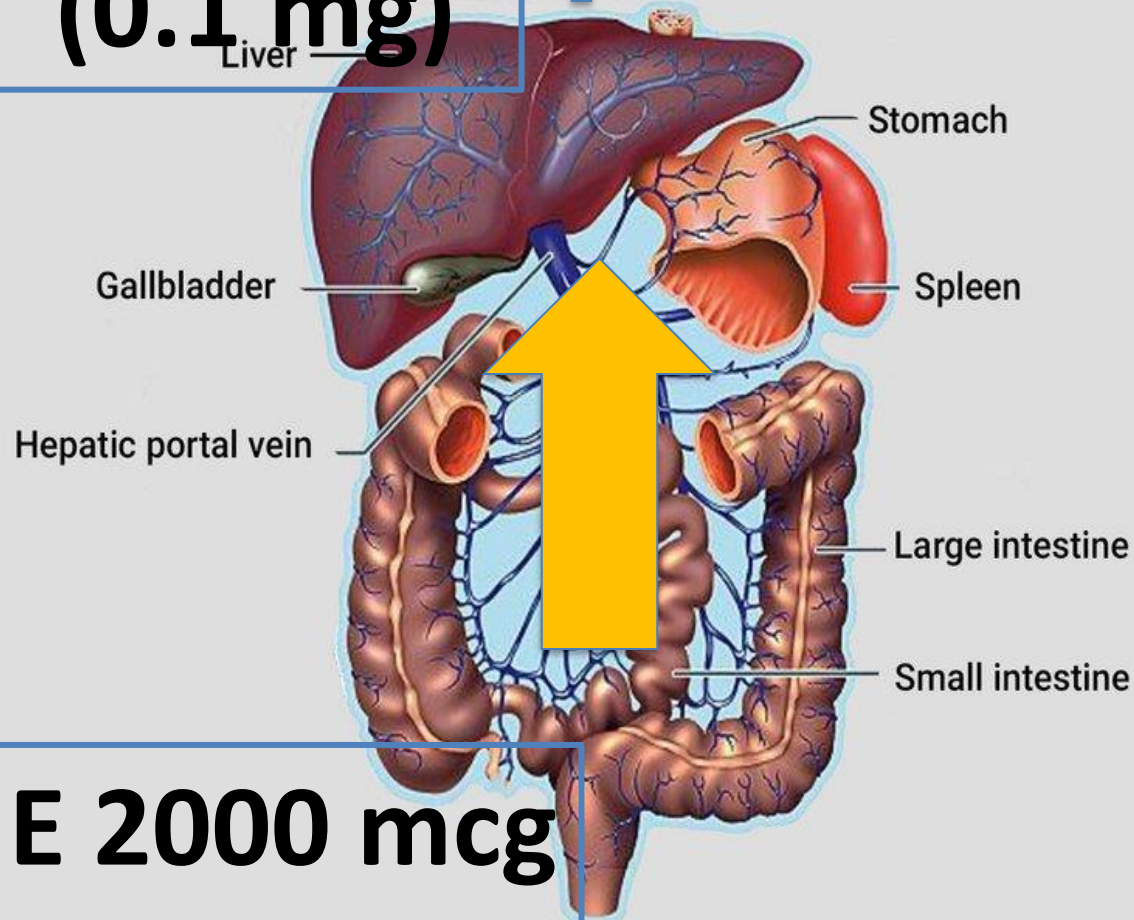
Estetrolo



Metabolismo

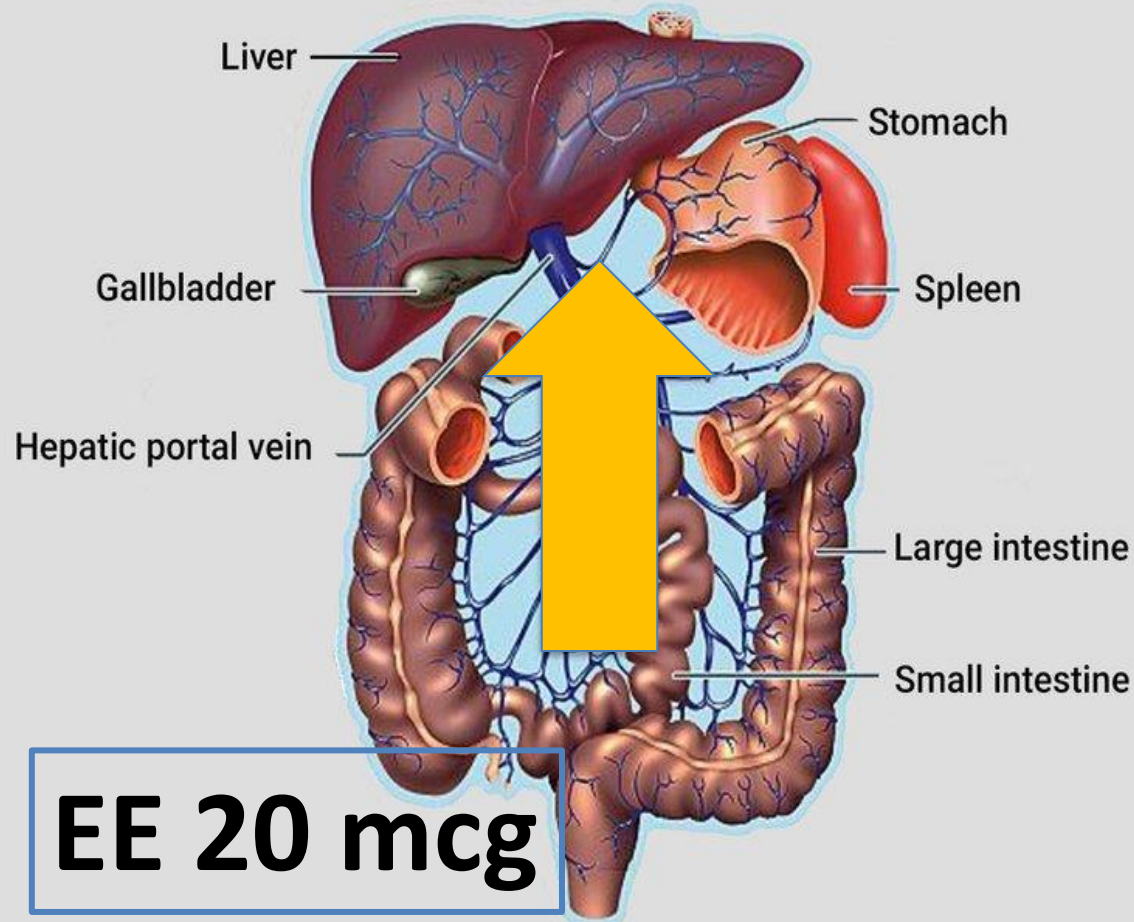


**E 100 mcg
(0.1 mg)**



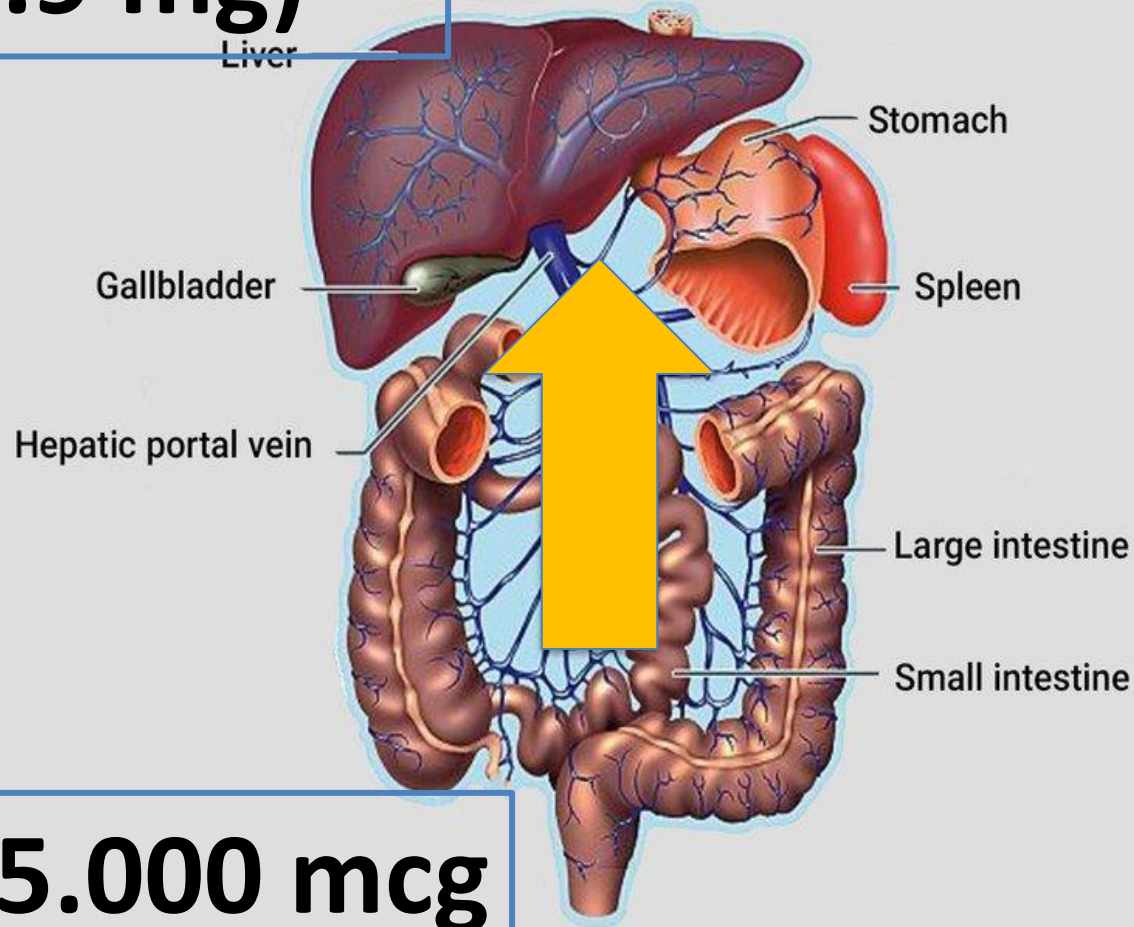
**E 2000 mcg
(2 mg)**

EE 19.9 mcg



EE 20 mcg

**E4 14.900 mcg
(14.9 mg)**



**E4 15.000 mcg
(15 mg)**

Diversità Tra i vari Estrogeni

	EE	E2	E4
Emivita	26+/-7 hr	20-30 min	28-32 hr
SHBG aumento	250%	60%	50%
SHBG legame	Molto bassa	38% alta affinità	assente
Albumina legame	98.5%	60% bassa affinità	Bassa affinità 50%
Biodisponibilità	38-48%	3-5%	70%
Recettori	Alfa/Beta	Alfa/Beta	Alfa/Beta
Inibizione FSH	-70% (20 mcg)	-41/-54% (2mg)	-12% (-15 mg)

Progesterone derivati

Didrogesterone
Medrogestone

✓ 17-OH Progesterone

Medrossiprogesterone Ac 1°
Ciproterone Ac 3°
Clormadinone Ac 2°
Megestrol Ac

✓ 19-nor progesterone

Nestorone
Nomegestrol ac 4°
Trimegestone 4°

Testosterone derivati

✓ Estrani

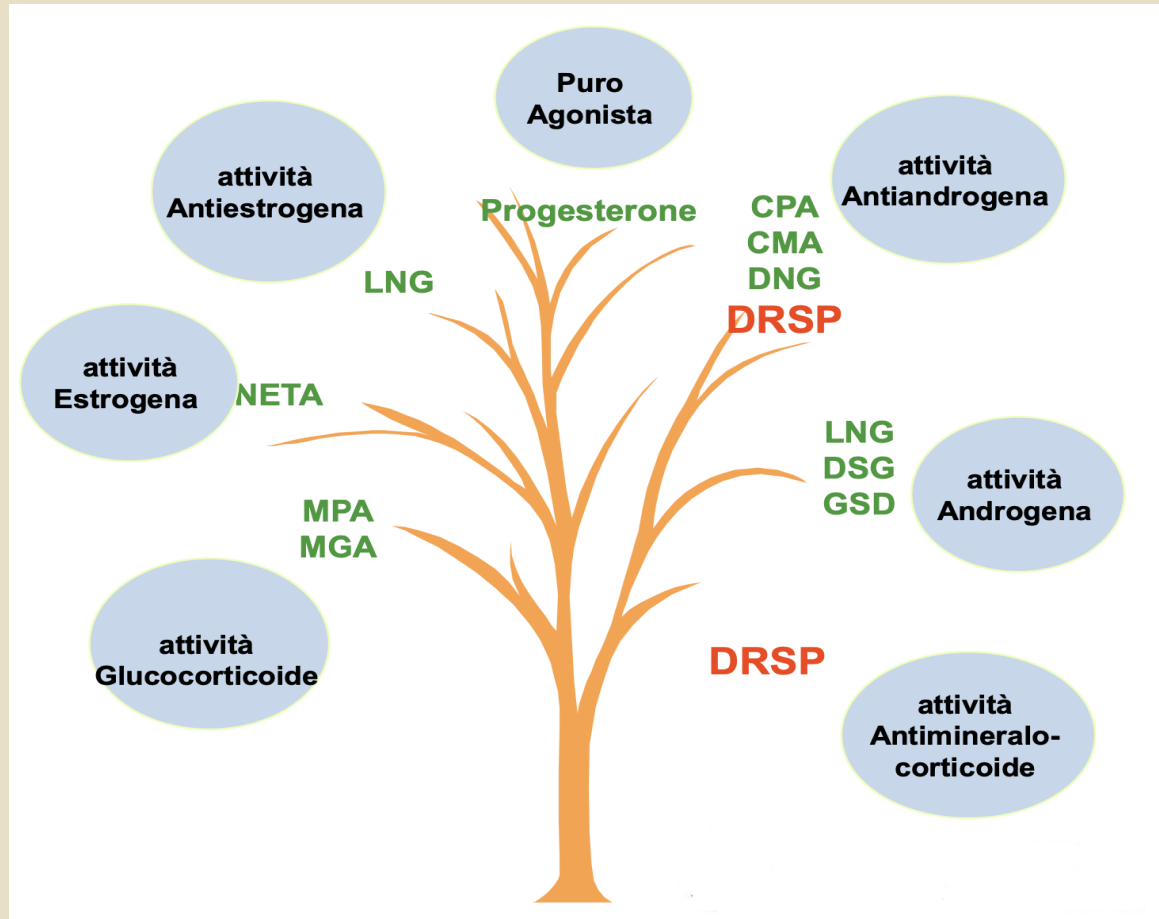
Norethisterone 1°
Dienogest

✓ 13-etil Gonani

Levonorgestrel 2°
Desogestrel
Gestodene } 3°
Norgestimate

Spirolactone derivati

Drospirenone 4°



Controllo del Ciclo

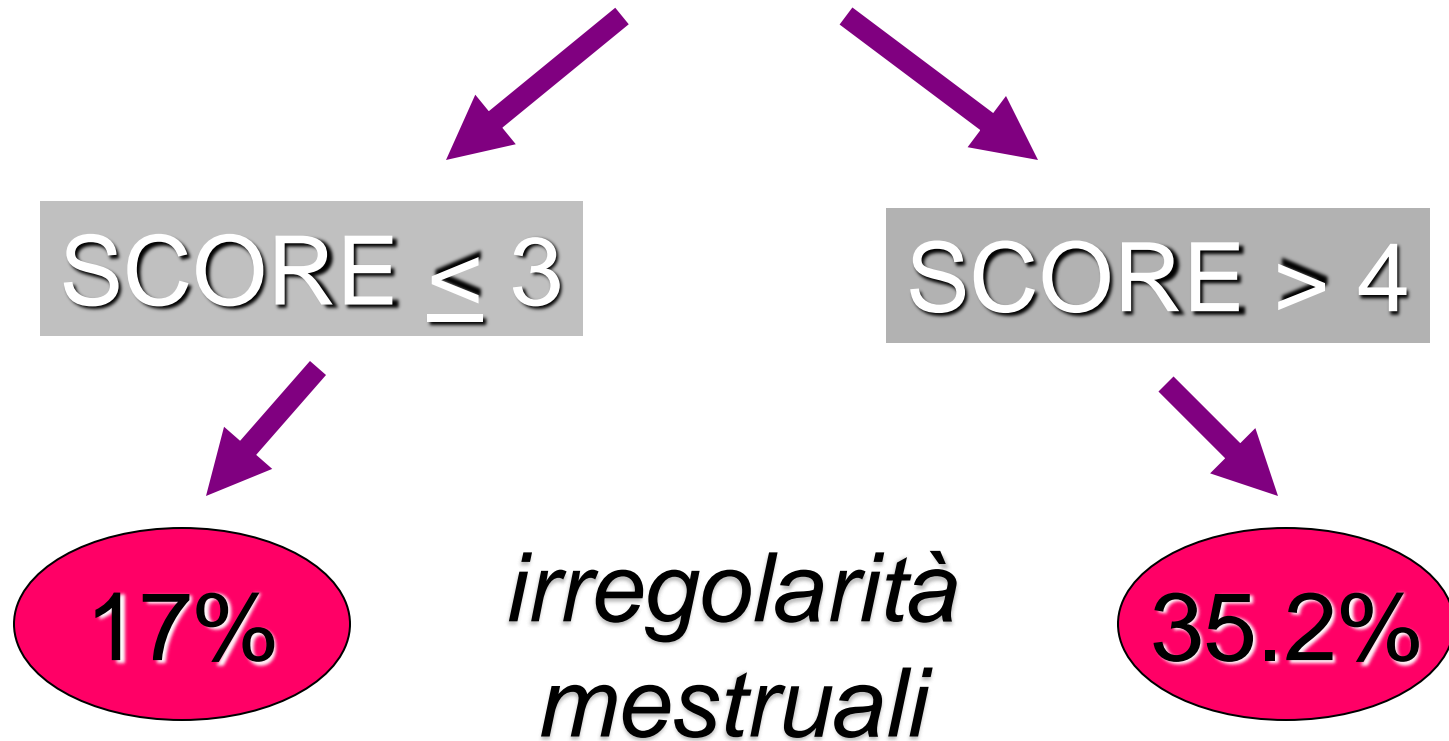


Diversità Tra i vari Estrogeni

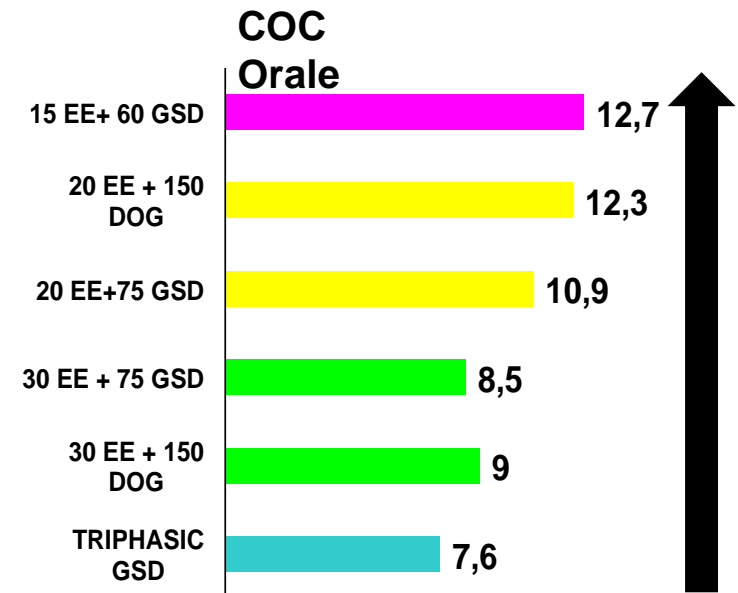
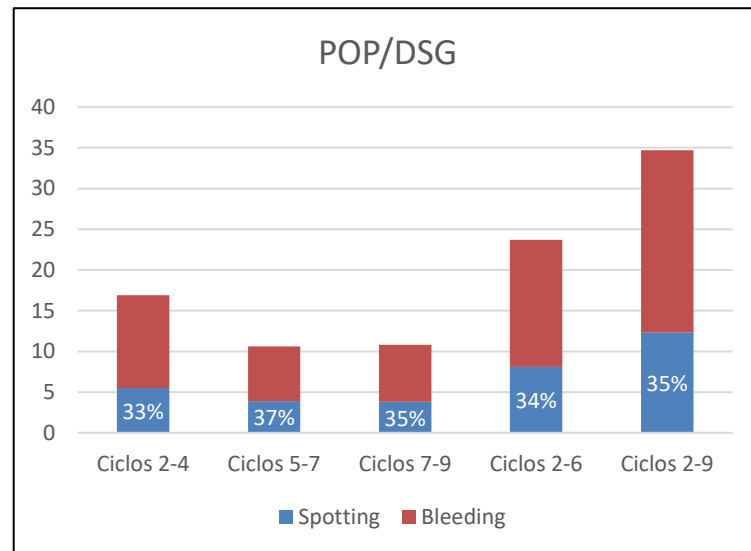
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Recettori	Alfa/Beta	Alfa/Beta	Alfa/Beta
Inibizione FSH	-70% (20 mcg)	-41/-54% (2mg)	-12% (-15 mg)

Soppressione della funzione ovarica

HOOGLAND SCORE
(diametro follicolare/livelli ormonali)



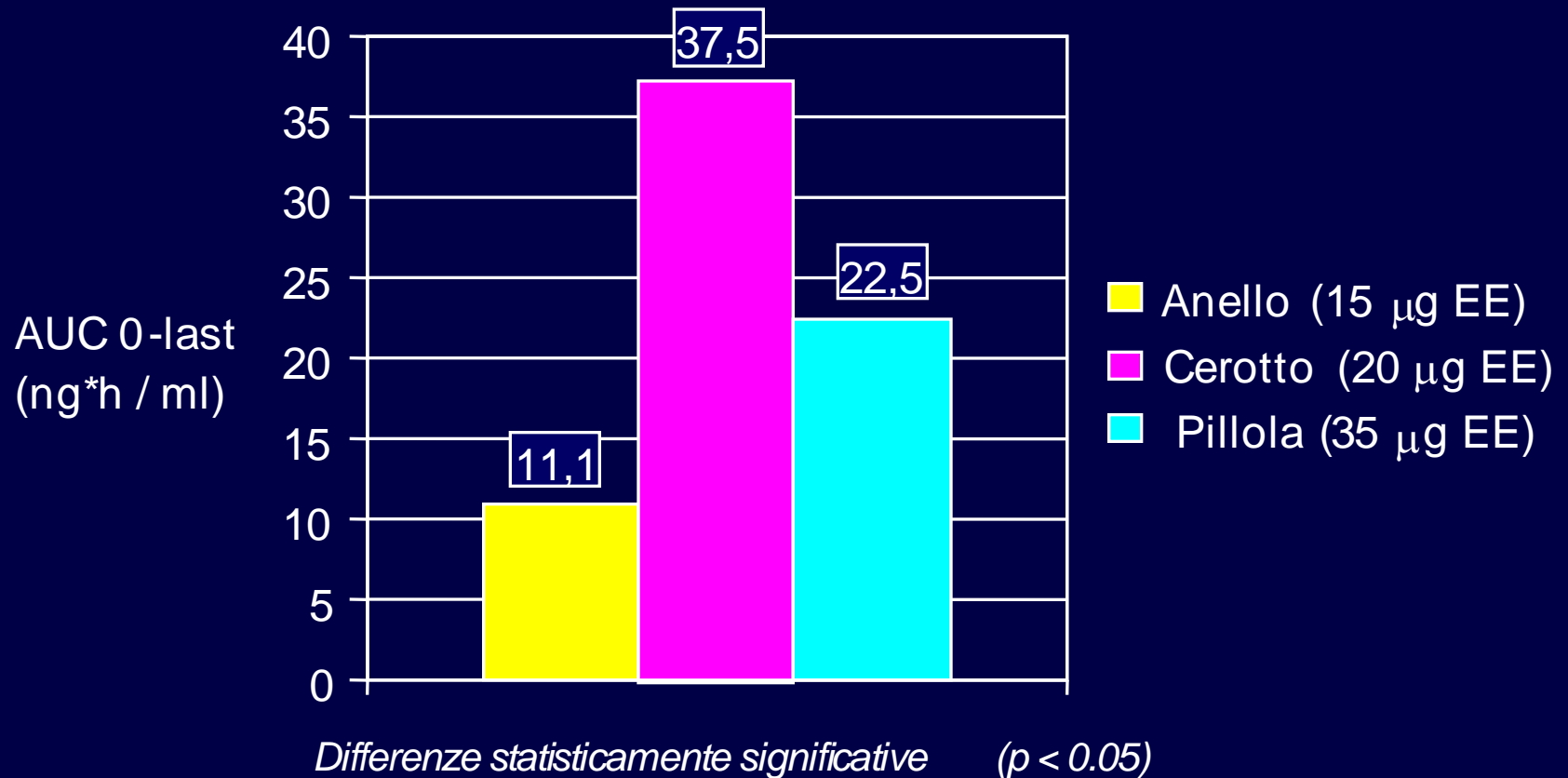
CONTROLLO DEL CICLO



cortesia da F. Fruzzetti

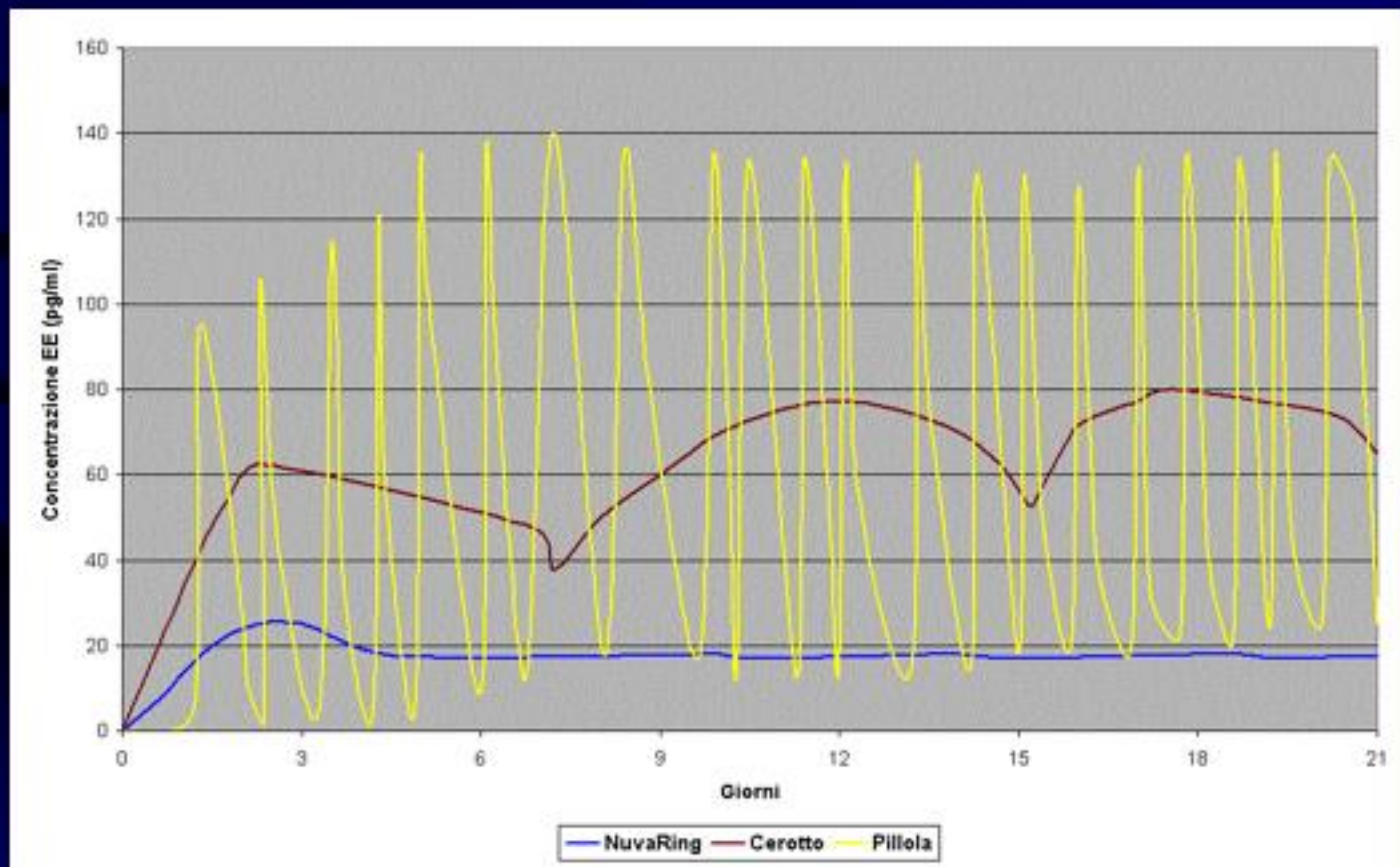
Ring vs. Patch vs. OC

Esposizione sistemica mensile all'EE



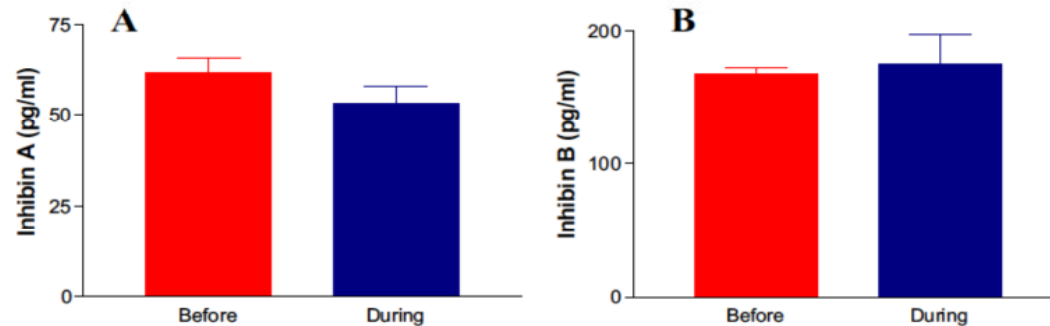
Livelli sierici di Etinilestradiolo

Dati di confronto: anello / cerotto / pillola

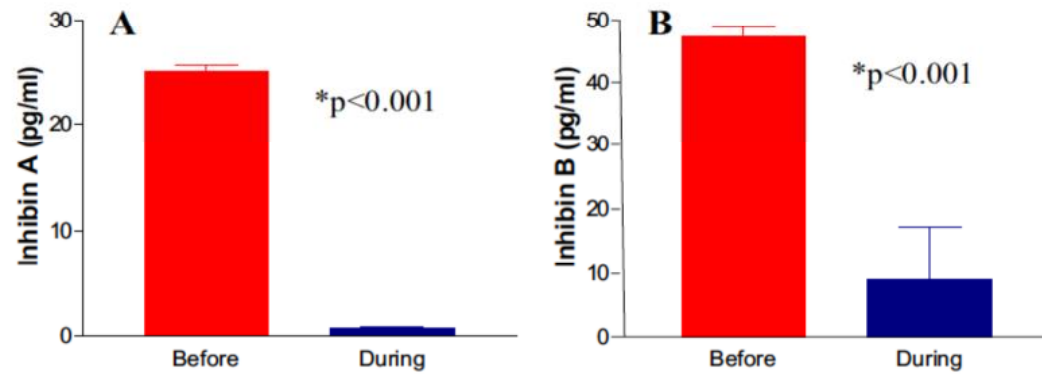


Soppressione Ovarica e Contraccezione Ormonale

Serum inhibin A (**A**), inhibin B (**B**), FSH (**C**), and LH (**D**) levels 8–10 days after the last spontaneous menstrual period (before estroprogestinic administration) and 8–10 days of oral contraceptive administration.

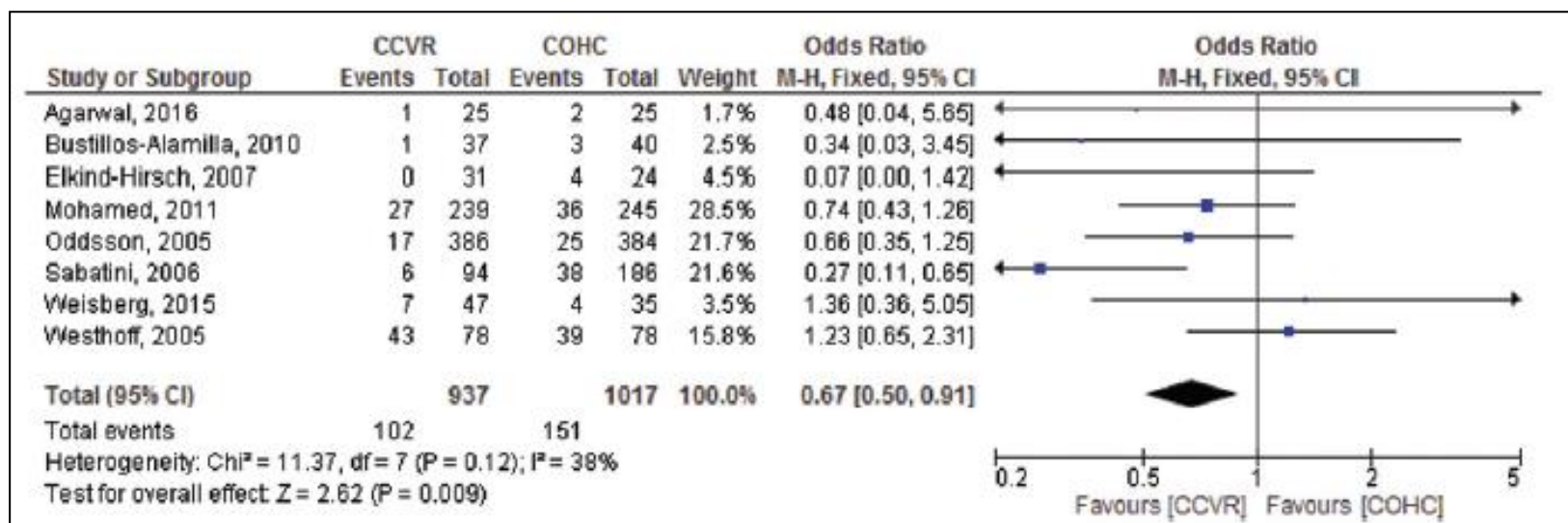


Serum inhibin A (**A**), inhibin B (**B**), FSH (**C**), and LH (**D**) levels 8–10 days after the last spontaneous menstrual period (before estroprogestinic administration) and 8–10 days during vaginal ring insertion.



CONTROLLO DEL CICLO ANELLO VS. COC

Breakthrough Bleeding



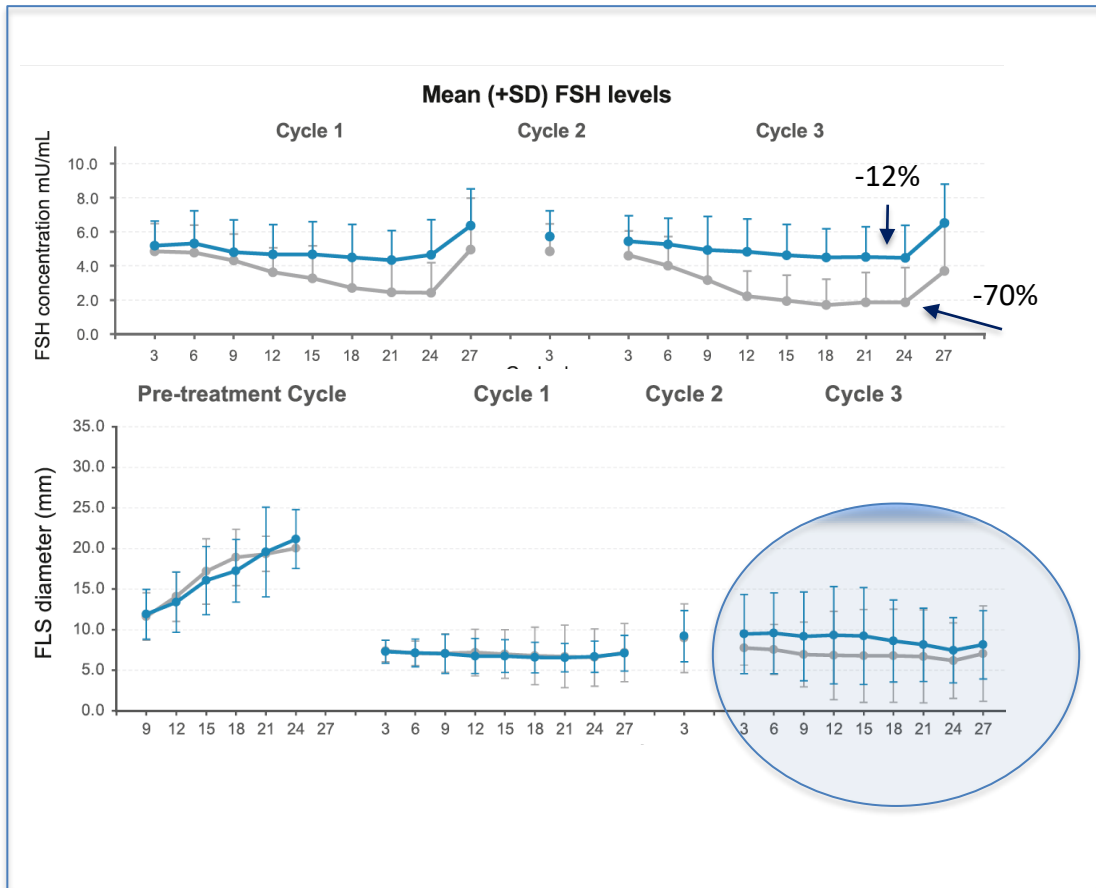
Effects of an oral contraceptive containing estetrol and drospirenone on ovarian function☆☆☆

Ingrid Duijkers^a, Christine Klipping^a, Virginie Kinet^b, Maud Jost^{b,*}, Adriana Bastidas^b, Jean-Michel Foidart^{b,c}

— E4-DRSP
— EE 20 mcg/DRSP


Hoogland Score

	E4-DRSP	EE 20-DRSP
No Activity	66.8%	83.8%
Potential activity	10.8%	8.1%
Non active	2.6%	0
Active	21.1%	5.4%



Review

Bleeding Patterns of Oral Contraceptives with a Cyclic Dosing Regimen: An Overview

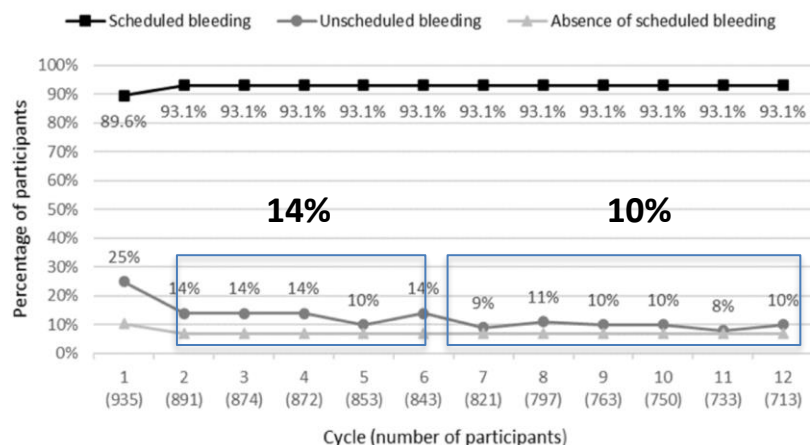
David F. Archer ¹, Diana Mansour ² and Jean-Michel Foidart ^{3,4,*} 

Unscheduled Bleedings

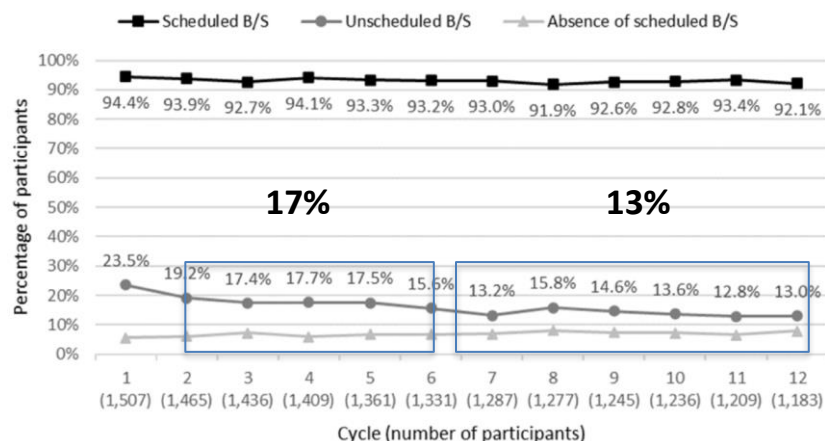
EE 30 mcg= 8%

Ring=5%

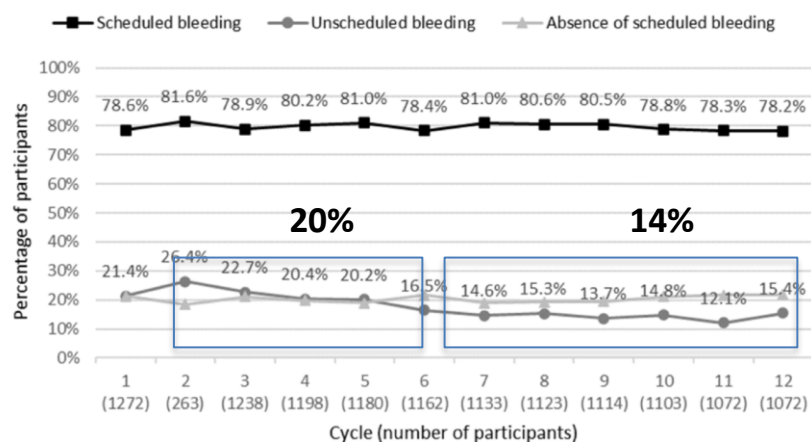
EE 20µg/DRSP (24/4 regimen)



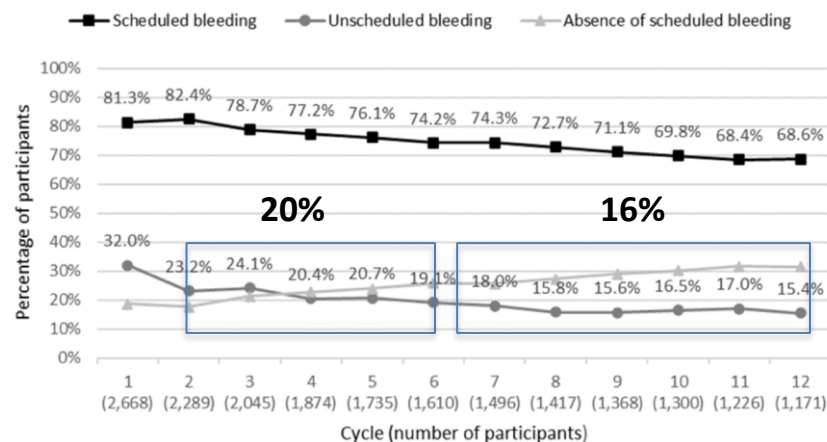
E4/DRSP phase 3 EU/RUS (24/4 regimen)



E2V/DNG Phase 3 trial EU (2/22/2/2 regimen)



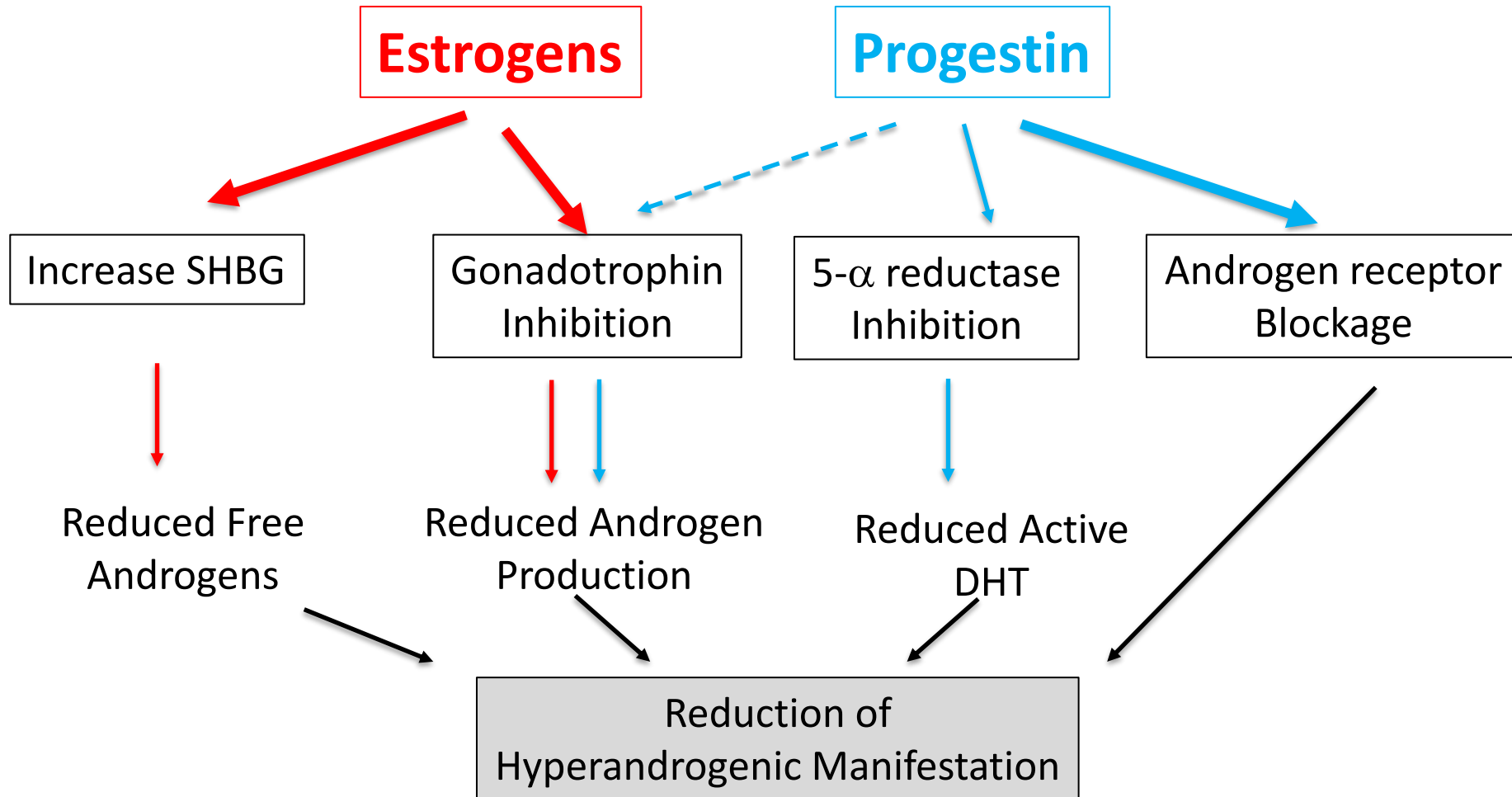
E2/NOMAC pooled phase 3 data (24/4 regimen)



Controllo di Acne e Irsutismo



Hormonal Contraception and Hyperandrogenism

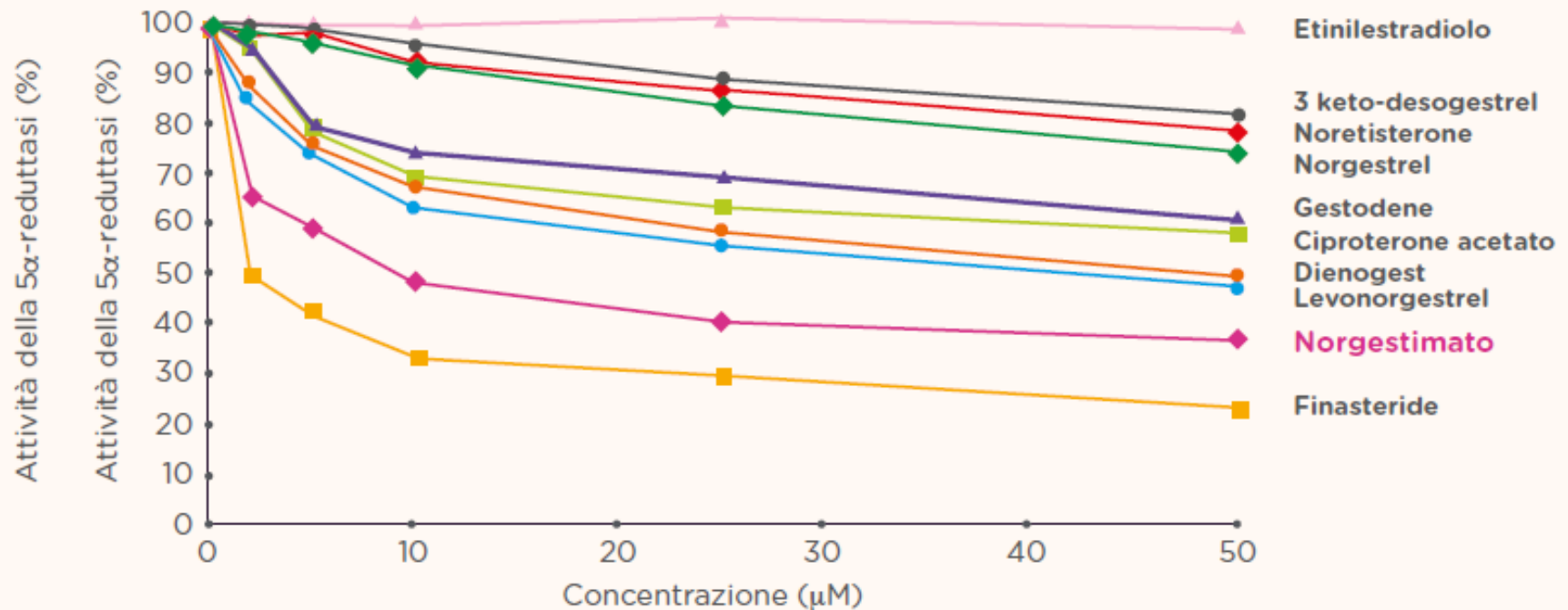


Diversità Tra i vari Estrogeni

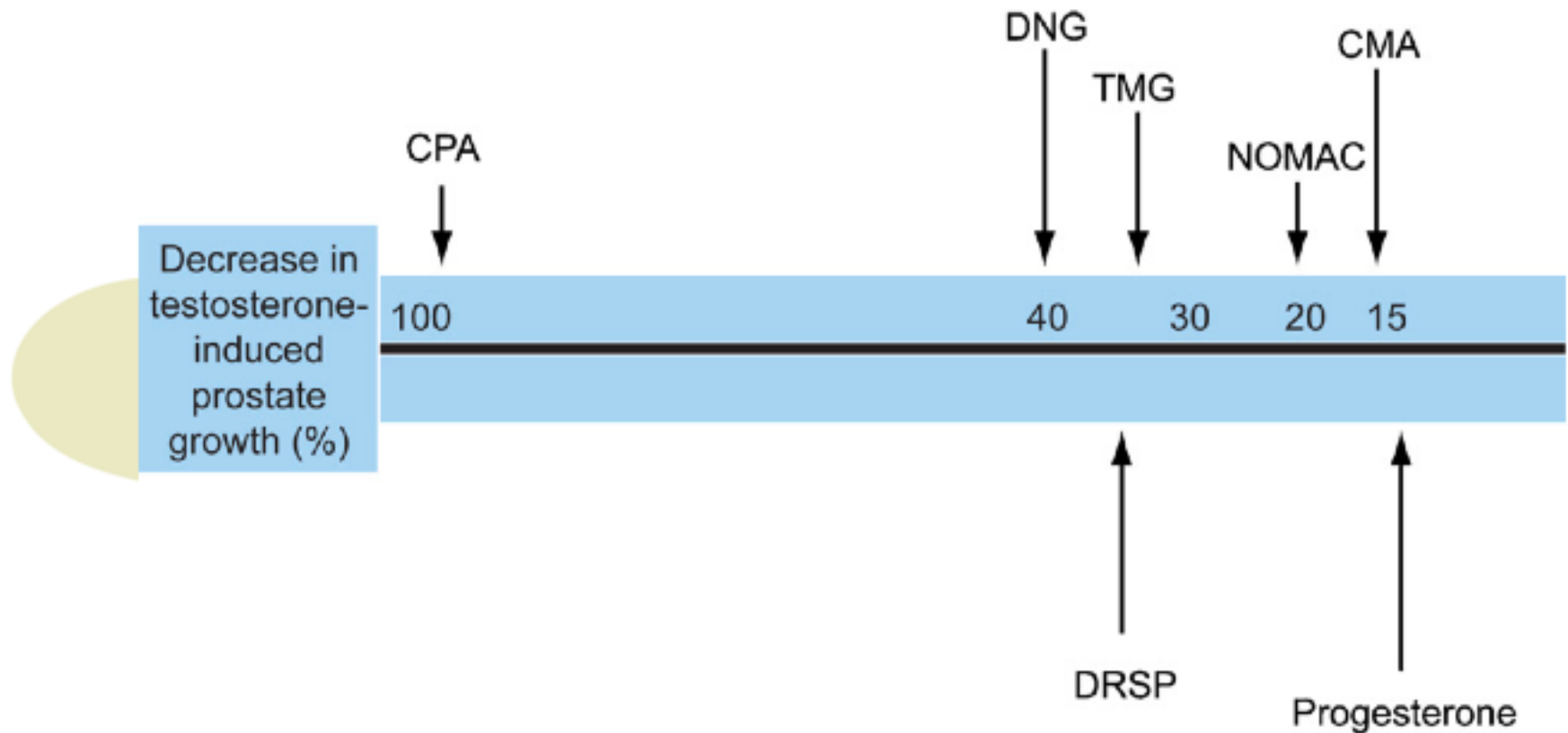
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Albumina legame	98.5%	60% bassa affinità	Bassa affinità 50%
Biodisponibilità	38-48%	3-5%	70%
Recettori	Alfa/Beta	Alfa/Beta	Alfa/Beta
Inibizione FSH	-41% (20 mcg)	-41/-54% (2mg)	-12% (15 mg)

Inibizione della 5 α -reduttasi

- La 5 α -reduttasi è l'enzima che converte a livello periferico il testosterone in deidrotestosterone, il suo metabolita attivo a livello della cute e dell'unità pilosebacea.
- Tutti i COC inibiscono questo enzima, ma il NGM ha dimostrato in uno studio *in vitro* di essere il più potente inibitore di questo enzima, subito dopo la finasteride.



