Centro Salute Donna
Azienda USL Ferrara

OSTETRICIA e GINECOLOGIA

2018

Estradiolo in contraccezione ormonale: vera evoluzione o vino vecchio in una nuova botte?

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S.I.C. Società Italiana della Contraccezione

ESC THE EUROPEAN SOCIETY OF CONTRACEPTION AND REPRODUCTIVE HEALTH

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Conflicts of interest

Giovanni Grandi M.D. has been lecturer and member of advisory boards for TEVA/Theramex, Bayer HealthCare, Effik Italia, Sandoz and Sanofi-Aventis.

EDITORIAL

Estradiol in hormonal contraception: real evolution or just same old wine in a new bottle?

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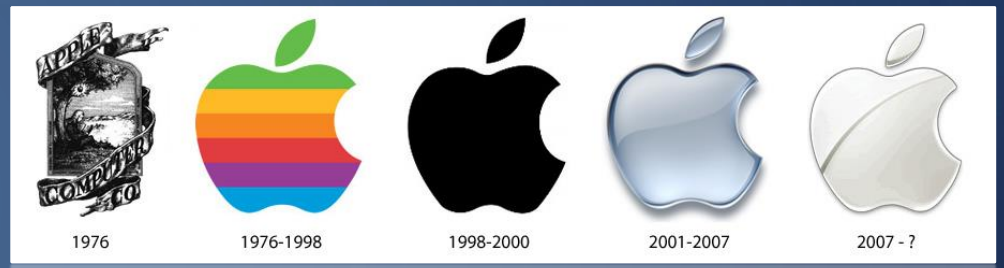
2017 Aug;22(4):245-246

THE EUROPEAN SOCIETY OF CONTRACEPTION AND REPRODUCTIVE HEALTH

The European Journal of Contraception & Reproductive Health Care

Come sono cambiati i contraccettivi ormonali



Administration

Classic 21/7 >> Extended/continuous regimens

Oral >> Others ways of administration

Progestin component

- Androgenic >> Non androgenic >> Anti androgenic

Estrogenic component

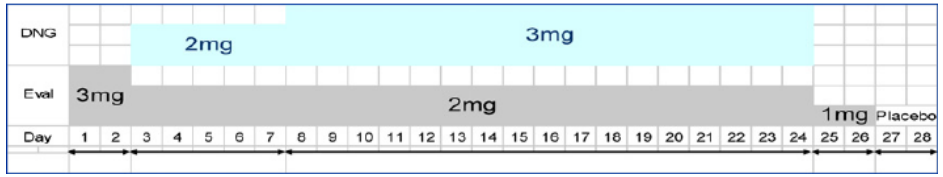
- Mestranol >> Ethinyl-estradiol >> Reduction of doses (15 mcg)>> Estradiol

Grandi G, Cagnacci A & Volpe A.
Exp Opinion Drug Metab Toxicol
2014;10:1-10

L'estradiolo in contraccezione ormonale

- Estradiol Valerate/Dienogest

quadriphasic regimen (26+2)



- Estradiol 1.5 mg/
Nomegestrol Acetate 2.5 mg

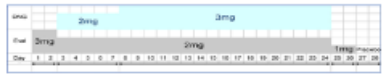
monophasic regimen (24+4)

E2-NOMAC Vs E2V/DNG 2012-2018?

L'estradiolo in contraccezione ormonale

- Estradiol 1.5 mg/
  Nomegestrol Acetate 2.5 mg
  monophasic regimen (24+4)

- Estradiol Valerate/Dienogest
  quadriphasic regimen (26+2)

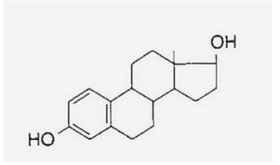


Grandi G, Facchinetti F.
News of Women's Health 2016;dicembre

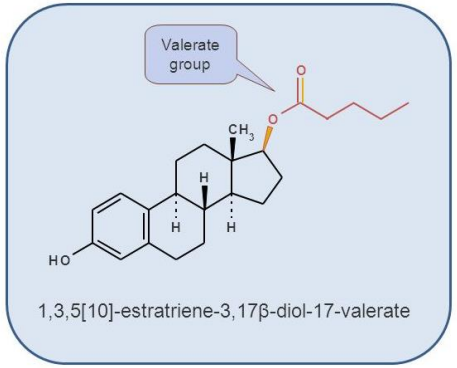
Tabella 1. Similarità e differenze dal punto di vista clinico dei contraccettivi a base di estradiolo (E2) o del suo estere estradiolo valerato (E2V) presenti in commercio.
+ vantaggio (considerando i dati esistenti in letteratura e la plausabilità farmacologica); – nessun vantaggio, non dati positivi.