Antiandrogenic Potency of Progestins



Sicurezza Contraccettiva

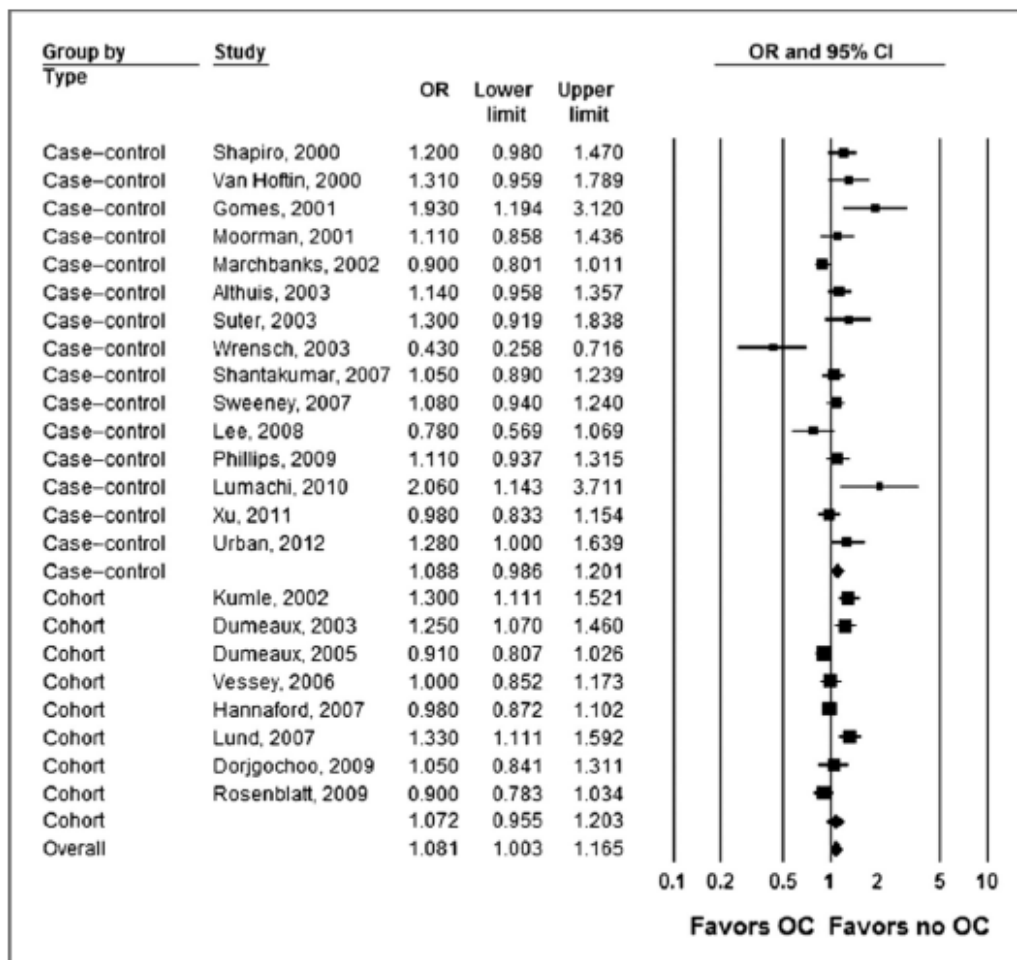
Tumore della Mammella



Oral Contraceptive Use and Risk of Breast, Cervical, Colorectal, and Endometrial Cancers: A Systematic Review

Jennifer M. Gierisch^{1,2,3}, Remy R. Coeytaux^{2,4}, Rachel Peragallo Urrutia⁹, Laura J. Havrilesky^{5,7}, Patricia G. Moorman⁴, William J. Lowery⁵, Michaela Dinan⁸, Amanda J. McBroom², Vic Hasselblad⁶, Gillian D. Sanders^{2,3}, and Evan R. Myers⁵

Breast Cancer Risk



+2 BC/100.000 women

Breast Cancer Risk and COCs With Natural Estrogens

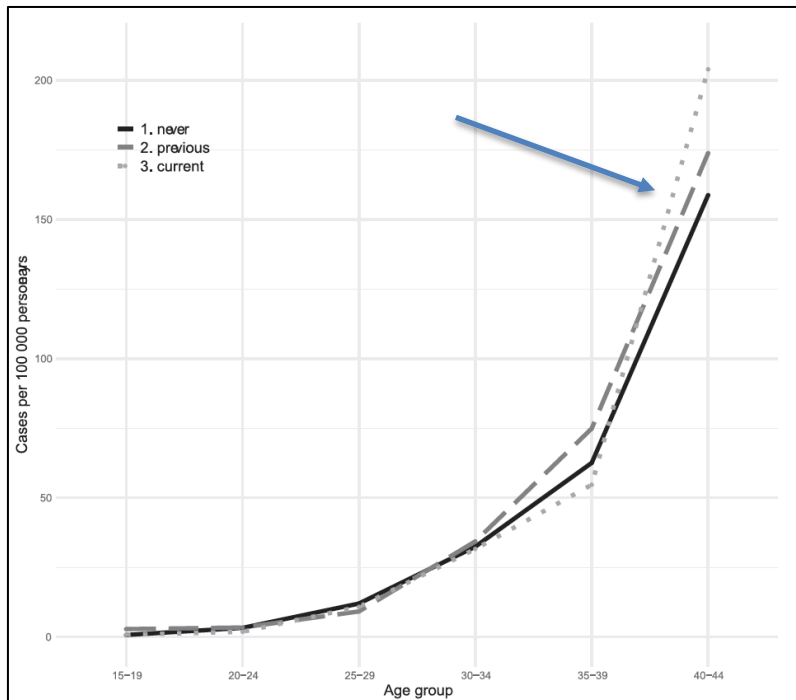
E2: No epidemiological data

E4: No epidemiological data

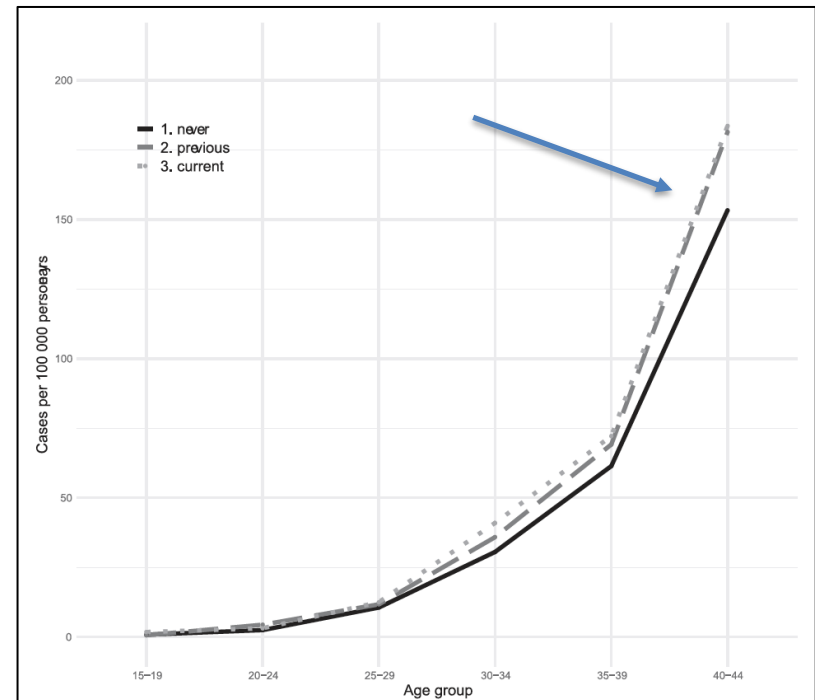
Hormonal contraception and risk of breast cancer and breast cancer in situ among Swedish women 15–34 years of age: A nationwide register-based study

Jenny Niemeyer Hultstrand,^a Kristina Gemzell-Danielsson,^b Helena Kopp Kallner,^b Henrik Lindman,^c Per Wikman,^a and Inger Sundström-Poromaa^{a*}

Combined Hormonal Contraceptives



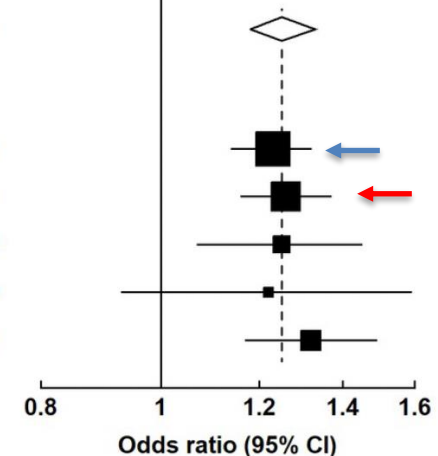
Contraceptives with only Progestins



Combined and progestagen-only hormonal contraceptives and breast cancer risk: A UK nested case-control study and meta-analysis

Danielle Fitzpatrick^{1,2}, Kirstin Pirie^{1*}, Gillian Reeves¹, Jane Green¹, Valerie Beral^{1†}

	Number of cases/controls	Mean years since last prescription	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	p-value	Adjusted OR (95% CI)
No hormonal contraceptive prescriptions	5303/11079	-	1.00 (reference)	1.00 (reference)		
Any hormonal contraceptive prescription	4195/7092	3.1	1.33 (1.26-1.41)	1.25 (1.18-1.33)	<i><0.001</i>	
By type last prescribed:						
Combined oral	1968/3407	3.7	1.32 (1.23-1.42)	1.23 (1.14-1.32)	<i><0.001</i>	
Progestagen-only oral	1308/2137	2.6	1.36 (1.26-1.47)	1.26 (1.16-1.37)	<i><0.001</i>	
Progestagen injected	308/536	2.8	1.30 (1.12-1.50)	1.25 (1.07-1.45)	<i>0.004</i>	
Progestagen implant	87/161	2.3	1.26 (0.96-1.64)	1.22 (0.93-1.59)	<i>0.2</i>	
Progestagen Intra-uterine device (IUD)	509/834	3.0	1.35 (1.20-1.52)	1.32 (1.17-1.49)	<i><0.001</i>	



Combined and progestagen-only hormonal contraceptives and breast cancer risk: A UK nested case-control study and meta-analysis

Danielle Fitzpatrick^{1,2}, Kirstin Pirie^{1*}, Gillian Reeves¹, Jane Green¹, Valerie Beral^{1†}

	Number of exposed cases/controls	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	p-value	Adjusted OR (95% CI)
A. Characteristics of the contraceptives					
Number of hormonal contraceptive prescriptions					
1	61/123	1.09 (0.80-1.49)	1.02 (0.74-1.40)	0.9	
2-9	684/1089	1.38 (1.24-1.53)	1.28 (1.15-1.42)	<0.001	
10+	792/1181	1.55 (1.40-1.72)	1.42 (1.28-1.58)	<0.001	
Estimated duration of use					
<1 year	202/385	1.12 (0.94-1.34)	1.06 (0.88-1.27)	0.5	
1-4 years	599/890	1.49 (1.33-1.67)	1.38 (1.22-1.55)	<0.001	
5+ years	736/1118	1.54 (1.38-1.71)	1.40 (1.26-1.57)	<0.001	
Phasic (combined oral contraceptives only)					
No	799/1204	1.54 (1.39-1.70)	1.41 (1.27-1.57)	<0.001	
Yes	70/127	1.23 (0.91-1.65)	1.10 (0.82-1.49)	0.5	
Progestagen type					
(Levo)norgestrel	487/734	1.52 (1.34-1.72)	1.40 (1.24-1.59)	<0.001	
Norethisterone	319/526	1.33 (1.15-1.53)	1.22 (1.05-1.41)	0.009	
Gestodene, Desogestrel, Norgestimate	573/909	1.43 (1.28-1.60)	1.32 (1.18-1.48)	<0.001	
Cyproterone, Drospirenone	79/117	1.55 (1.16-2.07)	1.40 (1.05-1.87)	0.02	
Other type	79/107	1.60 (1.19-2.15)	1.50 (1.11-2.02)	0.008	
Prior use of other hormonal contraceptives					
Only used oral combined	703/1118	1.43 (1.29-1.59)	1.32 (1.19-1.47)	<0.001	
Only used oral progestagen	314/483	1.38 (1.19-1.59)	1.29 (1.11-1.50)	<0.001	
Prior use of other hormonal contraceptives	520/792	1.51 (1.34-1.70)	1.37 (1.21-1.55)	<0.001	
B. Characteristics of the tumour					
Oestrogen receptor status					
Positive	1039/1548	1.50 (1.36-1.64)	1.36 (1.24-1.50)	<0.001	
Negative	449/753	1.37 (1.19-1.58)	1.29 (1.12-1.49)	0.001	

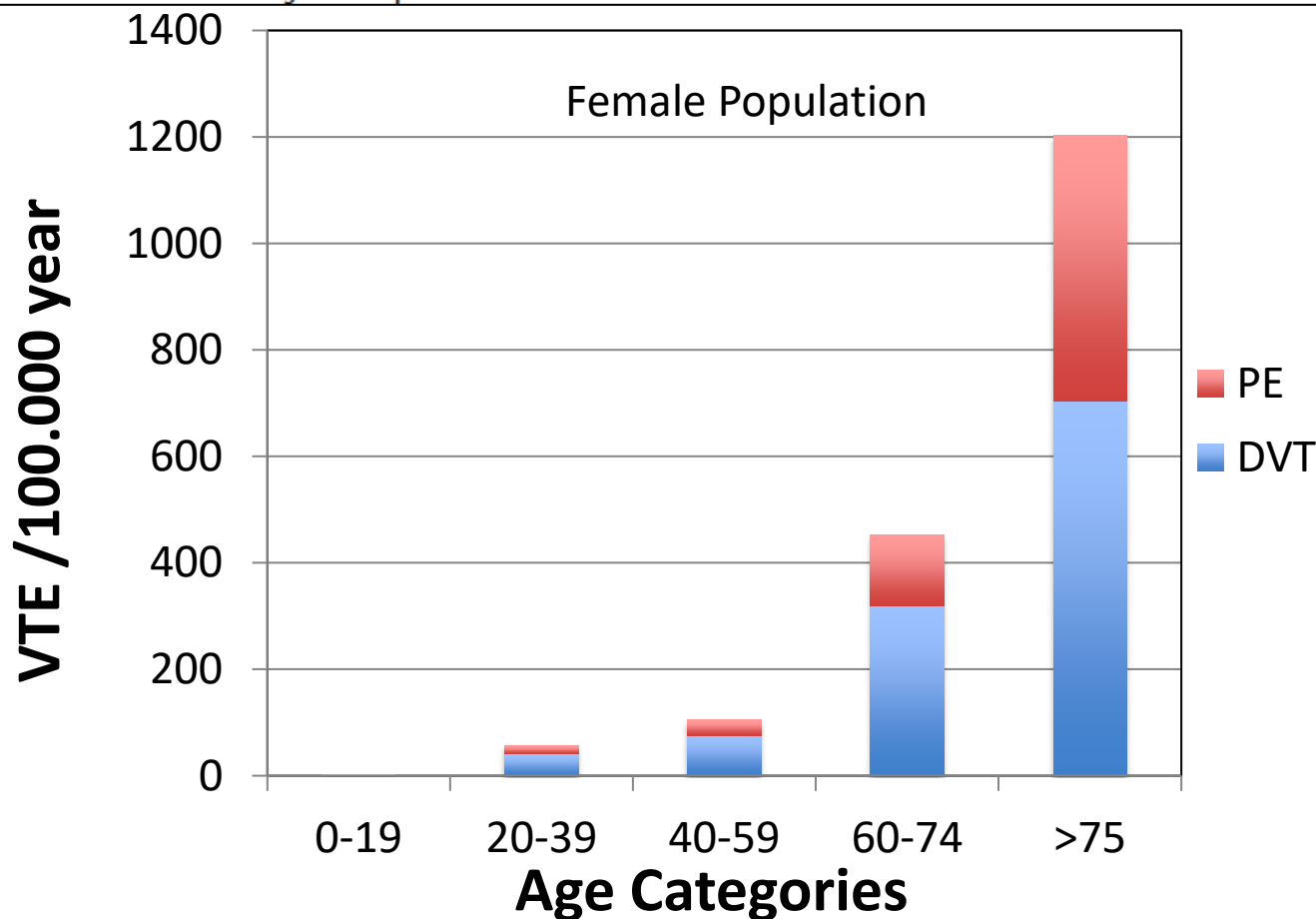
Sicurezza Contraccettiva

Sistema Cardiovascolare

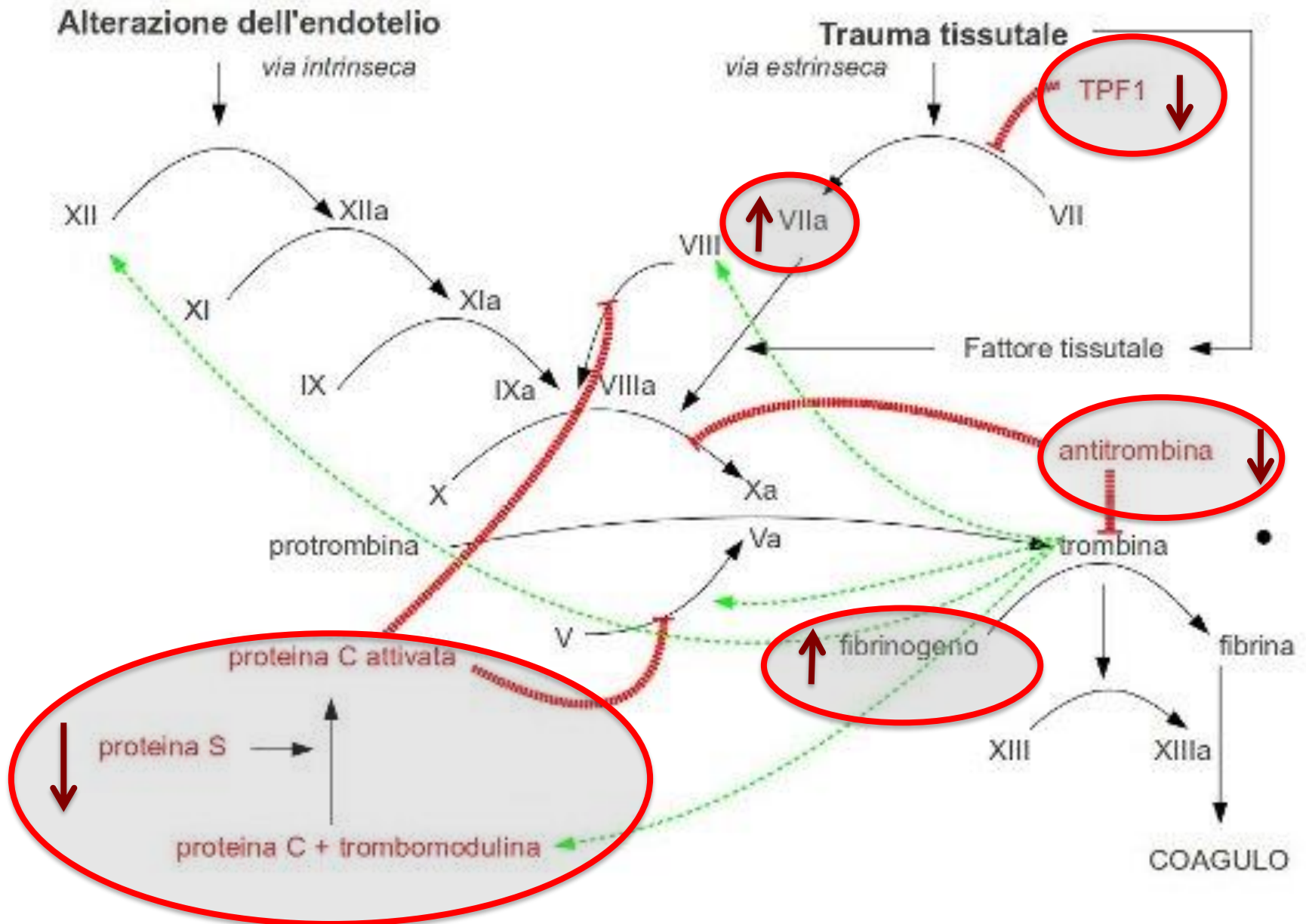


Incidence of Venous Thromboembolism: A Community-based Study in Western France

Emmanuel Oger
for the EPI-GETBO Study Group*



Effetto degli Estrogeni Sintetici od Orali



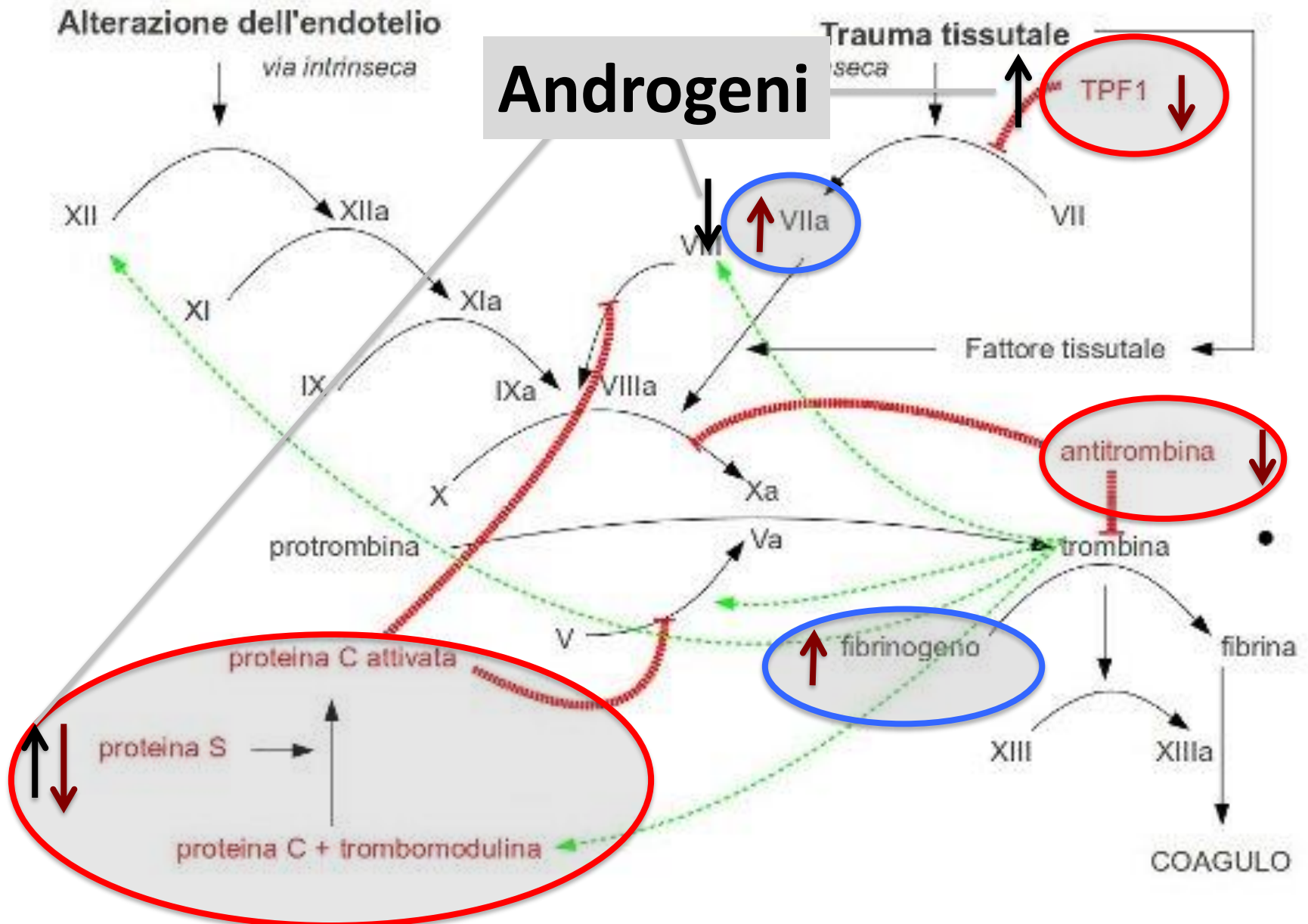
Oral contraceptives and venous thromboembolism: a five-year national case-control study☆

Øjvind Lidegaard*, Birgitte Edström, Svend Kreiner

	OR	95% CI
Estrogen dose		
50 μg EE	1.6	0.9–2.8
30–40 μg EE	1 reference	
20 μg EE	0.6	0.4–0.9
POP	—	

Effetto degli Androgeni sull'Azione degli Estrogeni Sintetici od Orali

Androgeni



Progestinici: Profilo Androgenico

L'affinità di NGM e NGMN per il recettore degli androgeni è simile a quella del progesterone naturale e ha una potente attività inibitoria dell'enzima 5 α -reduttasi nella pelle. Inoltre, non avendo legami con la globulina legante gli ormoni sessuali (SHBG), non causa lo spostamento del testosterone e non inibisce la sintesi epatica di SHBG che sarebbe indotta da EE, dimostrando così di essere un **progestinico neutro dal punto di vista androgeno**.

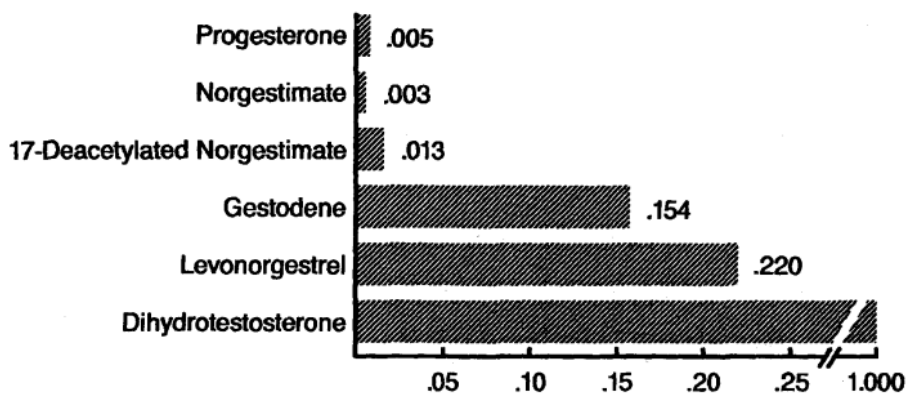


Fig. 4. Relative binding affinity for rat prostatic androgen receptors measured as displacement of ^3H -dihydrotestosterone. (Data from Phillips A, et al. Contraception 1990;41:399-410.)

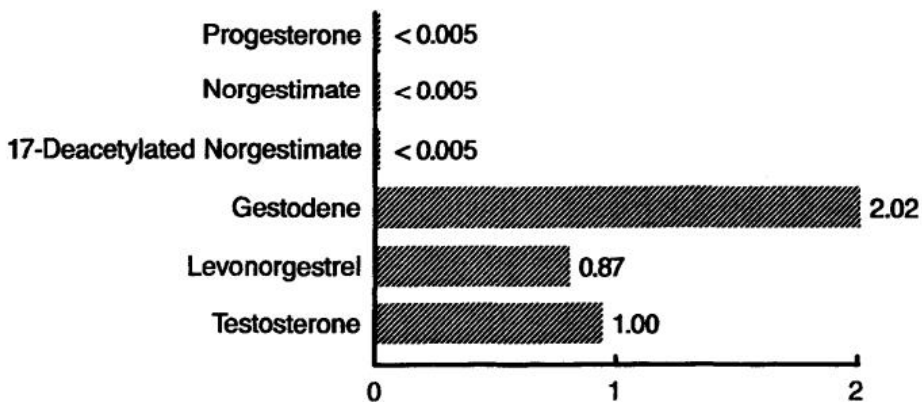
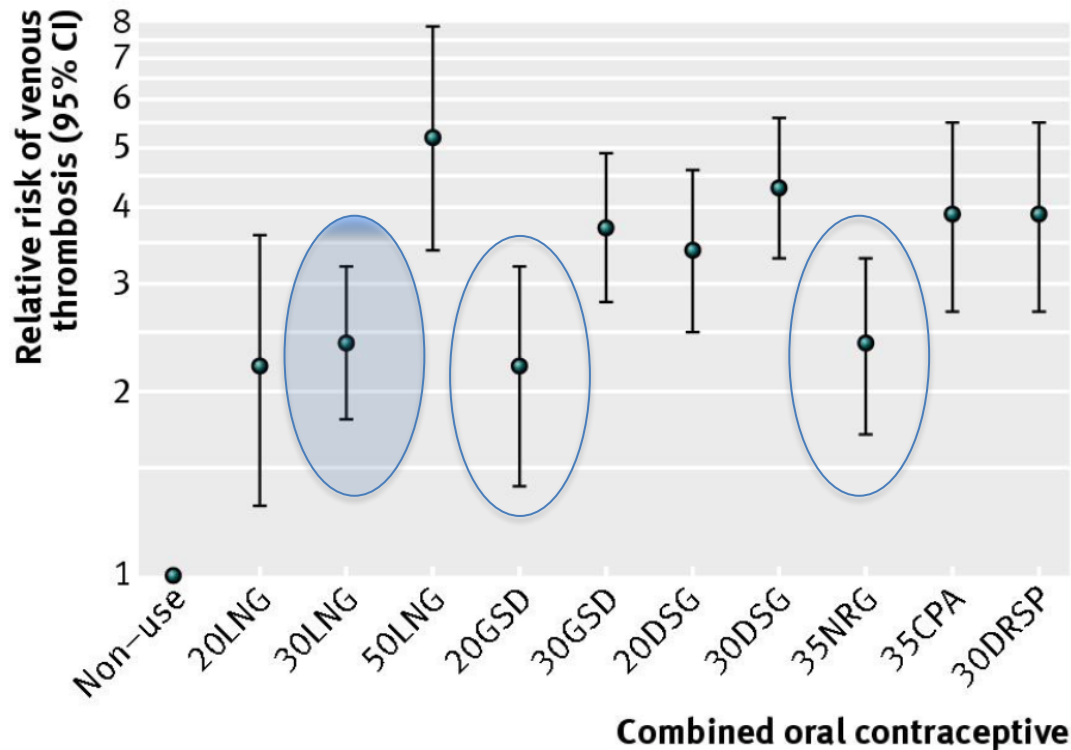


Fig. 6. Relative binding affinity for human SHBG measured as displacement of ^3H -testosterone. (Data from Phillips A, et al. Steroids 1990;55:373-5.)

Combined oral contraceptives: venous thrombosis (Review)

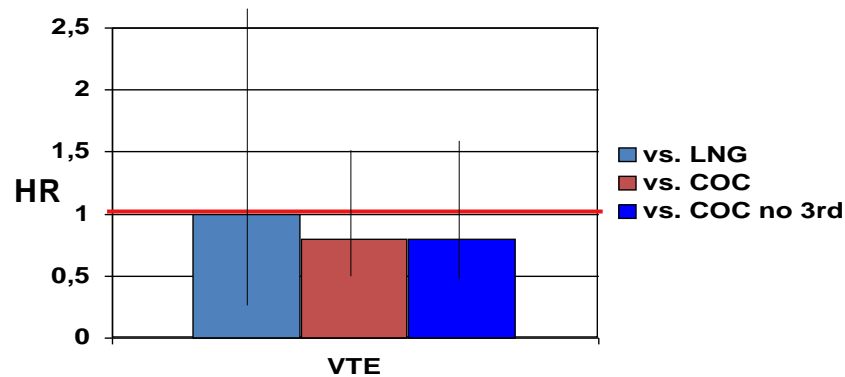
de Bastos M, Stegeman BH, Rosendaal FR, Van Hylckama Vlieg A, Helmerhorst FM, Stijnen T, Dekkers OM

© 2014 The Cochrane Collaboration.



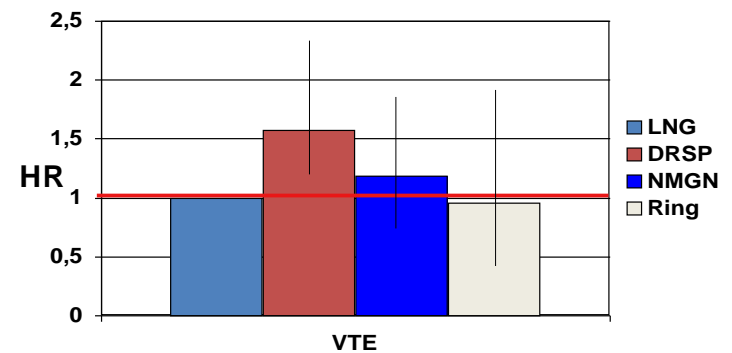
COC e Rischio Tromboembolico

HR of Venous Disease of Vaginal Ring vs. COC
(Ring user/anno; n=33.225)



Dinger et al., Obstet Gynecol 2013

HR of Venous Disease with Hormonal Contraception
(new users; n=573.680)



Sydney et al., Contraception 2013

VTE Risk of Natural Estrogens vs. EE-based contraceptives

NOMAC-E2 vs. LNG-EE (20-30 mcg, Multiphasic)

HR: 0.59 95% CI: 0.25 - 1.35

DNG-EV vs. LNG-EE (20-30 mcg)

HR: 0.4 95% CI: 0.20 - 1.10

COC e Rischio Tromboembolico

Tabella 1 Rischio di TEV con contraccettivi ormonali combinati (nuove informazioni in grassetto)

Progestinico nei COC (in combinazione con etinilestradiolo, se non diversamente indicato)	Rischio relativo vs Levonorgestrel	Incidenza stimata (per 10.000 donne per anno di utilizzo)
Non utilizzatrici-non in gravidanza	-	2
Levonorgestrel	Ref	5-7
Norgestimato/Noretisterone	1.0	5-7
Nomegestrolo (più estradiolo)	Può presentare un rischio di TEV nello stesso intervallo di quello osservato in un COC contenente levonorgestrel.	
Dienogest (più estradiolo valerato)	Può presentare un rischio di TEV nello stesso intervallo di quello osservato in un COC contenente levonorgestrel.	
Clormadinone acetato	1.25	6-9
Dienogest	1.6	8-11
Gestodene/Desogestrel/Drospirenone	1.5-2.0	9-12
Etonorgestrel/ Norelgestromin	1.0-2.0	6-12

VTE Risk of Natural Estrogens vs. EE-based contraceptives

DRSP-E4 vs. LNG-EE

HR: Unknown



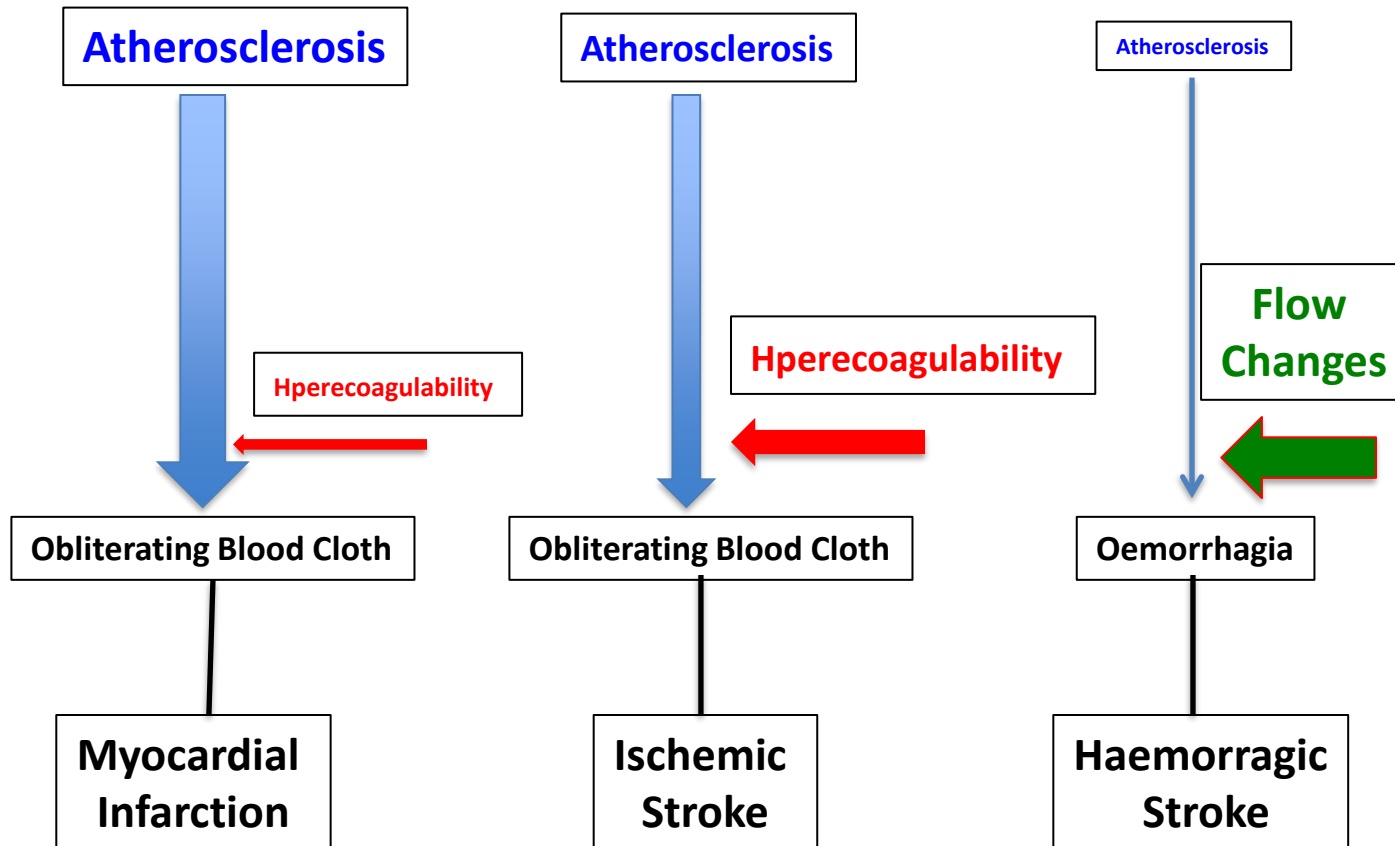
Estetra Study Protocol

Supporting document SOP PM01 – Doc PM3004.03

Estetra Post Authorisation study information

Title	International Active Surveillance Study: Native Estrogen Estetrol (E4) Safety Study (INAS-NEES)
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Risk Factors of Arterial Events



REVIEW ARTICLE

Estrogens, progestogens and thrombosis

F. R. ROSENDAAL,* A. VAN HYLCKAMA Vlieg,* B. C. TANIS† and F. M. HELMERHORST‡

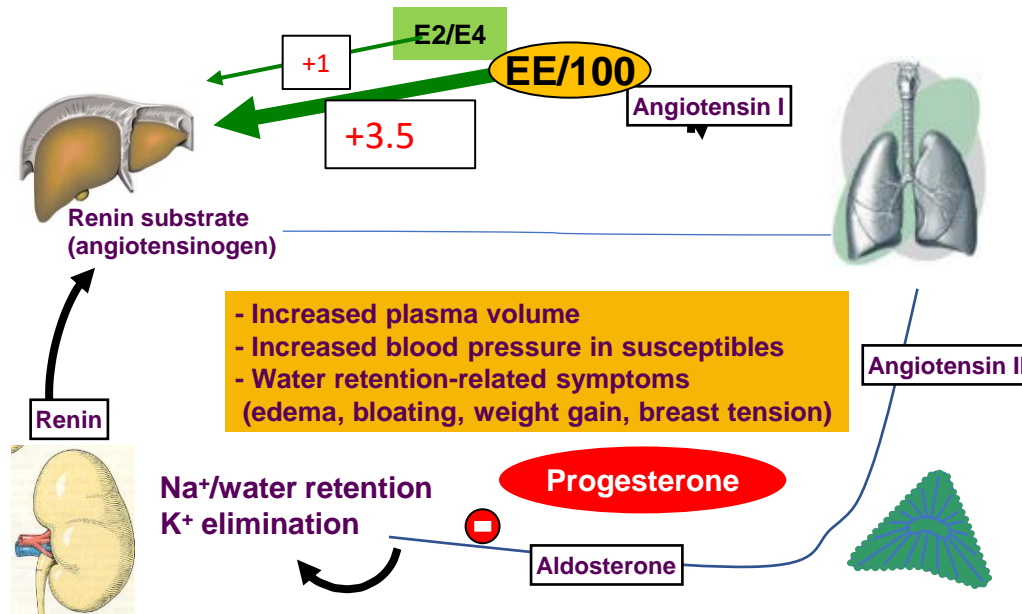
Table 1 Risk factors for thrombosis

Stasis	Vessel wall changes	Hypercoagulability
Venous thrombosis		
age	age	antithrombin deficiency
previous thrombosis	previous thrombosis	protein C deficiency
surgery		protein S deficiency
pregnancy		FV Leiden
puerperium		prothrombin 20210A
plaster casts		antiphospholipid syndrome
prolonged travel		dysfibrinogenemia
immobilization		high levels of prothrombin
		high levels of FVIII
		high levels of FIX
		high levels of FXI
		high levels of TAFI
		pregnancy
		malignant disease
		estrogens
Arterial thrombosis		
—	age	estrogens
	smoking	antiphospholipid syndrome
	hypertension	hyperhomocysteinemia
	hypercholesterolemia	FV Leiden (?)
	diabetes mellitus	prothrombin 20210A (?)
	lack of exercise	high levels of FVIII (?)
		high levels of FIX (?)

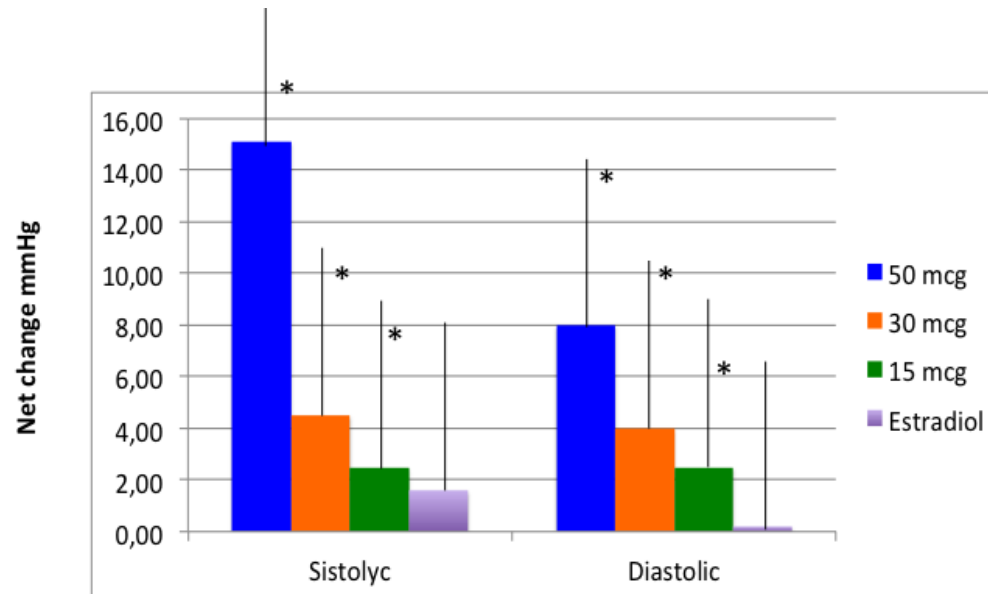
Quali caratteristiche distintive di estetrol?

	EE	E2	E4
Incremento			
SHBG	+250%	+60%	+50%
Angiotensinogeno	+206.5%	+80%	+75%

Renin-angiotensin-aldosterone system (RAAS)



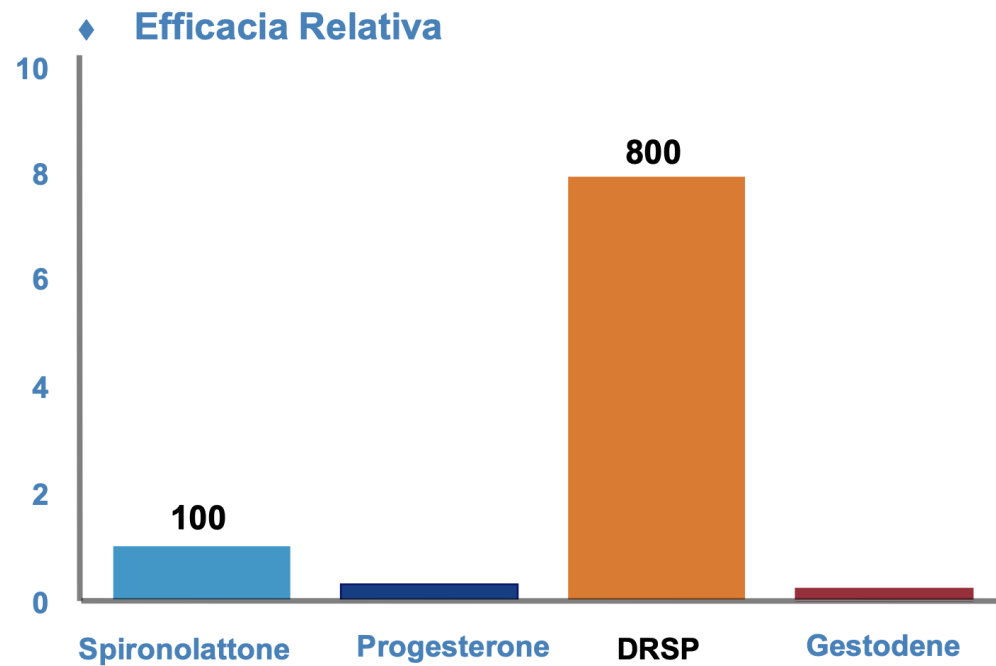
Quali caratteristiche distintive di estetrol?



Weir et al, 1974, Godsland et al. 1995, Cagnacci et al. 2013, Cagnacci et al. 2014

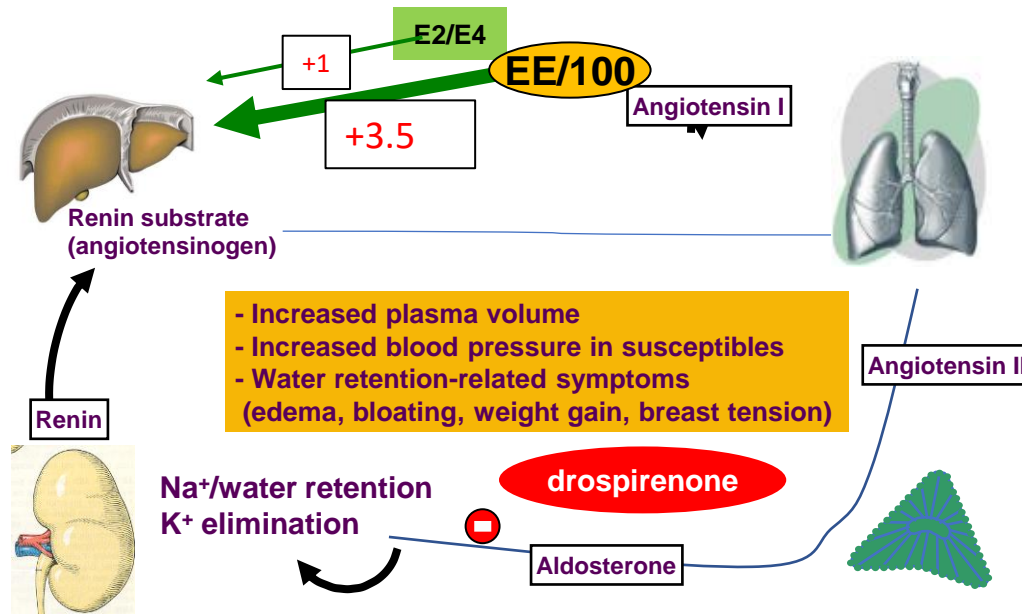
No data with E4

Attività Antimineralocorticoide



Losert et al. Drug Res. 35 (1985), 459-471

Renin-angiotensin-aldosterone system (RAAS)



Modificazioni della Pressione Arteriosa con EE/LNG, EE/DRSP ed E/NOMAc

	EV/NOMAc (6-13 cycles)		DRSP / EE 30 µg (13 cycles)		LNG / EE 30 µg (6 cycles)	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
syst. BP (mmHg)	3,103	- 0.1 (11.2)	1,013	- 0.1 (11.5)	57	+ 4.5 (12.1)
diast. BP (mmHg)	3,102	0.0	1,013	0.3 (8.7)	57	+ 2.5 (8.8)

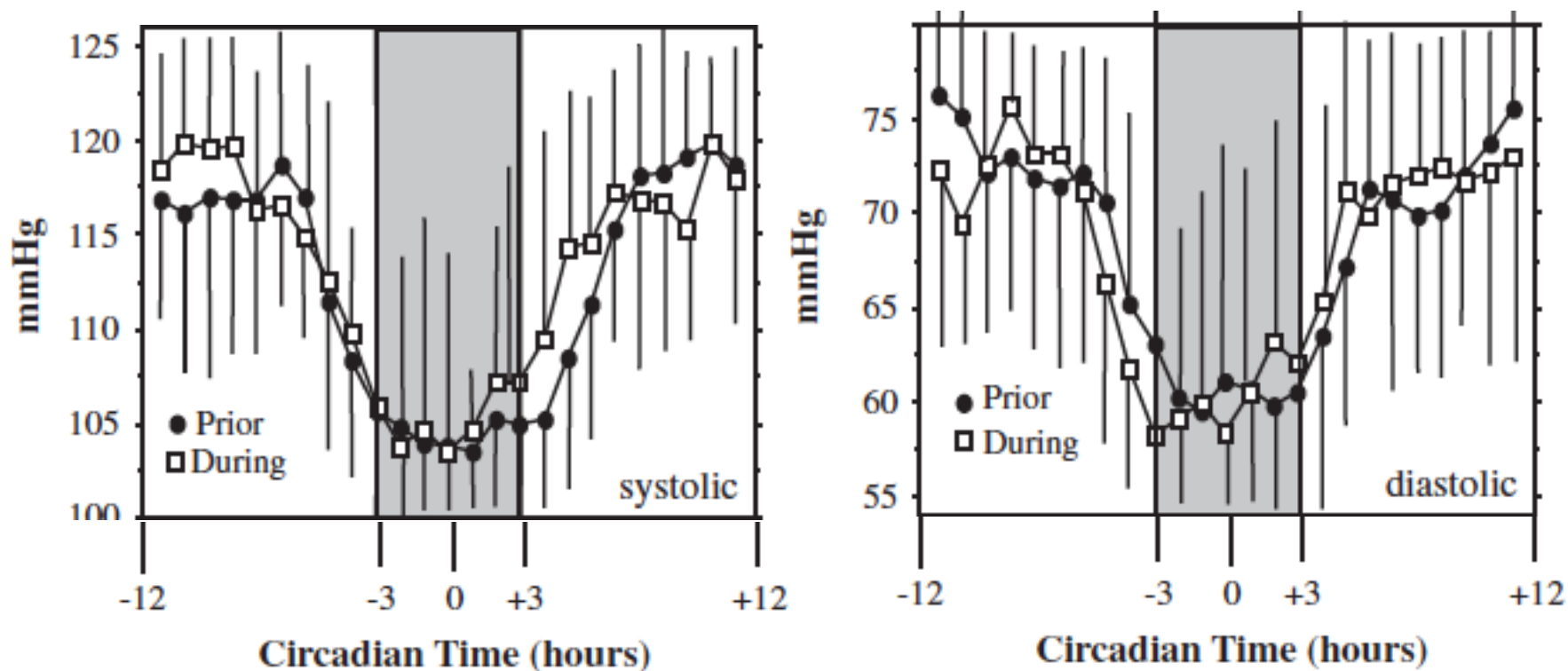
Original research article

Combined oral contraceptive containing **drospirenone** does not modify
24-h ambulatory blood pressure but increases heart rate in healthy
young women: prospective study

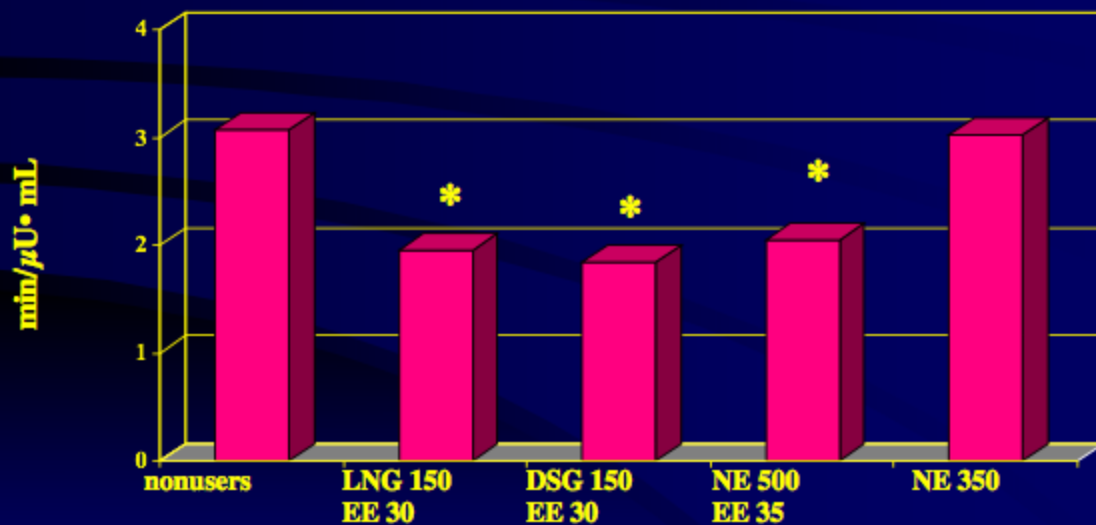
Angelo Cagnacci*, Serena Ferrari, Antonella Napolitano, Ilaria Piacenti,
Serenella Arangino, Annibale Volpe

Department of Obstetrics, Gynecology and Pediatrics, Obstetrics and Gynecology Unit, University of Modena, Modena, Italy

Received 2 October 2012; revised 29 November 2012; accepted 1 December 2012

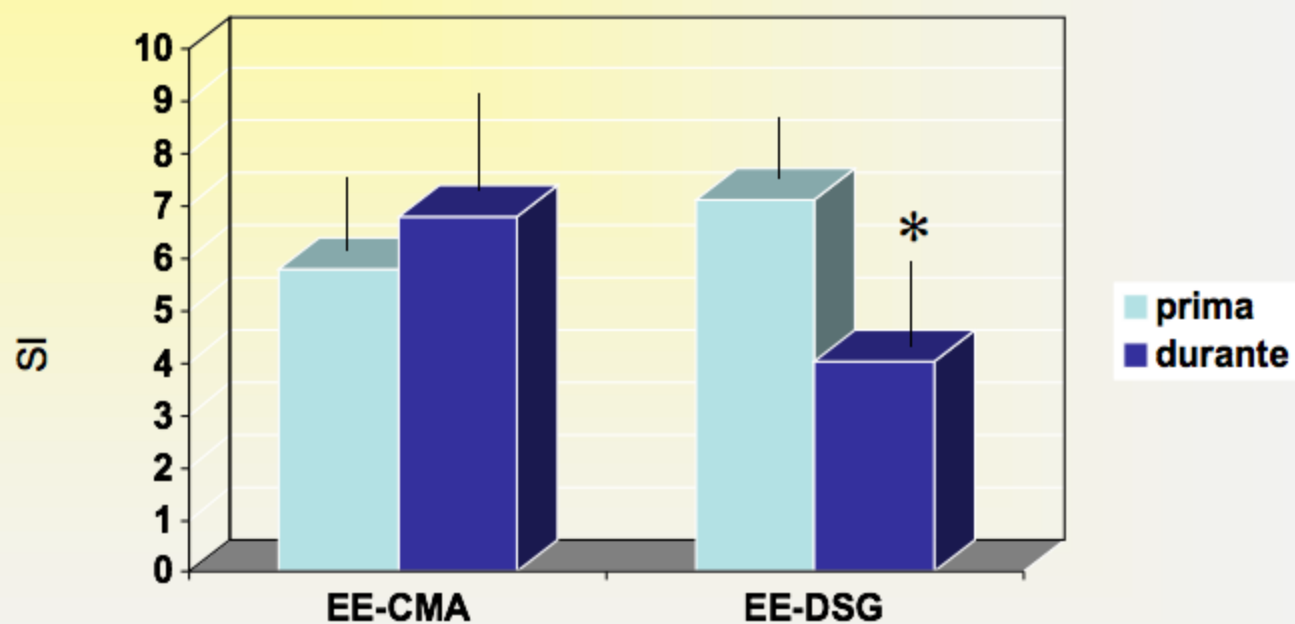


Insulin sensitivity index during OC



from Godsland I.F. et al., J Clin Endocrinol Metab 1991

Sensibilità all'Insulina in donne normali con CO contenenti CMA o DSG



Cagnacci et al., Contraception 2009

E2V/DNG (<i>n</i> = 16)			
	Before	During	<i>p</i>
Glucose, mmol/L	4.92 ± 0.49	4.94 ± 0.41	0.717
Insulin, pmol/L	34.68 ± 17.40	41.40 ± 19.68	0.650
HOMA-IR	1.13 ± 0.69	1.18 ± 0.69	0.642

European Journal of Obstetrics & Gynecology and Reproductive Biology 178 (2014) 68–70

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European Journal of Obstetrics & Gynecology and Reproductive Biology

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

Influence of an oral contraceptive containing drospirenone on insulin sensitivity of healthy women^a

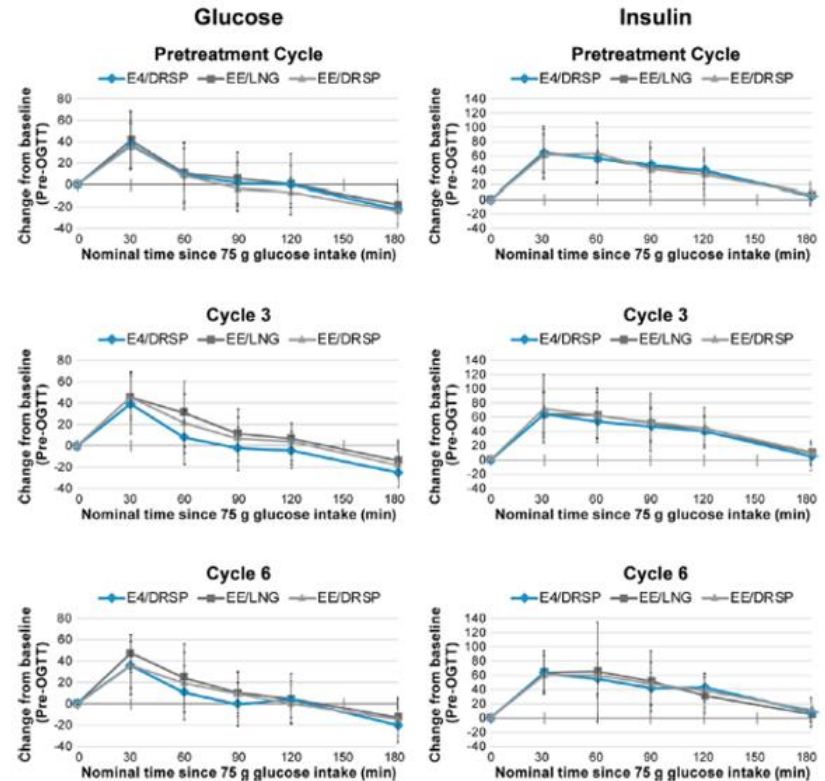
Angelo Cagnacci^a, Ilaria Piacenti, Renata Zanin, Anjeza Xholli, Alessandra Tirelli

Glucose metabolism, insulin sensitivity and lipid profile before after oral contraceptive pill containing drospirenone parameters.