	E2/NOMAc (monofasico)	E2/DNG (quadrifasico)
Effetto neutro su lipidi, glucidi ed SHBG	+++	+++
Rischio di accumulo (in caso di ridotta eliminazione)	+++	+
Attività progestazionale	+++	+++
Attività anti–gonadotropinica	+++	+
Attività glucorticoide	–	–
Attività mineralocorticoide	–	–
Attività anti–androgenica	+	+++
Efficacia contraccettiva in caso di compresse dimenticate	+++	–
Possibilità di regimi continuativi	+++	+
Possibilità di non avere sanguinamento da sospensione	+	+

Estradiolo ed estradiolo valerato



1,3,5[10]-estratriene-3,17β-diol



1,3,5[10]-estratriene-3,17β-diol-17-valerate

-E2V is the ester of 17β-Estradiol (E2).

-E2V is rapidly and completely metabolized to Estradiol (E2) during the first liver passage.

- E2V is virtually identical to E2 in pharmacokinetic and exactly identical in pharmacodynamic and clinical practice.

-1 mg of E2V is equivalent to 0.76 mg of E2.

Contraception
an international reproductive health journal

Fruzzetti F et Bitzer J.
Review of clinical experience with estradiol in combined oral contracepives.
Contraception 2010;81:8-15

Effetto biologico di EE vs E2

- The biological effects of E2V Vs EE can be compared only at specific target-organs level.

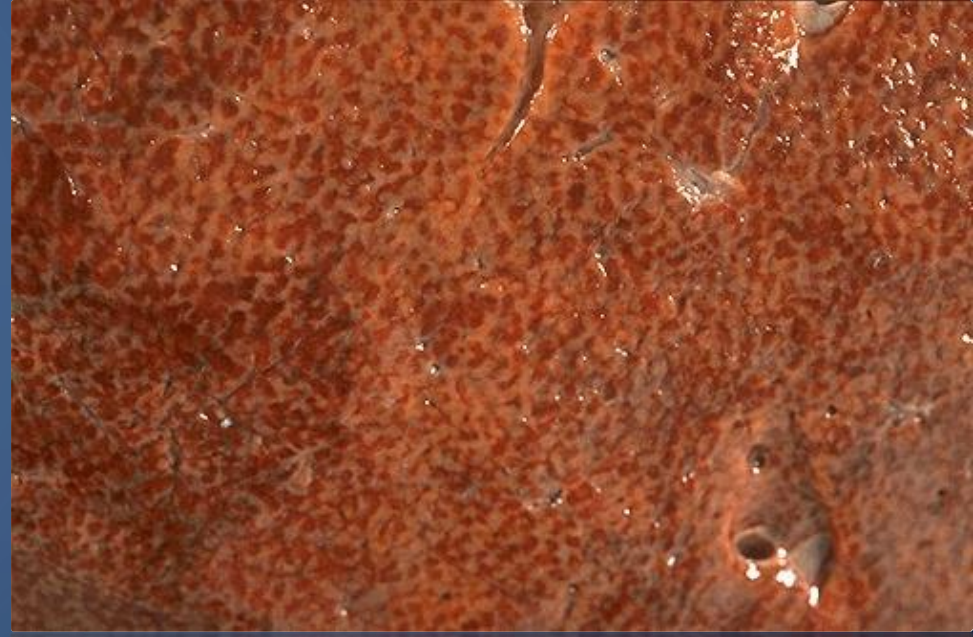
Biological effect	E2V effect versus EE effect
Suppression of FSH and ovulation inhibition	E2V 2mg = EE 20 µg
Endometrial stimulation	E2V 2mg = EE 20 µg
Maturation of vaginal epithelium cells	E2V 2mg slightly > EE 20 µg

Contraception
an international reproductive health journal

Endrikat J et al. Contraception 2008; 78: 218-25
Wiegratz I et al. Contraception 2004; 70: 97-106

Impatto epatico

Per il suo radicale etinilico, l'etinil-estradiolo compie molti passaggi epatici.
L'effetto dell'etinil-estradiolo su alcune proteine epatiche è fino a 500-600 volte maggiore dell'estradiolo.