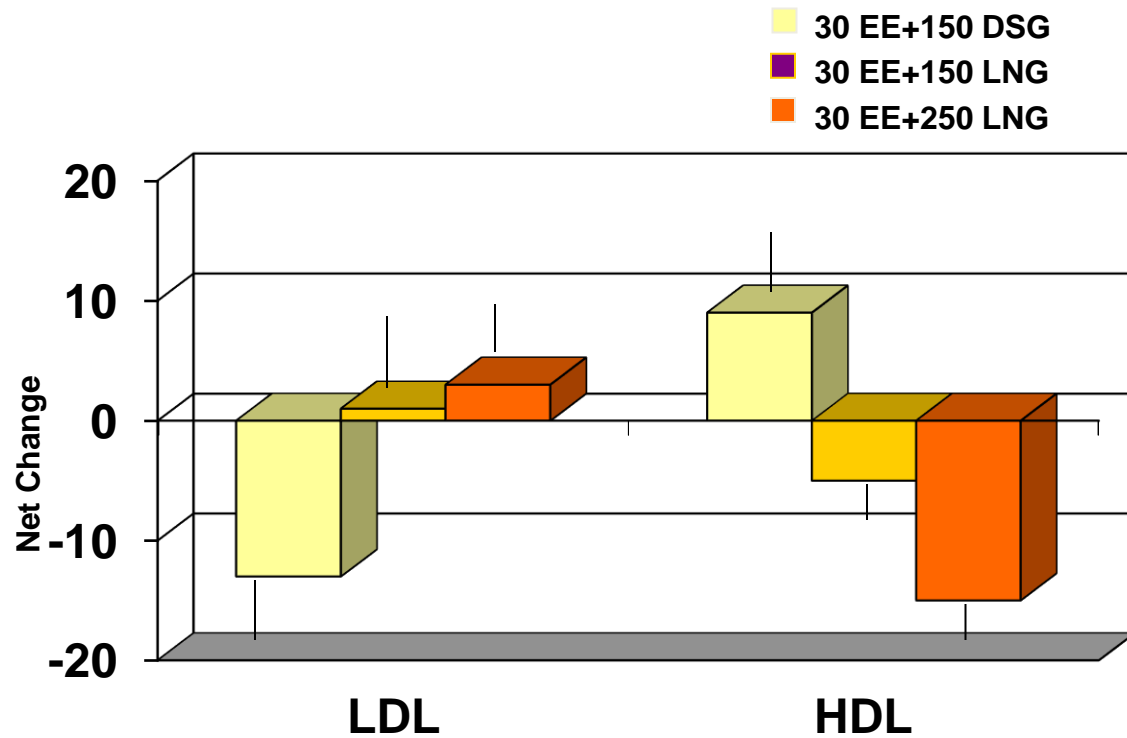
Parameters	Pretreatment	Posttreatment	Net difference	<i>P</i>
Glucose mg/dL	80.7 ± 6.9	80.7 ± 12.4	0.00 ± 10.8	0.99
Insulin mU/mL	10.6 ± 8.2	8.2 ± 2.6	−2.3 ± 7.9	0.33
HOMA/IR	2.2 ± 1.7	1.7 ± 0.76	−0.5 ± 1.7	0.34 ^a
SI	3.7 ± 2.6	3.29 ± 2.93	0.2 ± 3.9	0.73
Sg	0.03 ± 0.02	0.032 ± 0.014	−0.01 ± 0.02	0.87

E4-DRSP METABOLISMO DEI CARBOIDRATI

Dai dati sulla resistenza insulinica e tolleranza glucidica, appare un effetto neutro della combinazione E4/DRSP dopo 3, 6 cicli di trattamento



Lipoproteins and OC with DSG or LNG

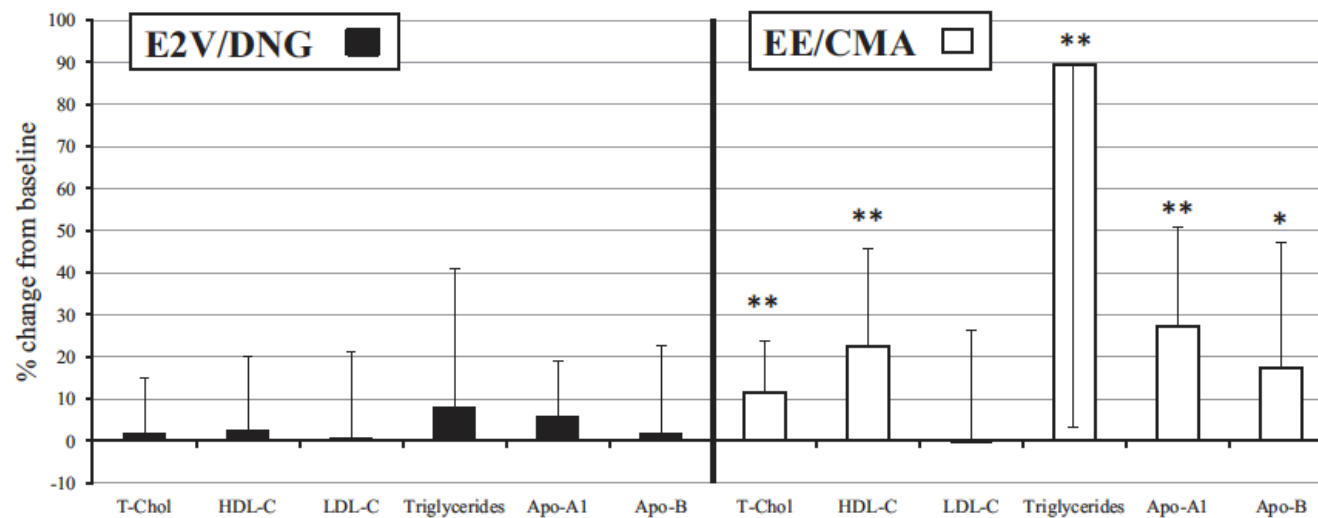


6 Months of treatment

Burkman, Am J Obstet Gynecol 1990

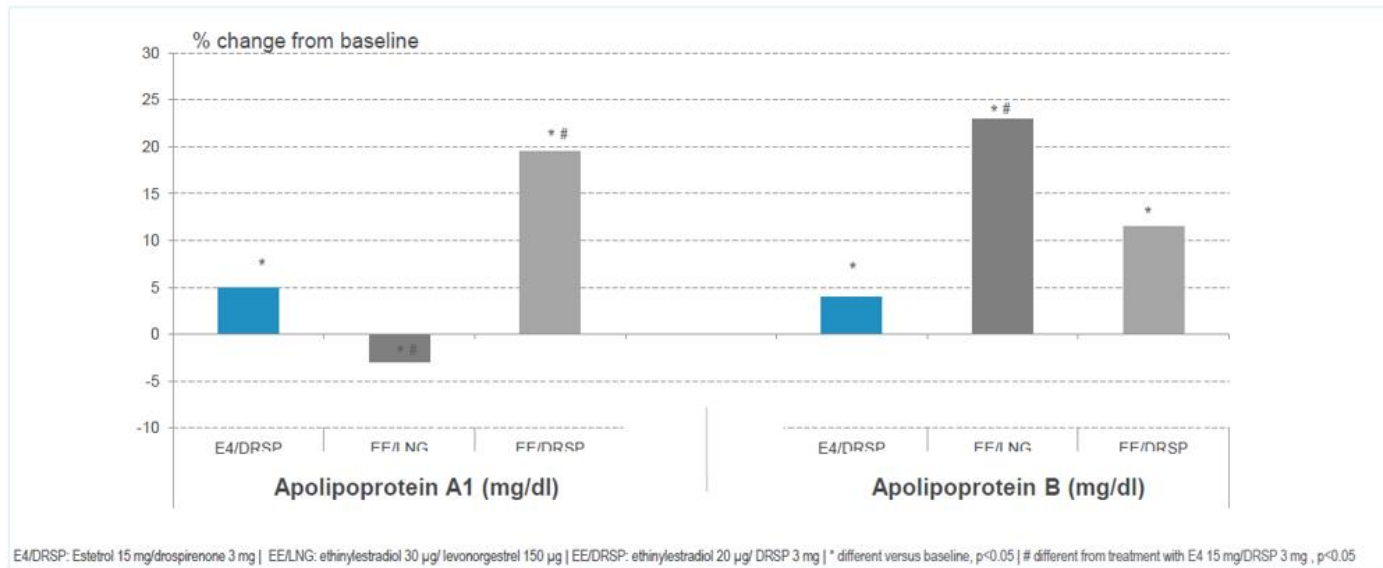
Modification of body composition and metabolism during oral contraceptives containing non-androgenic progestins in association with estradiol or ethinyl estradiol

Giovanni Grandi, Ilaria Piacenti, Annibale Volpe, and Angelo Cagnacci



E4-DRSP METABOLISMO DEI LIPIDI

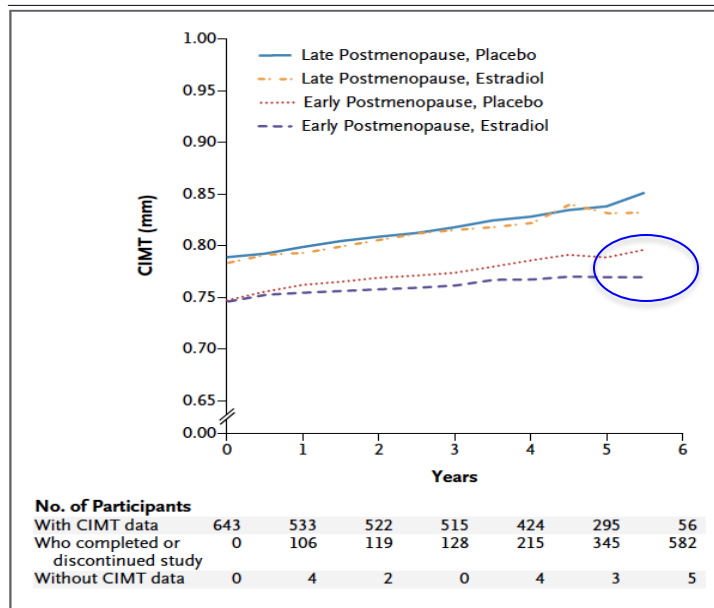
E4/DRSP - profilo lipidico cambiamenti dopo 6 cicli



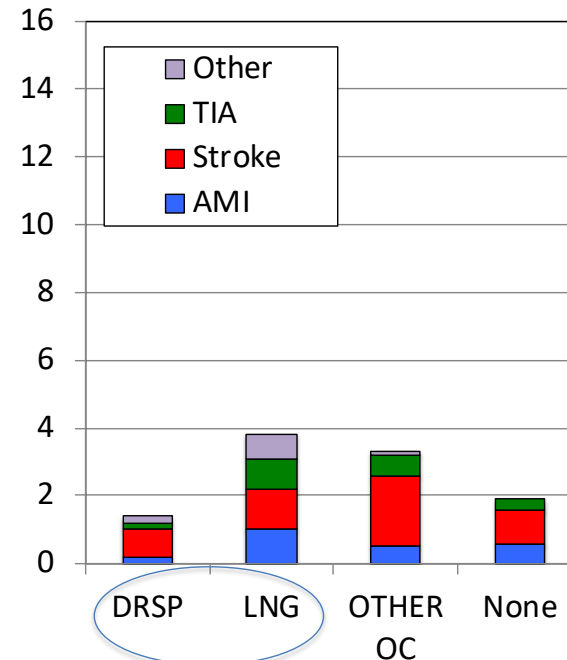
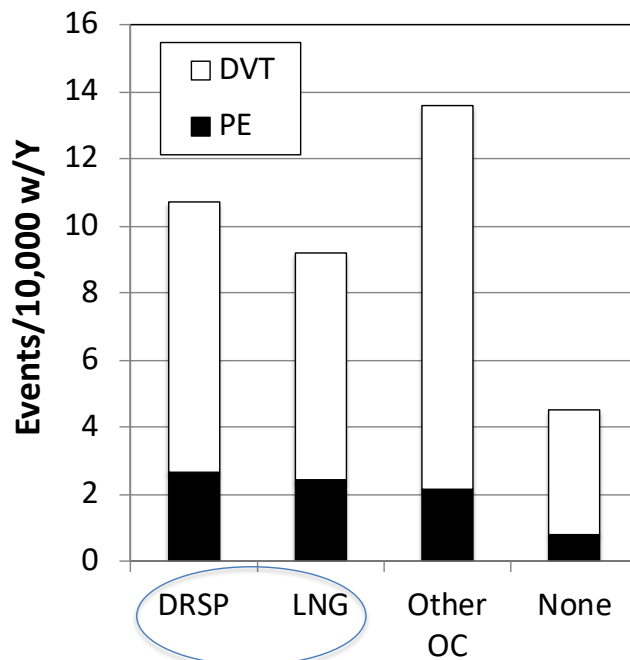
ORIGINAL ARTICLE

Vascular Effects of Early versus Late Postmenopausal Treatment with Estradiol

Howard N. Hodis, M.D., Wendy J. Mack, Ph.D., Victor W. Henderson, M.D., Donna Shoupe, M.D., Matthew J. Budoff, M.D., Juliana Hwang-Levine, Pharm.D., Yanjie Li, M.D., Mei Feng, M.D., Laurie Dustin, M.S., Naoko Kono, M.P.H., Frank Z. Stanczyk, Ph.D., Robert H. Selzer, M.S., and Stanley P. Azen, Ph.D., for the ELITE Research Group*



COC e Rischio Cardiovascolare



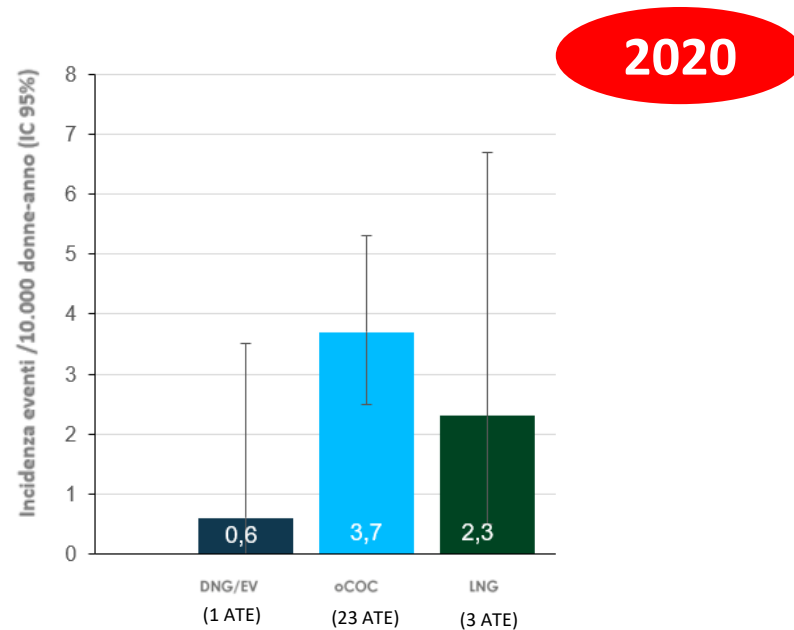
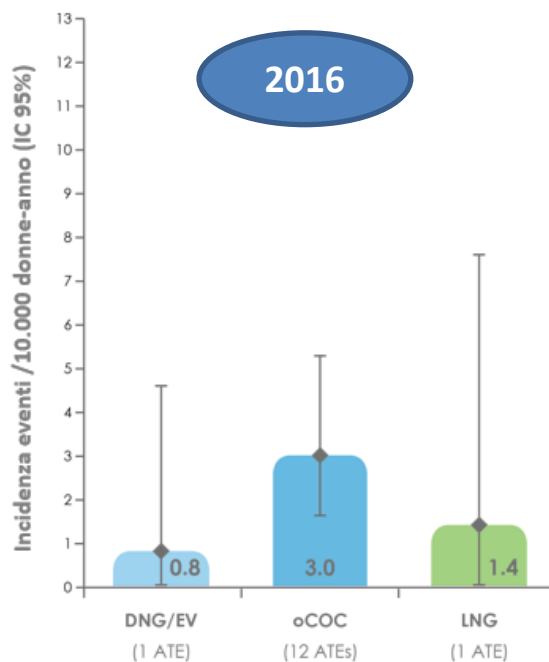
Modified by Cagnacci 2021



INAS-SCORE

Incidenza complessiva di tromboembolismo arterioso (TEA) (EU)
















Il tasso di incidenza di TEA è stato più basso per E2V/DNG rispetto agli altri COC, compresi quelli contenenti LNG



NB con estensione del follow up i casi ATE tot sono quasi raddoppiati in tutti i gruppi tranne con E2V/DNG dove resta 1 solo caso

Rischio Cardiovascolare e Contraccezione

Contraccezione con E2, E4 vs. EE/DRSP e EE/LNG

	E2	E4	EE/DRSP	EE/LNG
SHBG				
VTE				
Pressione Arteriosa	/		/	
Insulino Resistenza	/	/	/	
HDL/LDL	/	/		
Rischio arterioso	/		/	

Conclusioni

- Le azioni delle molecole estrogeniche e progestiniche utilizzate in contracccezione sono complesse e diverse tra di loro.
- L'ottimizzazione del risultato deriva dalla conoscenza delle proprietà delle singole molecole e dalla scelta mirata della giusta combinazione.



**Grazie per
l'attenzione!!**



**CORSO
SIGO
YOUNG**

in collaborazione con:
NOI GIOVANI
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DIRETTORE GENERALE
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S.I.C.
Società Italiana della Chimica

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MILANO
1 Luglio 2024

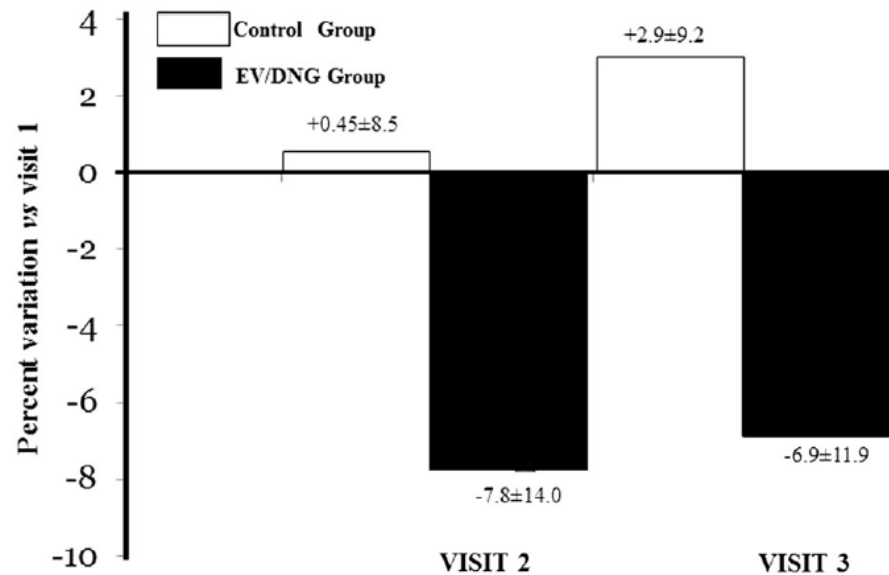
Coordinatori scientifici:
A. Cagnacci, N. Colacurci
Direttore del Corso
M. Vignali

HOTEL DEI CAVALIERI
Piazza Giuseppe Missori, 1

5 crediti ECM

Effect of Estradiol valerate plus dienogest on body composition of healthy women in the menopausal transition: a prospective one-year evaluation

Anna Maria Paoletti¹, Stefano Lello¹, Costantino Di Carlo², Marisa Orrù¹, Maria Elena Malune¹, Manuela Neri¹, Monica Pilloni¹, Pierina Zedda¹, Maurizio Nicola D'Alterio¹, Costantino Motzo¹, Gian Benedetto Melis¹, and Angelo Cagnacci³



Sicurezza Contraccettiva

Sistema Scheletrico



Hormonal contraception and bone metabolism. Emerging evidence from a systematic review and meta-analysis of studies on post-pubertal and reproductive-age women

Alice Tassi (1), Ambrogio P Londero (2,3), Anjeza Xholli (4), Giulia Lanzolla (5,6),
Serena Bertozzi (7), Federico Prefumo (3), Angelo Cagnacci (2,4)

Women 12-45 years of age

Controls: (no hormones)

Estrogens: EE, E2, E4

Progestins: Anti-Androgenic (CMA, DRSP, DNG, CPA)
Neutral (NGMN, P, SGA, DHPA)
Androgenic (LNG, GSD, NET, NGM, DSG, ENG, MPA)

Hormonal contraception and bone metabolism. Emerging evidence from a systematic review and meta-analysis of studies on post-pubertal and reproductive-age women

Alice Tassi (1), Ambrogio P Londero (2,3), Anjeza Xholli (4), Giulia Lanzolla (5,6), Serena Bertozzi (7), Federico Prefumo (3), Angelo Cagnacci (2,4)

Markers of Bone Formation

Osteocalcin, BPA, PA, P1NP

Markers of Bone Absorption

DPD, PYR, NTX, CTX

SMC (differenza standardizzata tra prima e durante trattamento)

SMC= Mean Difference/Standard Deviation

Results are expressed as variations in SD

Indici di Turnover Osseo e Contraccizione

Formazione

Controls	-0.12 (-0.35, 0.25)
E2V	-0.10 (-0.47, 0.27)
EE	-0.54 (-0.64, -0.43)
POP	0.55 (0.07, 1.04)

Osteocalcin

Riassorbimento

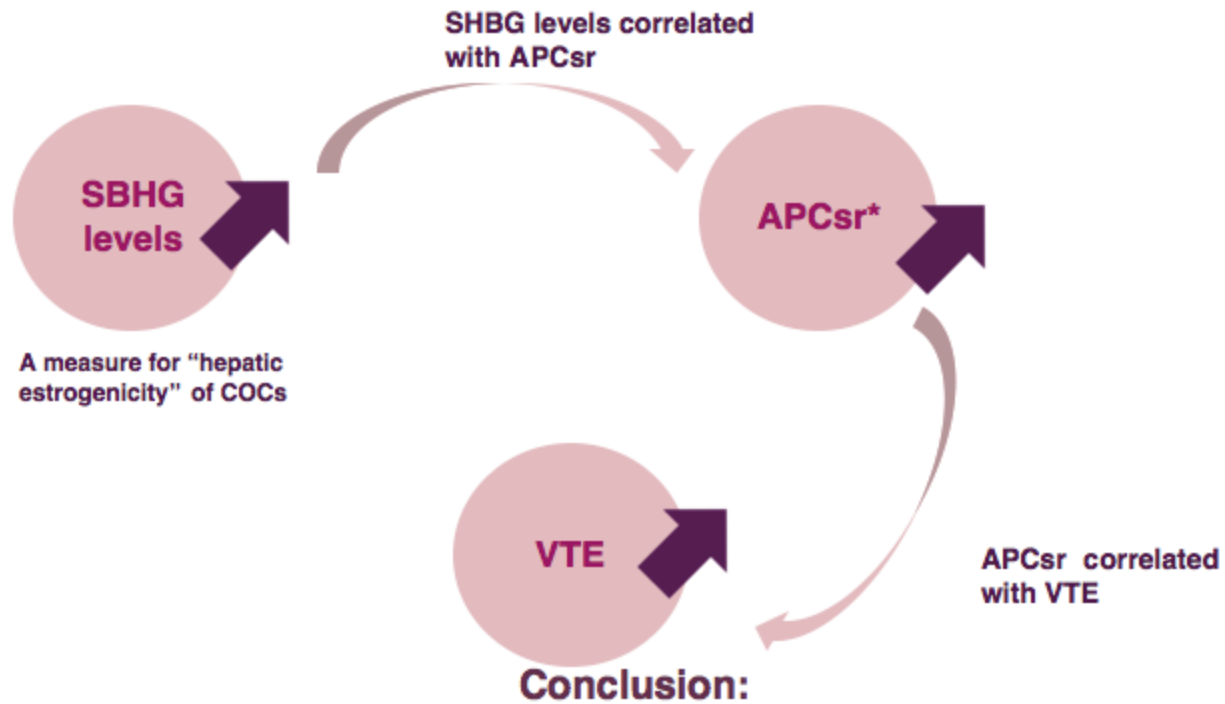
Controls	-0.02 (-0.14, 0.10)
EV	-1.57 (-2.13, -1.02)
EE	-0.33 (-0.43, -0.22)
POP	-0.07 (-0.34, 0.20)

DPD

Differenza tra Formazione E Riassorbimento

Controls	-0.1
EV	1.47
EE	-0.1
POP	0.62

SHBG come marker di TVP



- **SHBG levels are a marker for the thrombotic risk**

Tchaikovski et al., Thromb Res 2010;126(1):5-11

Diversità Tra i vari Estrogeni

	EE	E2	E4
Emivita	26+/-7 hr	20-30 min	28-32 hr
SHBG stimulus	250%	60%	50%
SHBG legame	Molto bassa	38% alta affinità	assente
Albumina legame	98.5%	60% bassa affinità	Bassa affinità 50%
Biodisponibilità	38-48%	3-5%	70%
Recettori	Alfa/Beta	Alfa/Beta	Alfa/Beta
Inibizione FSH	-41% (20 mcg)	-41/-54% (2mg)	-60% -79% (10 mg)(20 mg)



ELSEVIER

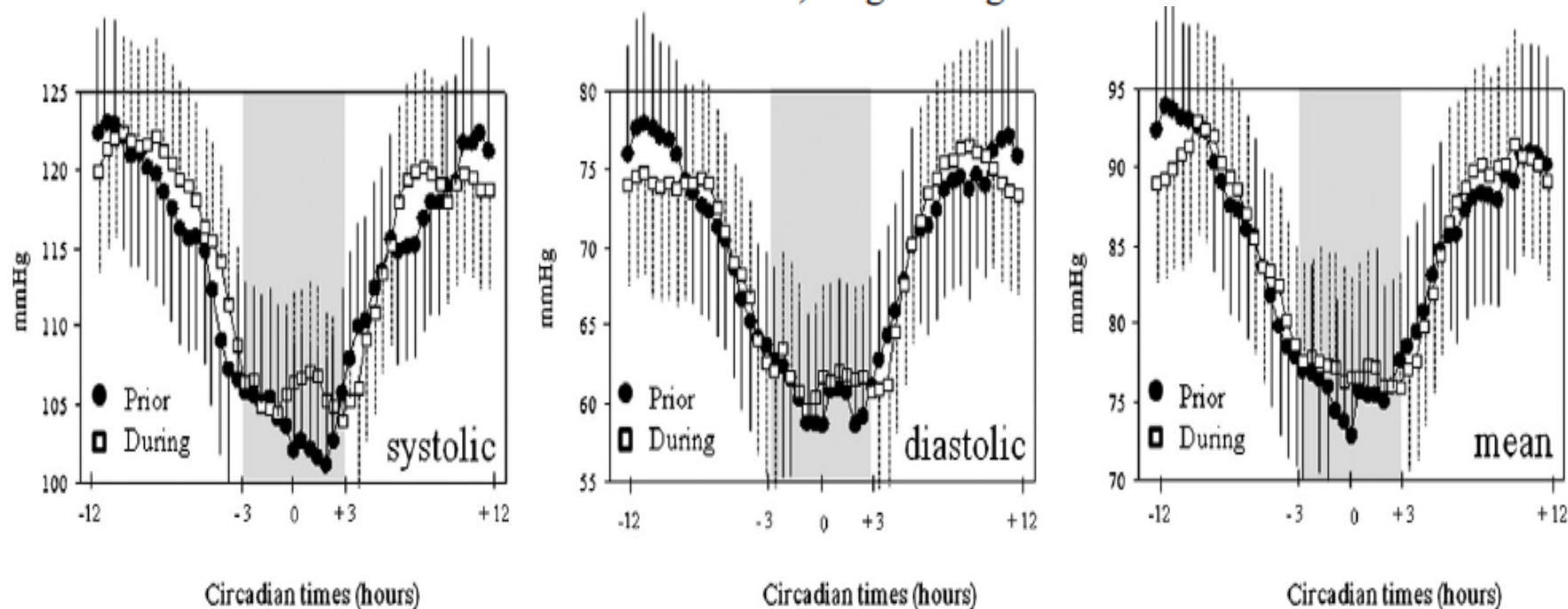


CrossMark

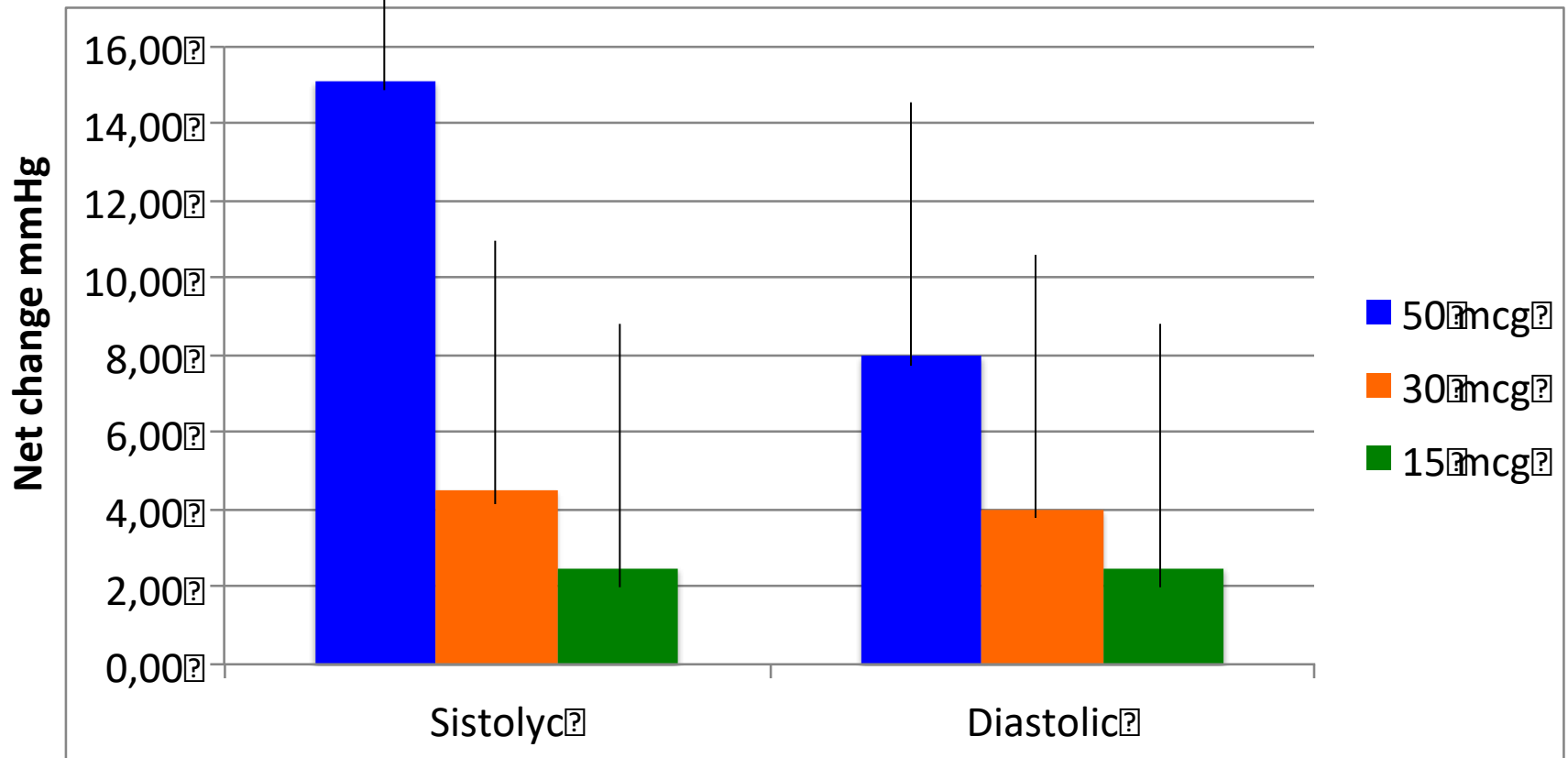
Original research article

Prospective measurement of blood pressure and heart rate over 24 h in women using combined oral contraceptives with estradiol^{☆,☆☆}

Giovanni Grandi, Anjeza Xholli, Antonella Napolitano, Ilaria Piacenti, Manuela Bellafronte, Angelo Cagnacci*



COC and Blood Pressure Increase



Weir et al, 1974, Godsland et al. 1995, Cagnacci et al. 2013

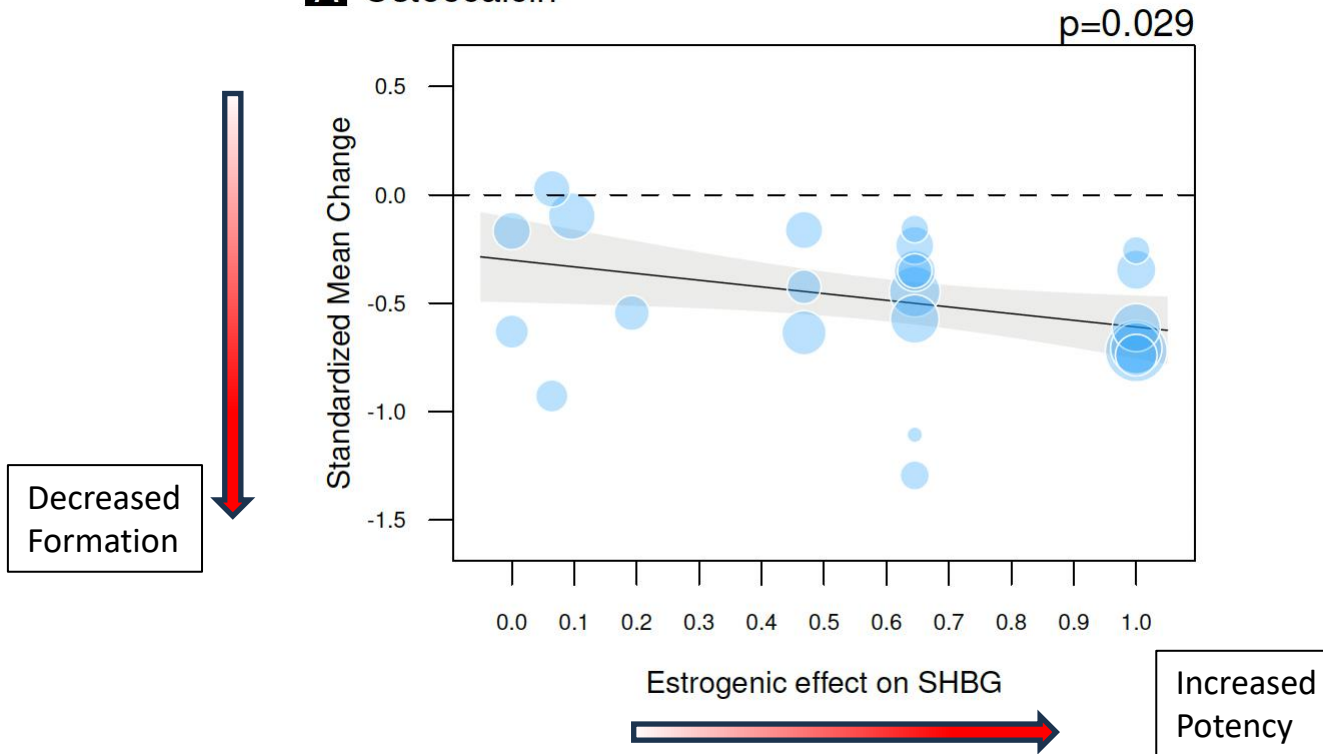
Hormonal contraception and bone metabolism. Emerging evidence from a systematic review and meta-analysis of studies on post-pubertal and reproductive-age women

Alice Tassi (1), Ambrogio P Londero (2,3), Anjeza Xholli (4), Giulia Lanzolla (5,6),
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Women of any age

Estrogen Effect on Formation

A Osteocalcin



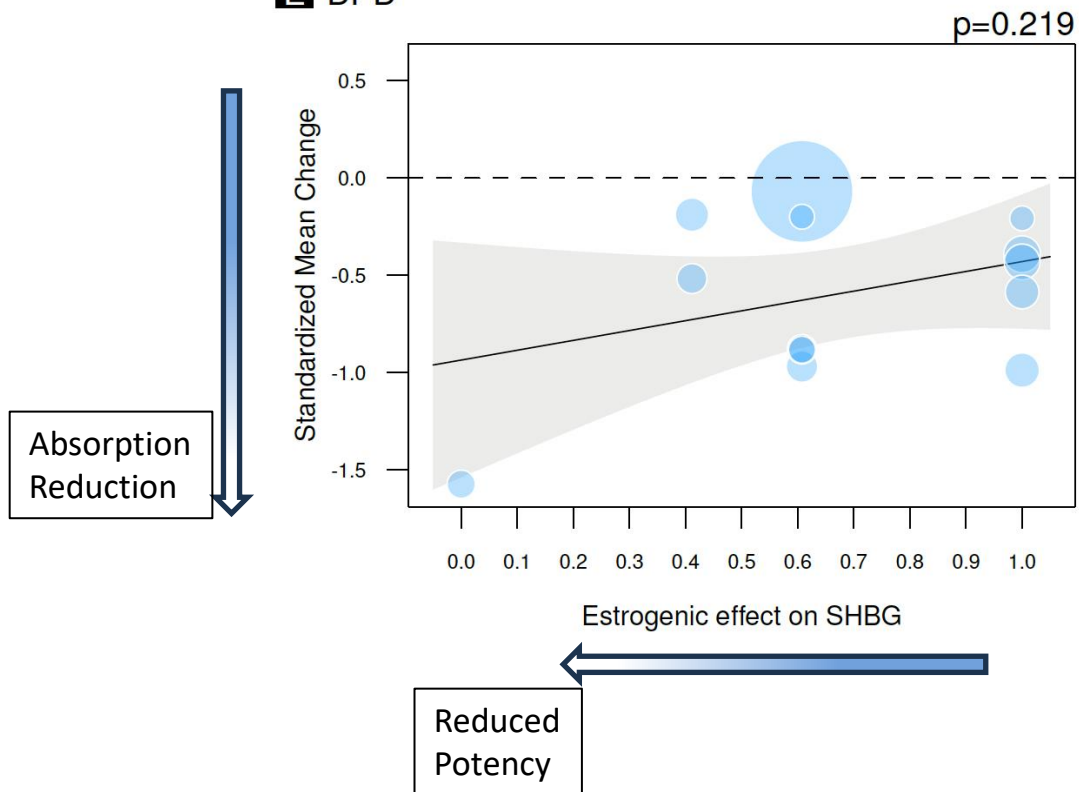
Hormonal contraception and bone metabolism. Emerging evidence from a systematic review and meta-analysis of studies on post-pubertal and reproductive-age women

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Women of any age

Estrogen Effect on Absorption

E DPD

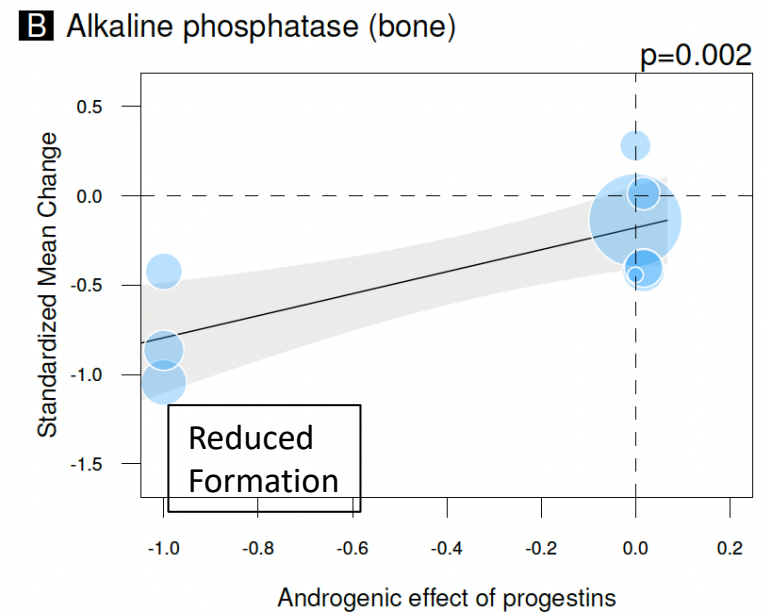
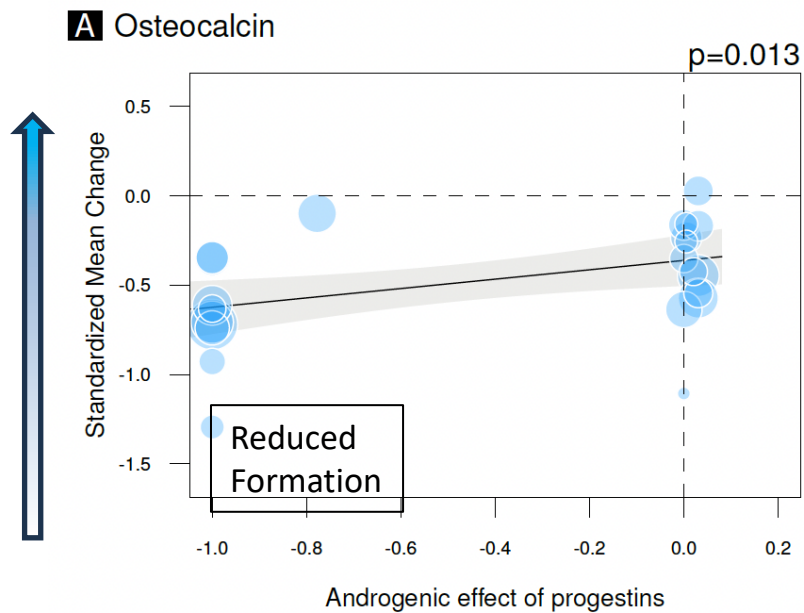


Hormonal contraception and bone metabolism. Emerging evidence from a systematic review and meta-analysis of studies on post-pubertal and reproductive-age women

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Women of any age

Progestin Effect on Bone Formation



BONE FORMATION

Controls	-0.12 (-0.35, 0.25)
E2V	-0.10 (-0.47, 0.27)
E4	-0.43 (-0.76, -0.10)
EE	-0.54 (-0.64, -0.43)
POP	0.55 (0.07, 1.04)

Osteocalcin

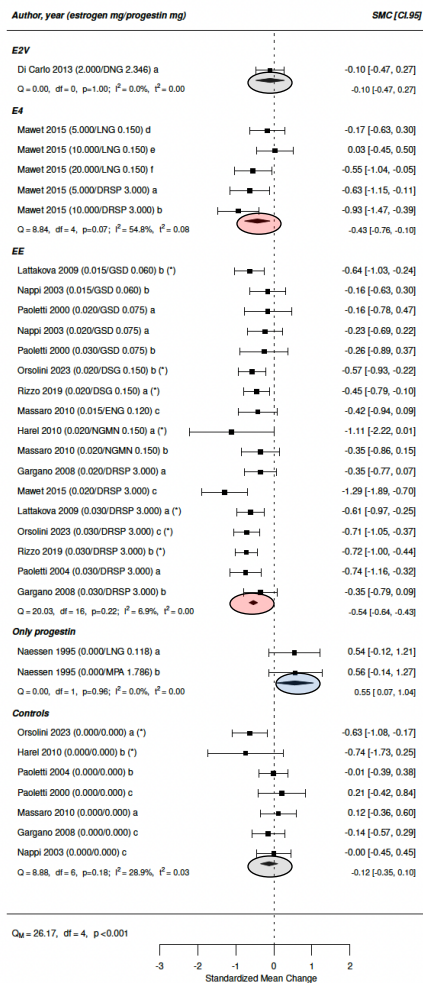
Controls	-0.40 (-0.93, 0.14)
EE	-0.39 (-0.67, -0.11)
POP	0.13 (-0.14, 0.40)

BPA

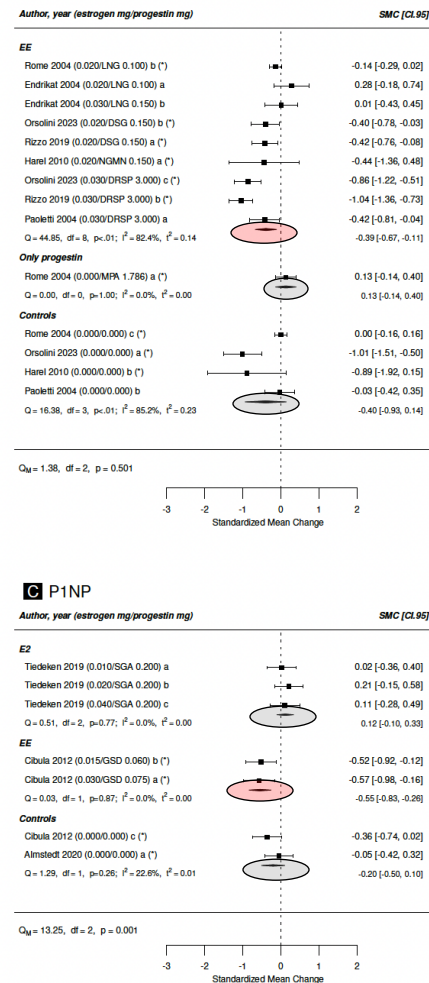
Controls	-0.20 (-0.50, 0.10)
E2	0.12 (-0.10, 0.33)
EE	-0.55 (-0.83, -0.26)

P1NP

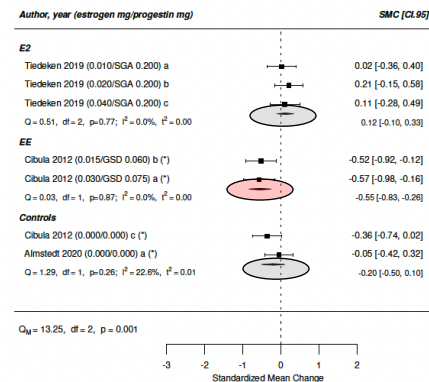
A Osteocalcin



B Alkaline phosphatase (bone)



C P1NP



BONE ABSORPTION

Controls	-0.02 (-0.14, 0.10)
EV	-1.57 (-2.13, -1.02)
EE	-0.33 (-0.43, -0.22)
POP	-0.07 (-0.34, 0.20)

DPD

Controls	-0.05 (-0.23, 0.13)
EV	-0.69 (-1.10, -0.27)
EE	-0.37 (-0.52, -0.21)

PYD

Controls	-0.23 (-0.56, 0.10)
E2 <small>transdermal/SGA</small>	0.25 (0.02, 0.48)
E4	-0.41 (-0.63, -0.20)
EE	-0.38 (-0.69, -0.07)

CTX

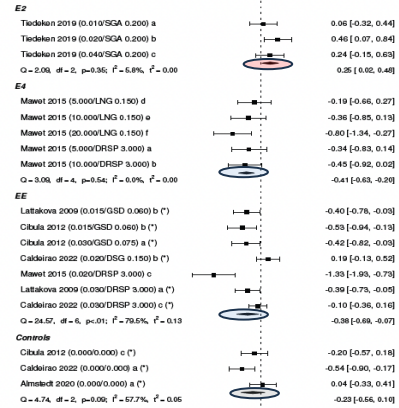
Controls	-1.65 (-3.0, -0.30)
EE	-0.43 (-0.74, -0.12)

NTX

A CTX

Author, year (estrogen mg/progestin mg)

SMC [CI.95]

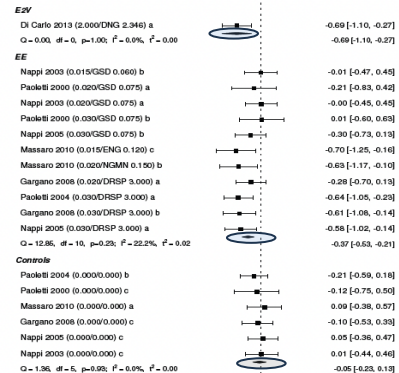


$Q_{adj} = 9.83$, $df = 3$, $p = 0.020$

C PYD

Author, year (estrogen mg/progestin mg)

SMC [CI.95]

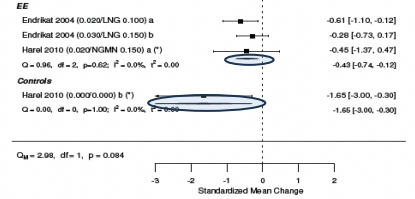


$Q_{adj} = 11.33$, $df = 2$, $p = 0.003$

B NTX

Author, year (estrogen mg/progestin mg)

SMC [CI.95]

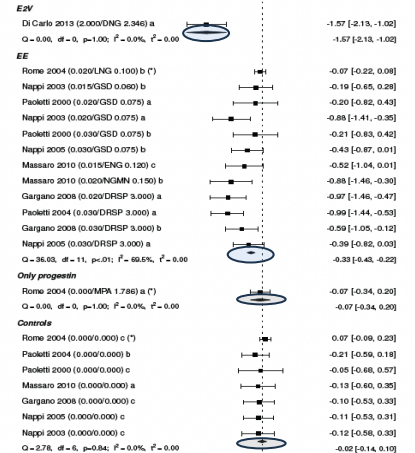


$Q_{adj} = 2.98$, $df = 1$, $p = 0.084$

D DPD

Author, year (estrogen mg/progestin mg)

SMC [CI.95]



$Q_{adj} = 38.77$, $df = 3$, $p < 0.001$

Original Article

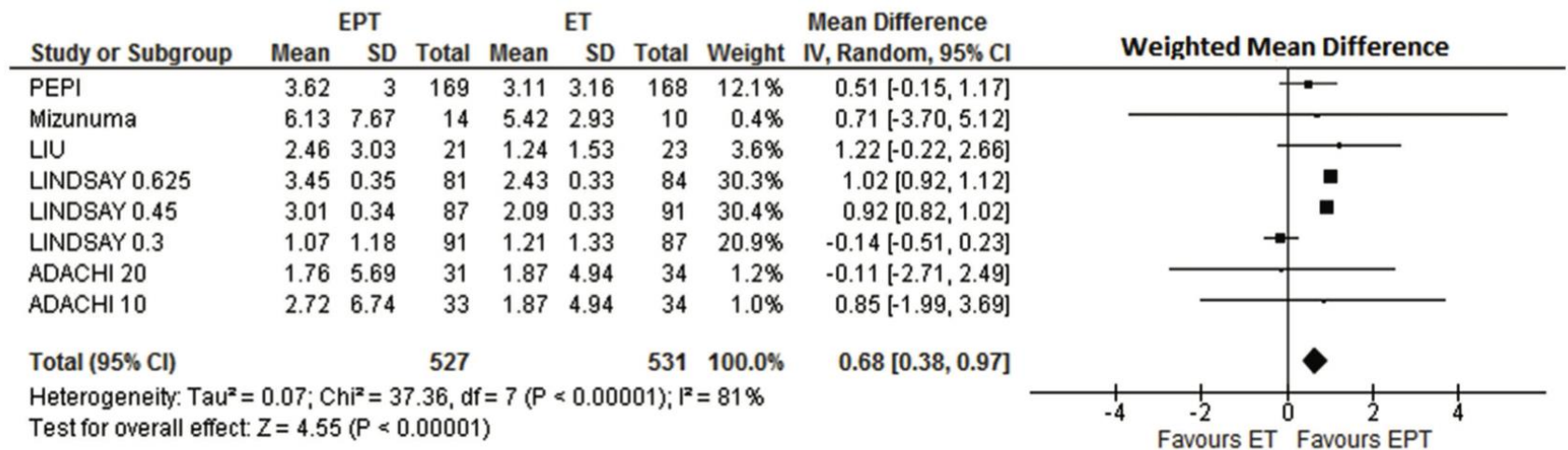

Estrogen-progestin therapy causes a greater increase in spinal bone mineral density than estrogen therapy - a systematic review and meta-analysis of controlled trials with direct randomizationJ.C. Prior^{1,2,3,4}, V.R. Seifert-Klauss^{1,7}, D. Giustini⁶, J.D. Adachi⁸, S. Kalyan^{1,2,4}, A. Goshtasebi^{1,5}

Figure 3. Forest plot comparing the Weighted Mean Difference in Percentage Annual Change in Spinal areal Bone Mineral Density (BMD) by Dual Energy X-ray Absorptiometry on Estrogen-Alone Therapy (ET) versus Estrogen-Progestin Therapy (EPT). This random effects meta-analysis model shows heterogeneity of the studies by I^2 .

Adolescent use of combined hormonal contraception and peak bone mineral density accrual: A meta-analysis of international prospective controlled studies

Azita Goshtasebi^{1,2} | Tatjana Subotic Brajic¹ | Delia Scholes³ |

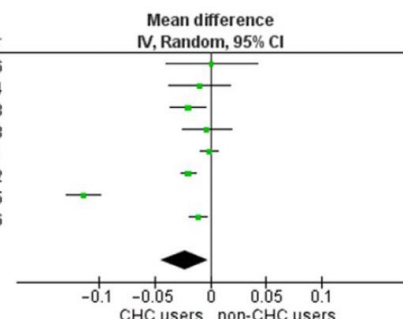
Tamara Beres Lederer Goldberg⁴ | Abbey Berenson⁵ | Jerilynn C. Prior^{1,2,6} 

Study or subgroup	Experimental			Control			Weight	Mean difference IV, Random, 95% CI	Year
	Mean	SD	Total	Mean	SD	Total			
Cromer	0.016	0.055	9	0.015	0.041	17	9.4%	0.00 [-0.04, 0.04]	1996
Lara-Tore	0.013	0.034	16	0.023	0.036	10	11.4%	-0.01 [-0.04, 0.02]	2004
Cromer'	0.02	0.056	62	0.04	0.04	95	12.9%	-0.02 [-0.04, -0.00]	2008
Berenson	0.008	0.042	36	0.011	0.032	14	12.3%	-0.00 [-0.02, 0.02]	2008
Scholes	0.007	0.041	115	0.008	0.014	75	13.6%	-0.00 [-0.01, 0.01]	2011
Gai	-0.01	0.027	277	0.01	0.035	136	13.7%	-0.02 [-0.03, -0.01]	2012
Blason	-0.01	0.03	26	0.104	0.03	35	13.0%	-0.11 [-0.13, -0.10]	2015
Gersten	0.015	0.06	240	0.026	0.036	372	13.6%	-0.01 [-0.02, -0.00]	2016

Total (95% CI) 781 754 100.0% -0.02 [-0.05, -0.00]

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 175.38$, $df = 7$ ($P < 0.00001$); $I^2 = 96\%$

Test for overall effect: $Z = 2.08$ ($P = 0.04$)

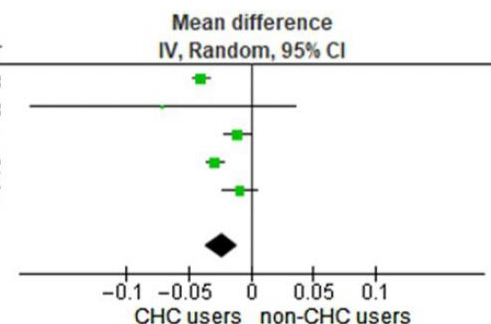


Study or subgroup	Experimental			Control			Weight	Mean difference IV, Random, 95% CI	Year
	Mean	SD	Total	Mean	SD	Total			
Cromer'	0.02	0.023	62	0.06	0.025	95	26.2%	-0.04 [-0.05, -0.03]	2008
Berenson	-0.039	0.29	29	0.032	0.02	8	1.6%	-0.07 [-0.18, 0.04]	2008
Scholes	0.011	0.037	93	0.0216	0.032	55	23.9%	-0.01 [-0.02, 0.00]	2011
Gai	-0.01	0.027	261	0.019	0.035	115	26.5%	-0.03 [-0.04, -0.02]	2012
Brajic	0.002	0.035	113	0.011	0.047	54	21.9%	-0.01 [-0.02, 0.01]	2017

Total (95% CI) 558 327 100.0% -0.02 [-0.04, -0.01]

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 26.29$, $df = 4$ ($P < 0.0001$); $I^2 = 85\%$

Test for overall effect: $Z = 3.41$ ($P = 0.0006$)



Hormonal contraception and bone metabolism. Emerging evidence from a systematic review and meta-analysis of studies on post-pubertal and reproductive-age women

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Serena Bertozzi (7), Federico Prefumo (3), Angelo Cagnacci (2,4)

Women 12-21 years of age

Controls (no hormones)

Estrogens: EE, E2, E4

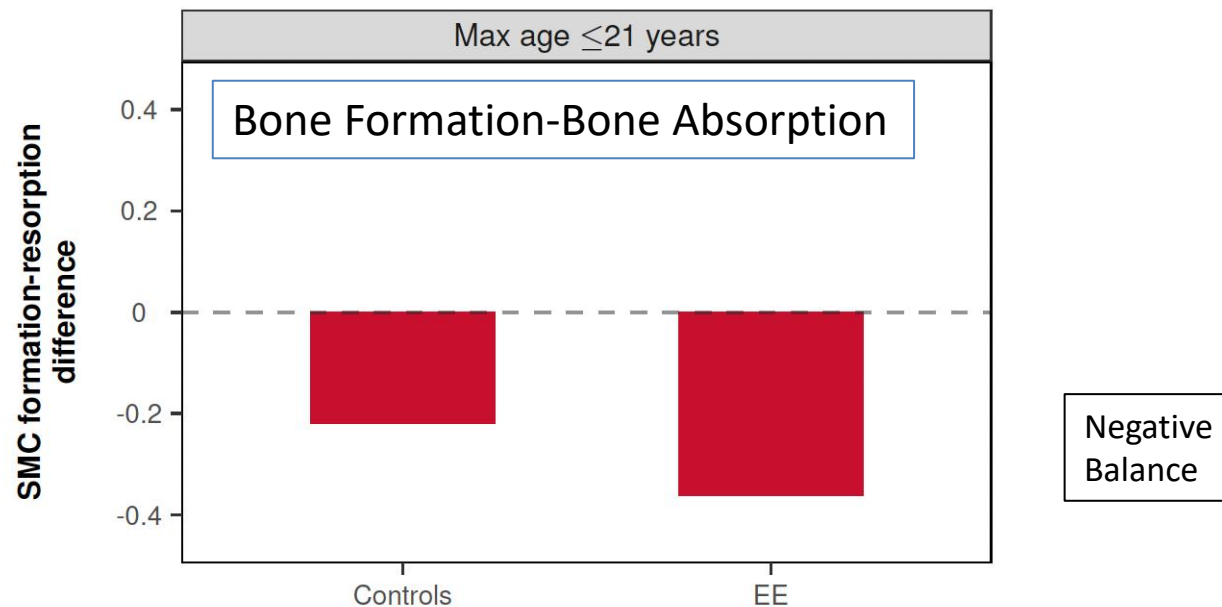
Progestins: Anti-Androgenic (CMA, DRSP, DNG, CPA)
Neutral (NGMN, P, SGA, DHPA)
Androgenic (LNG, GSD, NET, NGM, DSG, ENG, MPA)

Hormonal contraception and bone metabolism. Emerging evidence from a systematic review and meta-analysis of studies on post-pubertal and reproductive-age women

Alice Tassi (1), Ambrogio P Londero (2,3), Anjeza Xholli (4), Giulia Lanzolla (5,6),
Serena Bertozzi (7), Federico Prefumo (3), Angelo Cagnacci (2,4)

Women 12-21 years of age

Estrogens Effects

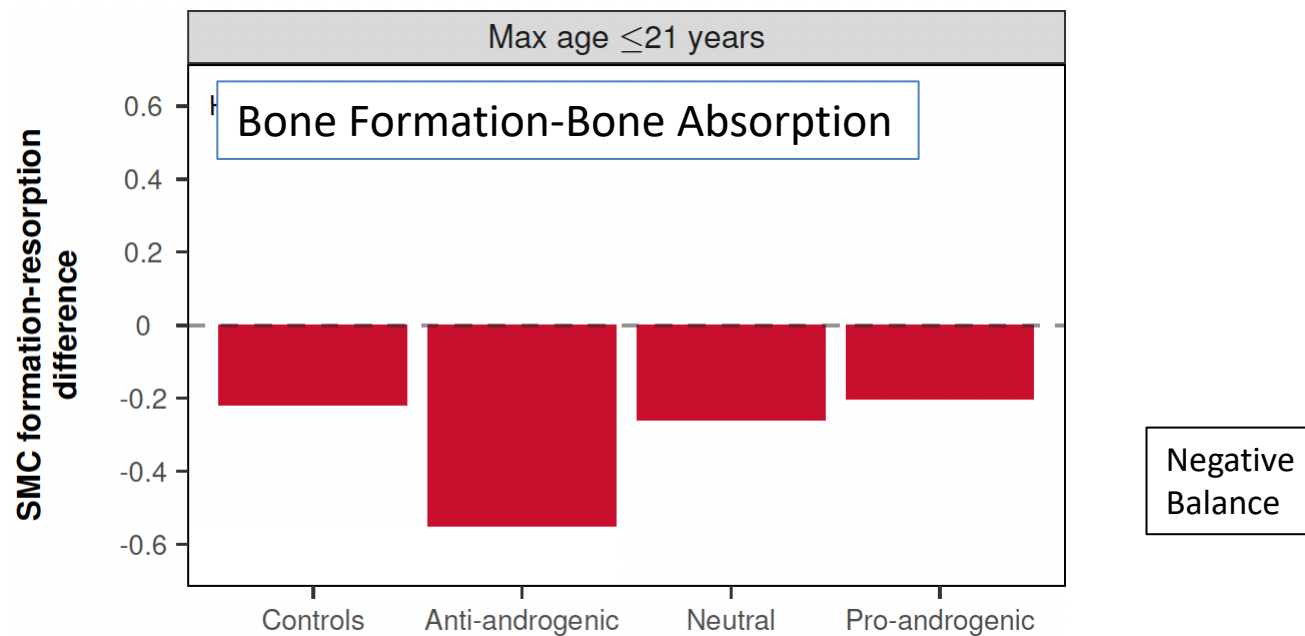


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Women 12-21 years of age

Progestin Effects



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Women 22-45 years of age

Controls (no hormones)

Estrogens: EE, E2, E4

Progestins: Anti-Androgenic (CMA, DRSP, DNG, CPA)
Neutral (NGMN, P, SGA, DHPA)
Androgenic (LNG, GSD, NET, NGM, DSG, ENG, MPA)

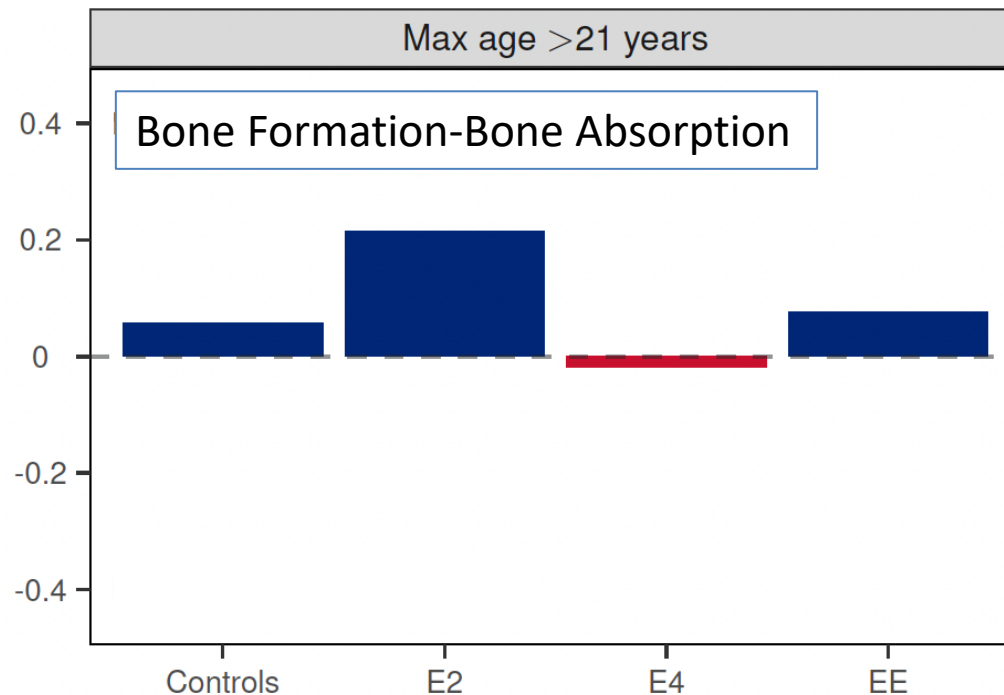
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Serena Bertozzi (7), Federico Prefumo (3), Angelo Cagnacci (2,4)

Women 22-45 years of age

Estrogens Effects

■ Positive balance
■ Negative balance

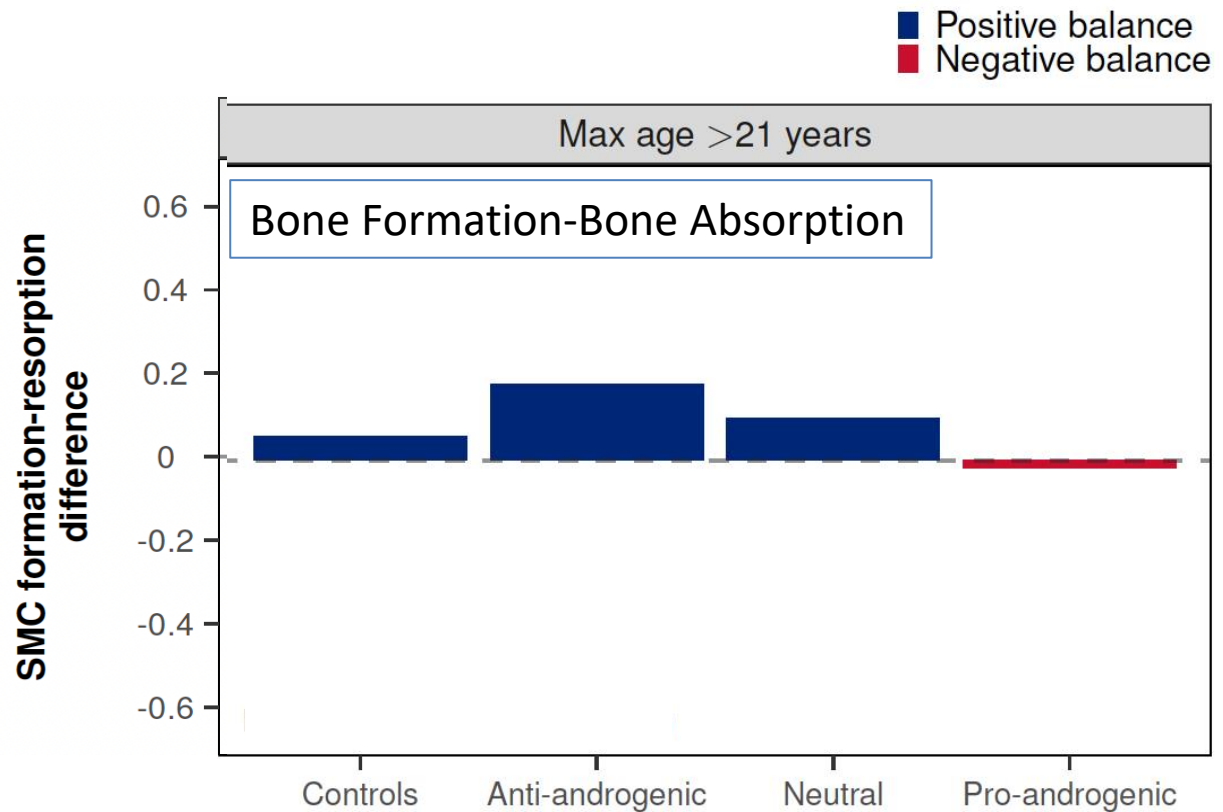


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Women 22-45 years of age

Progestin Effects



Tollerabilità: rischio TVP

L'attivazione del recettore glucocorticoide aumenta l'effetto della trombina e, in misura minore, amplifica l'attività dei fattori procoagulanti.

Ormone steroideo	Upregolazione del recettore della trombina	Affinità relativa di legame al recettore glucocorticoide
Desametasone	++	100%
Medrossiprogesterone acetato	+	29%
Gestodene	+	27%
3-Cheto-desogestrel	+	14%
Progesterone	+	10%
Levonorgestrel	-	1%
Norgestimato	-	1%
Noretisterone	-	0%
Etinilestradiolo	-	0%

- Nessun effetto; + effetto pronunciato; ++ effetto marcato.

Tab. 5 in ref. 6

Tabella 1: Rischio di TEV con i contraccettivi ormonali combinati

Progestinici COC (combinati con etinilestradiolo, se non specificato)	Rischio relativo verso Levonorgestrel	Incidenza stimata (per 10.000 donne/anno di utilizzo)
Non in gravidanza, non utilizzatrici	-	2
Levonorgestrel	Riferimento	5-7
Norgestimato/Noretisterone	1,0	5-7
Dienogest	1,6	8-11
Gestodene/Desogestrel/Drospirenone	1,5-2,0	9-12
Etonogestrel/Norelgestromina	1,0-2,0	6-12
Clormadinone/Nomegestroloacetato(E2)	DC ¹	DC ¹

E2=estradiolo; DC=da confermare

NGM, in associazione con EE, è il progestinico con **il più basso rischio di trombosi venosa profonda.**

Nota informativa AIFA/EMA 2019 (https://www.aifa.gov.it/sites/default/files/IT_NII_COC_02.01.2019.pdf)

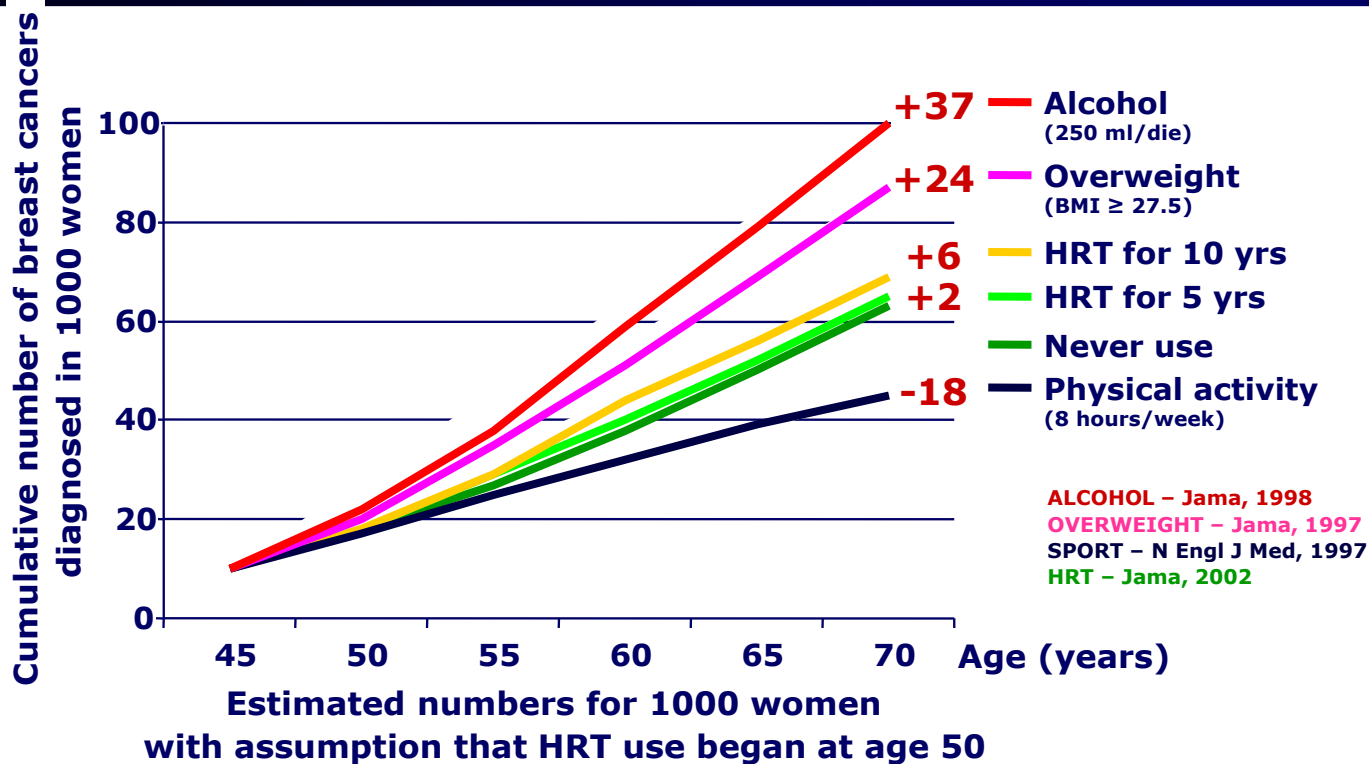
Kuhl H. J Reproduktionsmed. Endokrinol 2011;8:157-77

Scelta del Progestinico (E3N)

	Oral Estrogen		Transdermal/ Percutaneous estrogen	
	Cases/PY ^a	Relative risk ^b (95% CI)	Cases/PY ^a	Relative risk ^b (95% CI)
Estrogen alone	13/3,598	1.32 (0.76–2.29)	56/14,826	1.28 (0.98–1.69)
Estrogen combined with:				
Progesterone		– ^c	121/35,513	1.08 (0.89–1.31)
Dydrogesterone	7/3,217	0.77 (0.36–1.62)	90/25,405	1.18 (0.95–1.48)
Medrogestone	9/1,104	2.74 (1.42–5.29)	28/4,590	2.03 (1.39–2.97)
Chlormadinone acetate	8/1,431	2.02 (1.00–4.06)	35/7,774	1.48 (1.05–2.09)
Cyproterone acetate	34/4,779	2.57 (1.81–3.65)		– ^c
Promegestone	13/2,814	1.62 (0.94–2.82)	69/14,910	1.52 (1.19–1.96)
Nomegestrol acetate	8/2,623	1.10 (0.55–2.21)	91/18,826	1.60 (1.28–2.01)
Norethisterone acetate	46/7,401	2.11 (1.56–2.86)		– ^c
Medroxyprogesterone acetate	29/7,035	1.48 (1.02–2.16)		– ^c

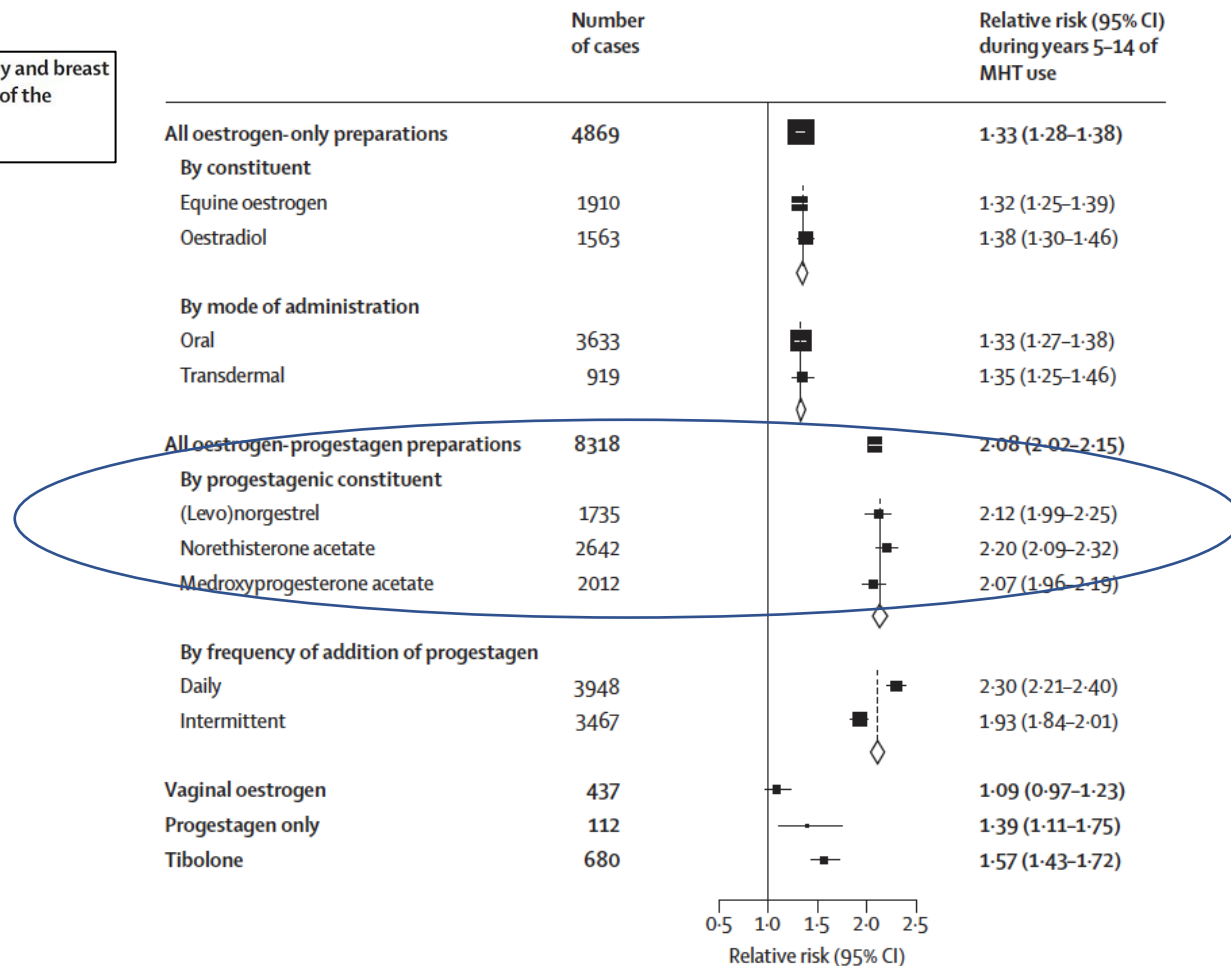
Fournier, Breast Cancer Res Treat 2008

BREAST CANCER



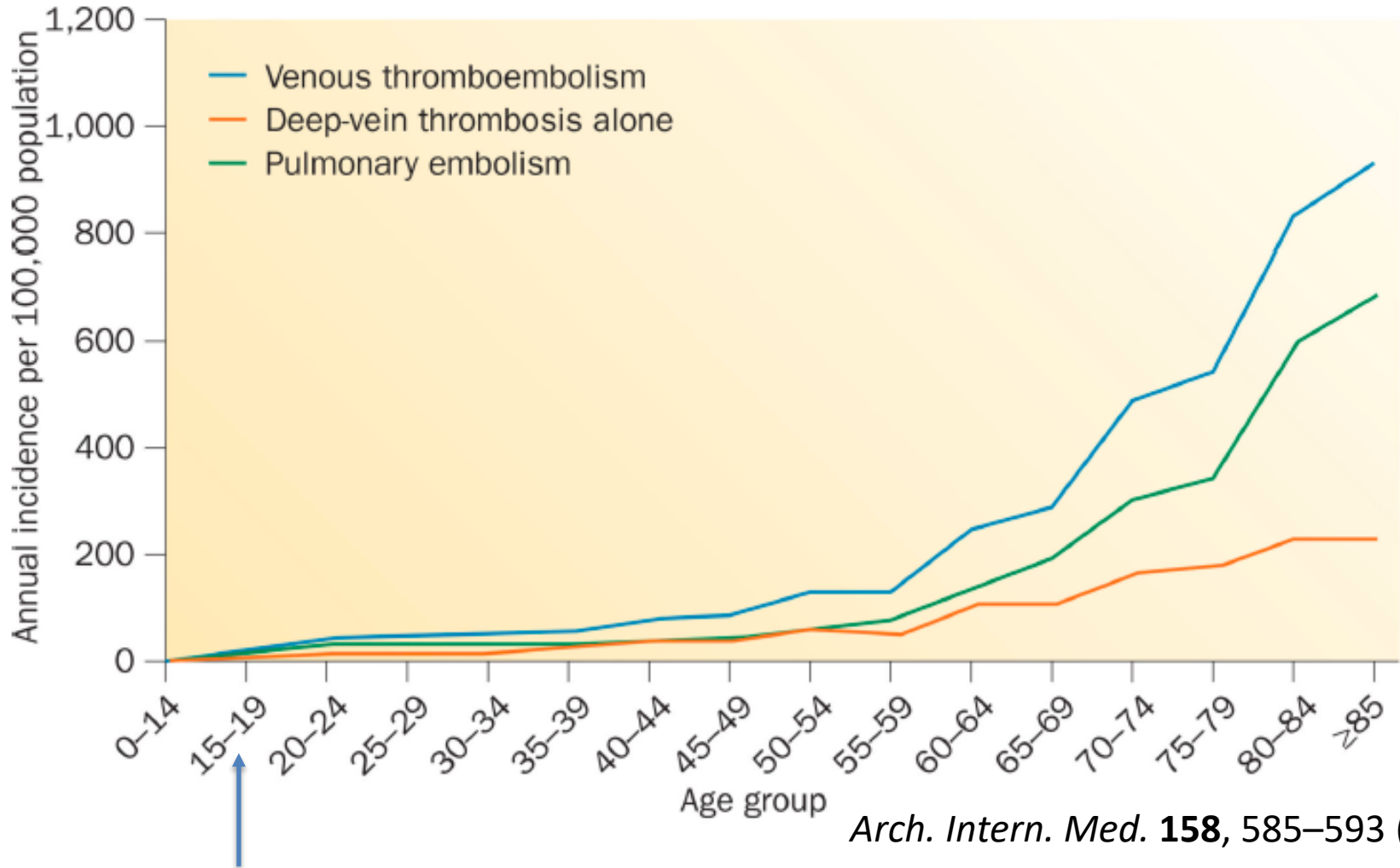
Type and timing of menopausal hormone therapy and breast cancer risk: individual participant meta-analysis of the worldwide epidemiological evidence

Collaborative Group on Hormonal Factors in Breast Cancer*



Epidemiology of Venous Thromboembolism

1966-1990 Olmsted County USA



Arch. Intern. Med. **158**, 585–593 (1998)

Prescrizione: quale Estrogeno?

Medico

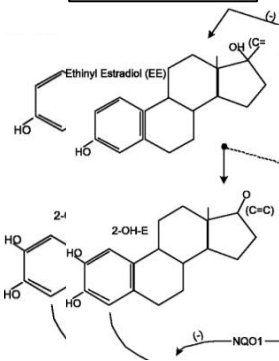
Profilo
della
donna

	Etinil Estradiolo	Estradiolo	Estetrolo	
SHBG	↑	↑	↑	EE meglio nelle donne iperandrogeniche
	Etinil Estradiolo	Estradiolo	Estetrolo	
Parametri metabolici	↑ (dose dipendente)	↑	↑	Estradiolo e estetrolo meno effetti
	Etinil Estradiolo	Estradiolo	Estetrolo	
Endometrio	Stabile	Instabile	Stabile	EE 30-35 mcg per controllo ciclo, Estetrolo
	Etinil Estradiolo	Estradiolo	Estetrolo	
Mammella	Effetto estrogenico	Effetto estrogenico	Minori effetti estrogenici Effetto antiestrogenico	Estetrolo ?

Metabolismo

A

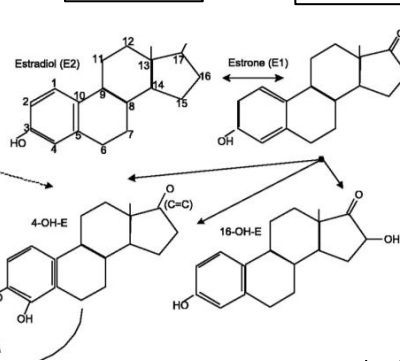
Etinilestradiolo



B

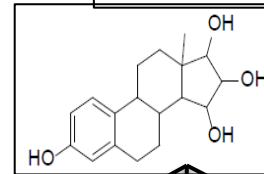
Estradiolo

Estrone



C

Estetrolo (E4)



Minima inibizione
(CYP3A4, UGT1A9, UGT2B7)

Non clinicamente
significativo

UGT

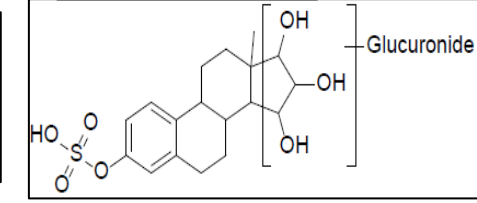
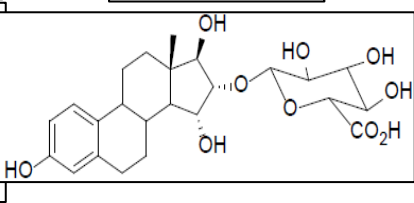
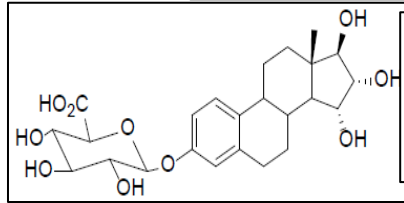
UGT2B7

UGT, SULT

E4-3-Glucuronide

E4-16-Glucuronide

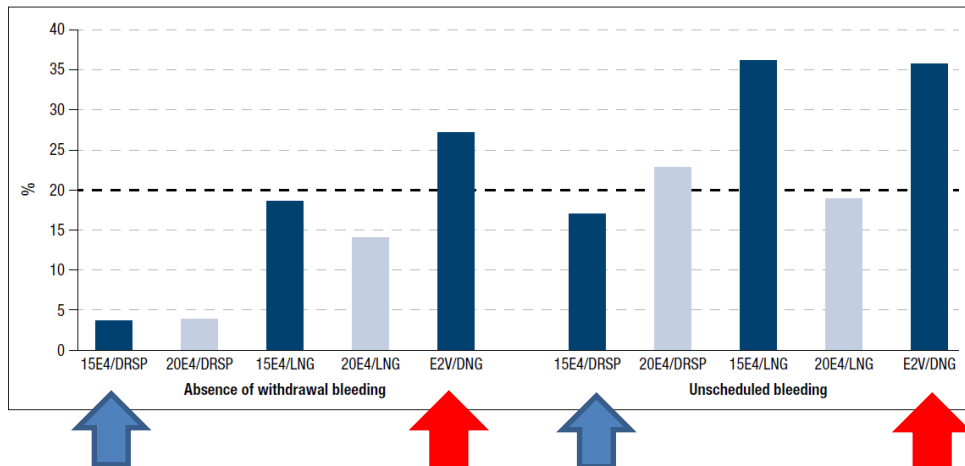
E4-Sulfate-Glucuronide



Contollo del Ciclo

FASE II: profilo di sanguinamento

la combinazione 15mgE4/DRSP risulta quella con miglior profilo di sanguinamento ➡ **dosaggio e combinazione scelta per lo sviluppo di Fase III**



con E415mg/DRSP il sanguinamento atteso si è verificato in circa il 95% delle utilizzatrici

Quali caratteristiche distintive di estetrol?

Estetrol (E4): Effetto sugli enzimi epatici

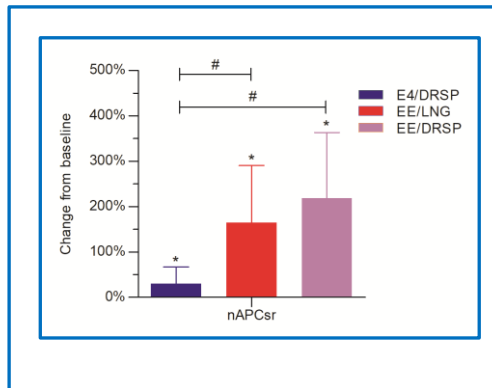
- Effetto trascurabile sui seguenti enzimi del cytP450 (<10%)

Estrogeni a 10 μmol/L	% P450 enzimi				
	CYP1A2	CYP2C9	CYP2C19	CYP2D6	CYP3A4
EE	<10	<10	82	<10	45
E2	19	<10	63	<10	<10
E4	<10	<10	<10	<10	<10

1. Visser M, et al. Climacteric 2008;11(Suppl.1):64–68

E4/DRSP – RESISTENZA ALLA PROTEINA C ATTIVATA

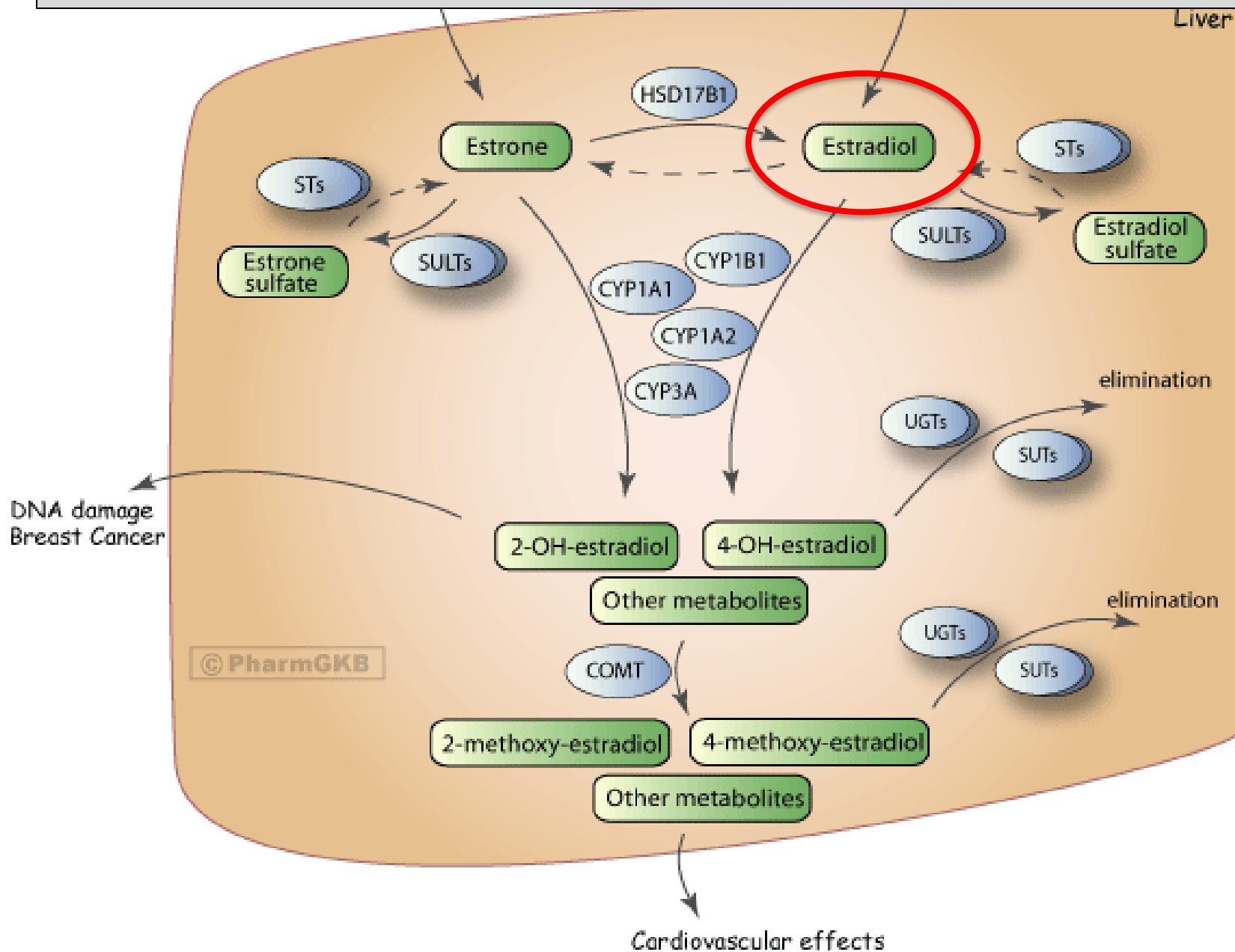
L'INNALZAMENTO dell' APC RESISTANCE solitamente CORRELA CON POSSIBILE INNALZAMENTO DI SHBG. Sia L'INNALZAMENTO DI APCr che delle SHBG POTREBBE ESSERE INDICATIVO DI POSSIBILE AUMENTATO RISCHIO TEV.



Incremento di APCr significativamente inferiore a EE/LNG e EE/DRSP

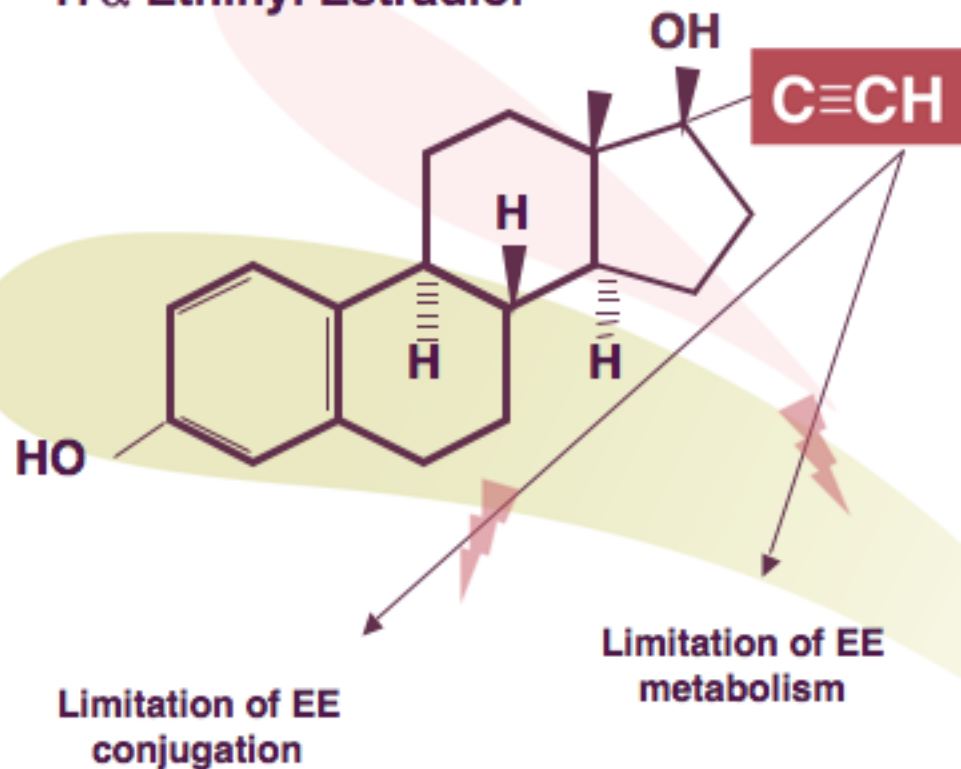
Il minimo aumento della **APCsr** con E4/DRSP è probabilmente il risultato della bassa potenza estrogenica dell'E4, in quanto DRSP, come progestinico antiandrogenico, non è in grado di contrastare gli effetti dell'estrogeno, come evidente dall'aumento di APC resistance con EE/DRSP

Estradiol Metabolism



17 β -E2 vs ethinylestradiol: Different metabolisms

17 α -Ethinyl Estradiol



Endogenous and synthetic exogenous estradiol are extensively biotransformed to estrogen conjugates⁽¹⁾

Unlike 17 β -E2, due to the presence of an ethynyl radical in C17, EE's metabolization and conjugation are limited⁽²⁾

1- Rattogianis R. *et al.* Chapter 6: Estrogen metabolism by conjugation. J Natl Cancer Inst Monogr 2000;27:113-24

2- Guengerich FP. Metabolism of 17 α -ethynylestradiol in humans. Life Sci 1990;47:1981-8

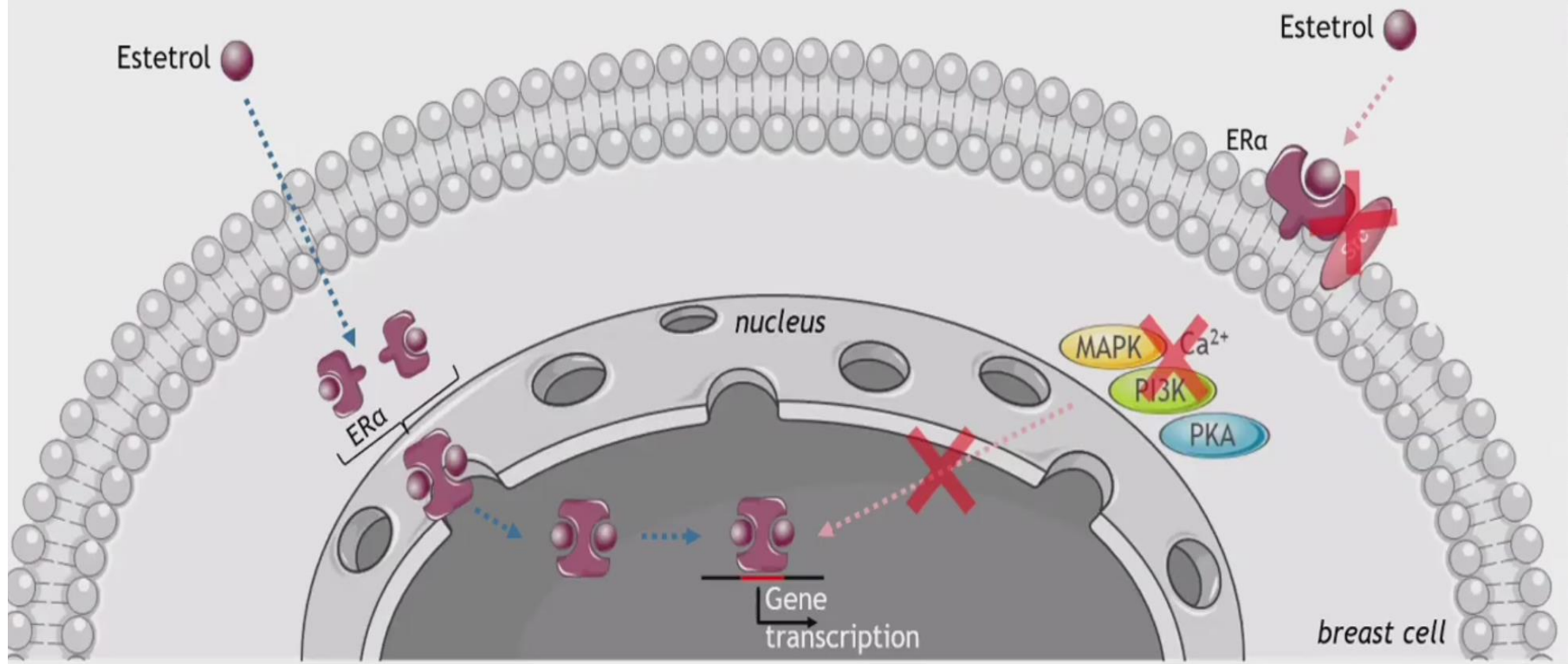
E4 acts differently on Estrogen Receptors

E4 **activates**, nucleus ER α

E4, **blocks** membrane ER α

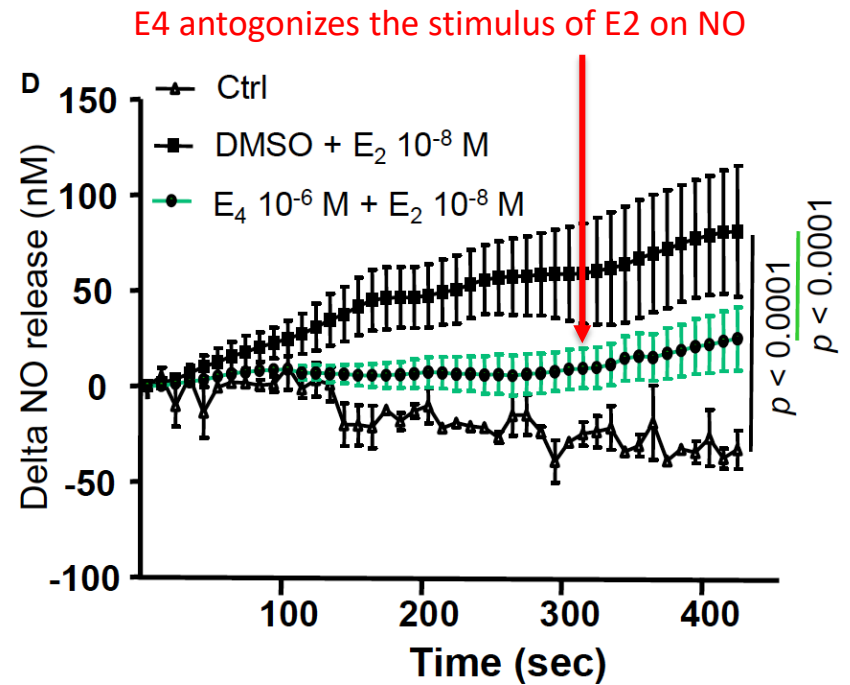
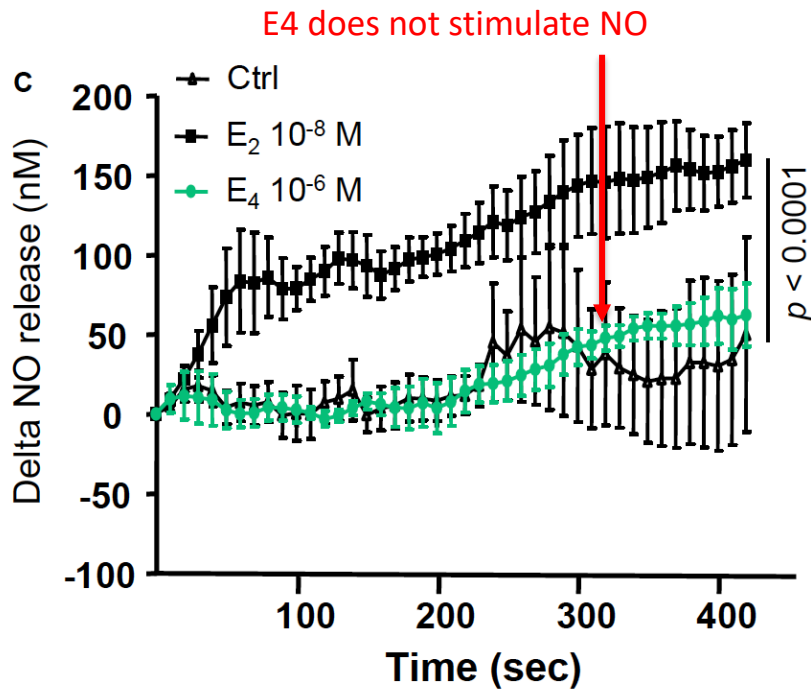
- **Nuclear**-initiated steroid signaling (NISS):

- **Blockade of membrane**-initiated steroid signaling (MISS):

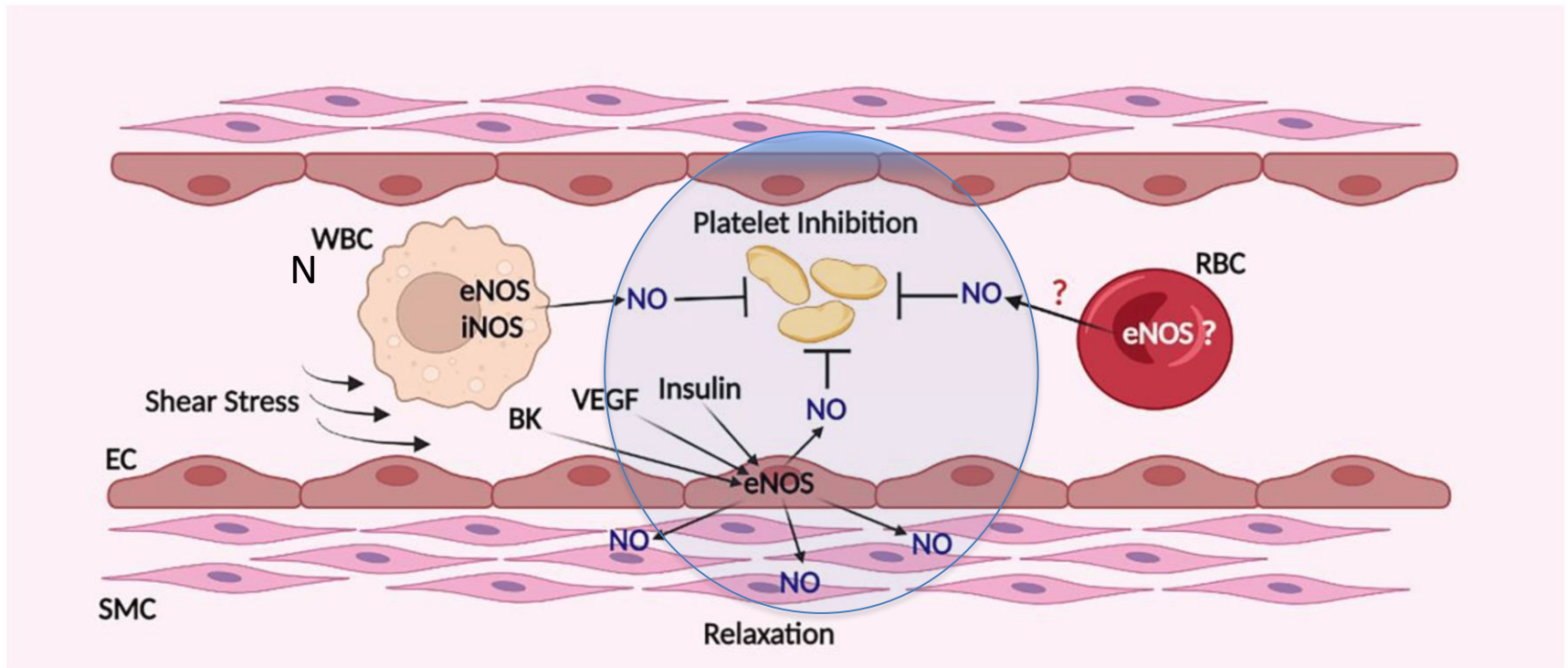


The uterine and vascular actions of estetrol delineate a distinctive profile of estrogen receptor α modulation, uncoupling nuclear and membrane activation

Ex vivo Rat Aorta



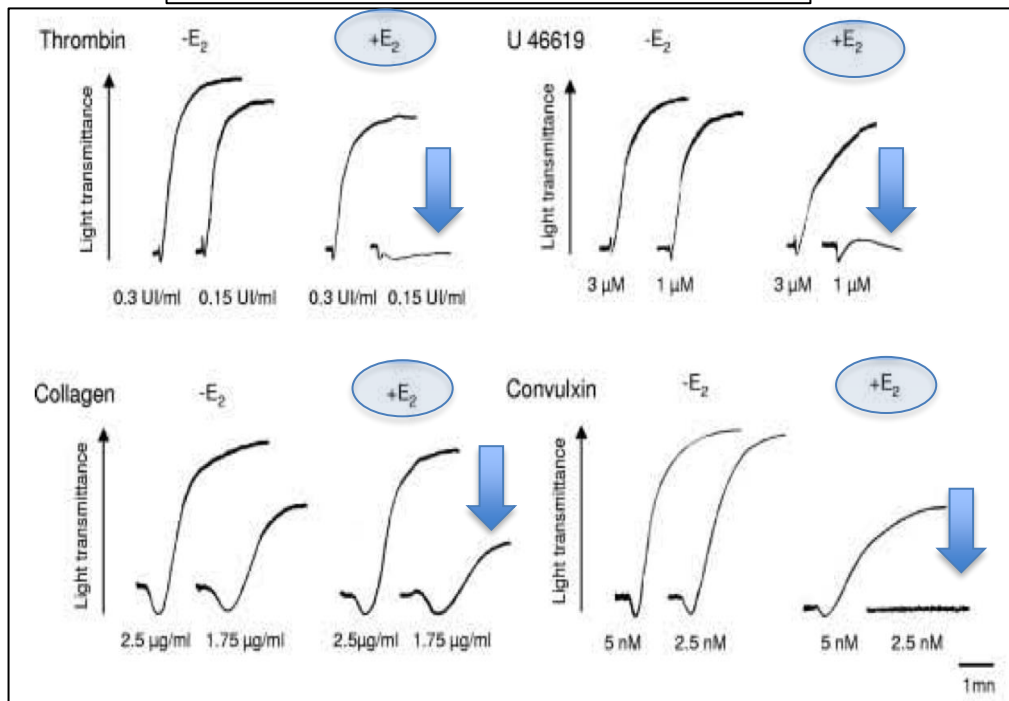
Nitric Oxide Inhibits Platelet Aggregation