Relative potency of estrogens

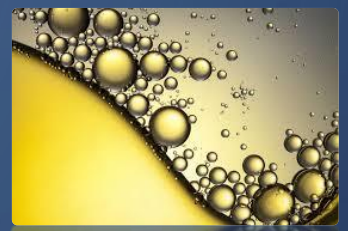
Estrogen	FSH	SHBG	CBG	Angiotensinogen
17β-E2	1	1	1	1
EE	120	600	500	350

Contraception
an international reproductive health journal

Fruzzetti F & Bitzer J.
Review of clinical experience with estradiol in combined oral contracepives.
Contraception 2010;81:8-15

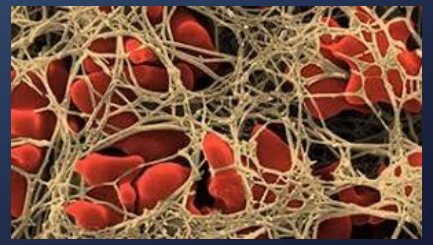
Effetti E2-COC sugli outcomes minori/secondari (2009-2016)

Lipidemia



Metabolismo glucidico

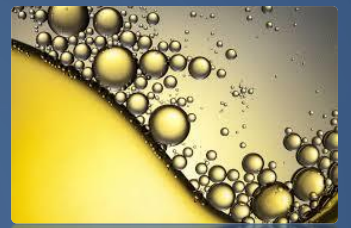
Emostasi



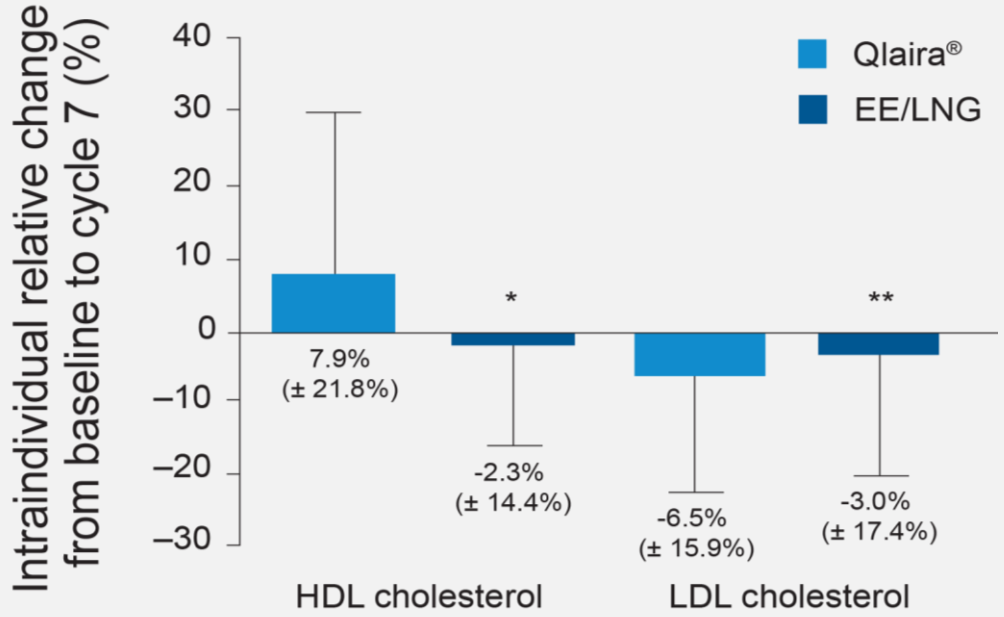
Pressione arteriosa

?

Lipidemia

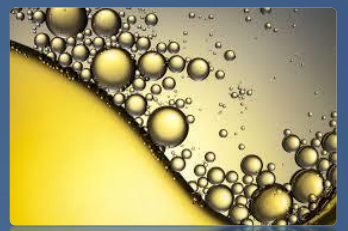


Mean (SD) intraindividual relative change from baseline to cycle 7 in HDL and LDL cholesterol in women treated with E2V/DNG or EE/LNG† (full analysis set; *p=0.055; **p=0.458 vs Qlaira®)