Inhibition of Platelet Aggregation

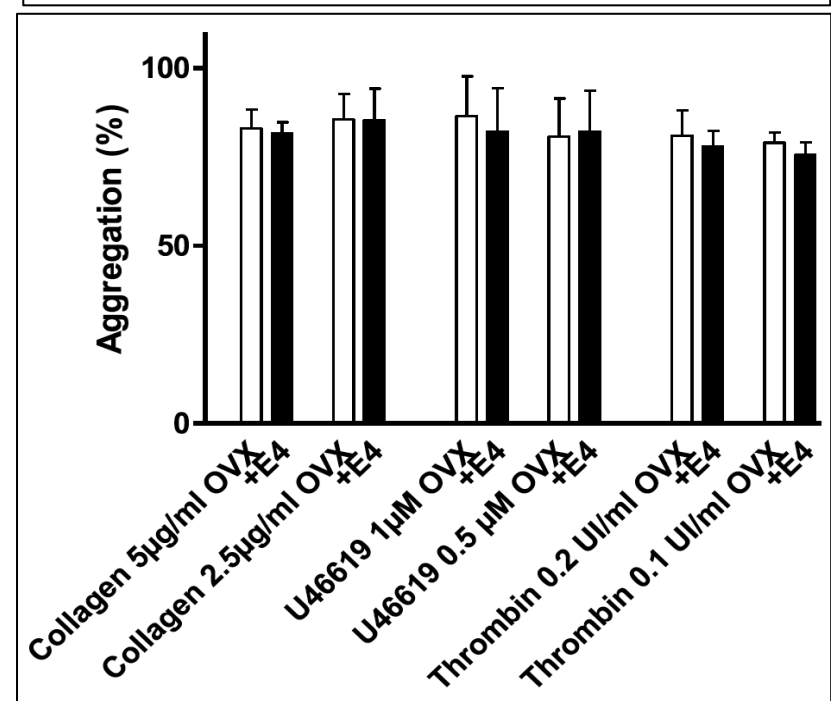
Washed platelets from treated rats

E2 inhibits platelet aggregation



Valéra MC et al. Blood 2012; 120:1703-12

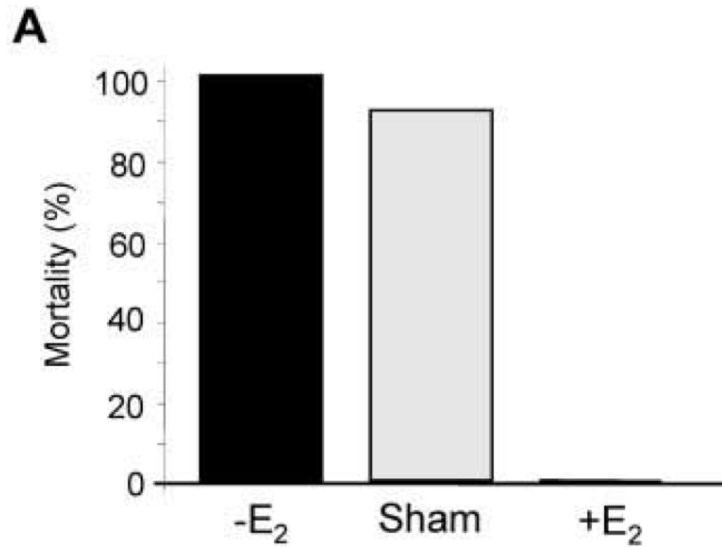
E4 does not inhibit platelet aggregation



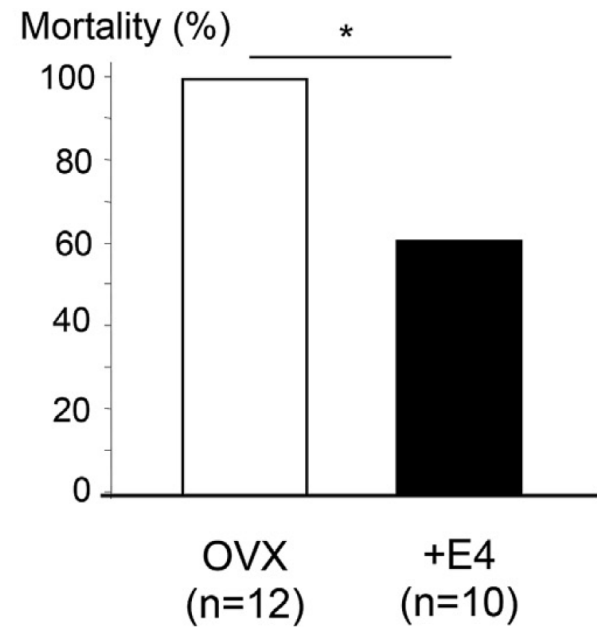
Valéra MC et al. mol Cell Endocrinol 2018; 477:132-139

Mortality by Ischemic Stroke

Collagen plus Epinephrine in in the Jugular vein

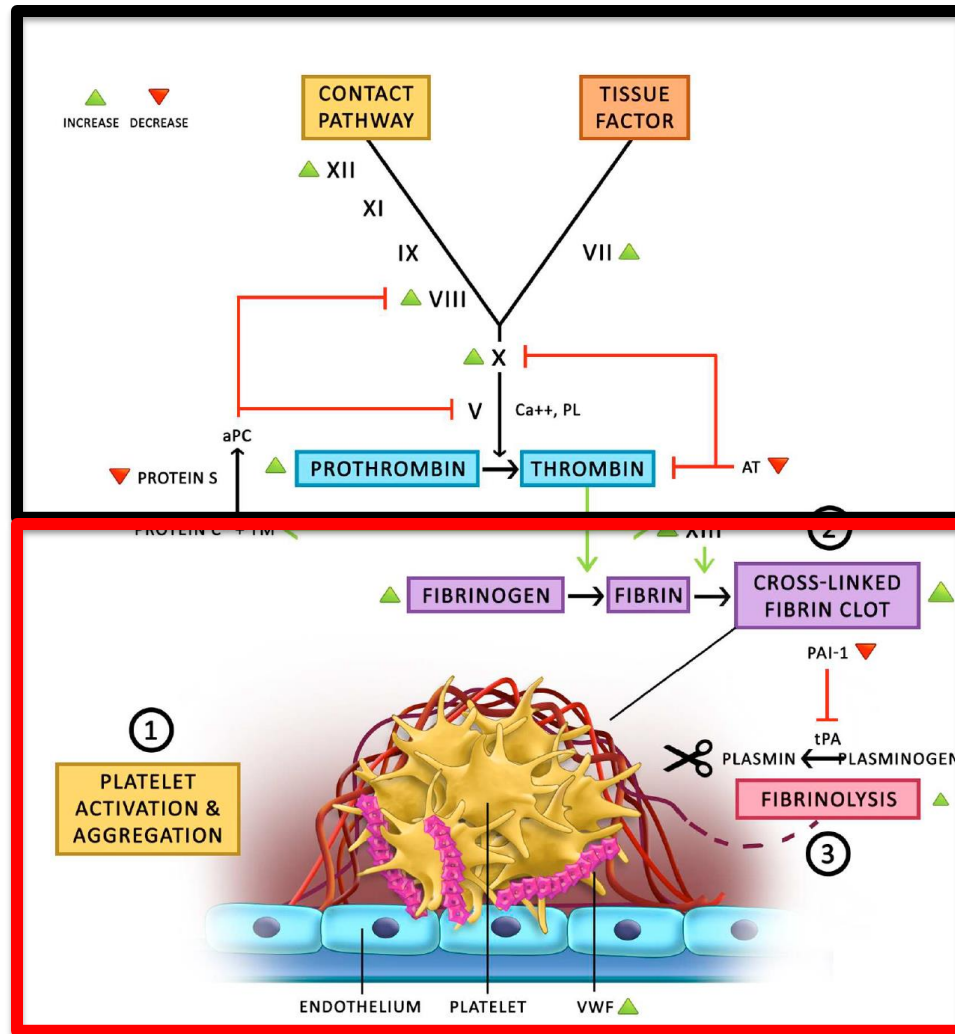


Valéra MC et al. Blood 2012; 120:1703-12



Valéra MC et al. mol Cell Endocrinol 2018; 477:132-139

Coagulation System



E4 = 😊

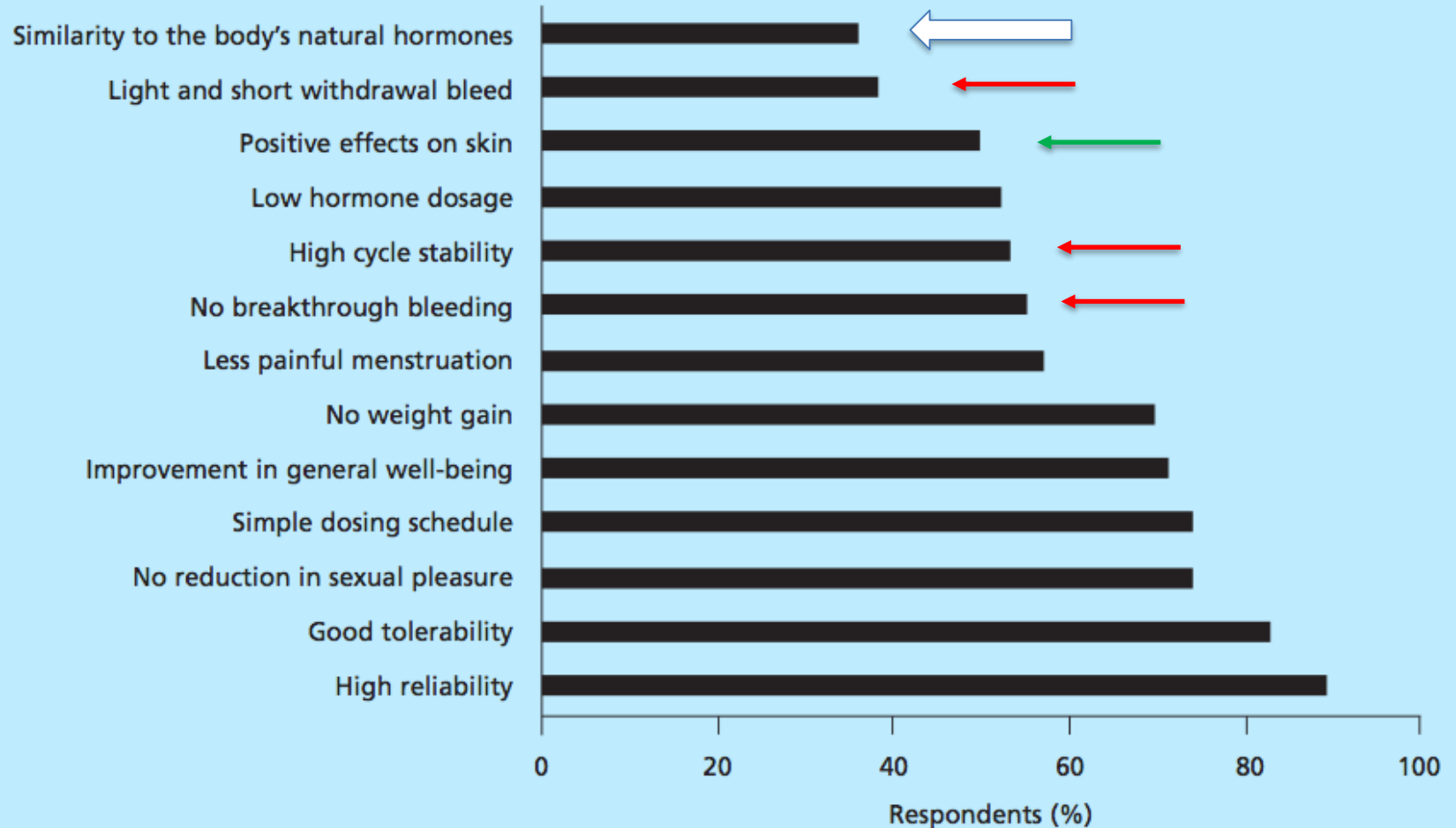
E4 = ?

Why to prescribe EE COC as first choice

1. Cycle Control

2. Therapeutic effects on hyperandrogenism

Survey: Characteristics of an Ideal Hormonal Contraceptive



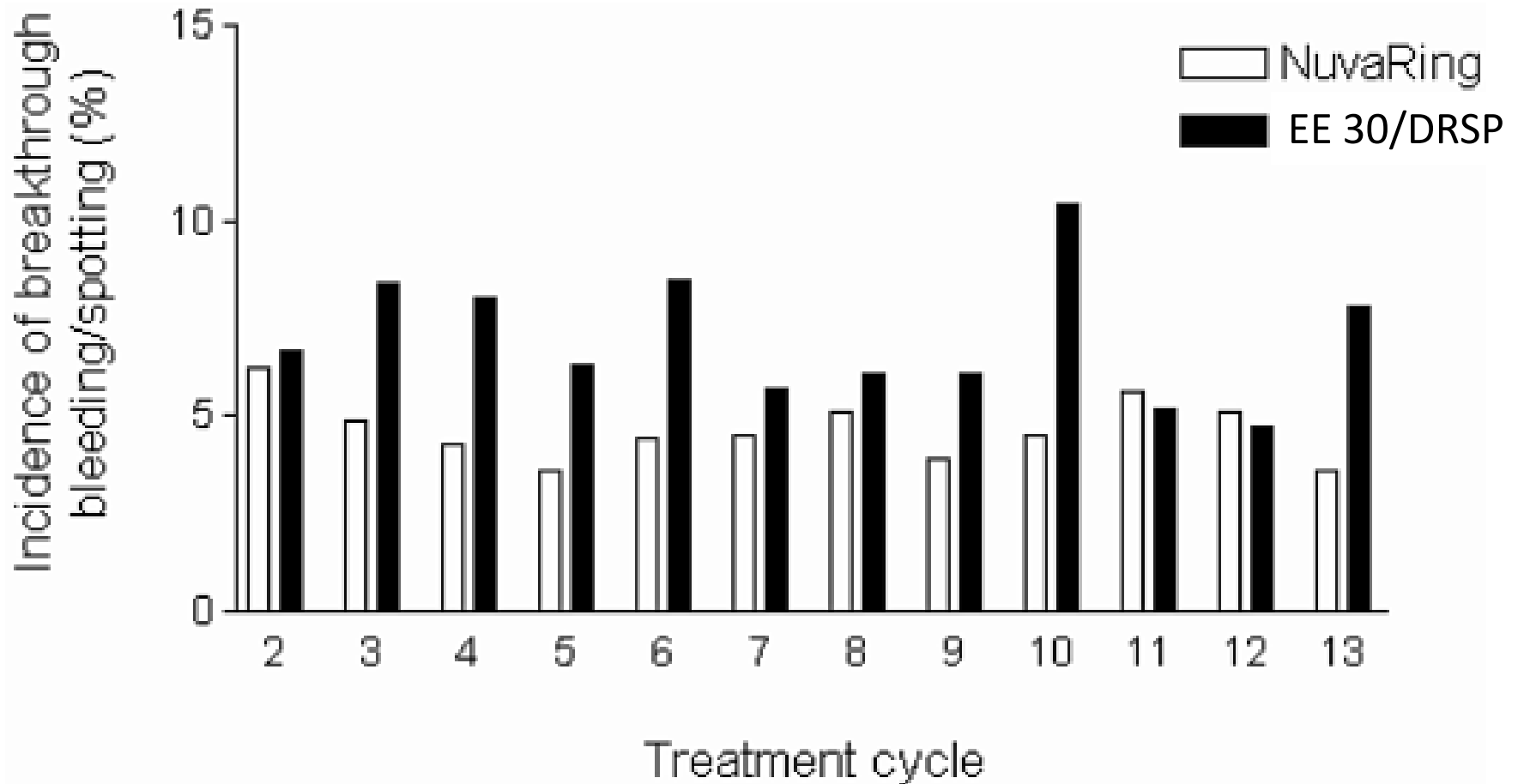
How often is oral contraception used for contraception? The need of benefit's formalisation

Request for the Therapeutic effects of COCs

42.5% in Europe/61% in Italy

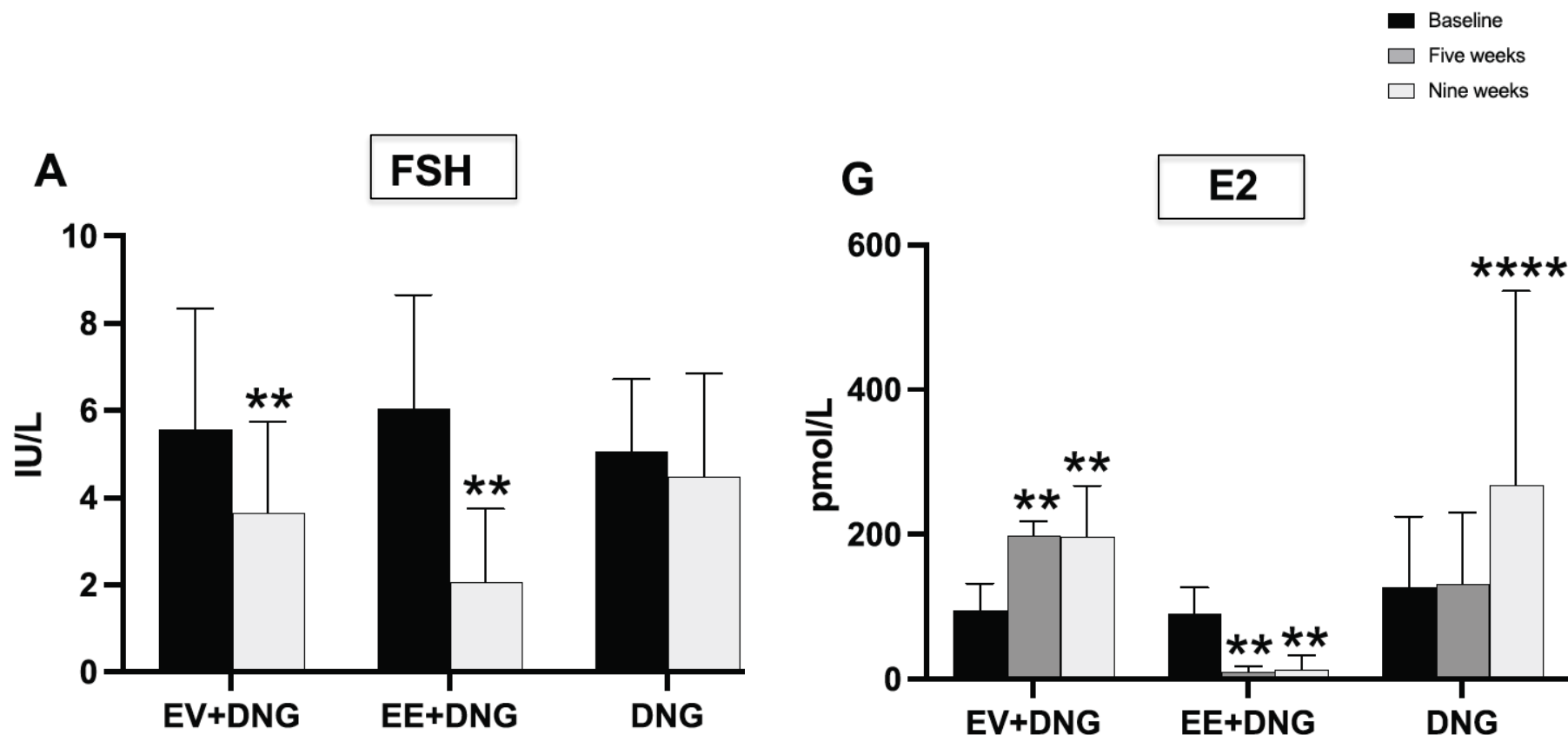
Cycle Irregularities	44.3%
Abnormal Bleedings	25.5%
Hyperandrogenism	15.2%
PMS	5.3%

Irregular Bleedings with Oral and Vaginal EE-based Contraceptives.



Estradiol Valerate vs Ethinylestradiol in Combined Oral Contraceptives: Effects on the Pituitary-Ovarian Axis

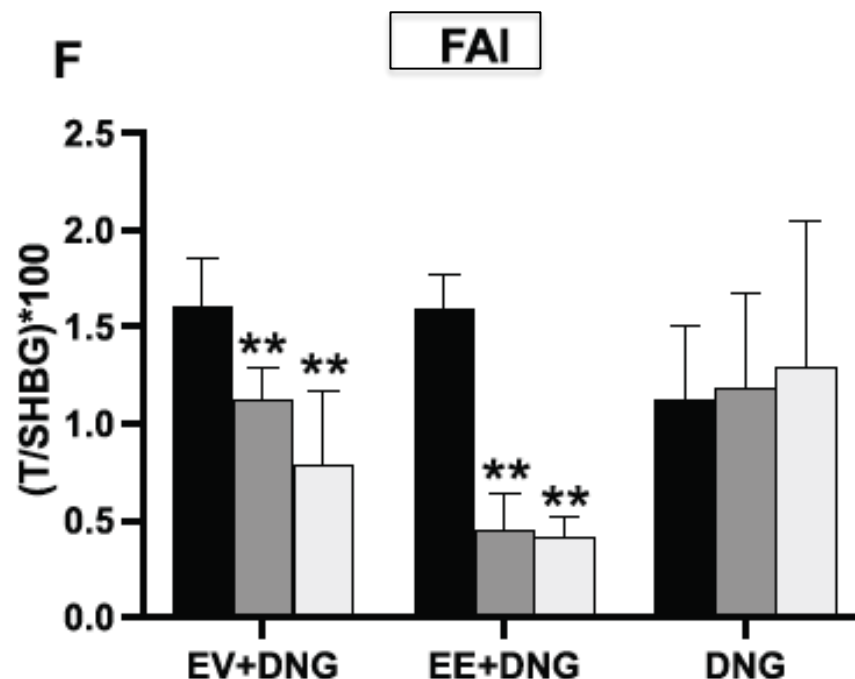
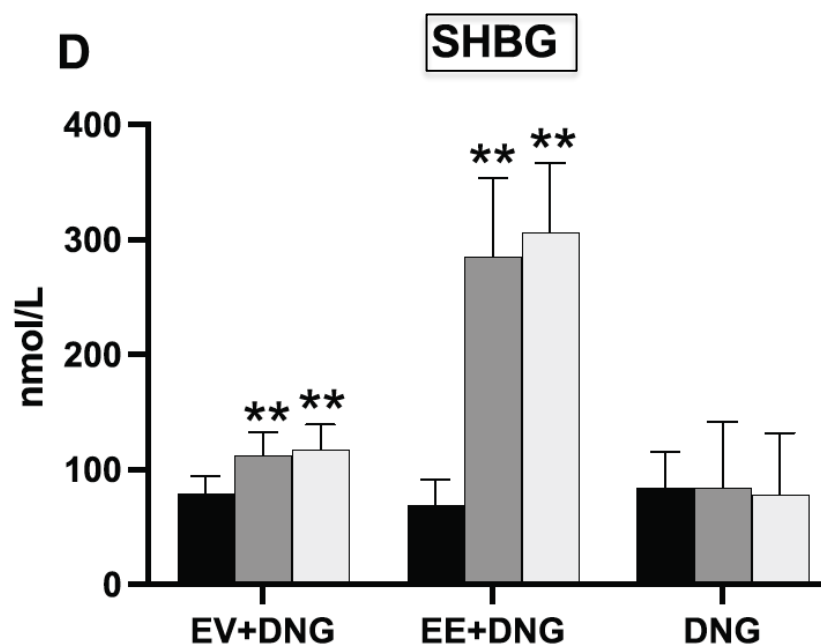
Annina Haverinen,^{1, ID} Kaisu Luiro,^{1, ID} Marika H. Kangasniemi,^{2, ID} Terhi T. Piltonen,^{2, ID}
Steinar Hustad,³ Oskari Heikinheimo,^{1, ID} Juha S. Tapanainen,^{1, ID}



Estradiol Valerate vs Ethinylestradiol in Combined Oral Contraceptives: Effects on the Pituitary-Ovarian Axis

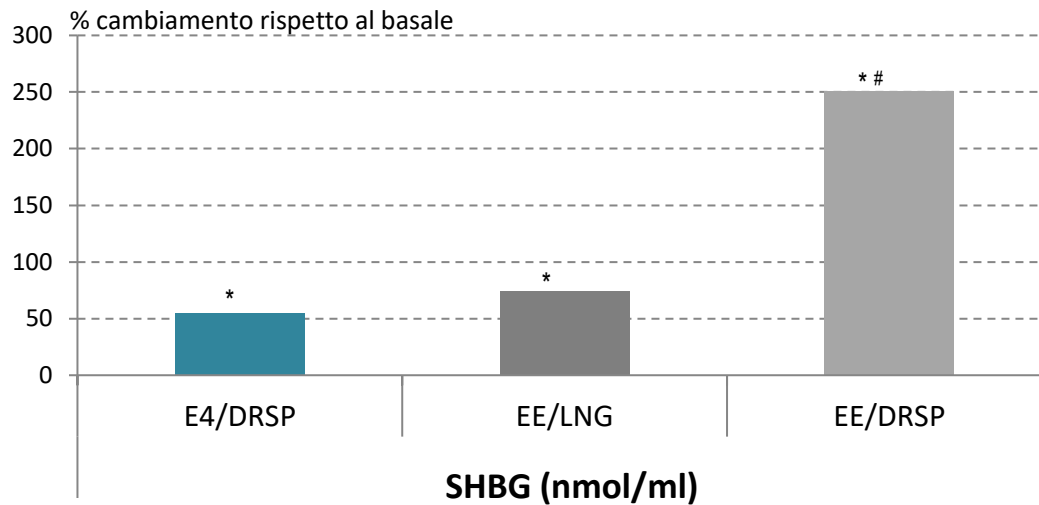
Annina Haverinen,^{1, ID} Kaisu Luiro,^{1, ID} Marika H. Kangasniemi,^{2, ID} Terhi T. Piltonen,^{2, ID}
Steinar Hustad,³ Oskari Heikinheimo,^{1, ID} Juha S. Tapanainen,^{1, ID}

■ Baseline
■ Five weeks
□ Nine weeks



Changes in SHBG

SHBG



* different versus baseline, $p < 0.05$ | # different from treatment with E4 15 mg/DRSP 3 mg, $p < 0.05$

Changes in Free Testosterone

	At 3 months	At 6 Months
E4/DRSP	-50*	-50*
EE/LNG	-60*	-50*
EE/DRSP	-75*	-71*

* $p < 0.05$ vs basale



Conclusions

Should Natural Estrogen Pills (estetrol, estradiol) be first Choice for COCs? Cons

1. COCs with natural estrogens are safer on the breast:
Unproven
2. COCs with natural estrogens are safer on VTE.
Unproven
3. The bleeding profile is worst with natural estrogens COCs-
4. Hyperandrogenic manifestations are better controlled with COCs containing EE

Thank you for your attention!!

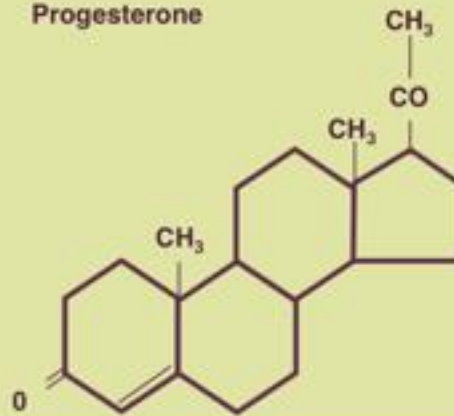
A broad spectrum of progestins

Reduced Androgenic Effect

Metabolic Neutrality

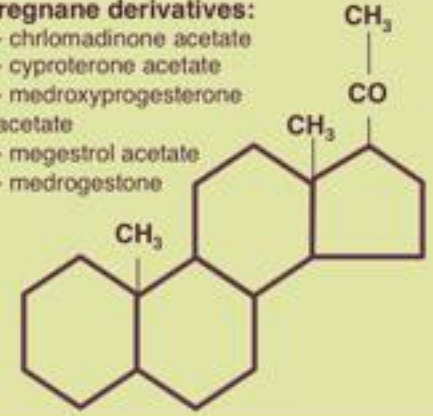
Related to Progesterone

Progesterone

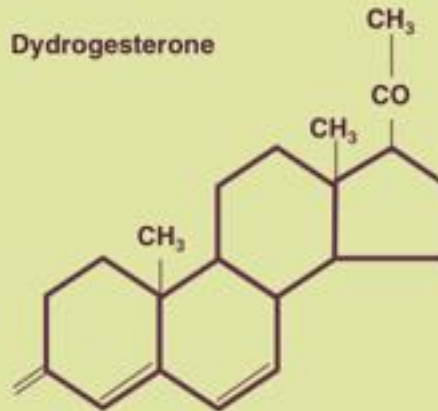


Pregnane derivatives:

- chlormadinone acetate
- cyproterone acetate
- medroxyprogesterone acetate
- megestrol acetate
- medrogestone

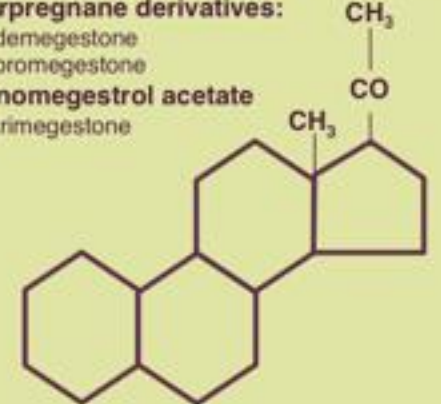


Dydrogesterone



Norpregnane derivatives:

- demegestone
- promegestone
- **nomegestrol acetate**
- trimegestone



Prescrizione: quale Estrogeno?

Medico

Profilo
della
donna

	Etinil Estradiolo	Estradiolo	Estetrolo	
SHBG	↑	↑	↑	EE meglio nelle donne iperandrogeniche
	Etinil Estradiolo	Estradiolo	Estetrolo	
Parametri metabolici	↑ (dose dipendente)	↑	↑	Estradiolo e estetrolo meno effetti
	Etinil Estradiolo	Estradiolo	Estetrolo	
Endometrio	Stabile	Instabile	Stabile	EE 30-35 mcg per controllo ciclo, Estetrolo
	Etinil Estradiolo	Estradiolo	Estetrolo	
Mammella	Effetto estrogenico	Effetto estrogenico	Minori effetti estrogenici Effetto antiestrogenico	Estetrolo ?

Estrogeni e mammella

17 β estradiolo

- Azione su ER α e ER β
- Stimola ERs nucleari e di membrana
- Metabolizzato da CYP450 metaboliti idrossilati

Estetrolo

- Azione su ER α , affinità minore di E2
- Antagonist action on membrane ERs
 - No stimulatory activity through membrane ERs
 - Block E2 action at this level
- No metabolizzato da CYP450
- No produzione metaboliti idrossilati

Visser M, 2008

Coelingh Bennink, H.J., 2008;

Abot A, 2014

Abot A, 2014

Alcuni metaboliti idrossilati sono cancerogeni

Yager JD., 2015

Abot A, et al. The uterine and vascular actions of estetrol delineate a distinctive profile of estrogen receptor alpha modulation, uncoupling nuclear and membrane activation. EMBO Mol Med.6(10):1328-46, 2014.

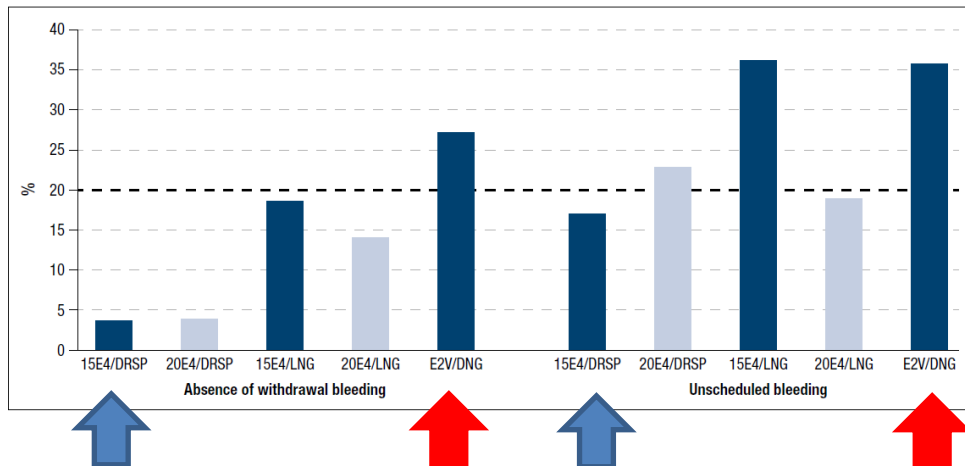
Coelingh Bennink HJ et al, Estetrol review: profile and potential clinical applications., Climacteric. 11 Suppl 1:47-58. 2008

Yager JD. Steroids. 2015 Jul;99(Pt A):56-60

Contollo del Ciclo

FASE II: profilo di sanguinamento

la combinazione 15mgE4/DRSP risulta quella con miglior profilo di sanguinamento ➡ **dosaggio e combinazione scelta per lo sviluppo di Fase III**



con E415mg/DRSP il sanguinamento atteso si è verificato in circa il 95% delle utilizzatrici

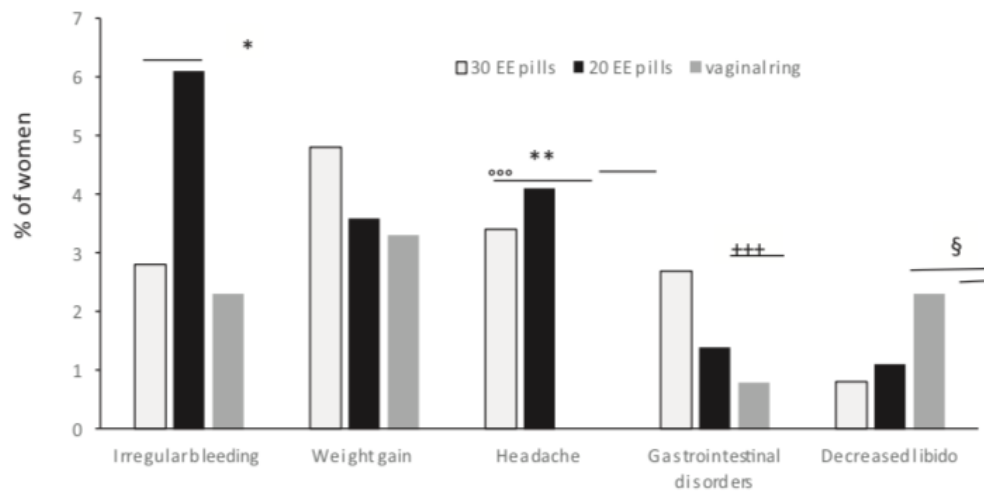


Figure 3. Reasons for discontinuation of hormonal contraception reported by women using the vaginal ring or pills containing 30 µg or 20 µg EE. * $p < .0008$ (20 µg vs 30 µg EE pills); ** $p < .01$ (20 µg EE pills vs vaginal ring); °°° $p < .02$ (30 µg EE pills vs vaginal ring); +++ $p < .02$ (20 µg vs 30 µg EE pills); § $p < .05$ (vaginal ring vs 20 µg and 30 µg EE pills).

Le donne interrompono la contraccezione ormonale se aumentano di peso

La donna che si avvicina alla contraccezione ha paura di aumentare di peso

Secondo motivo di interruzione

Italia

Table 2. Women who discontinued hormonal contraception due to minor side effects.

Reported symptom	N	% of all women examined (N = 1809)
Irregular bleeding	96	5.3
Weight gain and water retention	87	4.8
Headache	68	3.8
Gastrointestinal symptoms	34	1.9
Mood changes	31	1.7
Acne, hirsutism, alopecia	25	1.4
Decreased libido	18	1.0
Breast tenderness	11	0.6

Discontinuation of modern hormonal contraceptives: an Italian survey

Franca Fruzzetti, Daria Perini, Lara Fornaciari, Marinella Russo, Fiorella Bucci & Angiolo Gadducci

USA

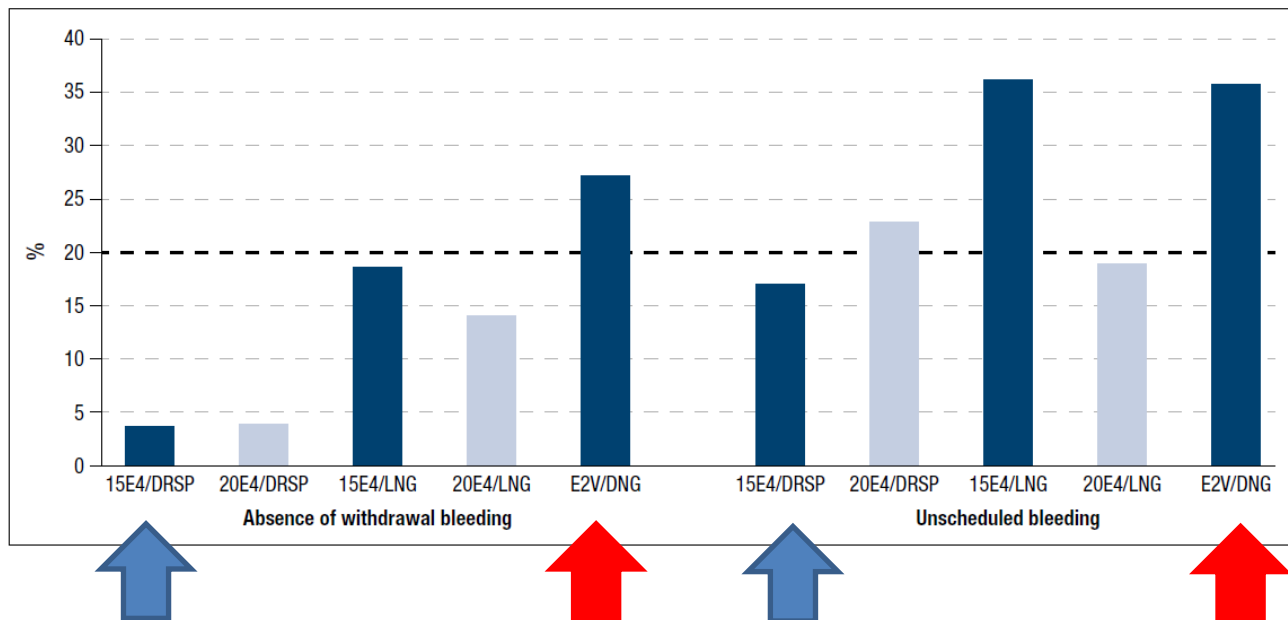
REASONS FOR DISCONTINUATION OF OCs



M.J. Rosenberg, M.S. Waugh, 1998

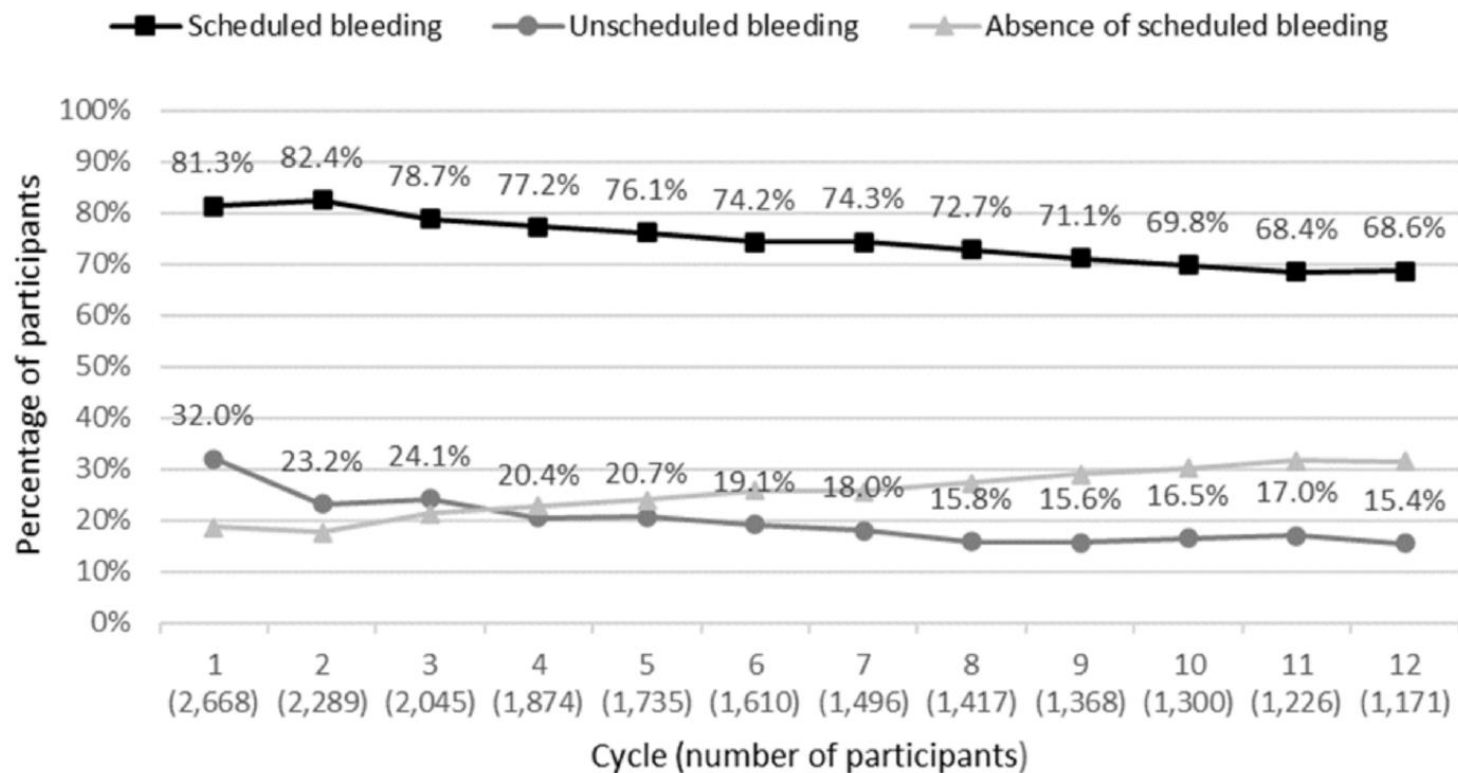
FASE II: profilo di sanguinamento

la combinazione 15mgE4/DRSP risulta quella con miglior profilo di sanguinamento ➡ **dosaggio e combinazione scelta per lo sviluppo di Fase III**



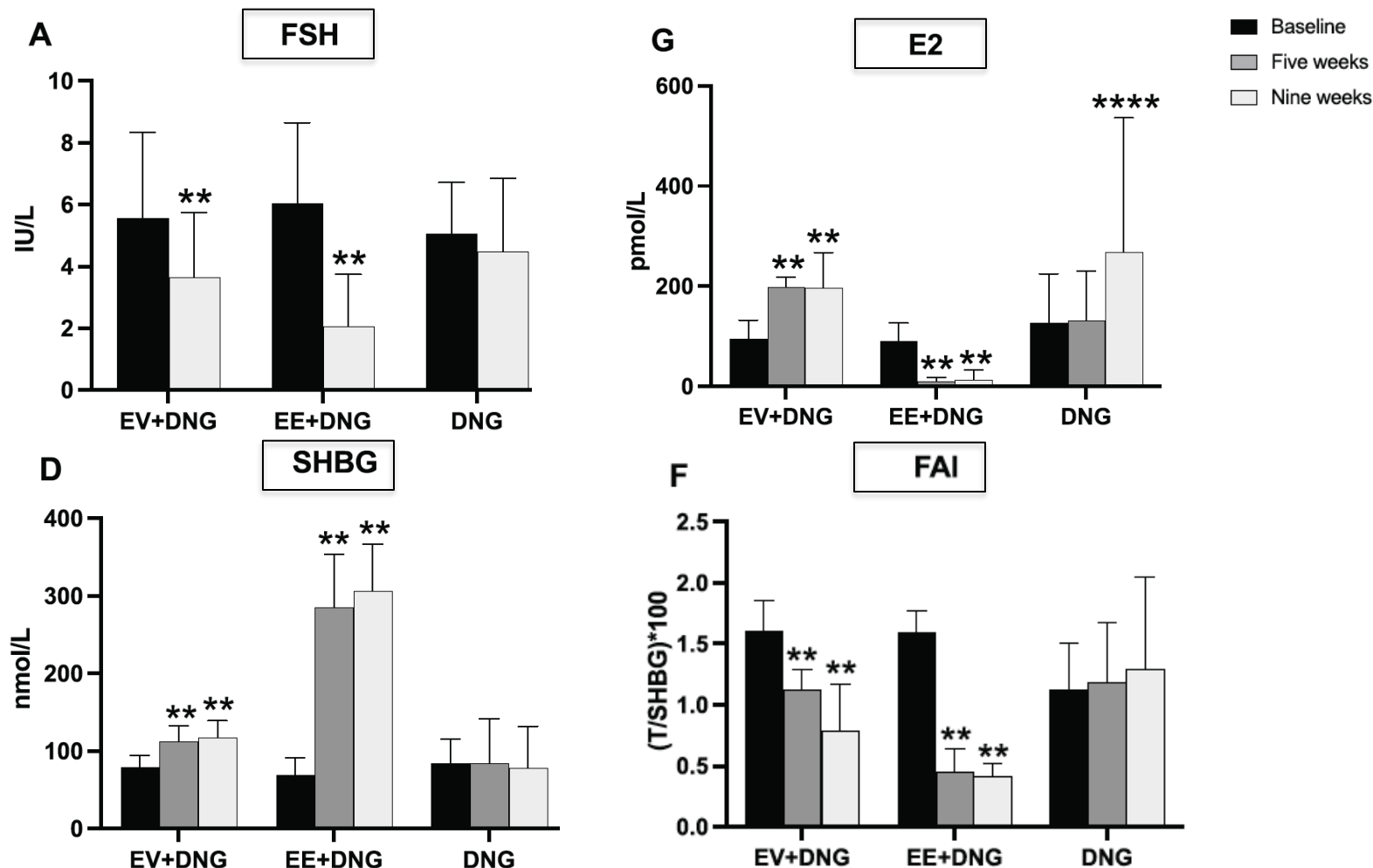
con E415mg/DRSP il sanguinamento atteso si è verificato in circa il 95% delle utilizzatrici

E2/NOMAC pooled phase 3 data (24/4 regimen)



Estradiol Valerate vs Ethinylestradiol in Combined Oral Contraceptives: Effects on the Pituitary-Ovarian Axis

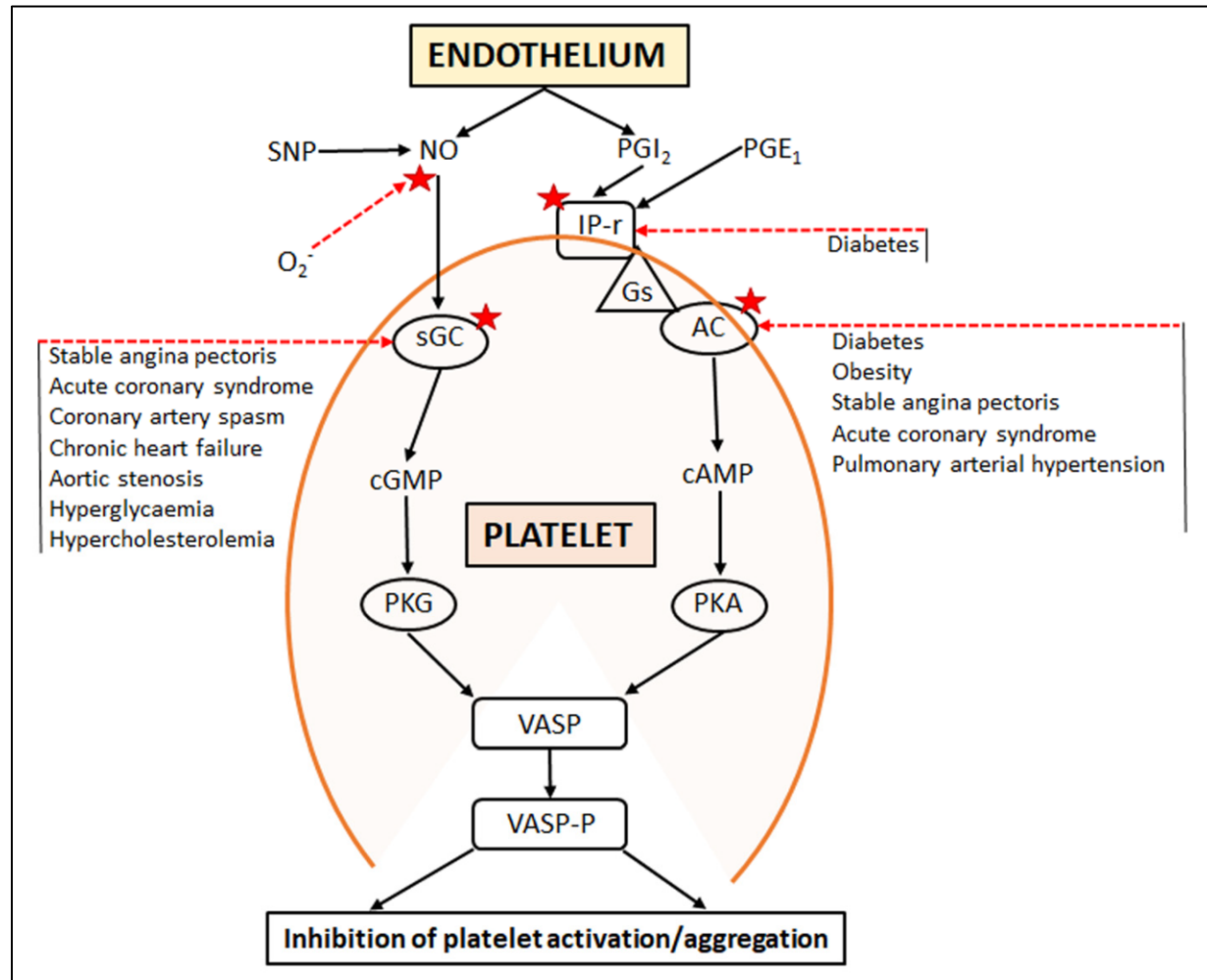
Annina Haverinen,^{1, ID} Kaisu Luiro,^{1, ID} Marika H. Kangasniemi,^{2, ID} Terhi T. Piltonen,^{2, ID}
Steinar Hustad,³ Oskari Heikinheimo,^{1, ID} Juha S. Tapanainen,^{1, ID}



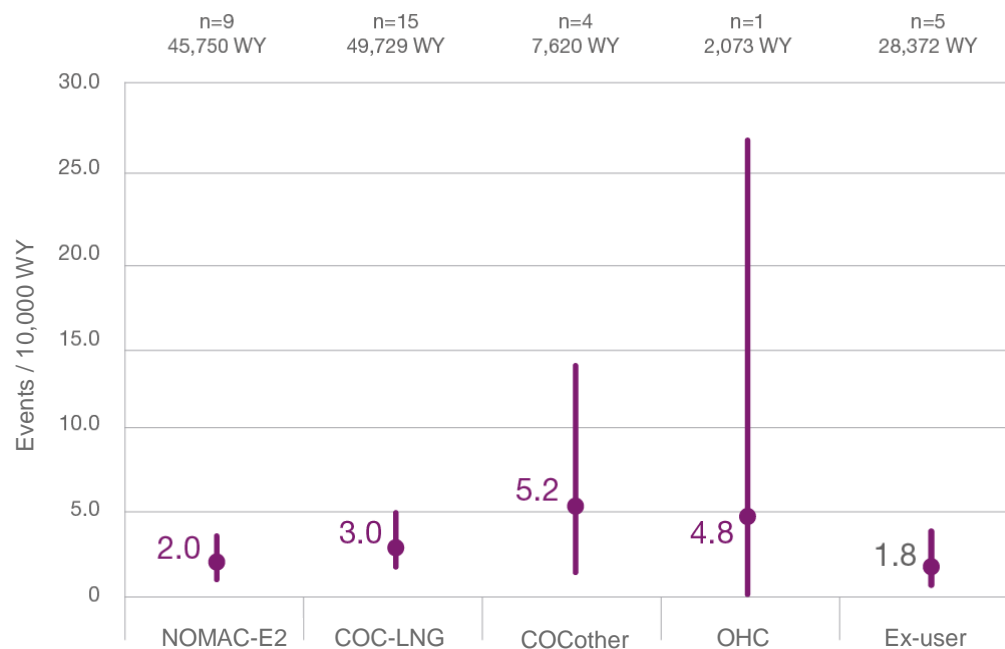
In che modo influisce la scelta dell'estrogeno nel contraccettivo e come orientarsi?