Junge W et al, Clin Drug Investig 2011;31:573-84

Lipidemia



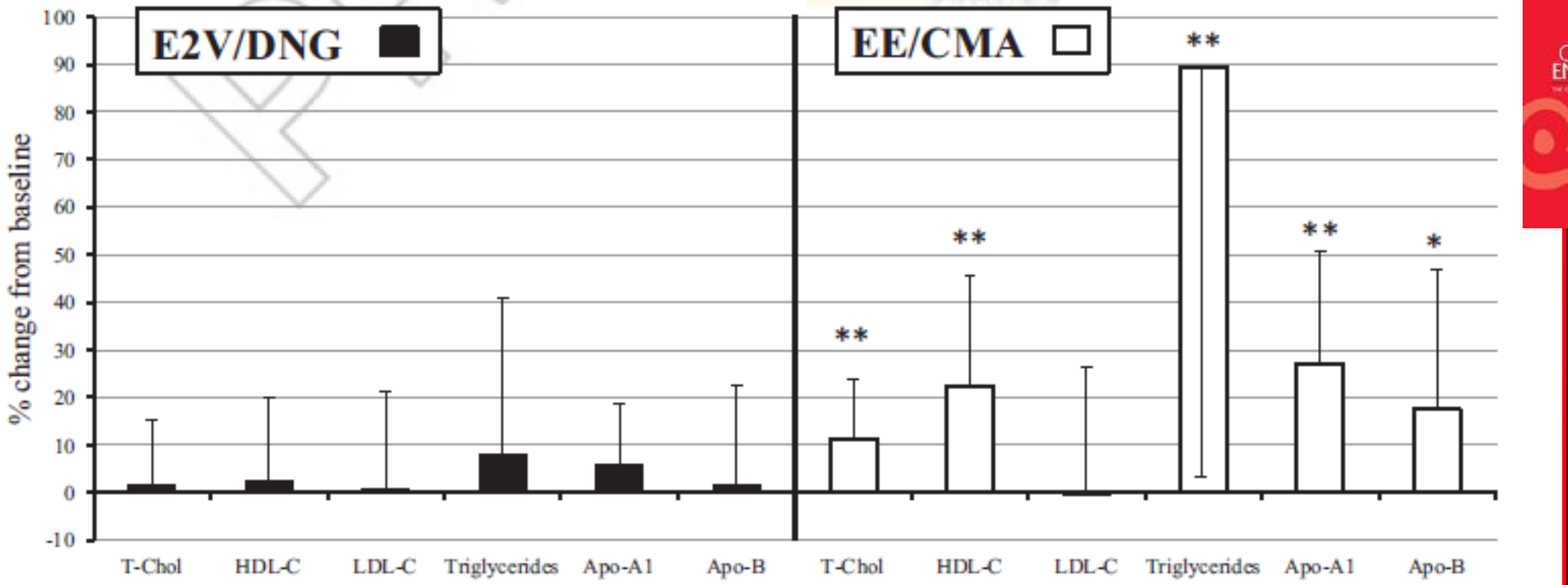
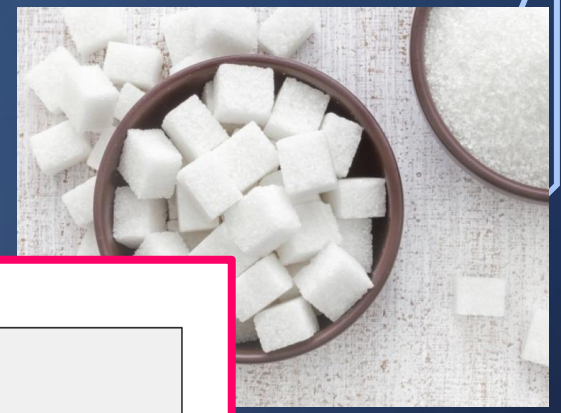
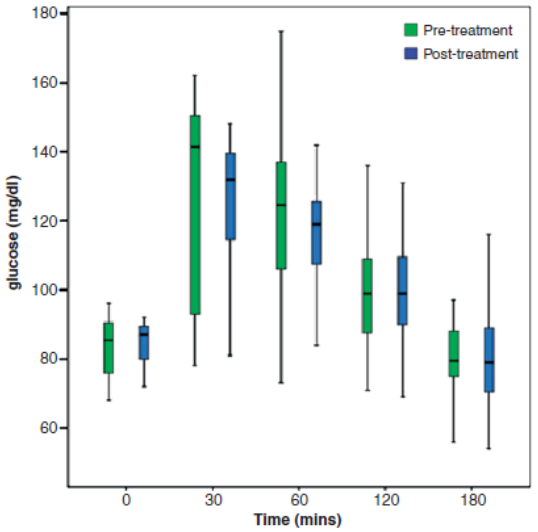


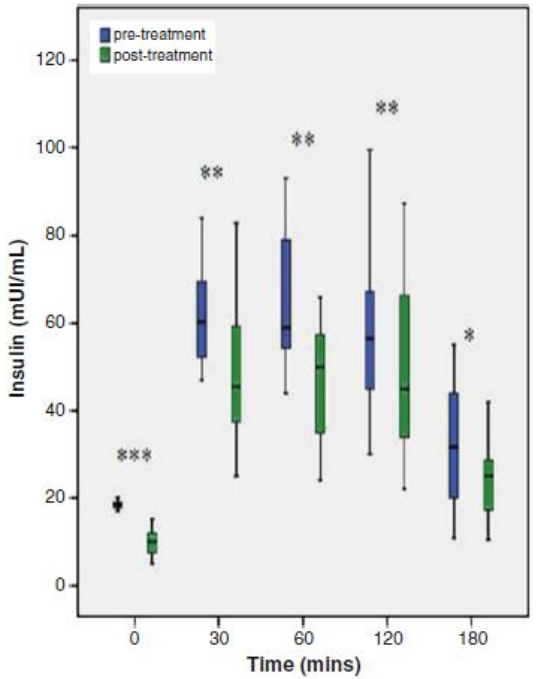
Figure 1. Mean (±SD) percent change from baseline to cycle three in total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, Apo-A1 and Apo-B in women treated with estradiol valerate/dienogest (E2V/DNG) or ethinyl estradiol/chlormadinone acetate (EE/CMA). $*p<0.05$; $**p<0.01$ versus basal.

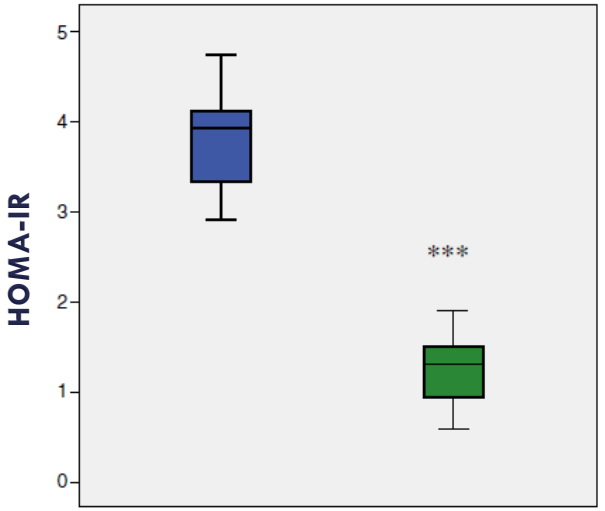
Grandi G et al, Gynecol Endocrinol 2014;30:676-80

Metabolismo glucidico









Contraception
an international reproductive health journal

De Leo V et al,
Contraception 2013:88;364-368

	E2V/DNG ($n = 16$)		
	Before	During	p
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