	EE	E2	E4
Emivita	26+/-7 hr	20-30 min	28-32 hr
SHBG legame	Molto bassa	38% alta affinità	assente
Albumina legame	98.5%	60% bassa affinità	Bassa affinità 50%
Biodisponibilità	38-48%	3-5%	70%
Recettori	Alfa/Beta	Alfa/Beta	Alfa/Beta
Inibizione FSH	-41/-70% (20/30 mcg)	-35/-41% (2mg)	-12% (15 mg)

Nitric Oxide Inhibits Platelet Aggregation



Rischio di TEV delle estremità inferiori e di ED



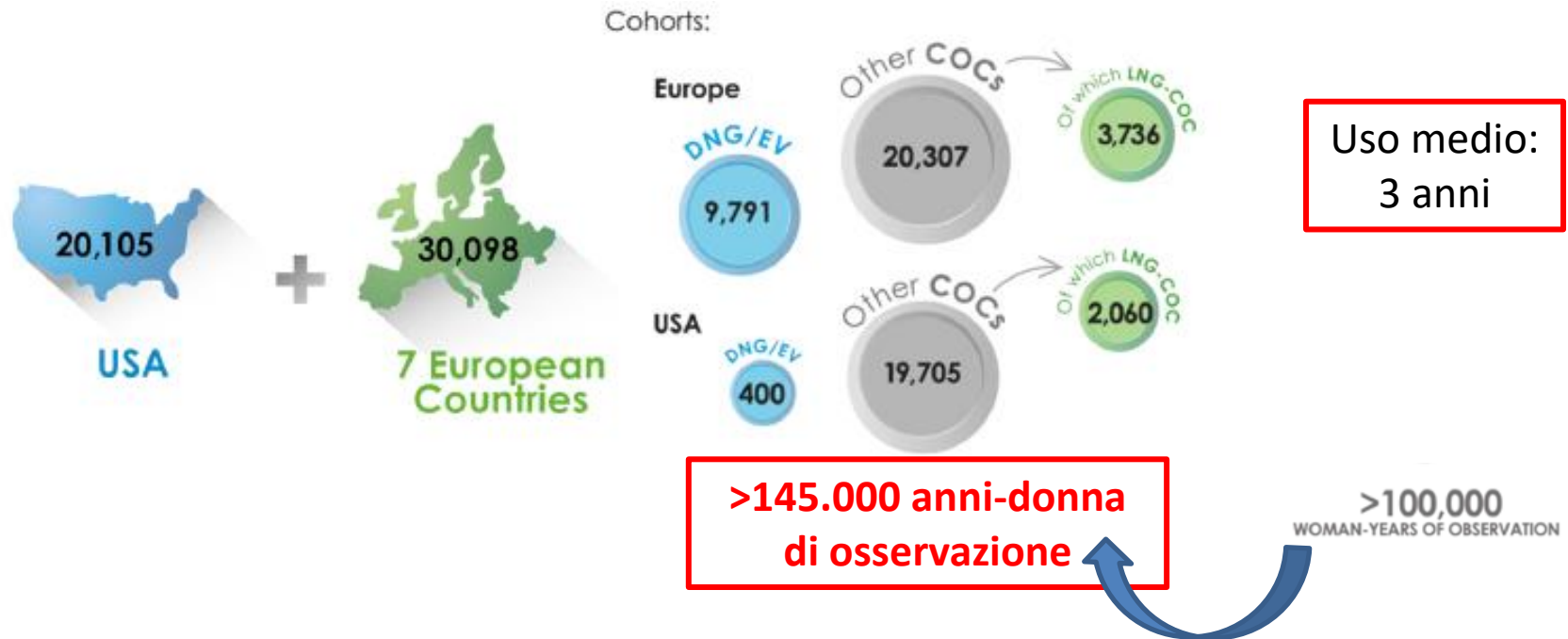
dati corretti per gravidanza entro 3 mesi da inizio trattamenti, storia di cancro/chemioterapia, aumentato rischio genetico di TEV(es. Factor V Leiden, Proteina S o C deficit)



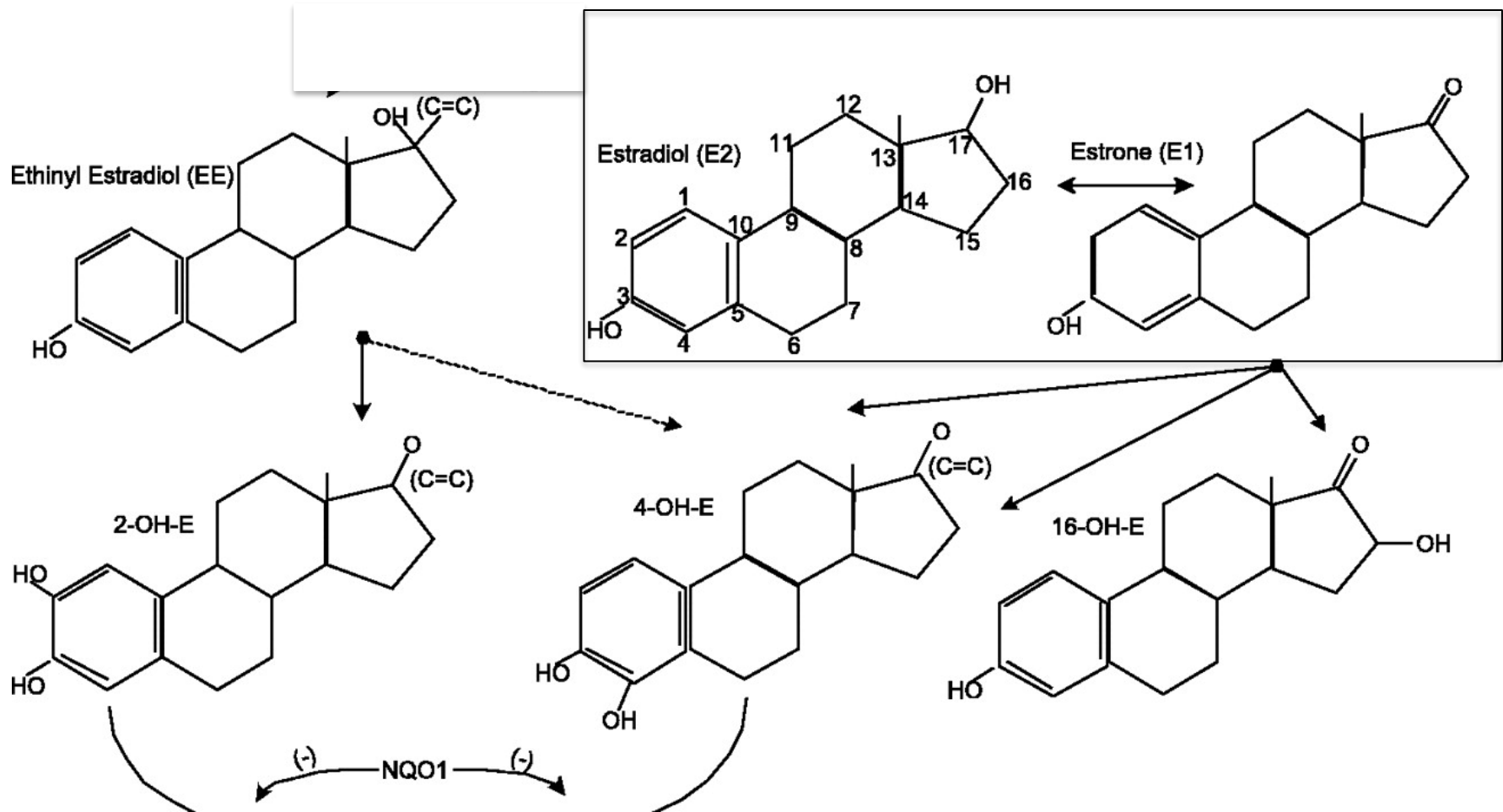
INAS SCORE: International Active Surveillance Study on the Safety of Contraceptive and the Role of Estrogens



Studio di coorte prospettico, controllato, non-interventistico, a lungo termine condotto in USA e EU su 50.203 nuove utilizzatrici di COC con follow up max fino a **7 anni (prima 5,5)**



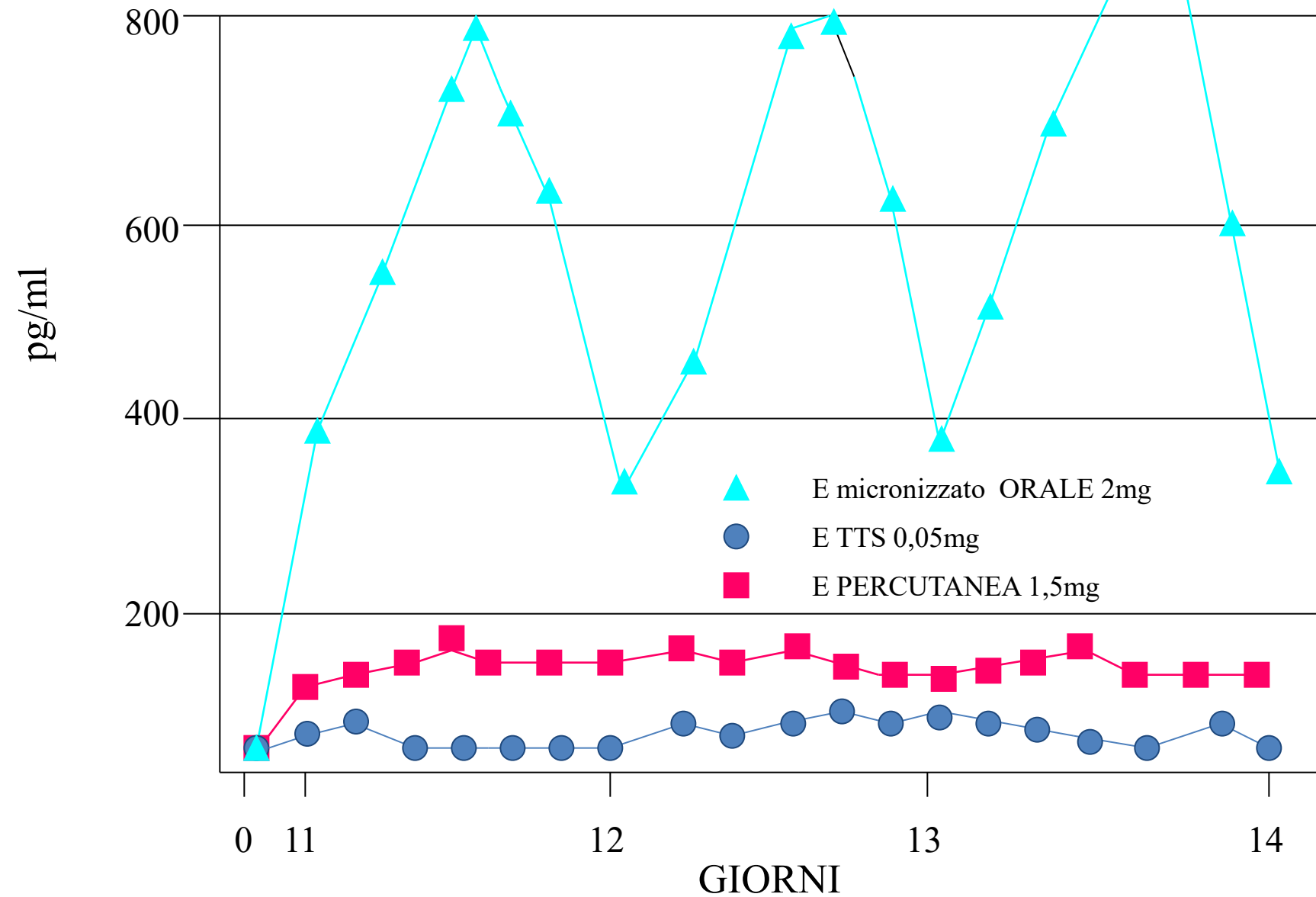
Different metabolism of E2 and EE



Etinil-Estradiolo (EE) vs. Estradiolo (E2)

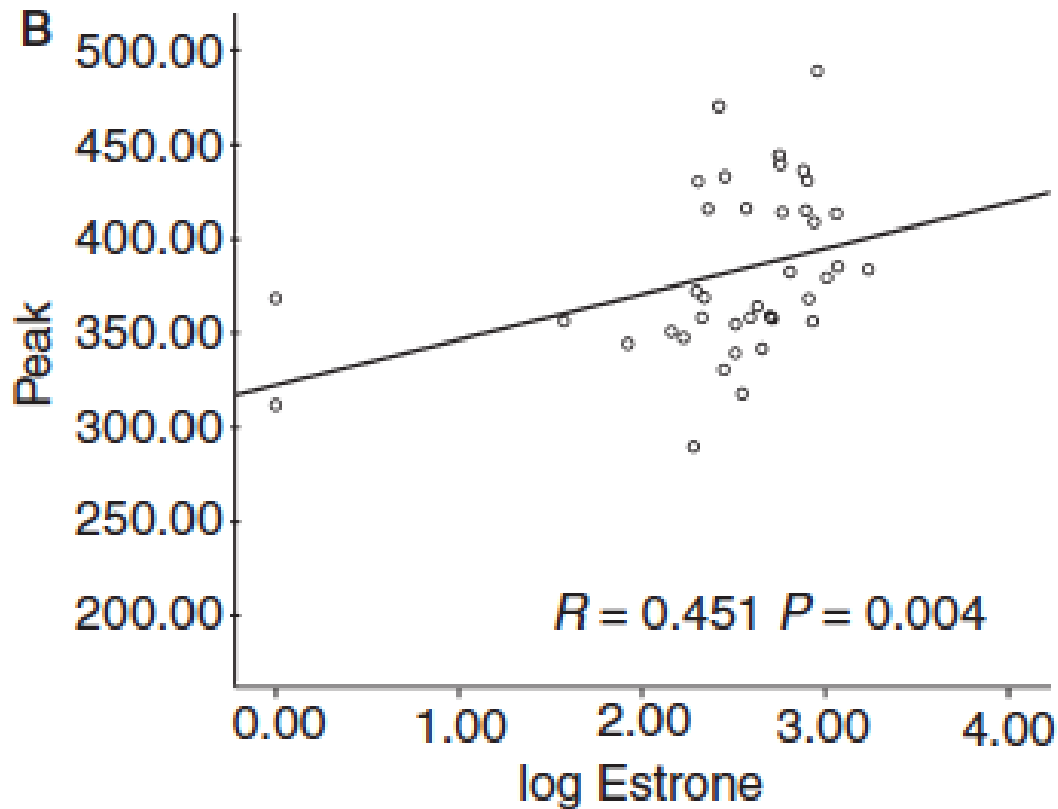
	EE	E2
Emivita	26+/-7 hr	20-30 min
SHBG legame	Molto bassa	38% alta affinità
Albumina legame	98.5%	60% bassa affinità
Biodisponibilità	38-48%	3-5%

Livelli Sierici di Estrone



The effect of estrone on thrombin generation may explain the different thrombotic risk between oral and transdermal hormone replacement therapy

C. N. BAGOT,* M. S. MARSH,† M. WHITEHEAD,† R. SHERWOOD,‡ L. ROBERTS,* R. K. PATEL* and R. ARYA*



Blood Pressure and COC with EE 50 mcg or Mestranol

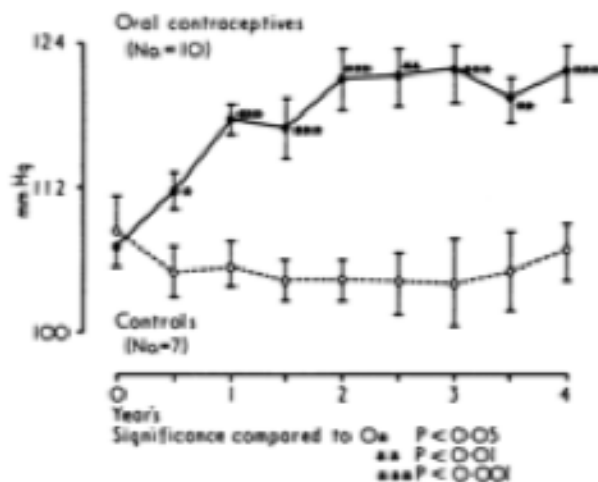


FIG. 1—Mean systolic blood pressure (\pm S.E.M.) after four years in a group of women taking oral contraceptives and in control group using mechanical methods of contraception.

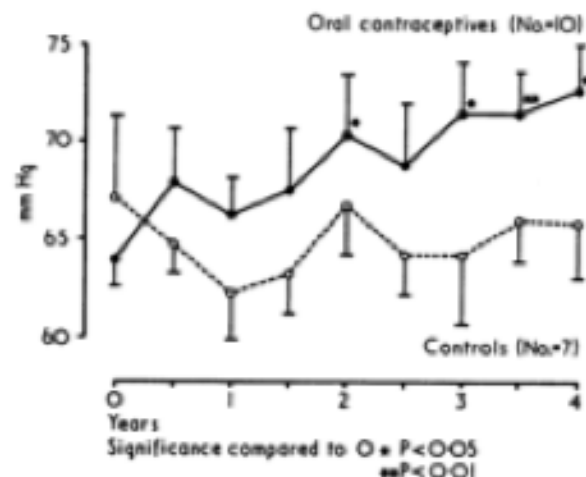


FIG. 2—Mean diastolic blood pressure (\pm S.E.M.) after four years in group of women taking oral contraceptives and in control group using mechanical methods of contraception.

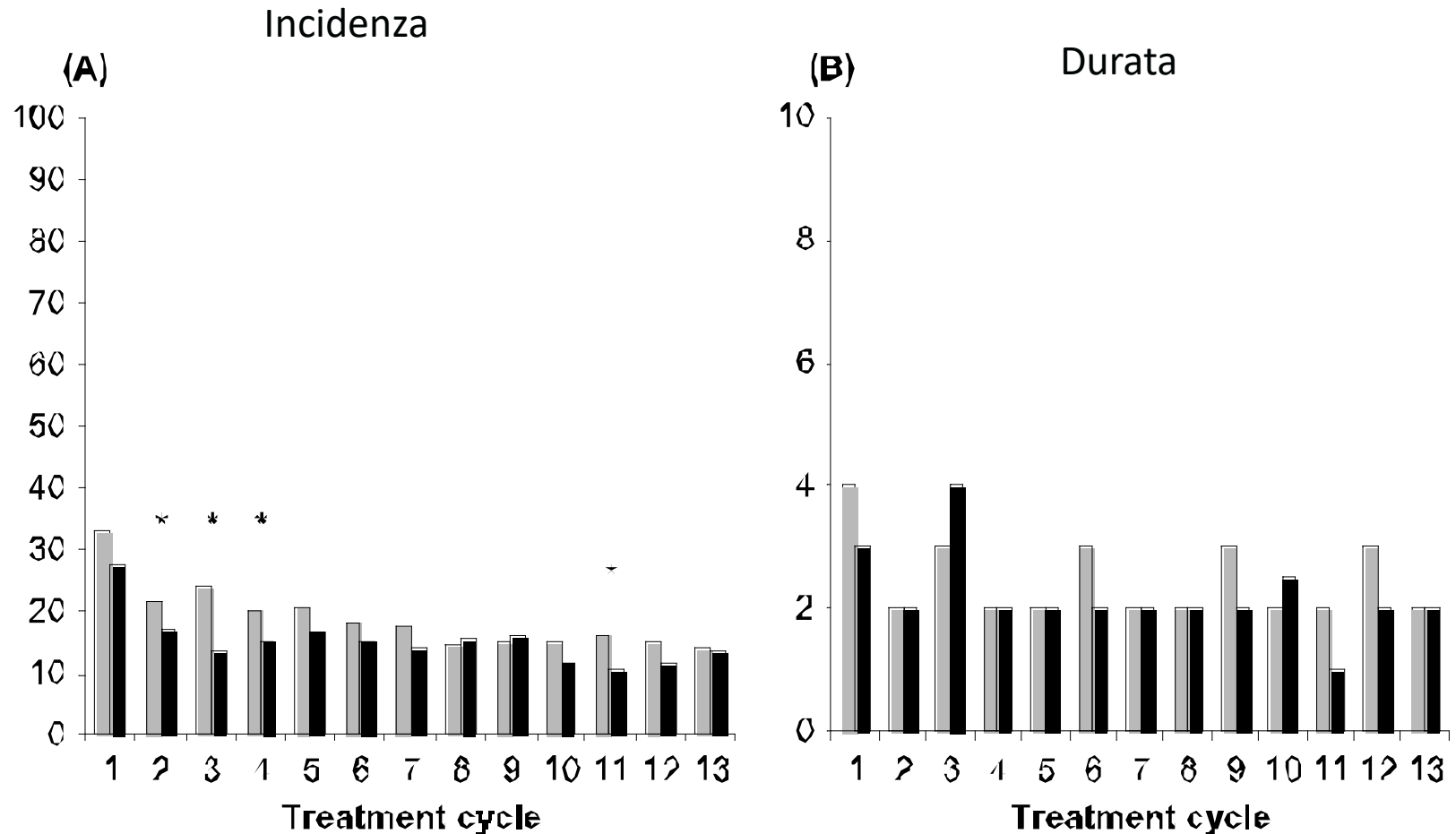
CO con Estradiolo: Aumento SHBG

- **Aumentate**
- **Simile al CO con EE/LNG**
- **Inferiore a EE/DRSP**

E2 1.5 mg /NOMAC 2.5 mg

CONTROLLO DEL CICLO

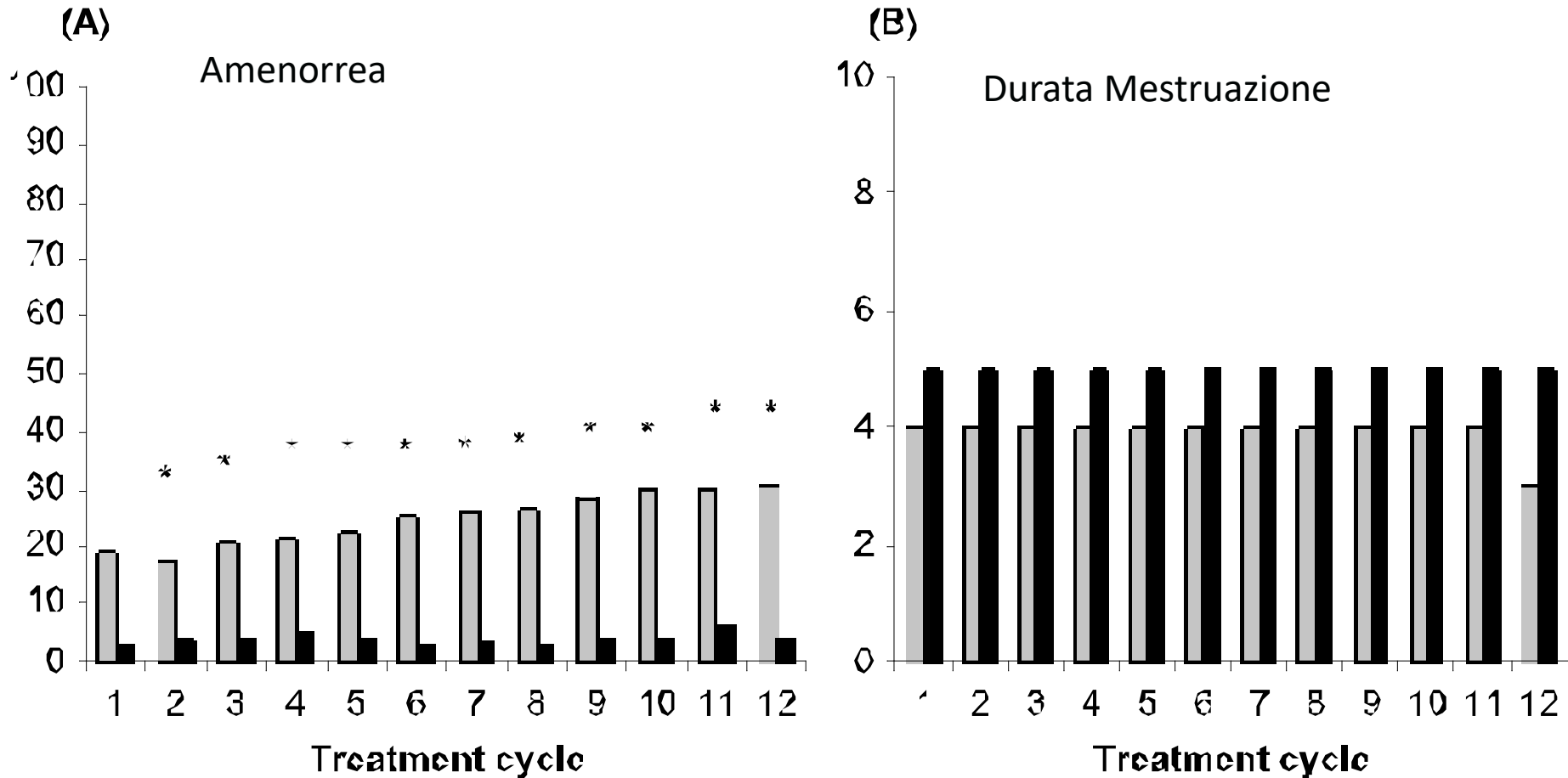
BTB-spotting for Nomac E2 (grey) or EE/DRSP (black)



E2 1.5 mg /NOMAC 2.5 mg

CONTROLLO DEL CICLO

(NOMAC/E2 (grey) and DRSP/EE (black)).



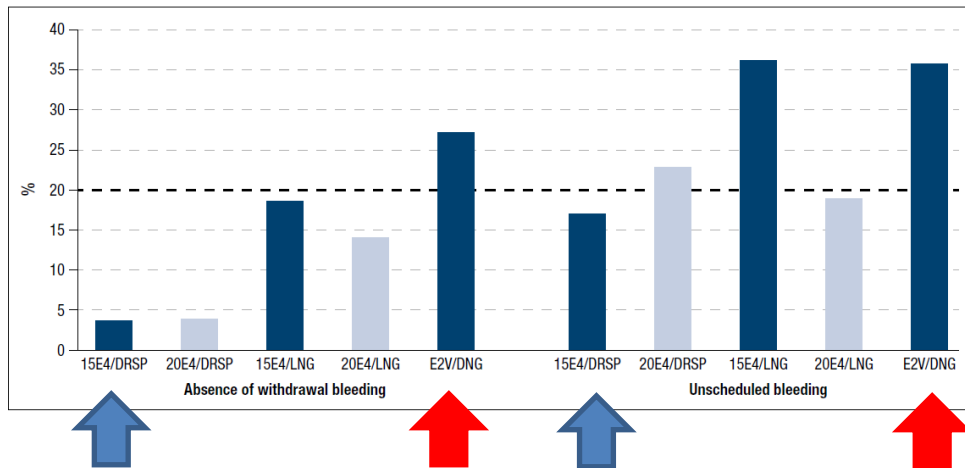
CO con Estradiolo: controllo del ciclo

- **Buono**
- **Simile al CO con EE/DRSP o EE/LNG**
- **Cicli più scarsi**
- **Più amenorrea**

Contollo del Ciclo

FASE II: profilo di sanguinamento

la combinazione 15mgE4/DRSP risulta quella con miglior profilo di sanguinamento ➡ **dosaggio e combinazione scelta per lo sviluppo di Fase III**



con E415mg/DRSP il sanguinamento atteso si è verificato in circa il 95% delle utilizzatrici

Quali caratteristiche distintive di estetrol?

Estetrol (E4): Effetto sugli enzimi epatici

- Effetto trascurabile sui seguenti enzimi del cytP450 (<10%)

Estrogeni a 10 μmol/L	% P450 enzimi				
	CYP1A2	CYP2C9	CYP2C19	CYP2D6	CYP3A4
EE	<10	<10	82	<10	45
E2	19	<10	63	<10	<10
E4	<10	<10	<10	<10	<10

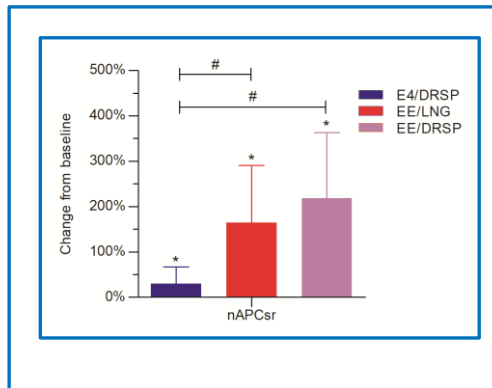
1. Visser M, et al. Climacteric 2008;11(Suppl.1):64-68

Quali caratteristiche distintive di estetrol?

	EE	E2	E4
Incremento	26+/-7 hr	20-30 min	28-32 hr
SHBG	+250%	+60%	50%
Angiotensinogeno	206.5%	80%	75%

E4/DRSP – RESISTENZA ALLA PROTEINA C ATTIVATA

L'INNalzAMENTO dell' APC RESISTANCE solitamente CORRELA CON POSSIBILE INNalzAMENTO DI SHBG. Sia L'INNalzAMENTO DI APCr che delle SHBG POTREBBE ESSERE INDICATIVO DI POSSIBILE AUMENTATO RISCHIO TEV.

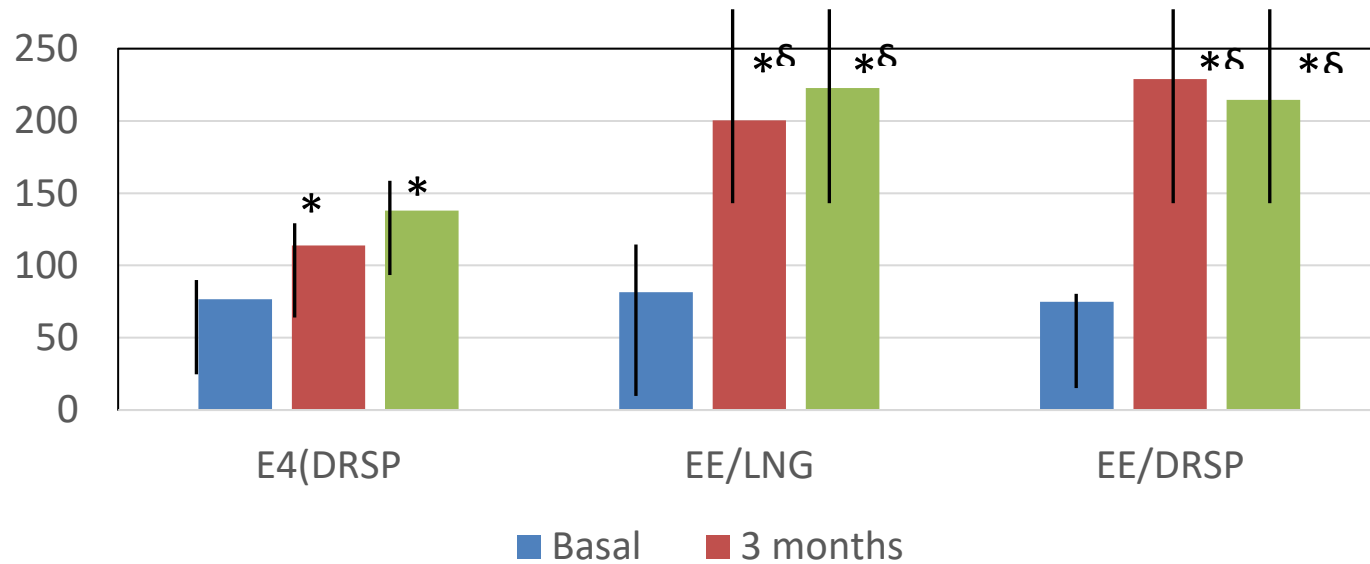


Incremento di APCr significativamente inferiore a EE/LNG e EE/DRSP

Il minimo aumento della **APCsr** con E4/DRSP è probabilmente il risultato della bassa potenza estrogenica dell'E4, in quanto DRSP, come progestinico antiandrogenico, non è in grado di contrastare gli effetti dell'estrogeno, come evidente dall'aumento di APC resistance con EE/DRSP

Incremento dell' Angiotensinogeno

Incremento di angiotensinogeno < 50% rispetto agli altri gruppi



Prescrizione: quale Estrogeno?

Medico

Profilo
della
donna

	Etinil Estradiolo	Estradiolo	Estetrolo	
SHBG	↑	↑	↑	EE meglio nelle donne iperandrogeniche
	Etinil Estradiolo	Estradiolo	Estetrolo	
Parametri metabolici	↑ (dose dipendente)	↑	↑	Estradiolo e estetrolo meno effetti
	Etinil Estradiolo	Estradiolo	Estetrolo	
Endometrio	Stabile	Instabile	Stabile	EE 30-35 mcg per controllo ciclo, Estetrolo
	Etinil Estradiolo	Estradiolo	Estetrolo	
Mammella	Effetto estrogenico	Effetto estrogenico	Minori effetti estrogenici Effetto antiestrogenico	Estetrolo ?

Estrogeni e mammella

17 β estradiolo

- Azione su ER α e ER β
- Stimola Ers nucleari e di membrana
- Metabolizzato da CYP450metaboliti idrossilati

Estetrolo

- Azione su ER α , affinità minore di E2
- Antagonist action on membrane ERs
 - No stimulatory activity through membrane ERs
 - Block E2 action at this level
- No metabolizzato da CYP450
- No produzione metaboliti idrossilati

Visser M, 2008

Coelingh Bennink, H.J., 2008;

Abot A, 2014

Abot A, 2014

Alcuni metaboliti idrossilati sono cancerogeni

Yager JD., 2015

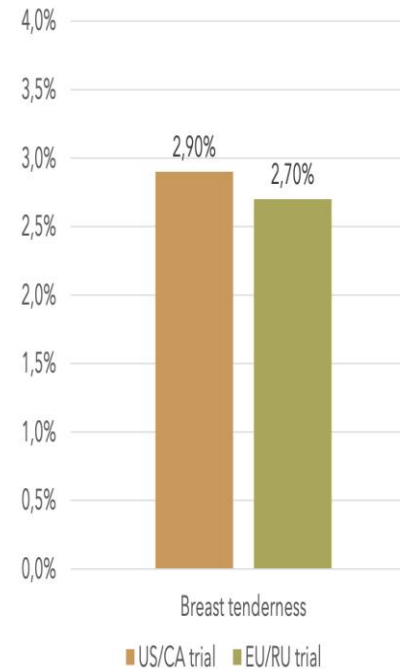
Abot A, et al. The uterine and vascular actions of estetrol delineate a distinctive profile of estrogen receptor alpha modulation, uncoupling nuclear and membrane activation. EMBO Mol Med.6(10):1328-46, 2014.
Coelingh Bennink HJ et al, Estetrol review: profile and potential clinical applications., Climacteric. 11 Suppl 1:47-58. 2008
Yager JD. Steroids. 2015 Jul;99(Pt A):56-60

Impatto sulla mammella : tensione mammaria

- E4/DRSP Phase 3 trials pooled data
- 3417 participants
- Designed to capture ALL breast complaints
- Breast pain or tenderness: 4.0% overall
 - 136 participants with complaint (4.0%)
 - ~75% in first 3 cycles
 - Rated severe in 3 participants (0.09%)
 - # affected cycles: 561 (1.6 cycles in participants with complaint)
 - Discontinuation for breast tenderness: 8 (0.2%) participants
 - Discontinuation for *any* breast complaint: 11 (0.3%) participants

Chen MJ, et al. Contraception 2022;116:44-50.

Difficile confronto con altri studi



Clinical trial publications

- Reported events $\geq 2\%$
- "Breast tenderness" reported

Creinin MD, et al. Contraception 2021;104:222-8.
Gemzell-Danielsson K, et al. BJOG 2022;129:63-71.

Fare clic per modificare stile

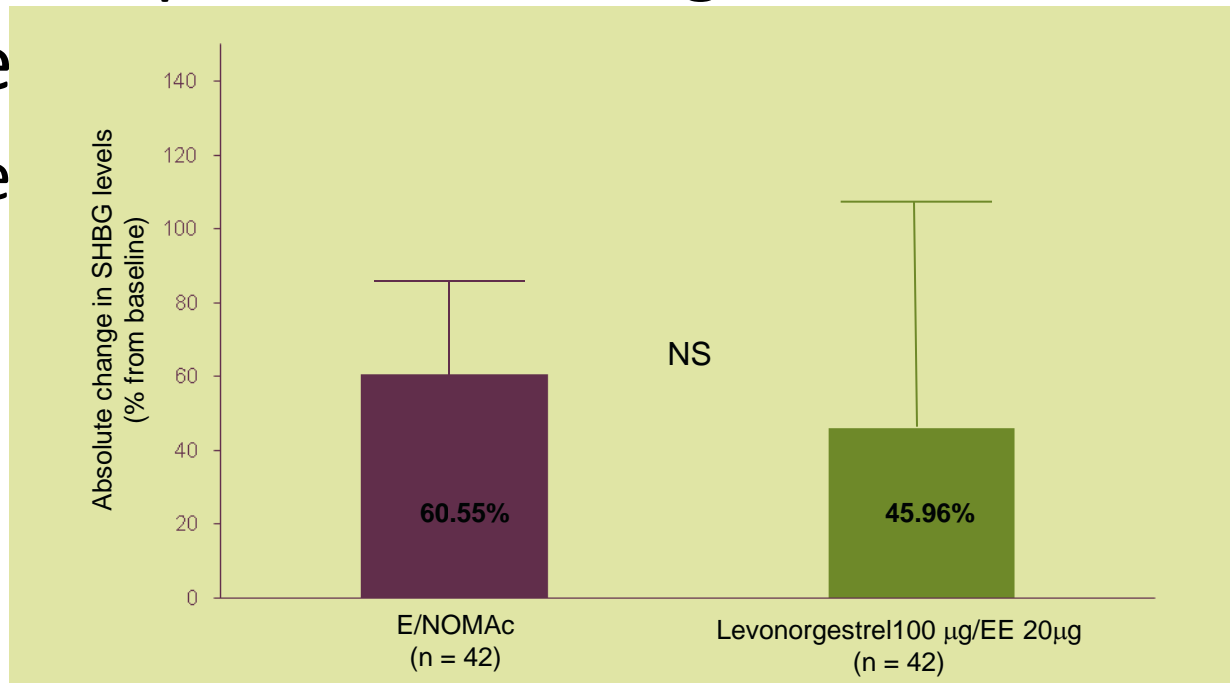
Changes in SHBG levels from baseline to Cycle 3 (mean \pm SEM)

- Fare clic per modificare gli stili del testo dello

sche

– Se

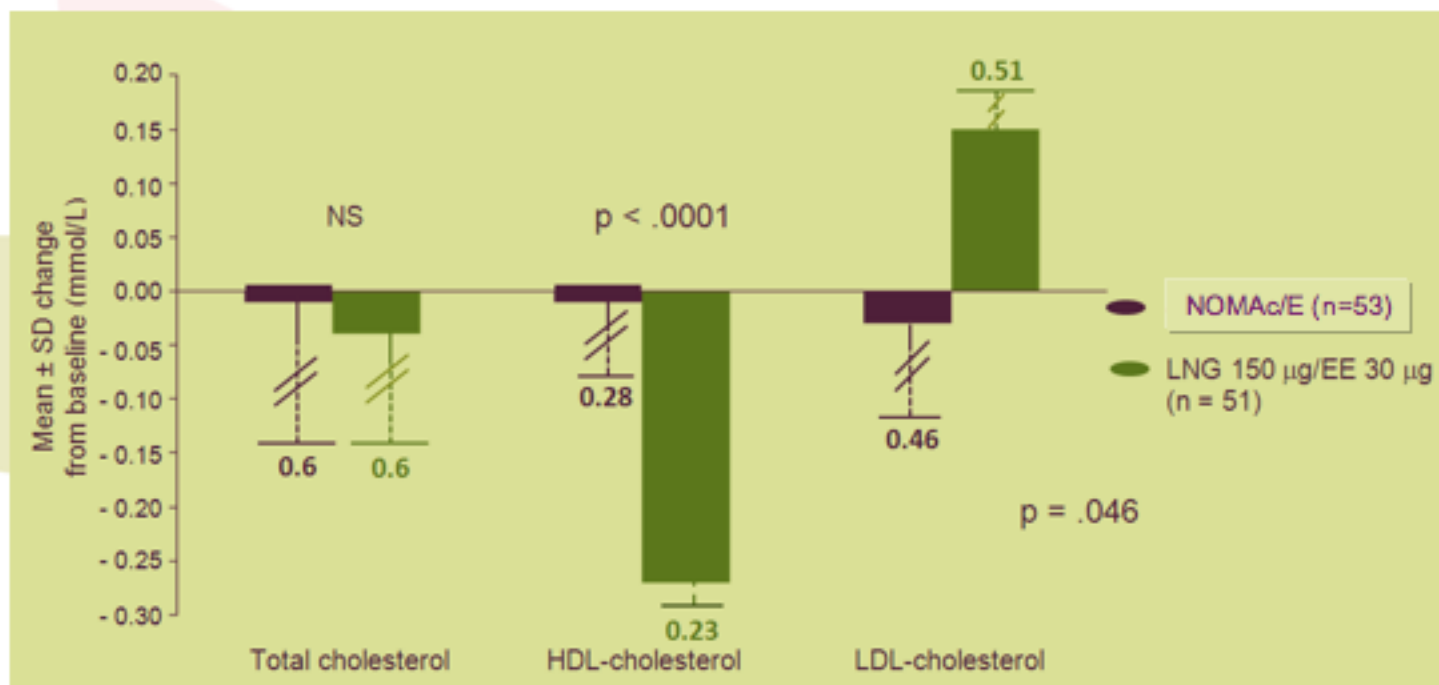
•



1 - Gaussem P *et al.* Thromb Haemost 2011;105:3

2 - Couzinet B *et al.* J Clin Endocrinol Metab 1996;81(12):4218-23

Metabolic markers: Lipids



E4 has a pro-apoptotic effect in humans

- Double-blinded, randomized, placebo-controlled, proof-of-concept study
- 15 post- and 15 premenopausal women with ER+ breast cancer
- Preoperative treatment for 14 days with E4 20 mg daily or placebo immediately followed by surgery
- Effect of E4 on tumor biology (Ki67 and apoptosis)

20 mg E4 increases the number of apoptotic cells in 30 women in pre and post-menopause with early breast cancer ER+ administered for 2 weeks before surgery

The increases in the number of apoptotic cells significantly different from placebo ($p < 0.005$)

No change in proliferation (Ki67)

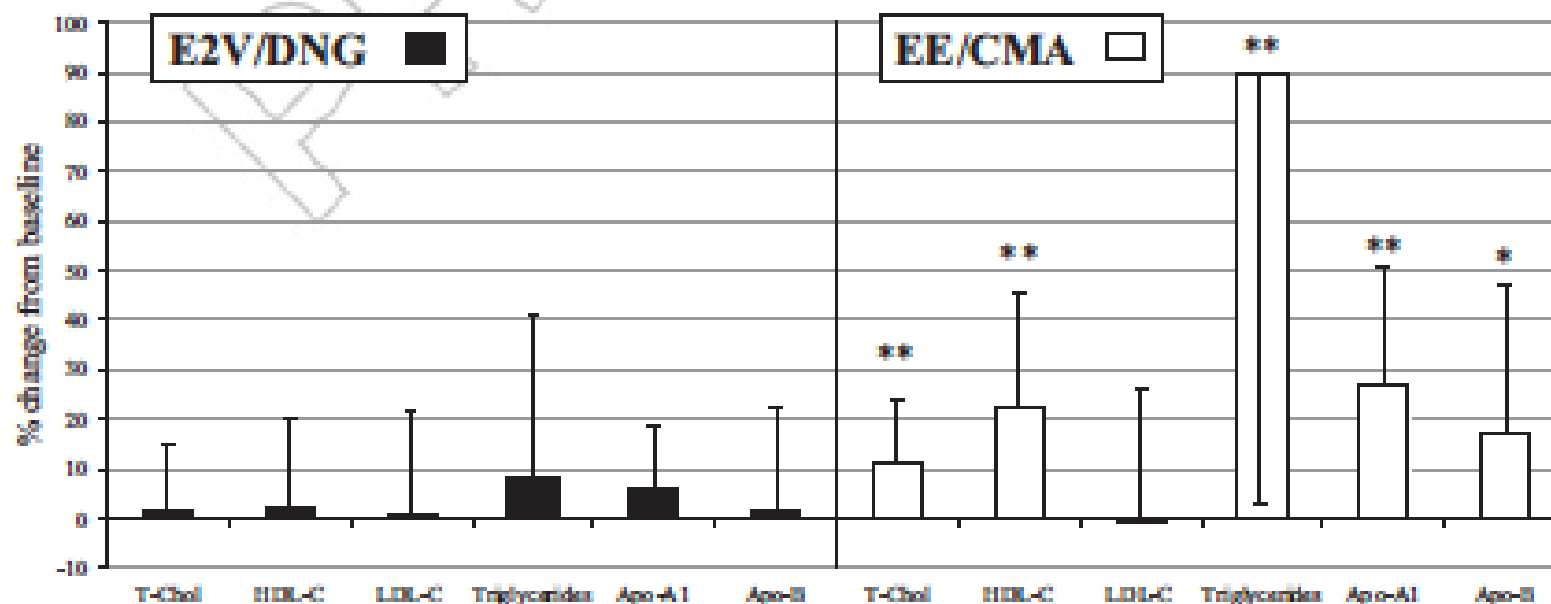
Singer CF, Bennink HJ, Natter C, Steurer S, Rudas M, Moirfar F, Appels N, Visser M, Kubista E.
Antiestrogenic effects of the fetal estrogen estetrol in women with estrogen-receptor positive early breast cancer.
Carcinogenesis 2014;35):2447-51

Singer CF, 2004

ORIGINAL ARTICLE

Modification of body composition and metabolism during oral contraceptives containing non-androgenic progestins in association with estradiol or ethinyl estradiol

Giovanni Grandi, Ilaria Piacenti, Annibale Volpe, and Angelo Cagnacci



CO con Estradiolo: Quadro Lipidico

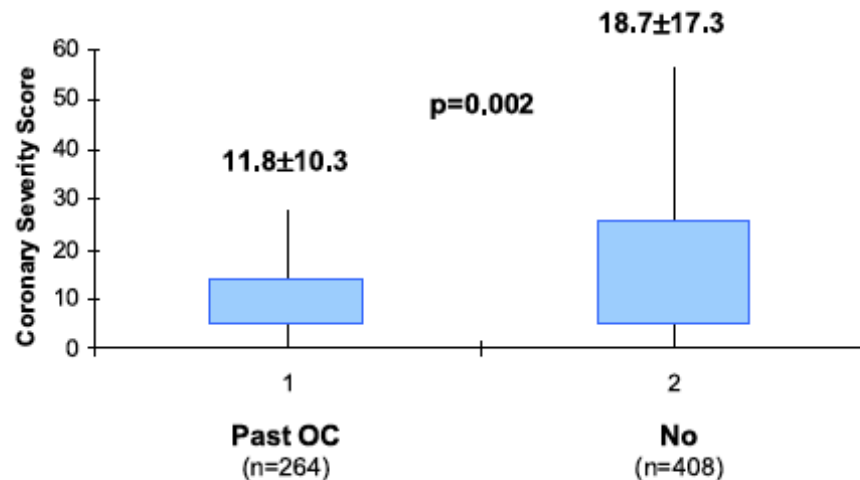
- **Neutrale**
- **Migliore dei CO con EE/LNG**
- **Peggior dei CO con EE/DRSP**

Past oral contraceptive use and angiographic coronary artery disease in postmenopausal women: data from the National Heart, Lung, and Blood Institute–sponsored Women’s Ischemia Syndrome Evaluation

C. Noel Bairey Merz, M.D., F.A.C.C.,^a B. Delia Johnson, Ph.D.,^b Sarah Berga, M.D.,^c Glenn Braunstein, M.D.,^a Steven E. Reis, M.D., F.A.C.C.,^b Vera Bittner, M.D., F.A.C.C.,^d and the WISE Study Group

FIGURE 1

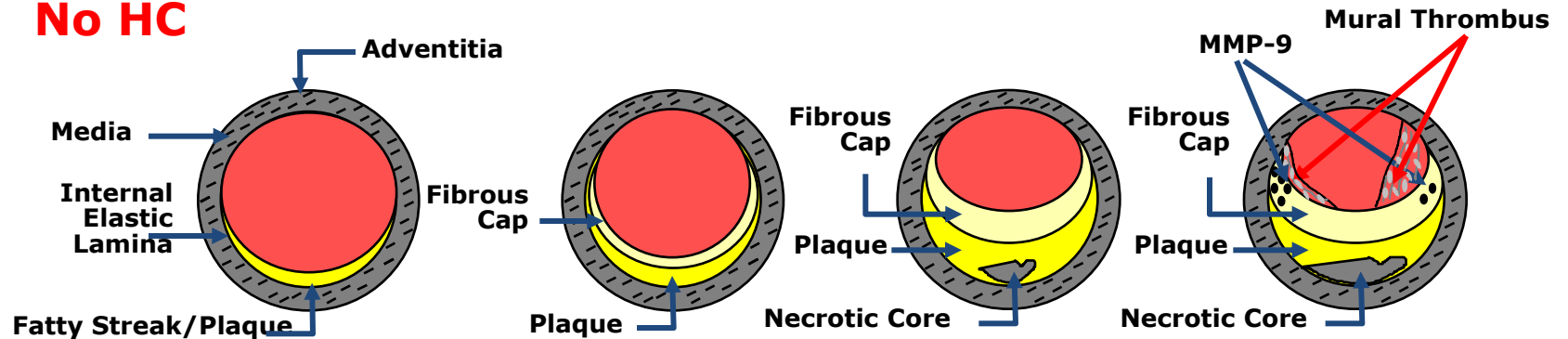
Coronary artery severity score, assessed by quantitative coronary angiography (17), stratified by reported prior oral contraceptive use.



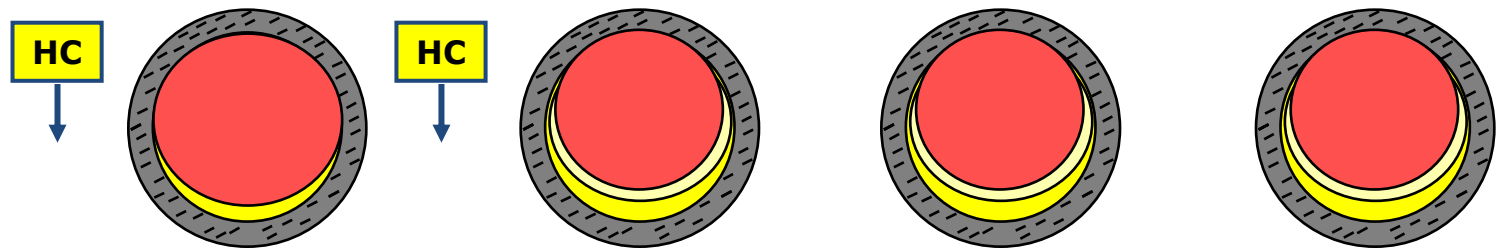
Bairey Merz. Oral contraceptives and CAD. *Fertil Steril* 2006.

Pathogenetic Sequence of ATE

No HC



HC with Non Androgenic Progestin



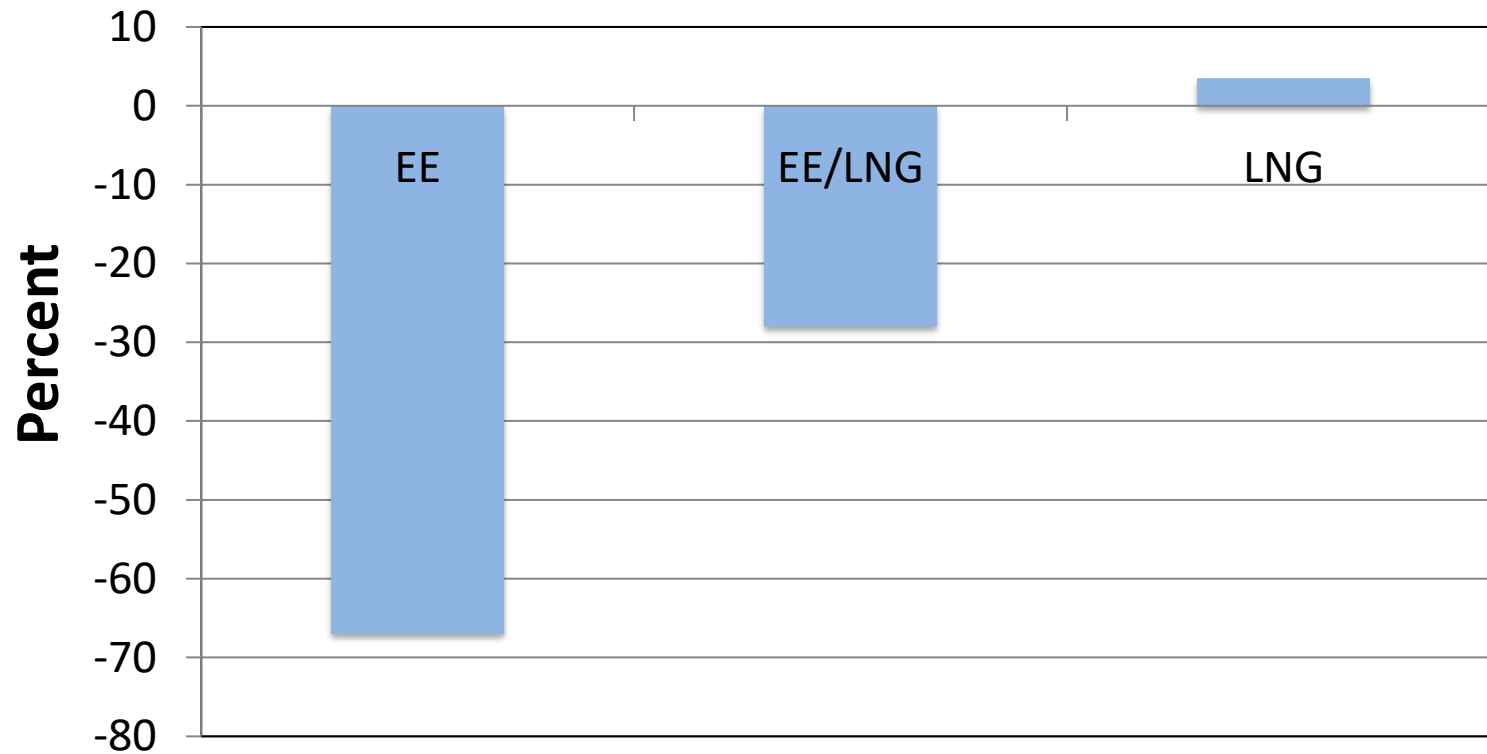
AGE

35-45

45-55

55-65

>65

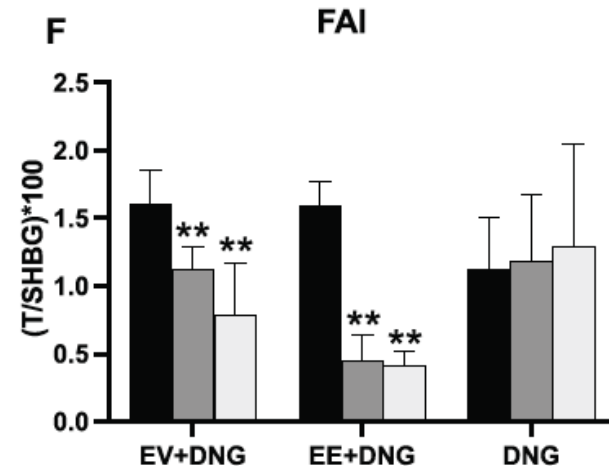
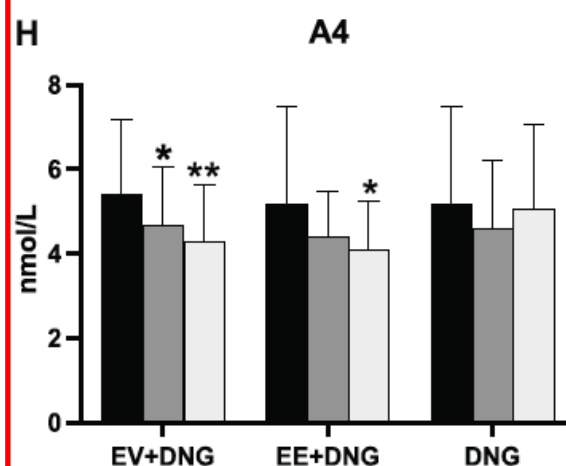
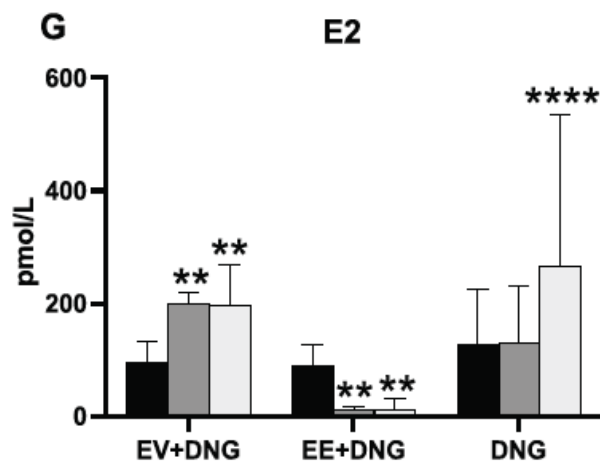


Adams et al, Obstet Gynecol 2000

Estradiol Valerate vs Ethinylestradiol in Combined Oral Contraceptives: Effects on the Pituitary-Ovarian Axis

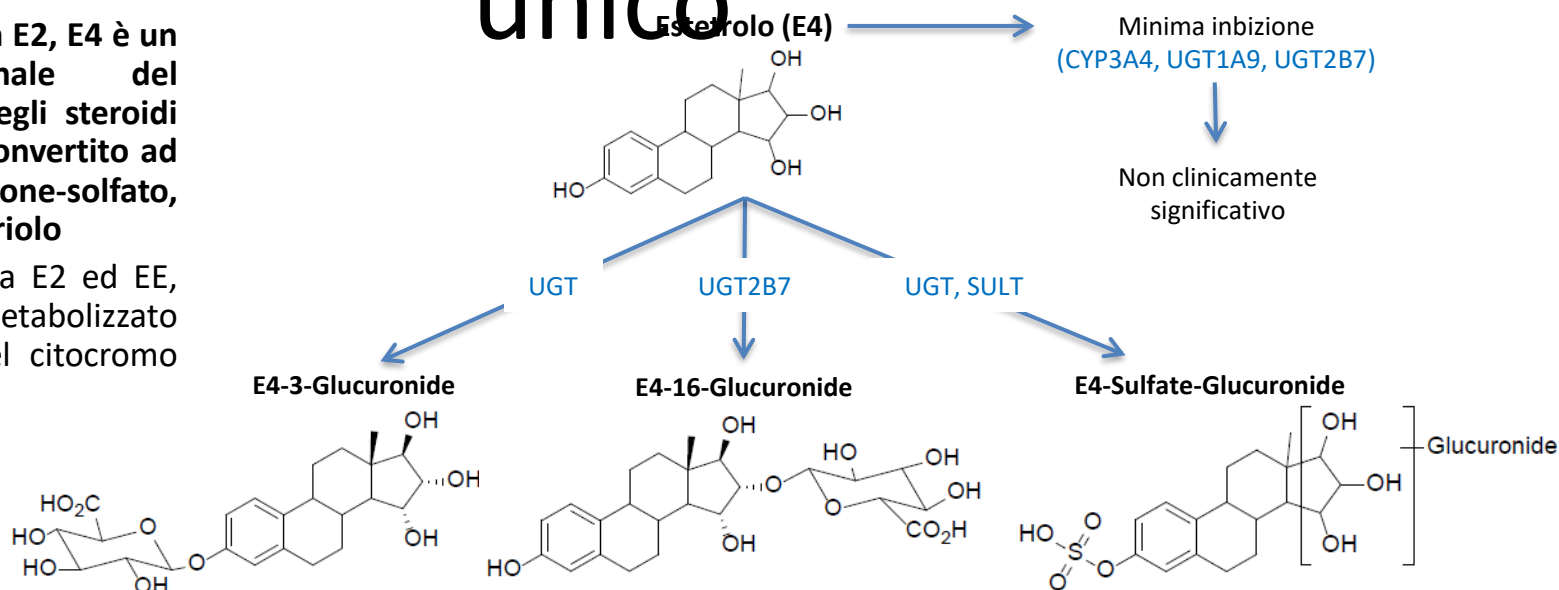
Annina Haverinen,^{1, ID} Kaisu Luiro,^{1, ID} Marika H. Kangasniemi,^{2, ID} Terhi T. Piltonen,^{2, ID}
Steinar Hustad,³ Oskari Heikinheimo,^{1, ID} Juha S. Tapanainen,^{1, ID}

■ Baseline
■ Five weeks
■ Nine weeks



E4 possiede un metabolismo unico

- In contrasto con E2, E4 è un prodotto finale del metabolismo degli steroidi e non viene riconvertito ad **estrone**, estrone-solfato, estradiolo o estriolo
- Diversamente da E2 ed EE, E4 non viene metabolizzato dagli enzimi del citocromo P450



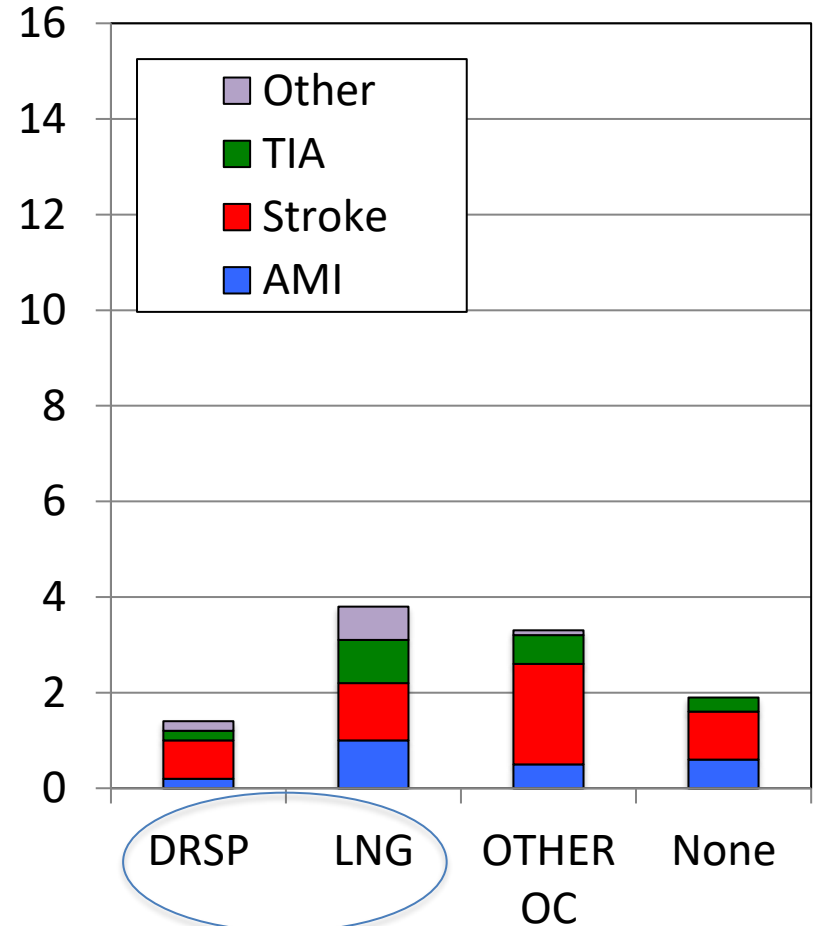
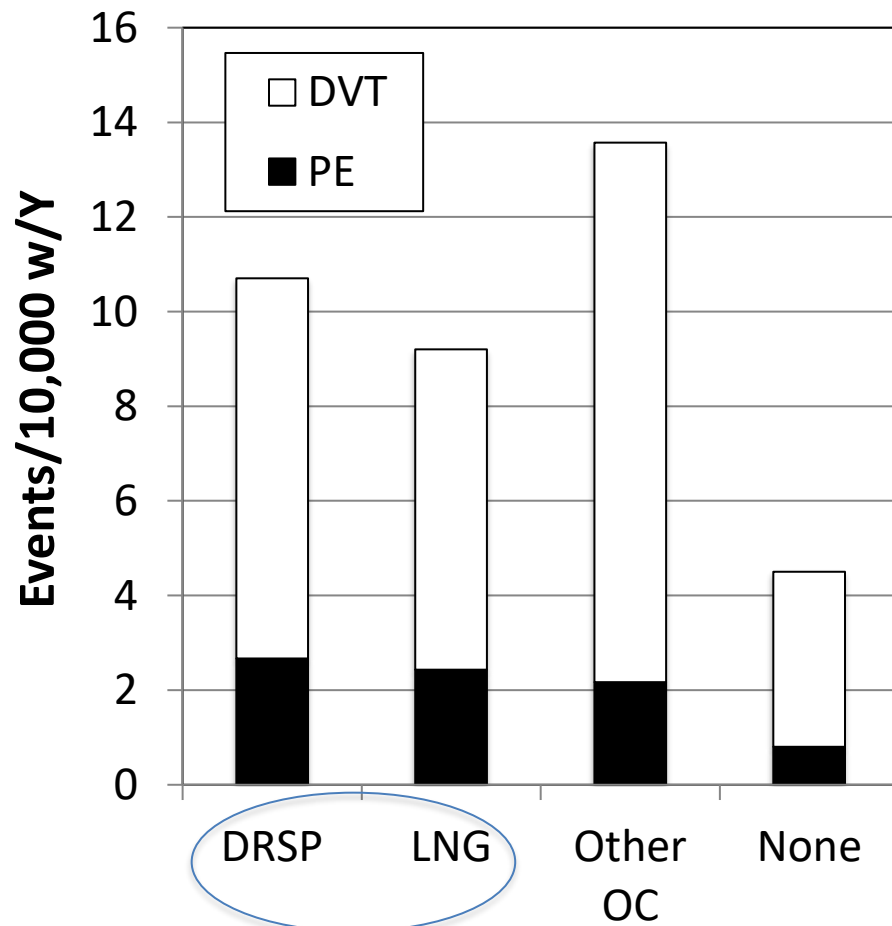
E2, estradiol; E4, estetrol; SULT, sulphotransferase; UGT, uridine 5'-diphospho-glucuronosyltransferase

Data on file. CSR MIT-Es0001-C105 (QCL114621), July 2016; Visser M, et al. Climacteric 2008;11(Suppl.1):64-68; Coelingh Bennink HJ, et al. Climacteric 2008;11 Suppl 1:47-58

Original research article

Cardiovascular risks associated with the use of drospirenone-containing combined oral contraceptives[☆]

Jürgen Dinger^{a,*}, Sabine Möhner^b, Klaas Heinemann^b

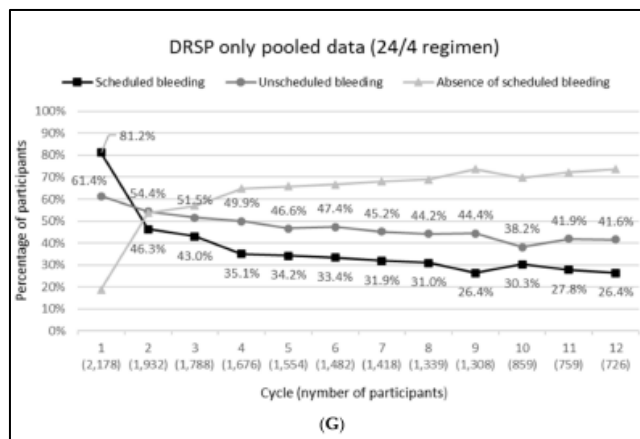


Conclusioni

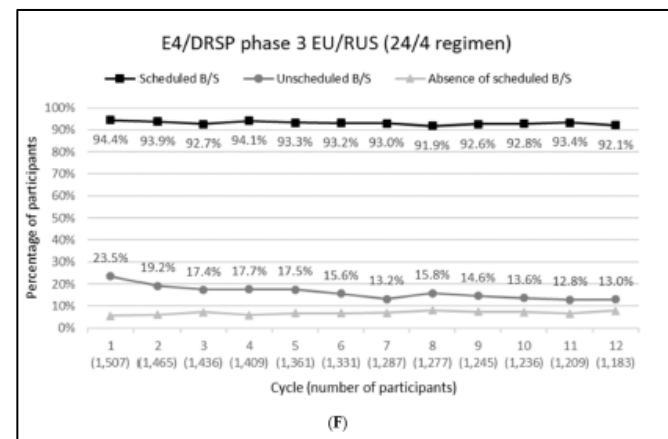
Contraccezione con Estradiolo vs EE/DRSP:

	EV/E2	EE/LNG	EE/DRSP
TEV	↑	↑	↑↑↑
Pressione Art.	/	↑↑↑	/
Insulino Res.	/	↑↑	/
HDL	/	↓	↑↑↑
SHBG	↑	↑	↑↑↑
Controllo Ciclo	/	/	/
Quantità flussi	↓	/	/
Amenorrea	↑↑	/	/

DRSP 24/4

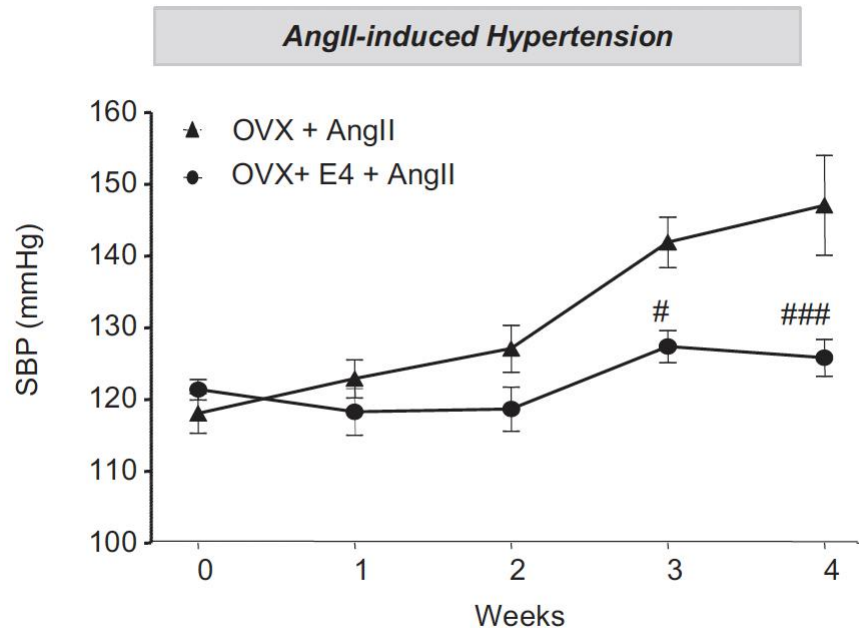


E4/DRSP 24/4



Predominant Role of Nuclear Versus Membrane Estrogen Receptor α in Arterial Protection: Implications for Estrogen Receptor α Modulation in Cardiovascular Prevention/Safety

Emmanuel Guivarc'h, PhD;* MéliSSa Buscato, BS;* Anne-Laure Guihot, BS; Julie Favre, PhD; Emilie Vessières, BS; Linda Grimaud, BS; Jamal Wakim, PhD; Nada-Joe Melhem, BS; Rana Zahreddine, BS; Marine Adlanmerini, PhD; Laurent Loufrani, PhD; Claude Knauf, PhD; John A. Katzenellenbogen, PhD; Benita S. Katzenellenbogen, PhD; Jean-Michel Foidart, MD, PhD; Pierre Gourdy, MD, PhD; Françoise Lenfant, PhD; Jean-François Arnal, MD, PhD; Daniel Henrion, PharmD, PhD;* Coralie Fontaine, PhD*



[#]P<0.05; ^{###}P<0.001 OVX+E4+AngII vs OVX+AngII mice

Treatment Options for Hirsutism: A Systematic Review and Network Meta-Analysis

Patricia Barrionuevo,^{1,2*} Mohammed Nabhan,^{1,3*} Osama Altayar,^{1,4*} Zhen Wang,¹ Patricia J. Erwin,^{1,5} Noor Asi,^{1,6} Kathryn A. Martin,⁷ and M. Hassan Murad¹

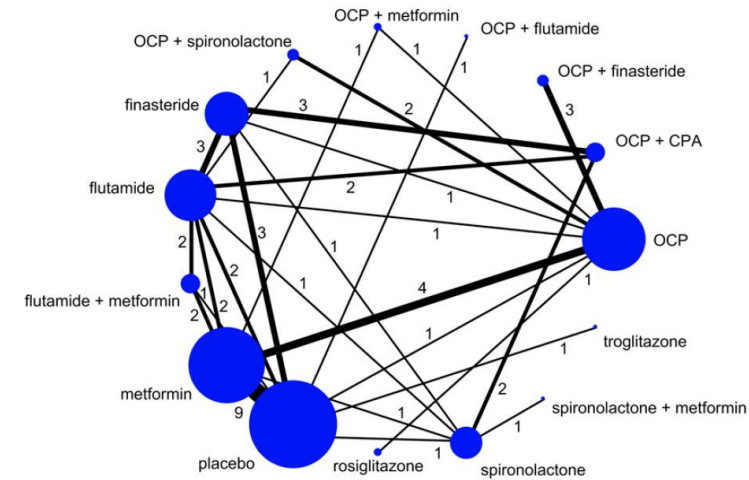


Table 2. Individual Medication Comparison

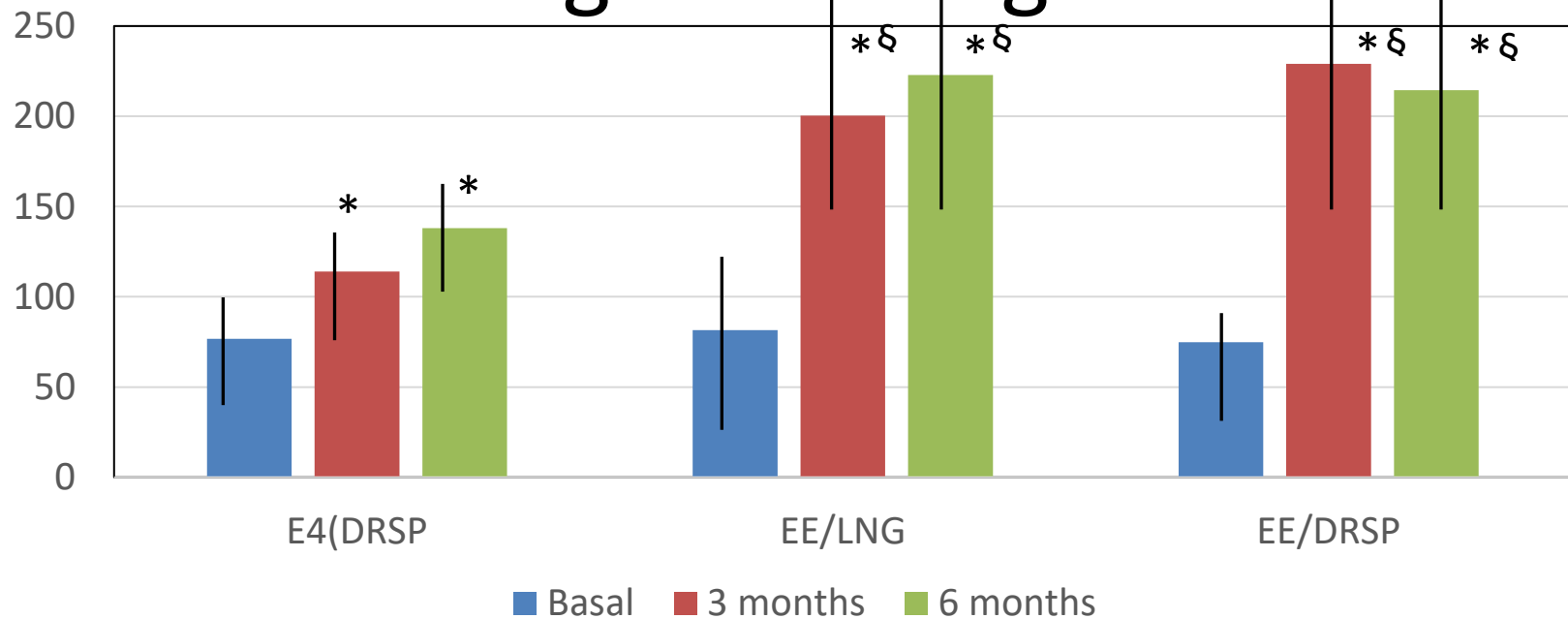
Variable	Placebo	OCP	OCP + CPA	OCP + Finasteride	OCP + Flutamide	OCP + Metformin	OCP + Spironolactone
OCP	-1.21 (-1.92 to -0.50) ^a						
OCP + CPA	-1.70 (-2.55 to -0.85) ^a	-0.49 (-1.41 to 0.43)					
OCP + finasteride	-1.64 (-2.72 to -0.55) ^a	-0.43 (-1.25 to 0.39)	0.06 (-1.17 to 1.29)				
OCP + flutamide	-0.70 (-1.95 to 0.56)	0.51 (-0.93 to 1.95)	1.00 (-0.52 to 2.52)	0.94 (-0.72 to 2.60)			
OCP + metformin	-2.09 (-3.33 to -0.85) ^a	-0.89 (-2.06 to 0.28)	-0.40 (-1.79 to 1.00)	-0.46 (-1.88 to 0.97)	-1.40 (-3.16 to 0.37)		
OCP + spironolactone	-1.90 (-2.88 to -0.93) ^a	-0.70 (-1.49 to 0.10)	-0.21 (-1.31 to 0.90)	-0.27 (-1.41 to 0.87)	-1.21 (-2.80 to 0.38)	0.19 (-1.19 to 1.58)	
Finasteride	-1.48 (-2.18 to -0.78) ^a	-0.28 (-1.05 to 0.50)	0.21 (-0.48 to 0.90)	0.15 (-0.97 to 1.28)	-0.79 (-2.22 to 0.65)	0.61 (-0.71 to 1.93)	0.42 (-0.58 to 1.42)
Flutamide	-1.85 (-2.55 to -1.14) ^a	-0.64 (-1.42 to 0.15)	-0.15 (-0.91 to 0.61)	-0.21 (-1.34 to 0.92)	-1.15 (-2.59 to 0.29)	0.25 (-1.06 to 1.56)	0.06 (-0.88 to 1.00)
Flutamide + metformin	-1.68 (-2.66 to -0.71) ^a	-0.48 (-1.55 to 0.59)	0.02 (-1.12 to 1.15)	-0.05 (-1.39 to 1.30)	-0.98 (-2.57 to 0.60)	0.41 (-1.07 to 1.89)	0.22 (-1.01 to 1.45)
Metformin	-0.73 (-1.18 to -0.27) ^a	0.48 (-0.13 to 1.09)	0.97 (0.14 to 1.80) ^a	0.91 (-0.11 to 1.93)	-0.03 (-1.37 to 1.31)	1.37 (0.20 to 2.53) ^a	1.17 (0.26 to 2.09) ^a
Rosiglitazone	-1.06 (-2.64 to 0.51)	0.14 (-1.26 to 1.55)	0.64 (-1.04 to 2.31)	0.57 (-1.05 to 2.20)	-0.37 (-2.38 to 1.65)	1.03 (-0.79 to 2.86)	0.84 (-0.77 to 2.45)
Spironolactone	-1.41 (-2.26 to -0.57) ^a	-0.21 (-1.14 to 0.73)	0.29 (-0.51 to 1.08)	0.22 (-1.02 to 1.47)	-0.72 (-2.23 to 0.80)	0.68 (-0.72 to 2.08)	0.49 (-0.64 to 1.62)
Spironolactone + metformin	-1.92 (-3.42 to -0.41) ^a	-0.71 (-2.27 to 0.85)	-0.22 (-1.69 to 1.26)	-0.28 (-2.04 to 1.48)	-1.22 (-3.18 to 0.74)	0.18 (-1.69 to 2.05)	-0.01 (-1.67 to 1.67)
Troglitazone	-0.65 (-1.88 to 0.58)	0.56 (-0.86 to 1.98)	1.05 (-0.45 to 2.54)	0.99 (-0.65 to 2.62)	0.05 (-1.71 to 1.80)	1.44 (-0.30 to 3.19)	1.25 (-0.32 to 2.82)

Table 2. Continued

Finasteride	Flutamide	Flutamide + Metformin	Metformin	Rosiglitazone	Spironolactone	Spironolactone + Metformin
-0.36 (-1.03 to 0.31)						
-0.20 (-1.25 to 0.85)	0.16 (-0.79 to 1.11)					
0.76 (0.05 to 1.46) ^a	1.12 (0.44 to 1.80) ^a	0.95 (0.01 to 1.89) ^a				
0.42 (-1.18 to 2.02)	0.78 (-0.82 to 2.39)	0.62 (-1.14 to 2.38)	-0.33 (-1.86 to 1.19)			
0.07 (-0.76 to 0.90)	0.43 (-0.41 to 1.28)	0.27 (-0.89 to 1.43)	-0.68 (-1.50 to 0.13)	-0.35 (-2.04 to 1.34)		
-0.43 (-1.93 to 1.06)	-0.07 (-1.57 to 1.43)	-0.23 (-1.93 to 1.46)	-1.19 (-2.67 to 0.30)	-0.85 (-2.95 to 1.24)	-0.50 (-1.75 to 0.74)	
0.83 (-0.58 to 2.25)	1.19 (-0.22 to 2.61)	1.03 (-0.54 to 2.60)	0.08 (-1.23 to 1.39)	0.41 (-1.58 to 2.41)	0.76 (-0.73 to 2.25)	1.27 (-0.68 to 3.21)

Incremento dell' Angiotensinogeno

Incremento di angiotensinogeno < 50% rispetto agli altri gruppi



Estetrol (E4): profile di pk unico

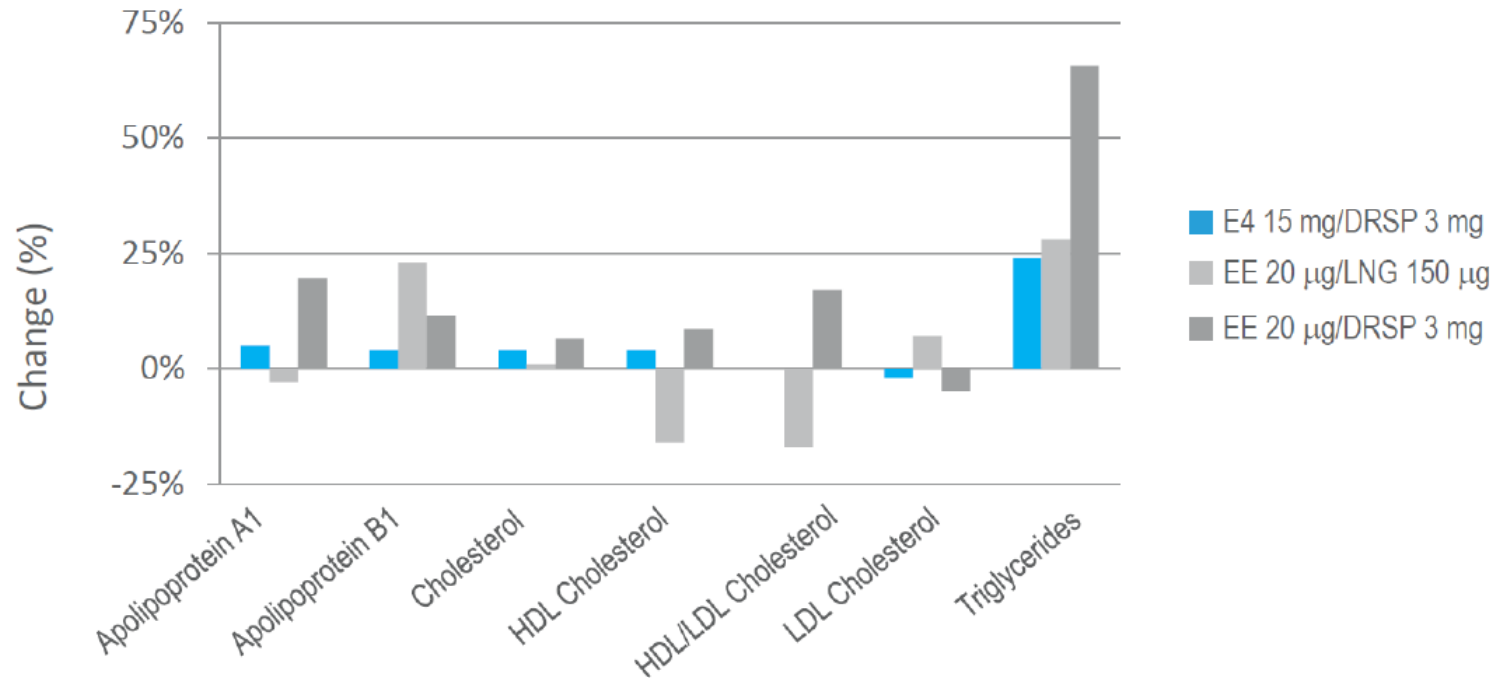
	E4 (in E4+DRSP) ¹	E2 (in E2/NOMAC) ³	EE (in EE/DRSP) ⁴
Oral bioavailability	~70% (rat) ²	1% (substantial first-pass effect after oral administration)	45%
Binding to circulating proteins	NON-SPECIFIC LOW AFFINITY BINDING → ~50% free active fraction • Negligible binding to SHBG	HIGH LEVELS OF BINDING • SHBG (37%) and albumin (61%) → 1–2% free active fraction	HIGH LEVELS OF BINDING • 98% bound to plasma proteins → 2% free active fraction • Induces hepatic synthesis of SHBG and CBG
Metabolites	No active metabolites • Inactive metabolites: mostly glucuronide conjugates formed by UGT2B7 • No relevant metabolism by cytochrome P450 enzymes	Active metabolites: mainly E1 • Oxidation of E1 and E2 involves cytochrome P450 enzymes: CYP1A2, CYP3A4, CYP3A5, CYP1B1 and CYP2C9	Hydroxylated and methylated metabolites are present in free or conjugated forms • EE is an inhibitor of cytochrome P450 enzymes
Elimination	t_{1/2} ~28-32 hours	t_{1/2} ~3.6 ±1.5 hours (dynamic equilibrium between estradiol, estrone and estrone-sulfate)	t_{1/2} ~20 hours Metabolites excreted at a urinary to biliary ratio of 4:6

CBG, cortisol binding globulin; DRSP, drospirenone; E1, estrone; E2, estradiol; E4, estetrol; NOMAC, norgestrel acetate; SHBG, sex hormone binding globulin; t_{1/2}, elimination half-life

MATERIALE CONFIDENZIALE AD ESCLUSIVO USO INTERNO

1. E4+DRSP 15 mg/3 mg film-coated tablet. SmPC, <<DRAFT>>
2. Coelingh Bennink HJ, et al. Climacteric 2008;11 Suppl 1:47–58
3. Zoely (norgestrel acetate/estradiol 2.5 mg/1.5 mg). SmPC, January 2019
4. Yasmin ethinylestradiol/drospirenone 0.03 mg/3 mg). SmPC, December 2018

EFFETTO SUI LIPIDI

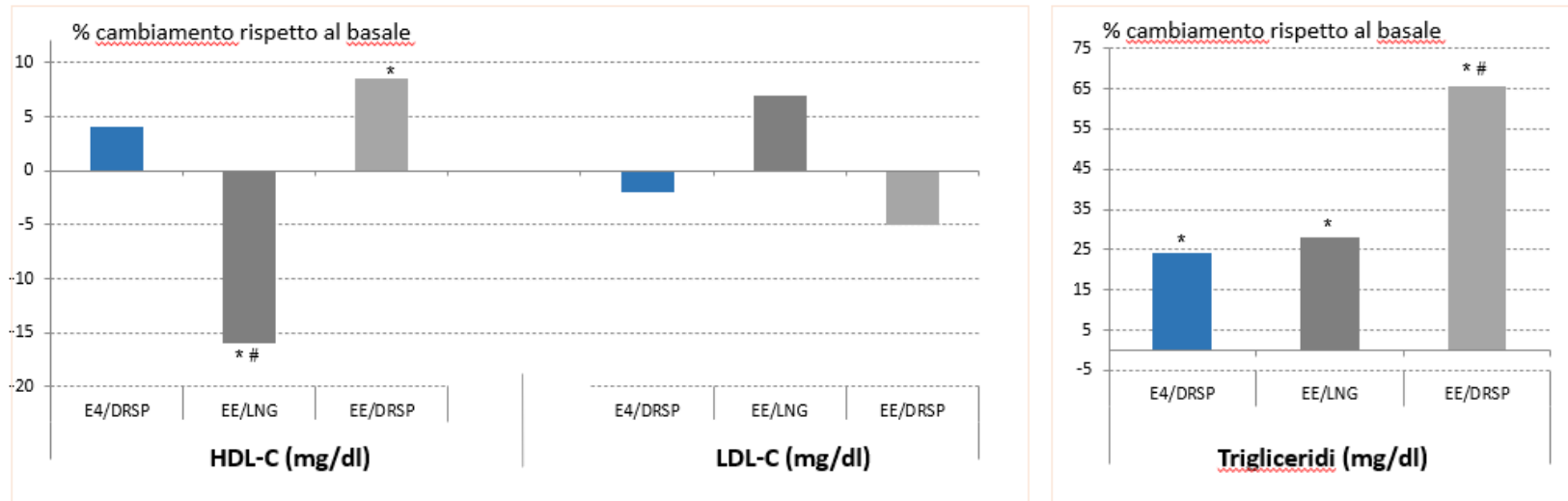


Data shown are median (vertical line in boxes), interquartile range (edges of the boxes) and min-max (lines)

Mawet M, et al. *Eur J Contracept Reprod Health Care*
2015;20:463-75

E4-DRSP METABOLISMO DEI LIPIDI

E4/DRSP PROFILO LIPIDICO NEUTRALE DOPO 6 CICLI DI TRATTAMENTO



E4/DRSP: Estetrol 15 mg/drospirenone 3 mg | EE/LNG: ethinylestradiol 30 µg/ levonorgestrel 150 µg | EE/DRSP: ethinylestradiol 20 µg/ DRSP 3 mg | * different versus baseline, $p < 0.05$ | # different from treatment with E4 15 mg/DRSP 3 mg, $p < 0.05$

Estetrolo (E4): Effetto sugli enzimi epatici

- Effetto trascurabile sui seguenti enzimi del cytP450 (<10%)

Estrogeni a 10 µmol/L	% P450 enzimi				
	CYP1A2	CYP2C9	CYP2C19	CYP2D6	CYP3A4
EE	<10	<10	82	<10	45
E2	19	<10	63	<10	<10
E4	<10	<10	<10	<10	<10

1. Visser M, et al. Climacteric 2008;11(Suppl.1):64–68

E4/DRSP – PARAMETRI EMOSTATICI

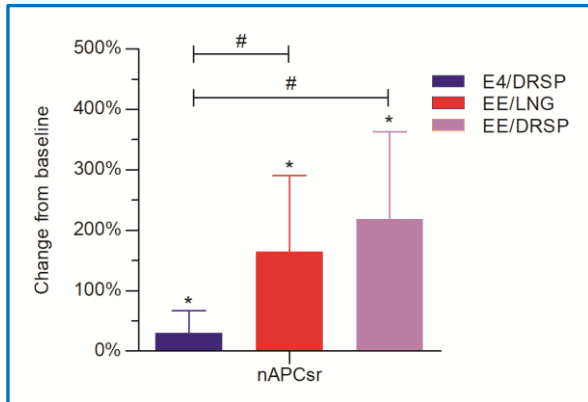
I parametri emostatici sono stati minimamente impattati dalla combinazione E4/DRSP; dose proporzionale cmq rimane bassa con 15 mg E4, molto più bassa rispetto EE/DRSP e in linea con EE/LNG

	Marker of estrogenicity	Global functional coagulation test	Markers of coagulation inhibition		Markers of ongoing coagulation	
	SHBG	APC resistance, ETP-based (nAPCsr)	Protein C activity	Protein S activity	D-dimer	Prothrombin fragment 1+2
5 mg E4/DRSP*	0 (-10; 25)	5 (-7; 29)	-1 (-12; 2)	7 (1; 16)	-26 (-52; -8)	-23 (-32; -17)
10 mg E4/DRSP*	43 (29; 76)	-1 (-13; 54)	-1 (-9; 6)	3 (-4; 17)	-26 (-43; -6)	-3 (-24; 14)
15 mg E4/DRSP**	51.5 (-23; 132) *	39.5 (-19; 117) *	1 (-14; 32)	1 (-22; 33)	0 (-36; 219)	7 (-39; 73)
20 mcg EE/DRSP study 1*	281 (213; 362)	175 (96; 248) §	11 (7; 25) §	-27 (-33; -20) §	27 (1; 54)	63 (31; -93) §
20 mcg EE/DRSP study 2**	239 (128; 608)	229 (91; 781) §	19.5 (-9; 46) §	-26 (-41; -6) §	0 (-46; 93)	47.5 (-6; 187) §
30 mcg EE/LNG**	67 (-10; 313) *	165 (33; 496) * §	12 (-11; 34) * §	2 (-32; 59) *	0 (-65; 59)	62 (2; 125) §

*p<0.05 vs EE/DRSP; § p<0.05 vs E4/DRSP

E4/DRSP – RESISTENZA ALLA PROTEINA C ATTIVATA

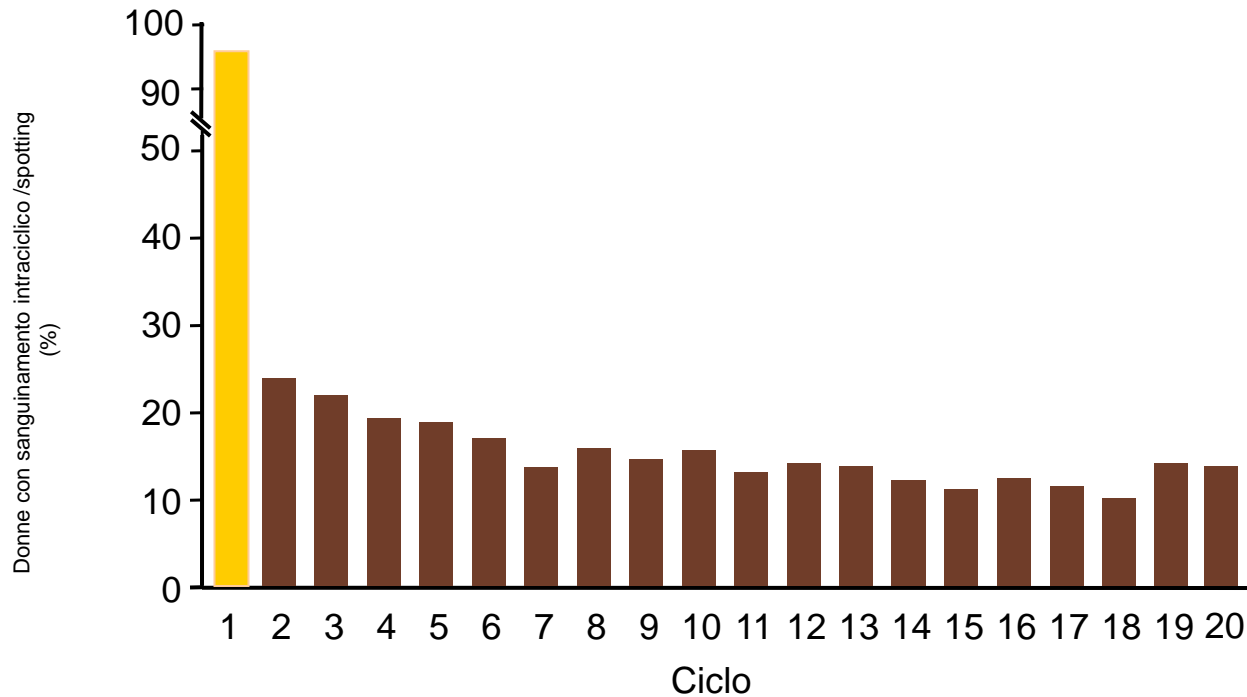
L'INNALZAMENTO dell' APC RESISTANCE solitamente CORRELA CON POSSIBILE INNALZAMENTO DI SHBG. Sia L'INNALZAMENTO DI APCr che delle SHBG POTREBBE ESSERE INDICATIVO DI POSSIBILE AUMENTATO RISCHIO TEV.



Incremento di APCr significativamente inferiore a EE/LNG e EE/DRSP

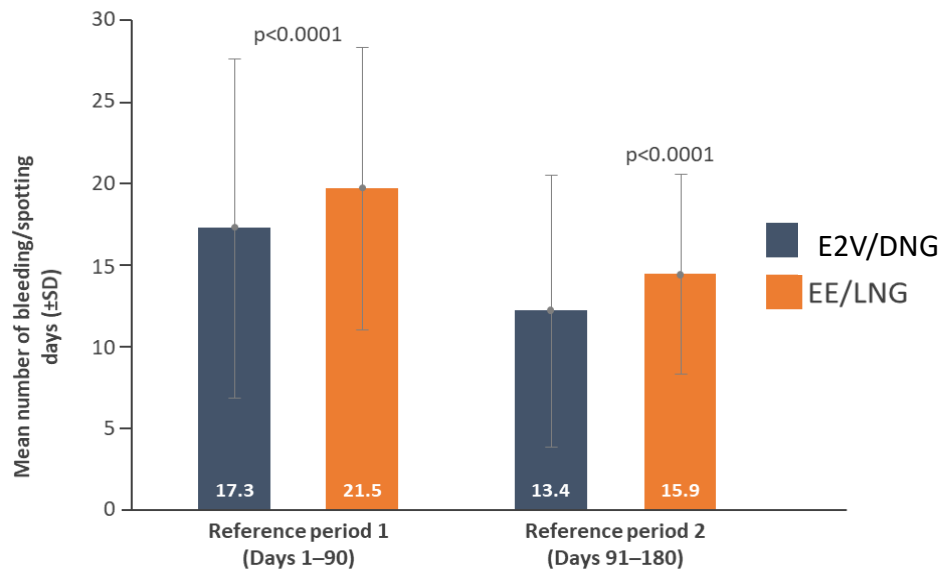
Il minimo aumento della **APCsr** con E4/DRSP è probabilmente il risultato della bassa potenza estrogenica dell'E4, in quanto DRSP, come progestinico antiandrogenico, non è in grado di contrastare gli effetti dell'estrogeno, come evidente dall'aumento di APC resistance con EE/DRSP

Fare clic per modificare lo stile del titolo dello schema



Fare clic per modificare stile

Giorni di sanguinamento/episodi di spotting durante il trattamento con E₂V/DNG e EE/LNG



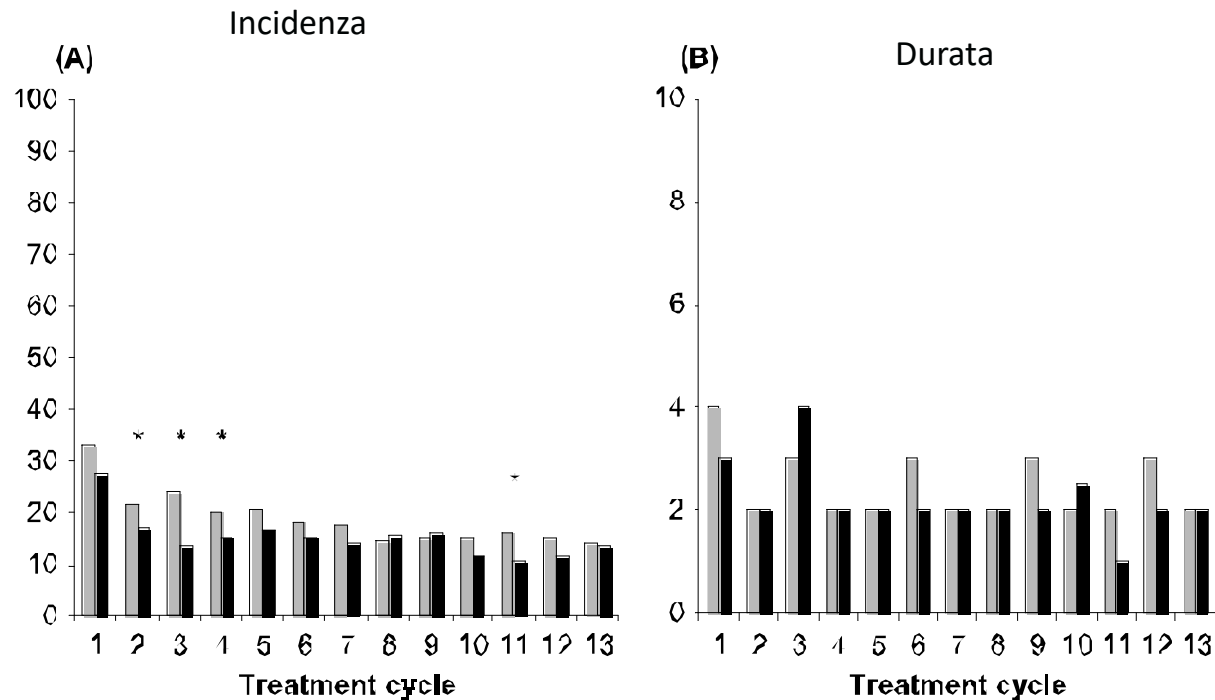
Complessivamente, le donne che assumono E2V/DNG hanno riportato un minor numero di giorni di sanguinamento e/o episodi di spotting rispetto alle donne con EE/LNG

COC – combined oral contraceptive; EE/LNG – ethinyl estradiol/levonorgestrel; SD – standard deviation.
1. Ahrendt HJ, et al. Contraception 2009;80(5):436–444

E2 1.5 mg /NOMAC 2.5 mg

CONTROLLO DEL CICLO

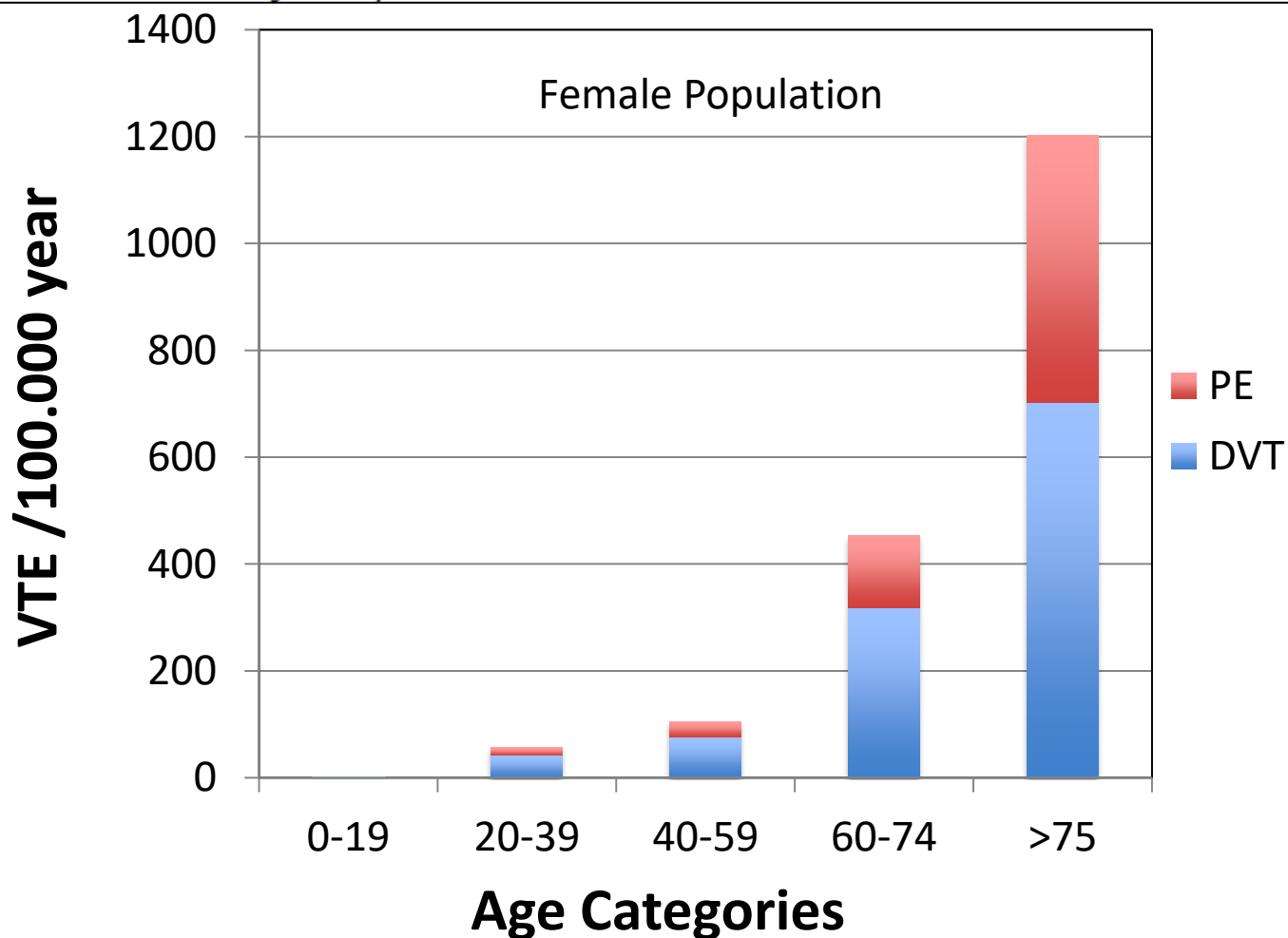
BTB-spotting for Nomac E2 (grey) or EE/DRSP (black)



Mansour et al. Eur J Contr Reprod 2011

Incidence of Venous Thromboembolism: A Community-based Study in Western France

Emmanuel Oger
for the EPI-GETBO Study Group*

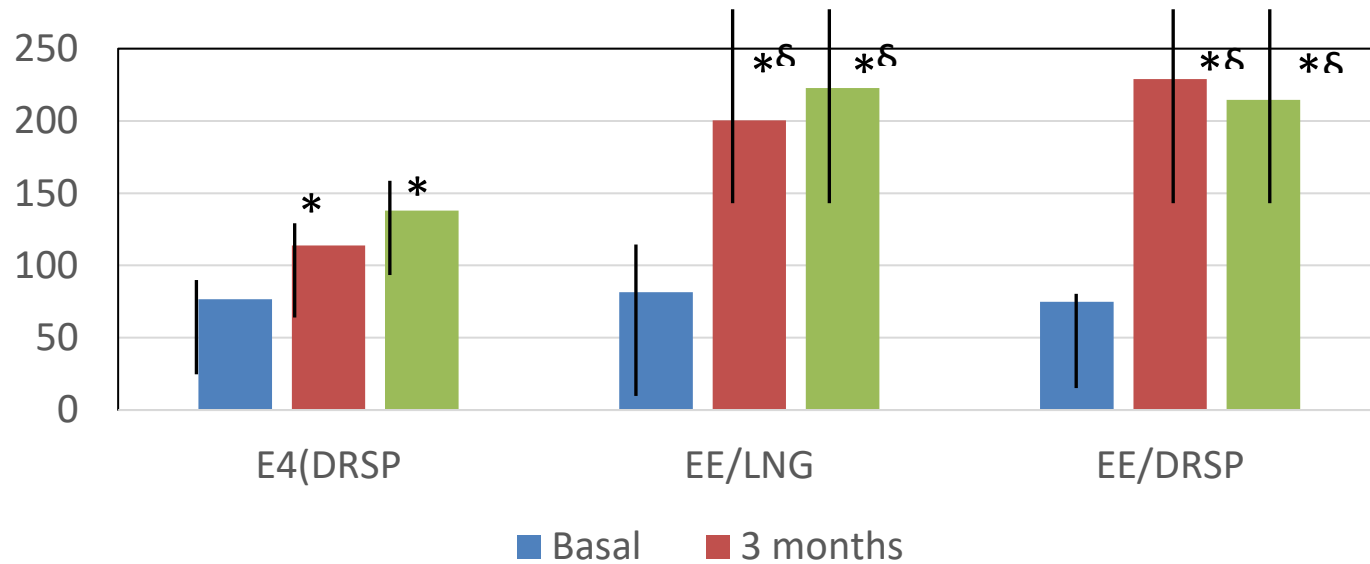


In che modo influisce la scelta dell'estrogeno nel contraccettivo e come orientarsi?

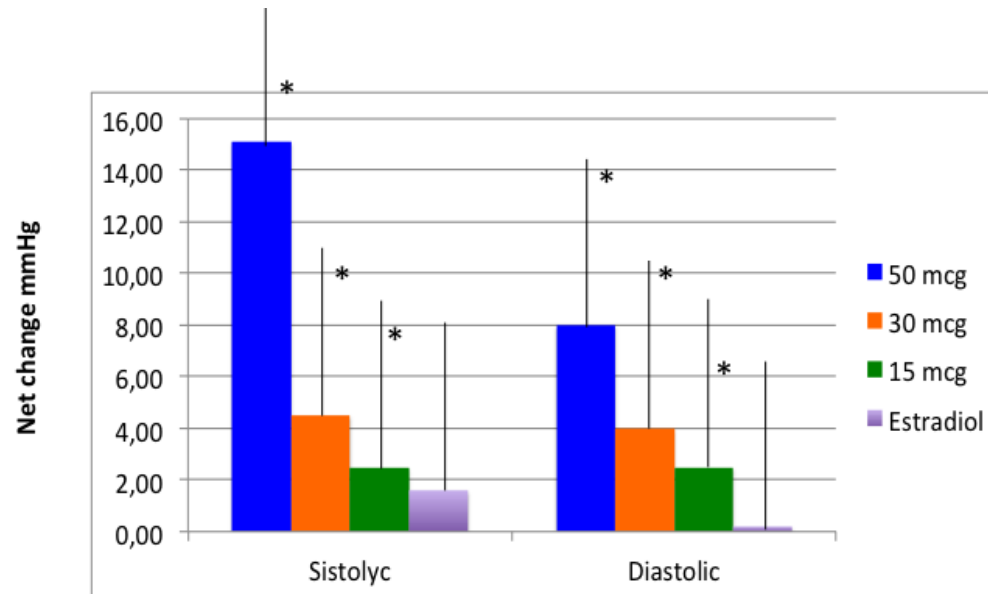
- Regolizzazione dei sanguinamenti
- Aumento dell'inibizione gonadotropinica (FSH)
- Supporto estrogenico in caso di carenza
- Personalizzazione della Contraccezione

Incremento dell' Angiotensinogeno

Incremento di angiotensinogeno < 50% rispetto agli altri gruppi



Quali caratteristiche distintive di estetrol?



Weir et al, 1974, Godsland et al. 1995, Cagnacci et al. 2013, Cagnacci et al. 2014

Estrogeni e mammella

17 β estradiolo

- Azione su ER α e ER β
- Stimola Ers nucleari e di membrana
- Metabolizzato da CYP450metaboliti idrossilati

Estetrolo

- Azione su ER α , affinità minore di E2
- Antagonist action on membrane ERs
 - No stimulatory activity through membrane ERs
 - Block E2 action at this level
- No metabolizzato da CYP450
- No produzione metaboliti idrossilati

Visser M, 2008

Coelingh Bennink, H.J., 2008;

Abot A, 2014

Abot A, 2014

Alcuni metaboliti idrossilati sono cancerogeni

Yager JD., 2015

Abot A, et al. The uterine and vascular actions of estetrol delineate a distinctive profile of estrogen receptor alpha modulation, uncoupling nuclear and membrane activation. EMBO Mol Med.6(10):1328-46, 2014.

Coelingh Bennink HJ et al, Estetrol review: profile and potential clinical applications., Climacteric. 11 Suppl 1:47-58. 2008

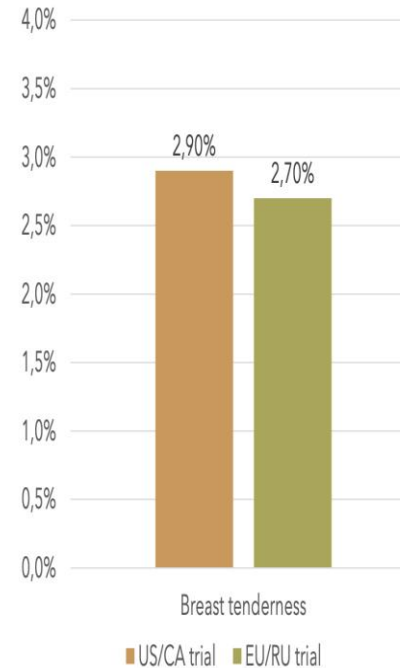
Yager JD. Steroids. 2015 Jul;99(Pt A):56-60

Impatto sulla mammella : tensione mammaria

- E4/DRSP Phase 3 trials pooled data
- 3417 participants
- Designed to capture ALL breast complaints
- Breast pain or tenderness: 4.0% overall
 - 136 participants with complaint (4.0%)
 - ~75% in first 3 cycles
 - Rated severe in 3 participants (0.09%)
 - # affected cycles: 561 (1.6 cycles in participants with complaint)
 - Discontinuation for breast tenderness: 8 (0.2%) participants
 - Discontinuation for *any* breast complaint: 11 (0.3%) participants

Chen MJ, et al. Contraception 2022;116:44-50.