Grandi G et al,
Gynecol Endocrinol 2014;30:676-80

GYNECOLOGICAL ENDOCRINOLOGY

COCs ed emostasi

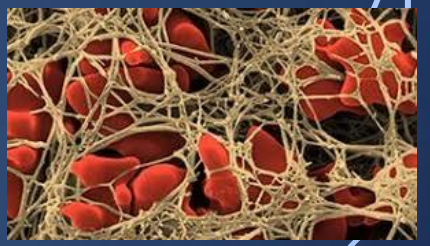
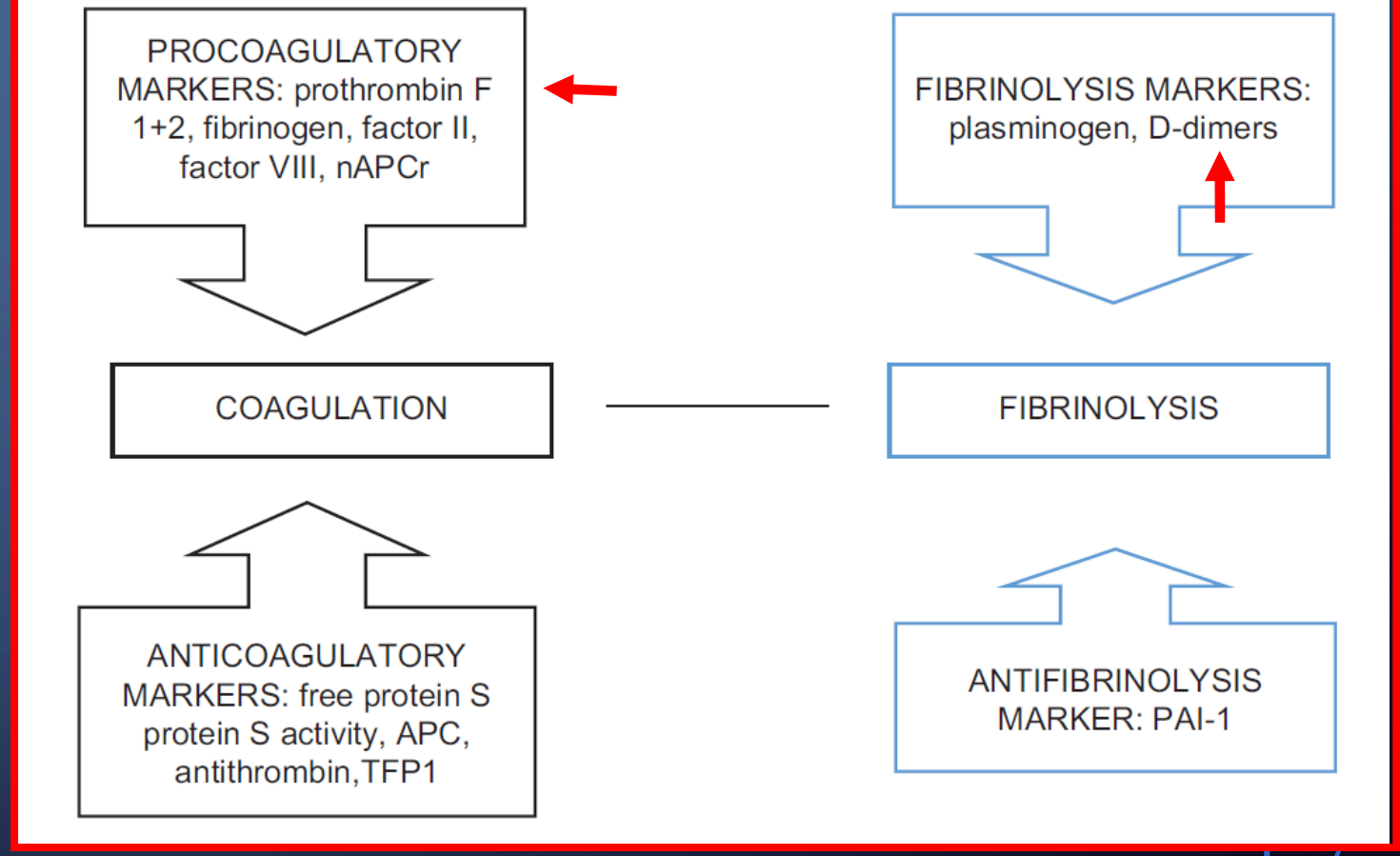


Table 2 Haemostatic changes during COC use (adapted from reference 17).

Factor	*Change during COC use*
Procoagulant factors	
Fibrinogen, V, VII, VIII, IX, X, XII	↑
XI	= or ↑
von Willebrand factor	=
Anticoagulant proteins	
Antithrombin	↓
Protein C	= or ↑
Protein S	↓
Resistance to APC	↑
Markers of thrombin formation	
F 1 + 2, TAT, fibrinopeptide A, D-dimer	↑
Fibrinolytic factors	
TAFI, PAI-1, PAI-2, t-PA	↑ ↓

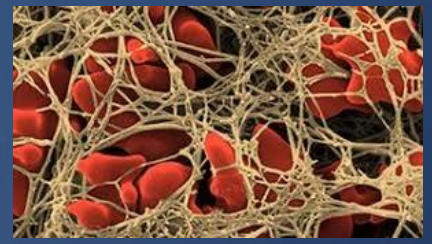
↑, increase; ↓, decrease; =, no change (vs. non-use of COCs).

TAT, thrombin–antithrombin complex; TAFI, thrombin-activatable fibrinolysis inhibitor; PAI, plasminogen activator inhibitor; t-PA, tissue plasminogen activator.

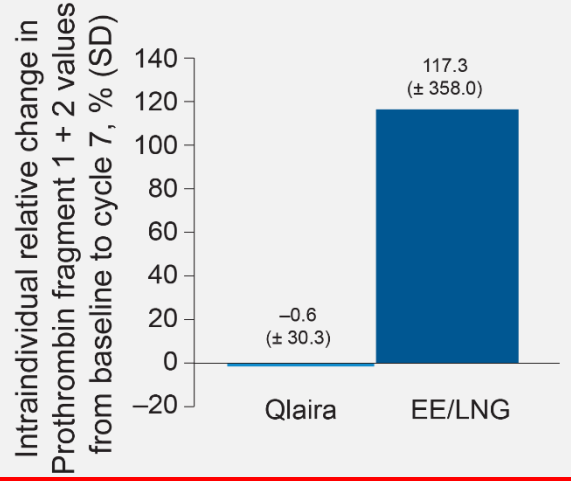


Lete I et al,
Eur J Contracept Reprod HealthCare 2015;20:329-43

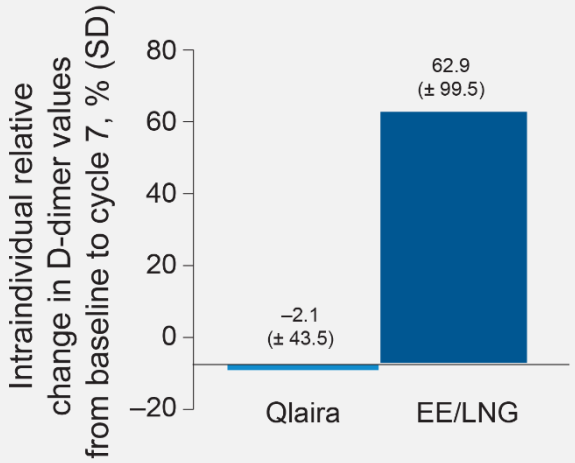
Emostasi



Changes in the mean (SD) prothrombin fragment 1 + 2 levels in the E2V/DNG group vs the EE/LNG* group (FAS)

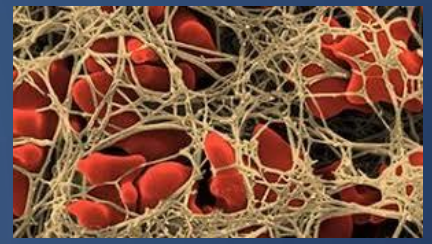


Changes in the mean (SD) D-dimer levels in the E2V/DNG group vs the EE/LNG* group (FAS)