Difficile confronto con altri studi



Clinical trial publications

- Reported events $\geq 2\%$
- "Breast tenderness" reported

Creinin MD, et al. Contraception 2021;104:222-8.
Gemzell-Danielsson K, et al. BJOG 2022;129:63-71.

Estetrol effect on breast cancer in humans

E4 has a pro-apoptotic effect in humans

- Double-blinded, randomized, placebo controlled, proof-of-concept study
- 15 post- and 15 premenopausal women with ER+ breast cancer
- Preoperative treatment for 14 days with E4 20 mg daily or placebo immediately followed by surgery
- Effect of E4 on tumor biology (Ki67 and apoptosis)

20 mg E4 increases the number of apoptotic cells in 30 women in pre and post-menopause with early breast cancer ER+ administered for 2 weeks before surgery

The increases in the number of apoptotic cells significantly different from placebo ($p < 0.005$)

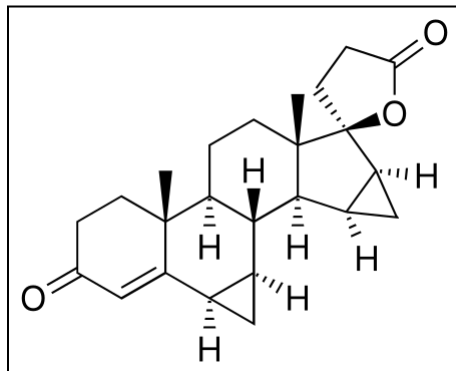
No change in proliferation (Ki67)

Singer CF, Bennink HJ, Natter C, Steurer S, Rudas M, Moïnfar F, Appels N, Visser M, Kubista E.
Antiestrogenic effects of the fetal estrogen estetrol in women with estrogen-receptor positive early breast cancer.
Carcinogenesis 2014;35):2447-51

Singer CF, 2004

Quale è il miglior risvolto clinico che secondo lei il drospirenone garantisce alla donna?

Drospirenone



Inhibition of Ovulation 2 mg

Half Life 25-33 hours

70% affinity of P to PR

30% affinity of CPA to AR

0% affinity of DXM to GR

0% affinity to ER

230% affinity of A to MR

Anti-androgenic properties

4 mg DRSP=33 mg spironolactone
Anti-hypertensive; Reduces coagulation
PAI-I reduction

Quale è il miglior risvolto clinico che secondo lei il drospirenone garantisce alla donna?

DRSP

Proprietà Anti-Androgeniche

Non Aumenta Resistenza all'Insulina

Effetto Diretto

No effetto

Riduzione

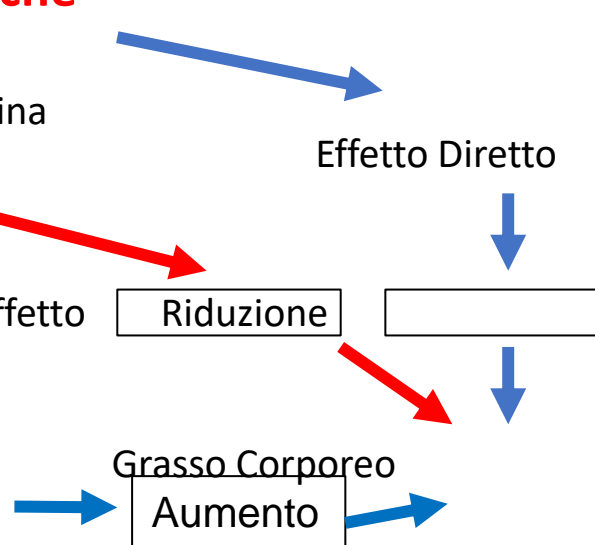
Aumenta Resistenza Insulina

Grasso Corporeo

Aumento

Proprietà Androgeniche

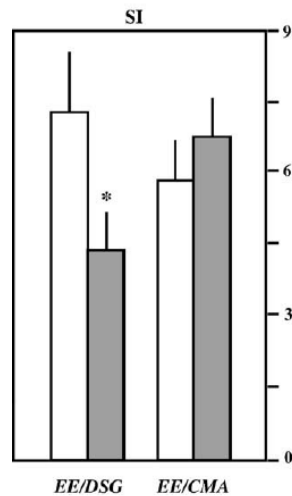
DSG



Original research article

Insulin sensitivity and lipid metabolism with oral contraceptives containing chlormadinone acetate or desogestrel: a randomized trial^{☆,☆☆}

Angelo Cagnacci*, Serena Ferrari, Alessandra Tirelli, Renata Zanin, Annibale Volpe



Contraception 79 (2009) 111–116

Influence of an oral contraceptive containing drospirenone on insulin sensitivity of healthy women[☆]

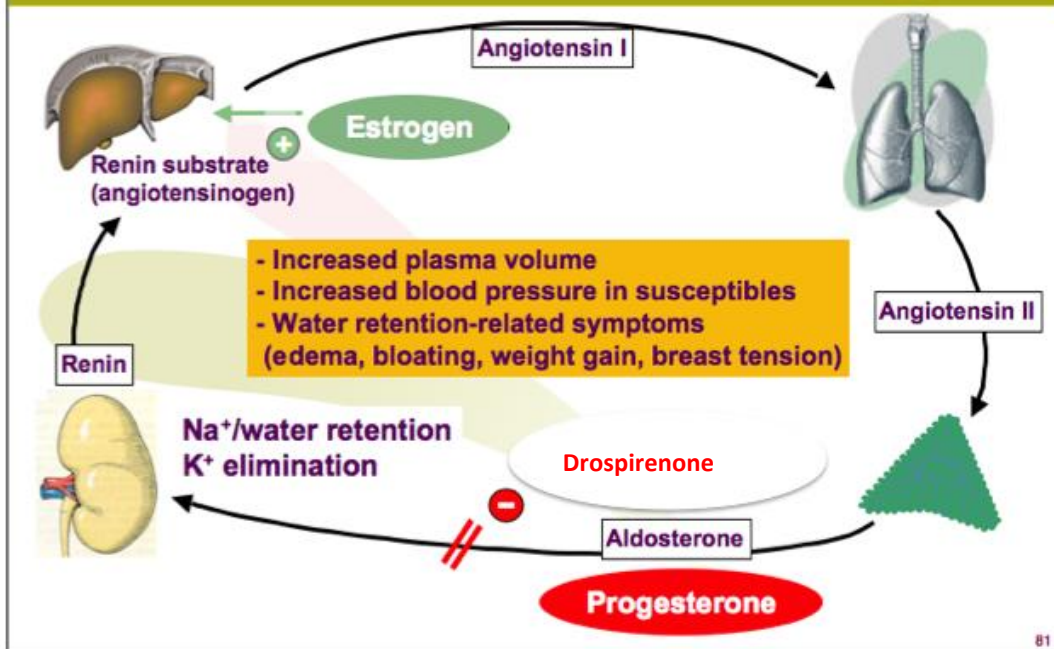
Angelo Cagnacci*, Ilaria Piacenti, Renata Zanin, Anjeza Xholli, Alessandra Tirelli

Glucose metabolism, insulin sensitivity and lipid profile before after oral contraceptive pill containing drospirenone parameters.

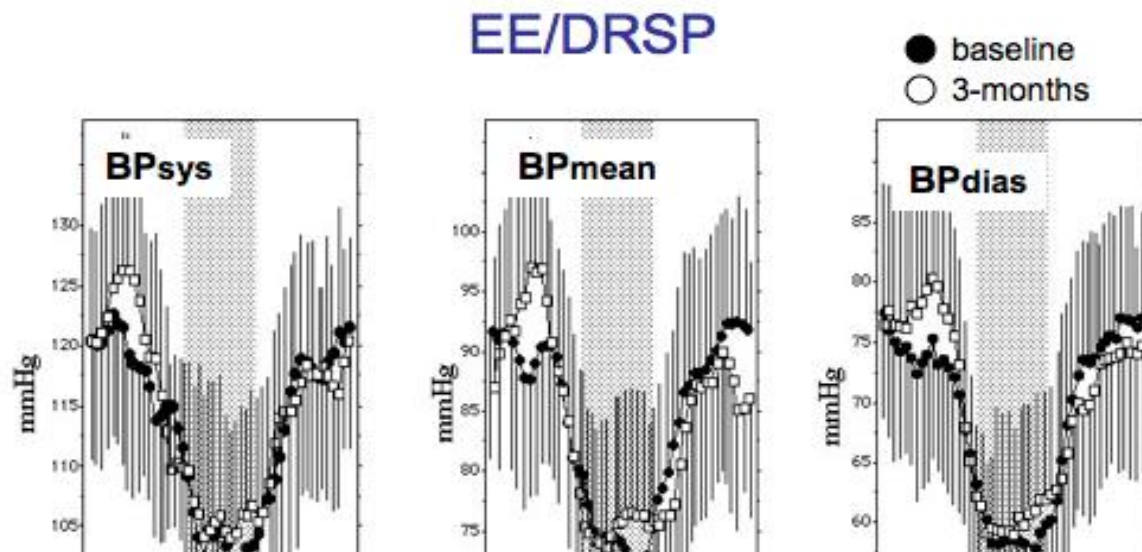
Parameters	Pretreatment	Posttreatment	Net difference	P
Glucose mg/dL	80.7 ± 6.9	80.7 ± 12.4	0.00 ± 10.8	0.99
Insulin mU/mL	10.6 ± 8.2	8.2 ± 2.6	−2.3 ± 7.9	0.33
HOMA-IR	2.2 ± 1.7	1.7 ± 0.76	−0.5 ± 1.7	0.34 ^a
SI	3.7 ± 2.6	3.29 ± 2.93	0.2 ± 3.9	0.73

European journal of Obstetrics & Gynecology and Reproductive Biology 178 (2014) 48–50

Renin-angiotensin-aldosterone system (RAAS)



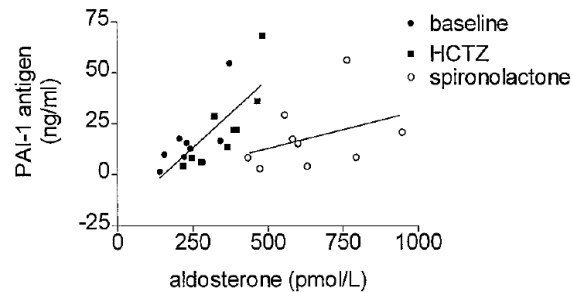
Quale è il miglior risvolto clinico che secondo lei il drospirenone garantisce alla donna?



Effetti Anti-Coagulanti del DRSP

Spironolactone Abolishes the Relationship between Aldosterone and Plasminogen Activator Inhibitor-1 in Humans

PAIRUNYAR SAWATHIPARNICH, SANDEEP KUMAR, DOUGLAS E. VAUGHAN, AND NANCY J. BROWN

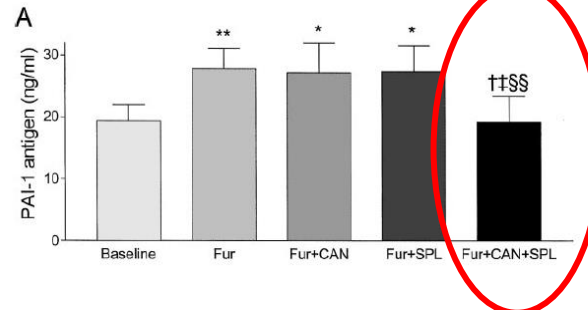


J Clin Endocrinol Metab, February 2002, 87(2):448-452

PAI-1 increases coagulation

Effect of Combined AT₁ Receptor and Aldosterone Receptor Antagonism on Plasminogen Activator Inhibitor-1

PAIRUNYAR SAWATHIPARNICH, LAINE J. MURPHEY, SANDEEP KUMAR, DOUGLAS E. VAUGHAN, AND NANCY J. BROWN



J Clin Endocrinol Metab, August 2003, 88(8):3867-3873

ORIGINAL ARTICLE

Drospirenone as estrogen-free pill and hemostasis: coagulatory study results comparing a novel 4 mg formulation in a 24 + 4 cycle with desogestrel 75 µg per day

Pedro Antonio Regidor^{1,2}, Enrico Colli³, and Adolf E. Schindler⁴

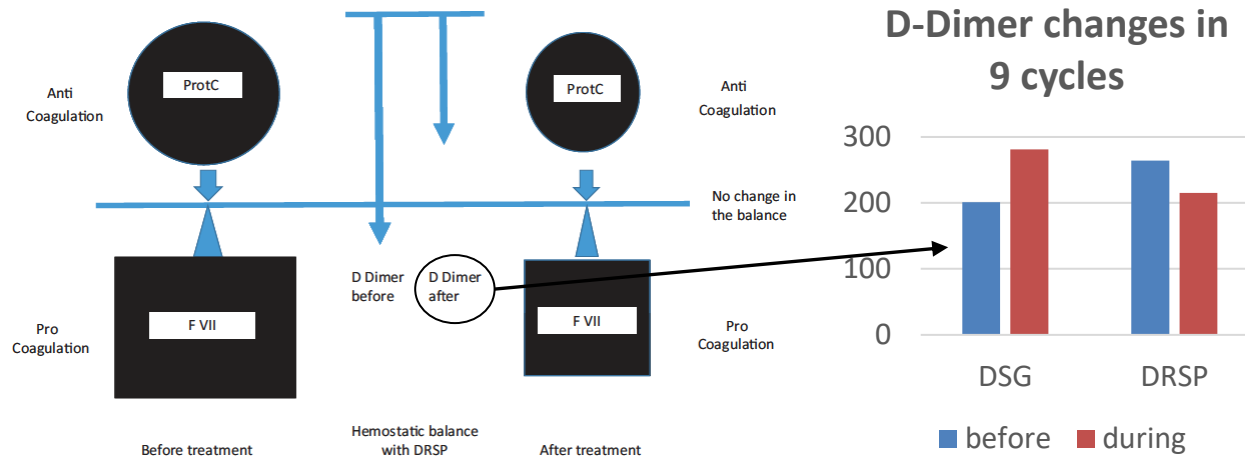


Figure 2. Balance of hemostasis after treatment with 4 mg drospirenone (DRSP).

The oral contraceptive containing 30 µg of ethinylestradiol plus 3 mg of drospirenone is able to antagonize the increase of extracellular water occurring in healthy young women during the luteal phase of the menstrual cycle: an observational study²⁵

Franca Fruzzetti^{a,*}, Stefano Lello^b, Veronica Lazzarini^a, Stefania Fratta^b, Marisa Orrù^b, Roberto Sorge^c, Luigi Minerba^d, Cabiria Ricci^a, Andrea Riccardo Genazzani^a, Gian Benedetto Melis^b, Anna Maria Paoletti^b

^aDepartment of Obstetrics and Gynecology, University of Pisa, 56100 Pisa, Italy

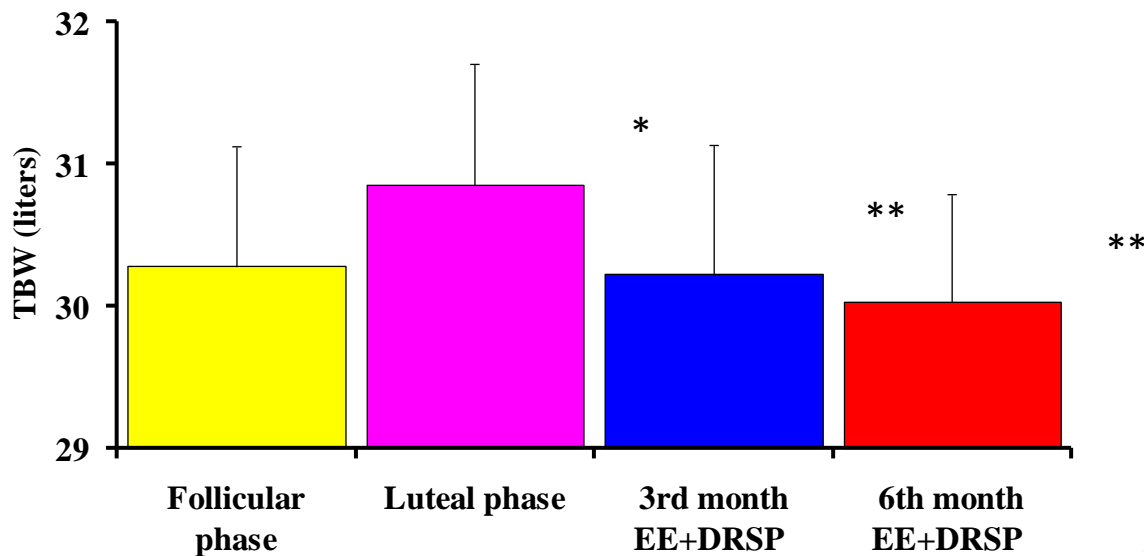
^bDepartment of Obstetrics and Gynecology, University of Cagliari, 09128 Cagliari, Italy

^cLaboratory of Biometry, University of Tor Vergata, Rome, 00133 Rome, Italy

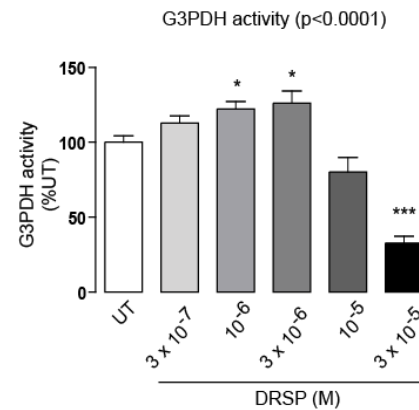
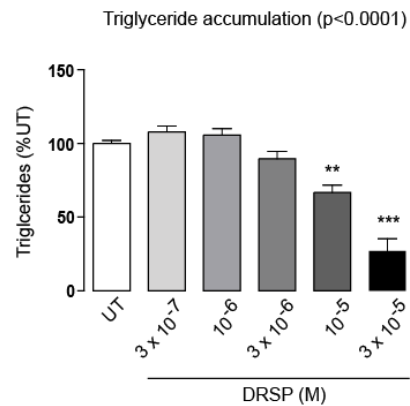
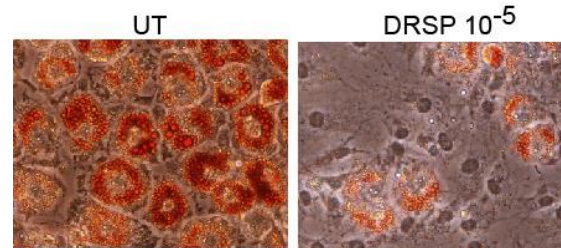
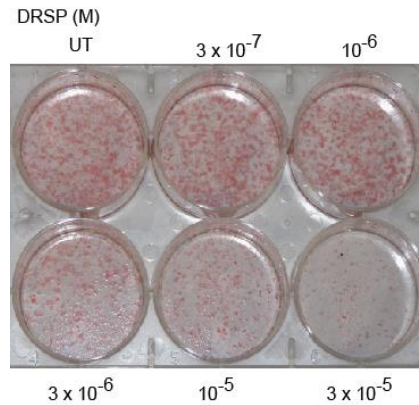
^dDepartment of Hygiene, University of Cagliari, 09124 Cagliari, Italy

Received 8 September 2006; revised 23 October 2006; accepted 30 October 2006

Total Body Water



Drospirenone inhibisce accumulo di trigliceridi nel tessuto adiposo



Caprio et al. European Heart Journal – Abstract supplement – Sept 2008



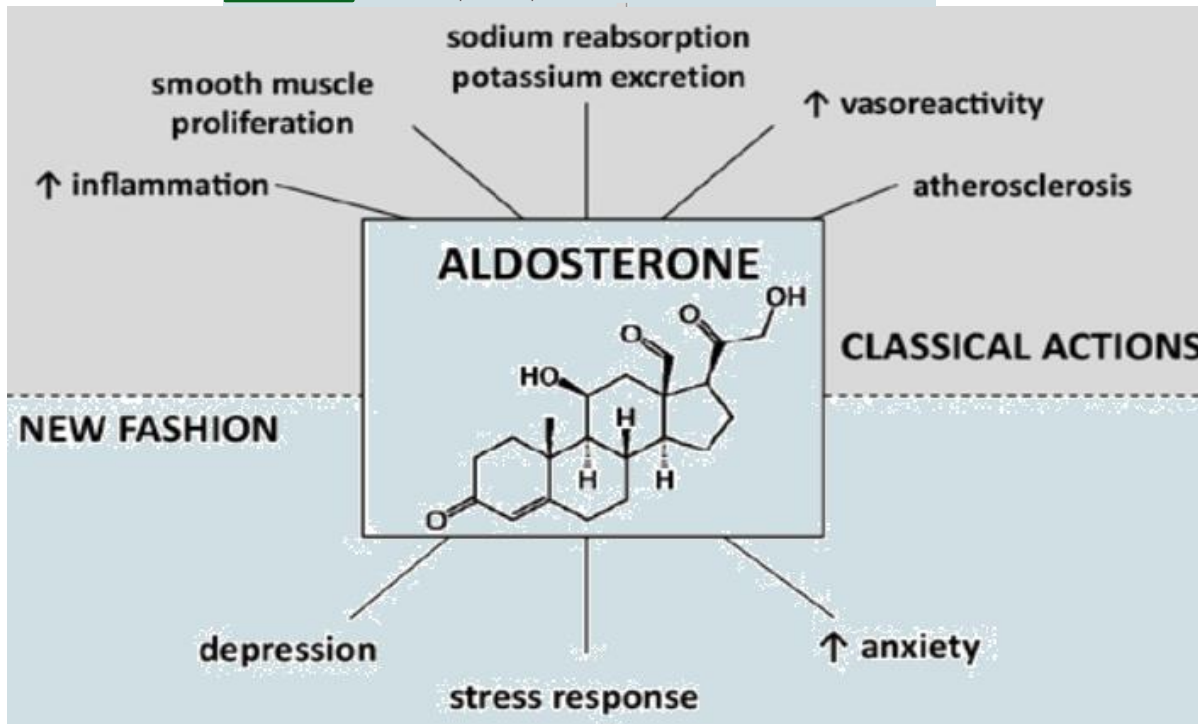
Review Article

Classical Steroids in a New Fashion: Focus on Testosterone and Aldosterone

Author(s): Daniela Jezova*, Lucia Balagova, Magdalena Chmelova and Natasa

Hlavacova

Volume 20 , Issue 11 , 2019





The potential pathophysiological role of aldosterone and the mineralocorticoid receptor in anxiety and depression – Lessons from primary aldosteronism

Harald Murck^a, Lena Schlageter^b, Anna Schneider^b, Christian Adolf^b, Daniel Heinrich^b, Marcus Quinkler^c, Felix Beuschlein^b, Martin Reincke^b, Heike Künzel^{b,*}

Depression

H. Murck et al.

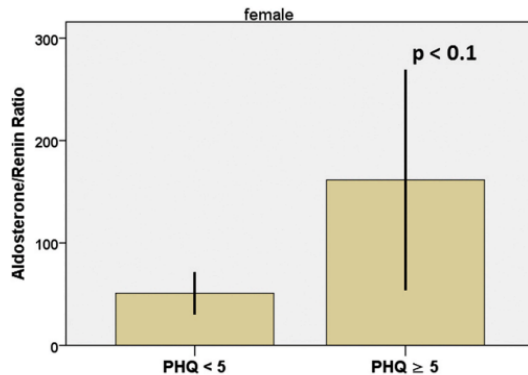


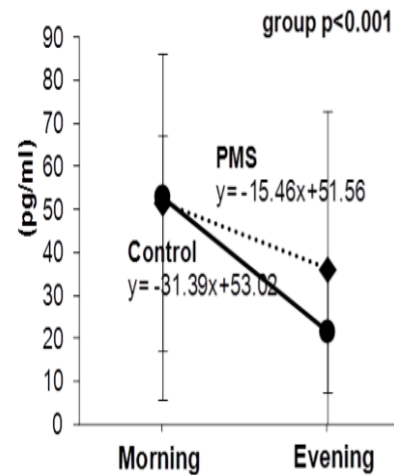
Fig. 1. Aldosterone/Renin Ratio in subjects with and without depressive symptom of depression.

Steroid stress hormone changes throughout the menstrual cycle: A rise in evening aldosterone concentration in early luteal phase precedes the symptoms of premenstrual syndrome

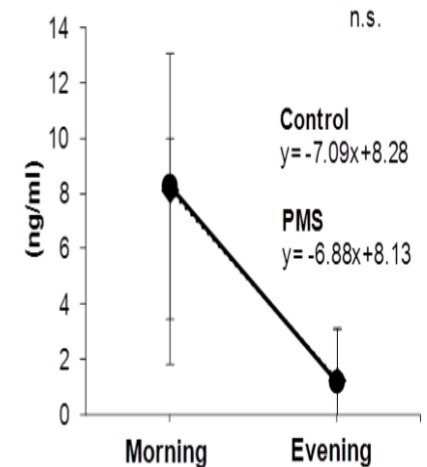
Lubomira Izakova¹, Natasa Hlavacova², Daniela Jezova²

Donne con PMS

(A) Salivary aldosterone



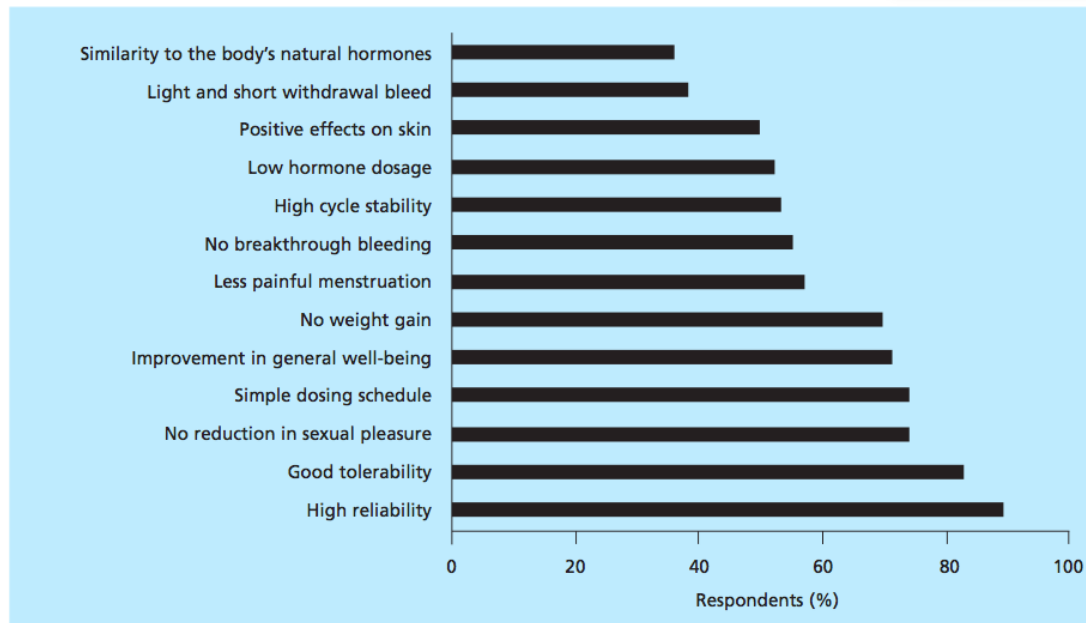
(B) Salivary cortisol



Età riproduttiva

Risultati di una survey in donne in età riproduttiva

Quali sono le qualità importanti di un contraccettivo ormonale?



Naturalezza

Leggerezza, bassi dosaggi

Controllo ciclo accettabile, simile
a COCs 20 mcg EE/DRSP

No aumento del peso

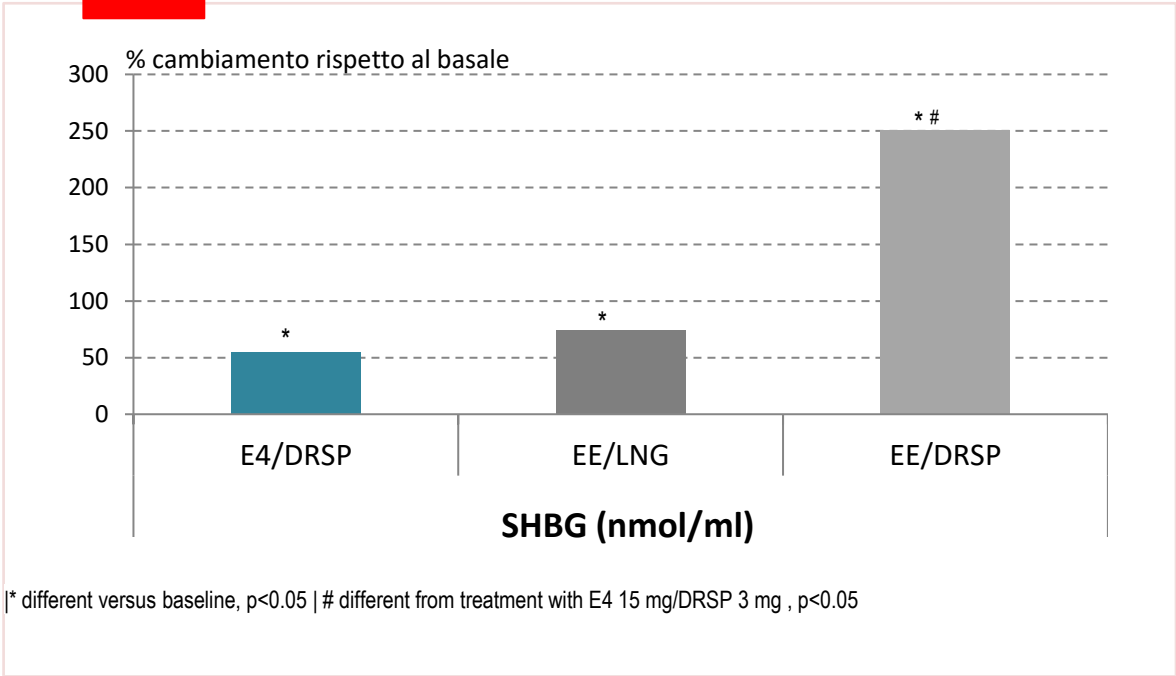
Ben tollerato

Hans-Joachim Ahrendt, 2009

Donne che riportano calo della libido durante uso del contraccettivo

E415 mg/DRSP3mg - SHBG . Confronto vs 30 EE/LNG e 20 EE/DRSP

SHBG



Modificazioni Testosterone Libero

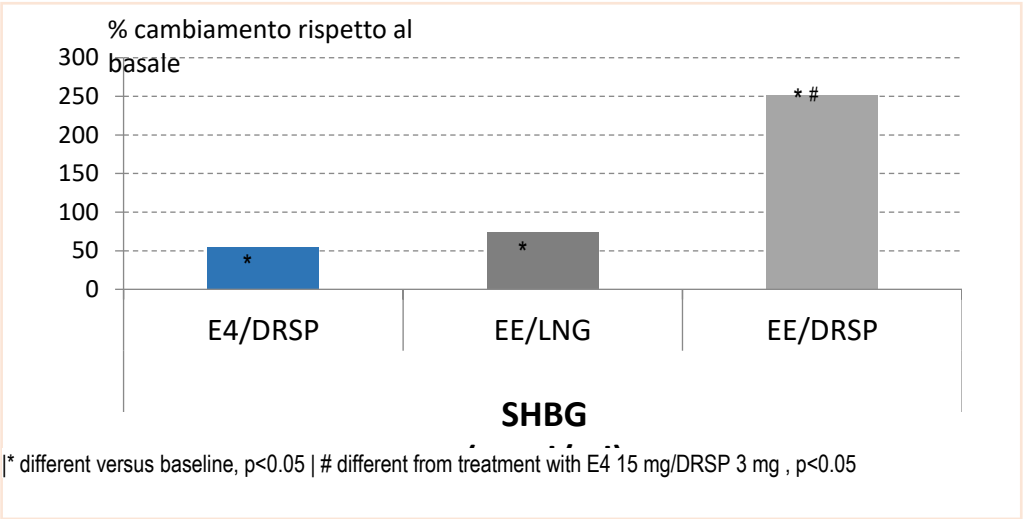
	Modificazioni vs basale -3^ mo	Modificazioni vs basale -6^mo
E4/DRSP	-50*	-50*
EE/LNG	-60*	-50*
EE/DRSP	-75*	-71*

*p<0.05 vs basale



Donna con sindrome dell'ovaio policistico

E415 mg/DRSP3mg - variazioni SHBG inferiori ad altri COCs



Klipping C et al. Contraception 2021

E415 mg/DRSP3mg - safety metabolica

Modificazioni Testosterone Libero

	Modificazioni vs basale -3^ mo	Modificazioni vs basale -6^mo
E4/DRSP	-50*	-50*
EE/LNG	-60*	-50*
EE/DRSP	-75*	-71*

*p<0.05 vs basale

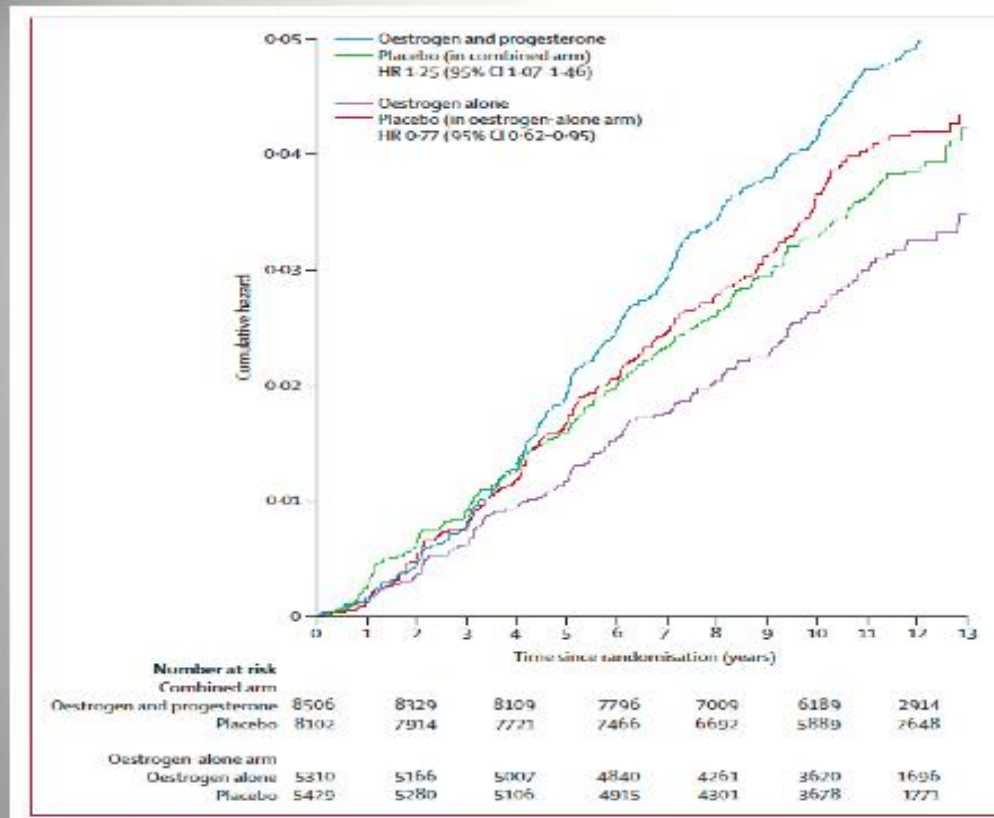


Klipping C et al. Contraception 2021

Interruzione per peggioramento acne: 0.8%

Chang JM, 2022

Estrogens and Breast Cancer



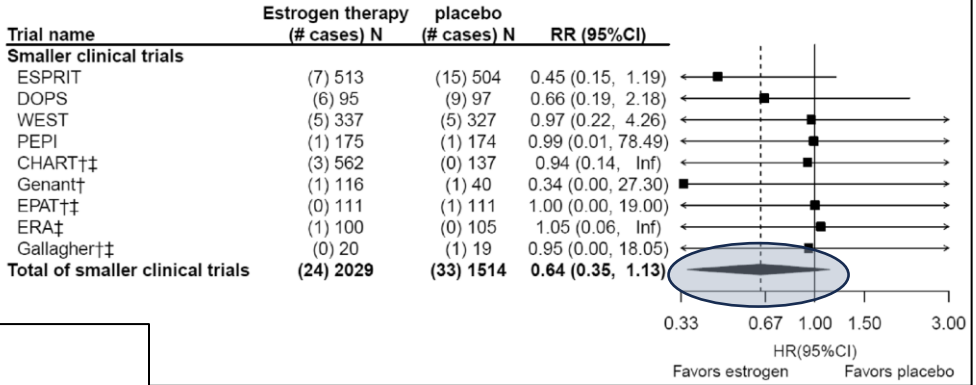
Anderson et al., Lancet Oncology 2012

RESEARCH

Randomized trials of estrogen-alone and breast cancer incidence: a meta-analysis

Rowan T. Chlebowski¹ · Aaron K. Aragaki² · Kathy Pan³ · Joanne E. Mortimer⁴ · Karen C. Johnson⁵ · Jean Wactawski-Wende⁶ · Meryl S. LeBoff⁸ · Sayeh Lavasani⁴ · Dorothy Lane⁷ · Rebecca A. Nelson⁴ · JoAnn E. Manson⁸

Without WHI



With WHI

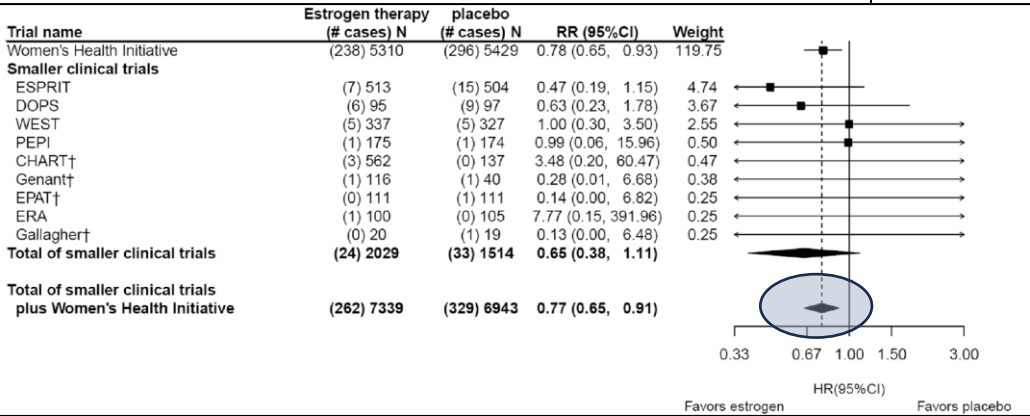


Table S18: Trials of oestrogen-progestagen hormone therapy (O+P HT) versus placebo

Trial name and year published (refs on p14)	Mean age at entry	Approximate years in trial and later FU	Cancers in HT group	Cancers in control group	Relative risk, RR (95%CI) with 99% CI for total	Weight, 1/var of $\log_e(RR)^*$	Weight times $\log_e(RR)$
PEPI 1995 ⁶³	~55	3+0	6/526, in 3 groups	1/174	-	1.3**	0.8**
WISDOM 2007 ⁶⁷	63	1+0	5/2196	7/2189	-	3.0**	-1.0**
HERS 1998 ⁶⁴	67	4+0	32/1380	25/1383	1.30 (0.77-2.19)	14.1	3.7
DOPS 2012 ⁶⁸ (open control)	50	10+6	18/407	17/407	1.05 (0.54-2.04)	8.7	0.5
Subtotal / mean in smaller trials [†]	60	6+2	57/4158 [‡]	50/4153	1.14 (0.78-1.65), z= 0.8; 2p=0.44	27.1	4.0
WHI trial of O+P HT vs placebo ^{60, 62}	63	5.6+8 [§]	434/8506	323/8102	1.28 (1.11-1.48), z= 3.4; 2p=0.001	185.7	45.8
WHI O+P trial plus the smaller trials	63	5.6+7	491/12,664	373/12,255	1.26 (1.10-1.45), z= 3.41; 2p=0.001; 99% CI 1.06-1.51	212.8	49.8

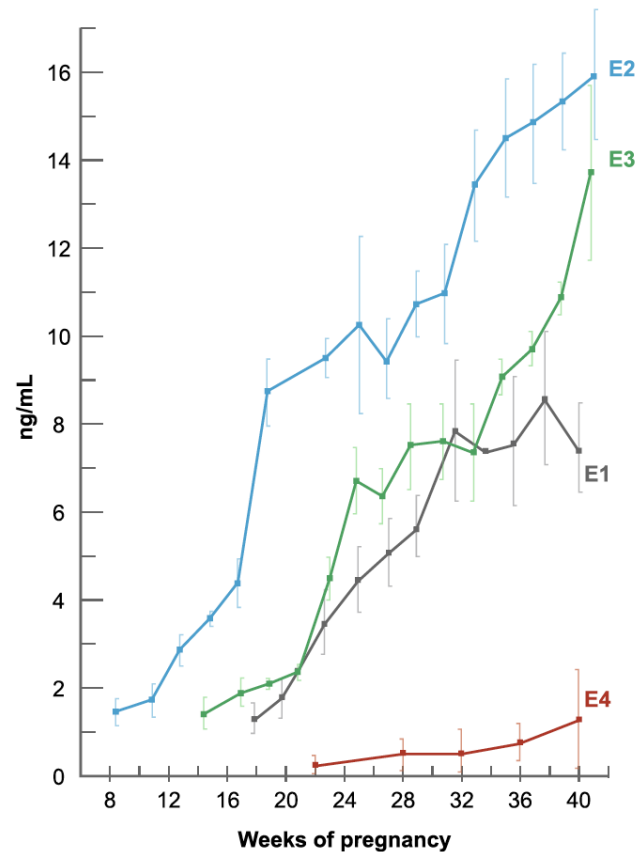
PERSPECTIVE

Open Access



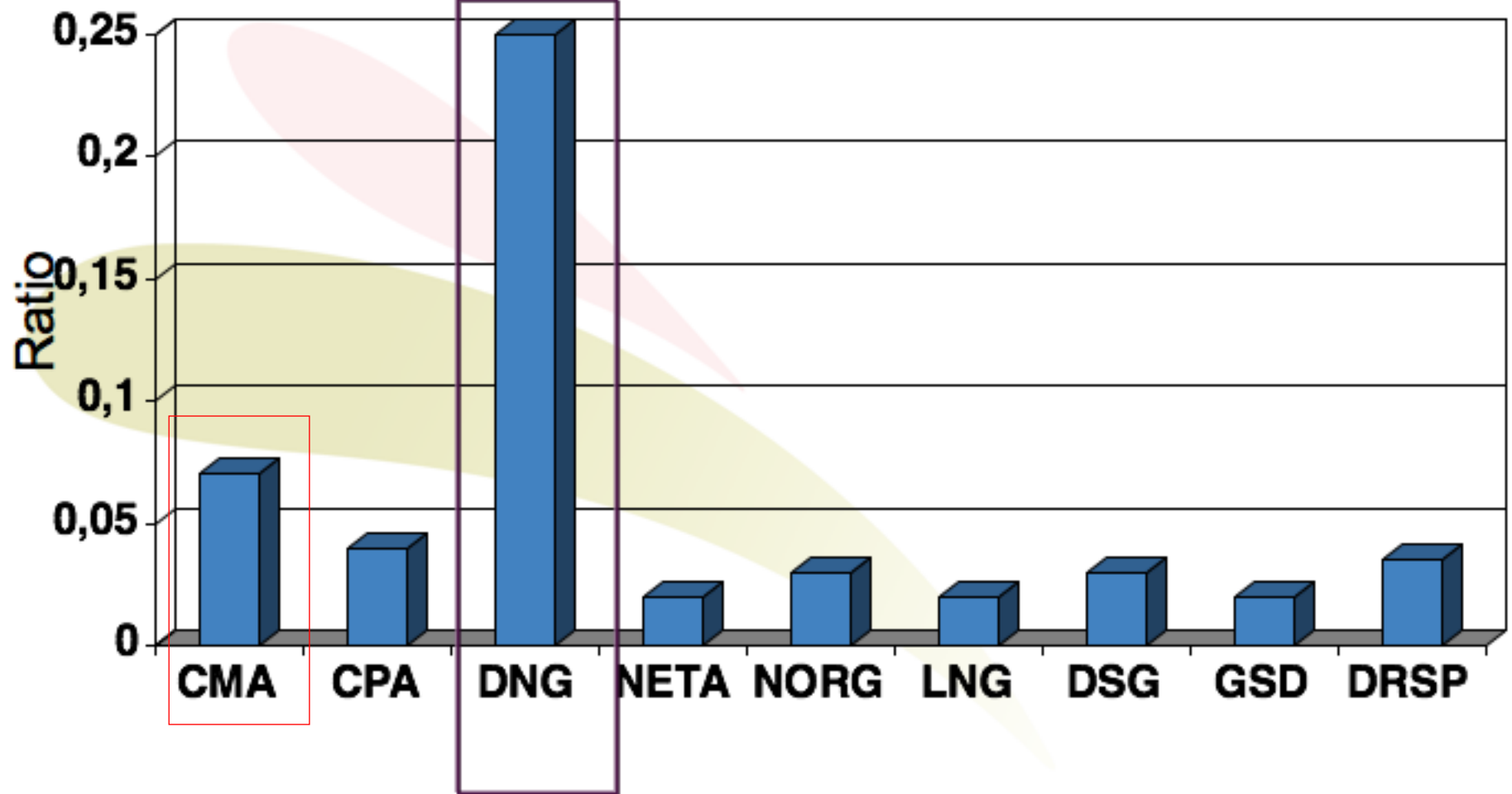
Progesterone from ovulatory menstrual cycles is an important cause of breast cancer

Herjan J. T. Coelingh Bennink^{1*}, Iman J. Schultz¹, Marcus Schmidt², V. Craig Jordan³, Paula Briggs⁴, Jan F. M. Egberts⁵, Kristina Gemzell-Danielsson⁶, Ludwig Kiesel⁷, Kirsten Kluivers⁸, Jan Krijgh¹, Tommaso Simoncini⁹, Frank Z. Stanczyk^{10†} and Robert D. Langer^{11†}

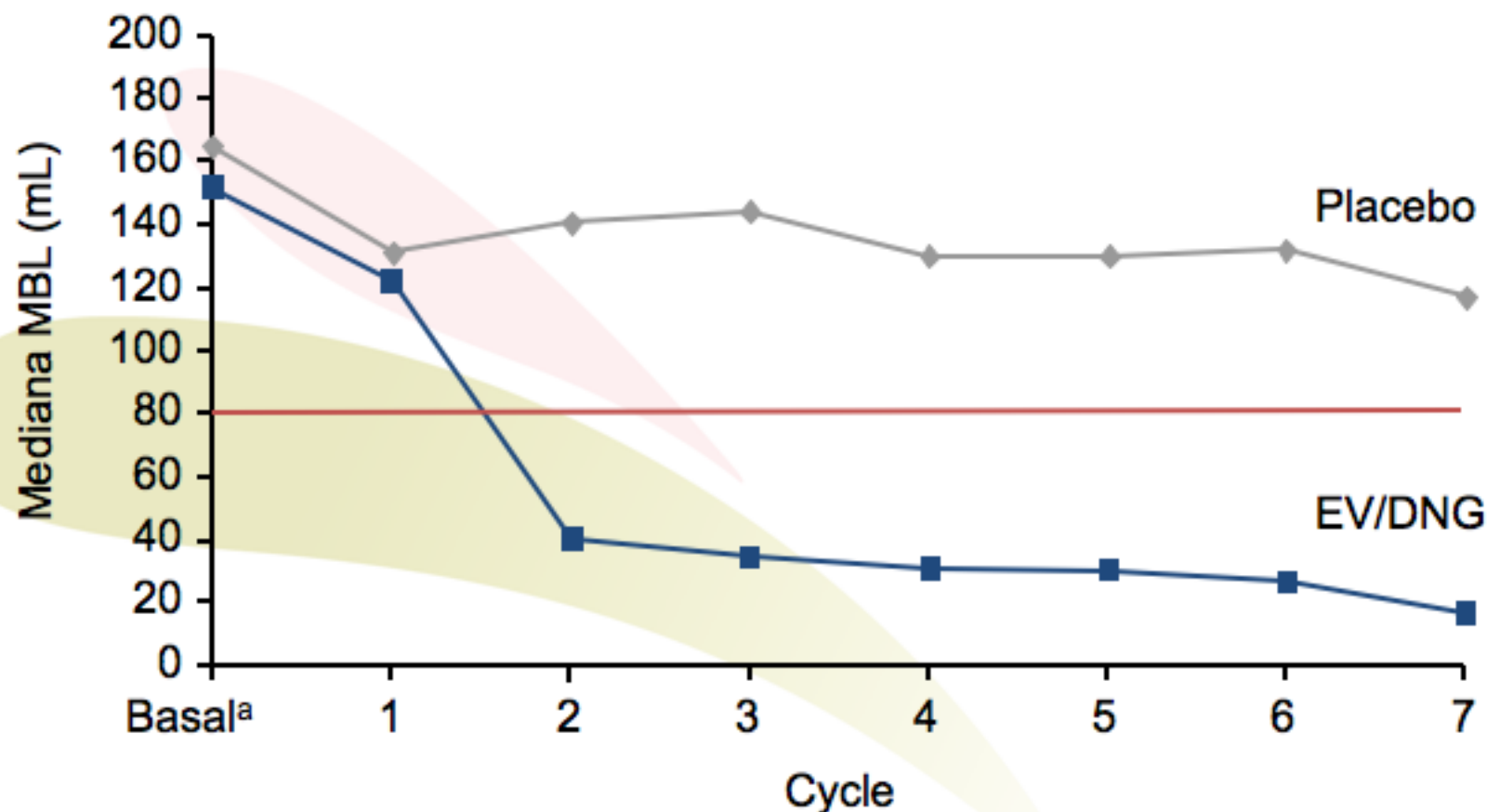


Progestogenic Potency

Ratio of daily dose for
ovulation inhibition/endometrial transformation

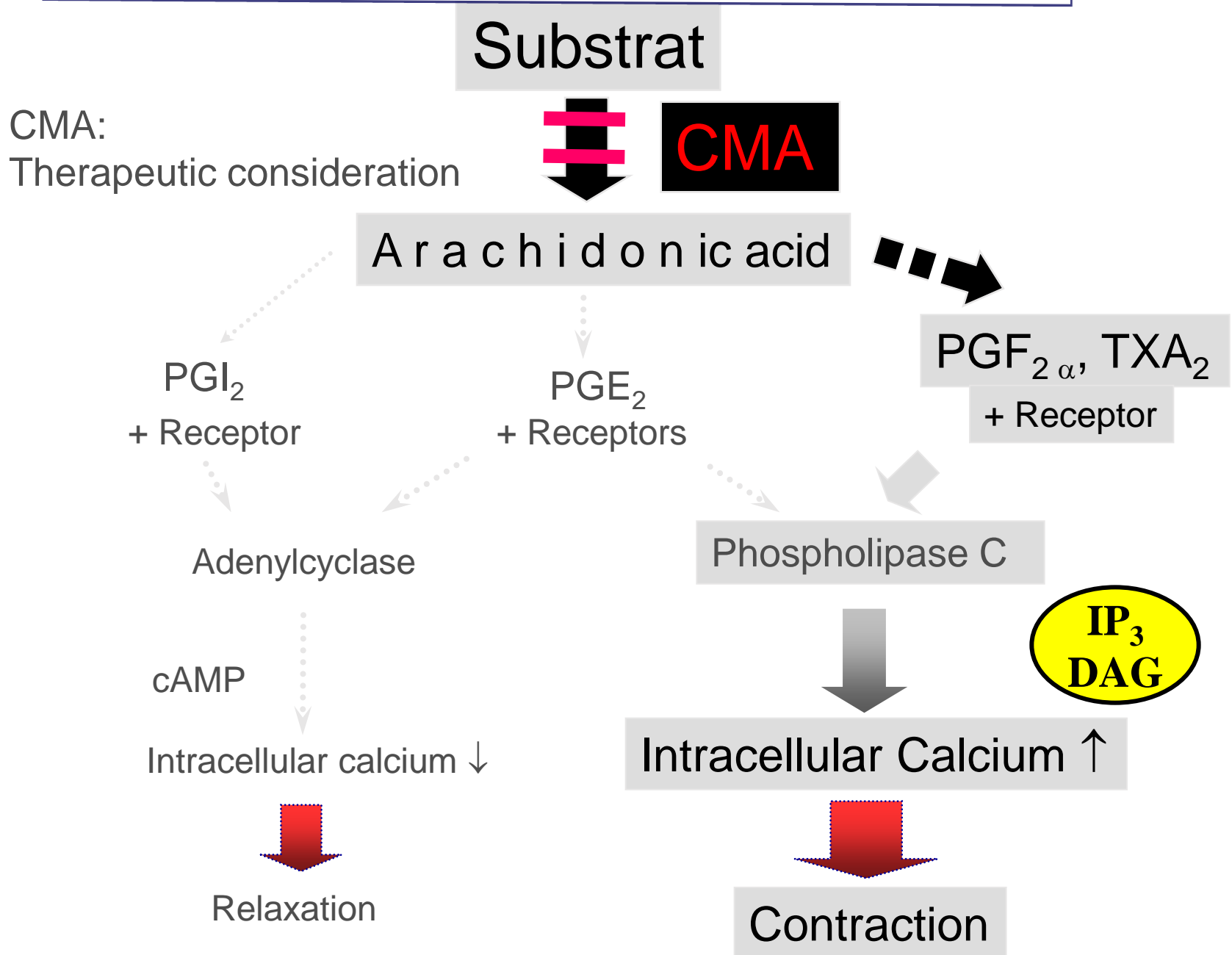


Median Blood Loss per Cycle



^aFor comparative purposes, baseline calculated as one-third of median MBL during 90-day run-in period. ITT population excluding missing data patients. $P < 0.0001$ for reduction in MBL between run-in and efficacy periods.

Dysmenorrhea and COC with CMA



Mortality in COVID-19 among women on hormone replacement therapy: a retrospective cohort study

Hajira Dambha-Miller¹, William Hinton², Christopher R. Wilcox^{1,*}, Mark Joy², Michael Feher², Simon de Lusignan^{2,3}

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²Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, UK

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Table 3. Association between HRT use and the likelihood of death in women diagnosed with COVID-19 during the observation period (1 January to 21 June 2020; $n = 5,451$).

	OR	95% CI		P-value
(i)Unadjusted models				
HRT use	0.15	0.061	0.366	0.000
(ii)Maximally adjusted models				
HRT use	0.22	0.05	0.94	0.041
Age 40–64 (years)	10.40	2.48	43.30	0.001
Age 65–74 (years)	58.90	14.00	249.00	0.000



Article

Estetrol Is Safe and Well Tolerated during Treatment of Hospitalized Men and Women with Moderate COVID-19 in a Randomized, Double-Blind Study



Jean Michel Foidart ^{1,2,*} , Krzysztof Simon ³, Wulf H. Utian ⁴, Franck Mauvais-Jarvis ⁵, Jonathan Douxflis ^{6,7} ,
Graham Dixon ¹ and Philip Barrington ⁸

Table 5. Cumulative proportion of patients with all-cause mortality during the study (ITT population).

Category	E4 15 mg (N = 85) n (%)	Placebo (N = 86) n (%)	Total (N = 171)
Day 14	3 (3.5%)	2 (2.3%)	5 (2.9%)
End of Treatment	5 (5.9%)	3 (3.5%)	8 (4.7%)
End of Study (Day 28)	6 (7.1%) ^a	3 (3.5%)	9 (5.3%)

E4: estetrol; ITT: intention-to-treat; N: number of patients in the study arm; n: number of patients. ^a There were two additional deaths in the E4 arm post-end-of-study (one on day 32 due to progressive disease and one on day 42 [unrelated]).