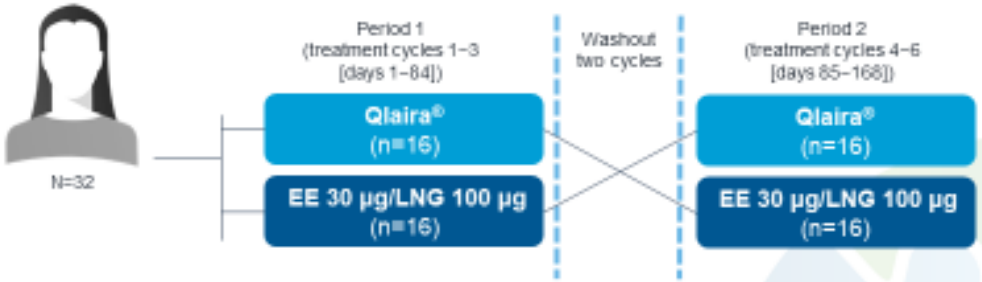


Junge W et al, Clin Drug Investig 2011;31:573-84

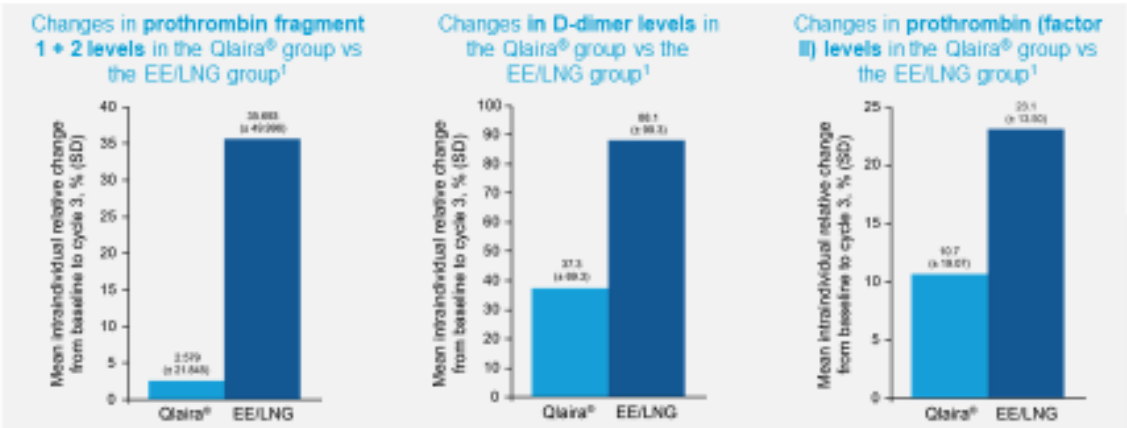
Emostasi



- A crossover, active-treatment-controlled, randomised, open-label, single-centre study in the Netherlands



Primary target parameters
Intraindividual absolute changes from baseline in thrombin and fibrin turnover (using the markers prothrombin fragment 1 + 2 and D-dimer) after three treatment cycles
Secondary target parameters
Intraindividual absolute changes from baseline in (pro)coagulatory parameters, anticoagulatory parameters, thrombin and fibrin turnover, and SHBG levels



- The reduced impact of Qlaira® on haemostatic parameters is probably due to the inclusion of E_2V instead of EE as the estrogenic component[1]
- E_2V is considerably less potent than EE in terms of inducing hepatic protein synthesis[2–5]

Klipping C et al. Drugs R D 2011;11:159–170

Pressione arteriosa

Blood Pressure in Women Taking Oral Contraceptives

R. J. WEIR, E. BRIGGS, A. MACK, L. NAISMITH, L. TAYLOR, E. WILSON

BRITISH MEDICAL JOURNAL 23 MARCH 1974

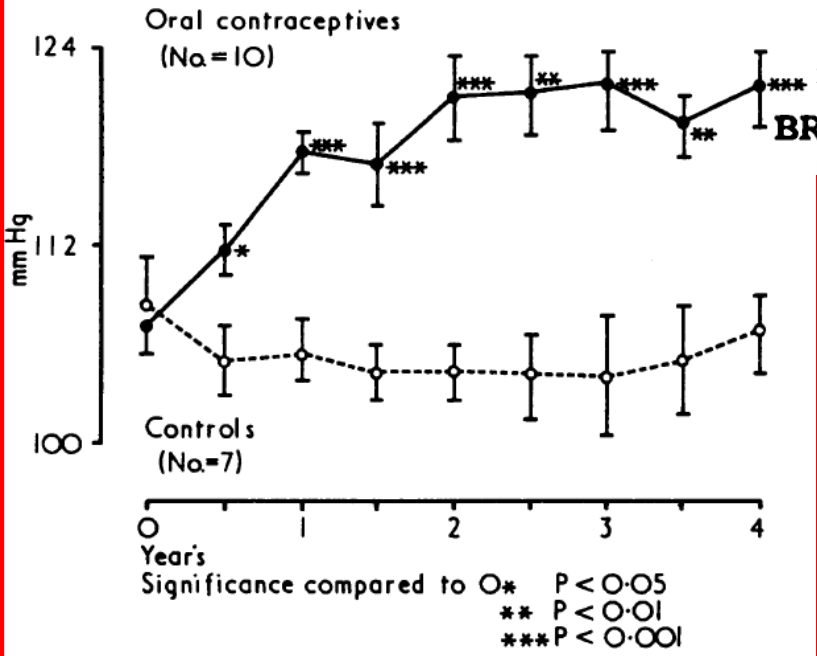


FIG. 1—Mean systolic blood pressure (±S.E.M.) after four years in a group of women taking oral contraceptives and in control group using mechanical methods of contraception

Mestranol (0·05 mg) and norethisterone (1 mg)
Ethinyloestradiol (0·05 mg) and lynestrenol (2·5 mg)
Ethinyloestradiol (0·05 mg) and norethisterone (3 mg)
Ethinyloestradiol (0·05 mg) and megestrol (4 mg)

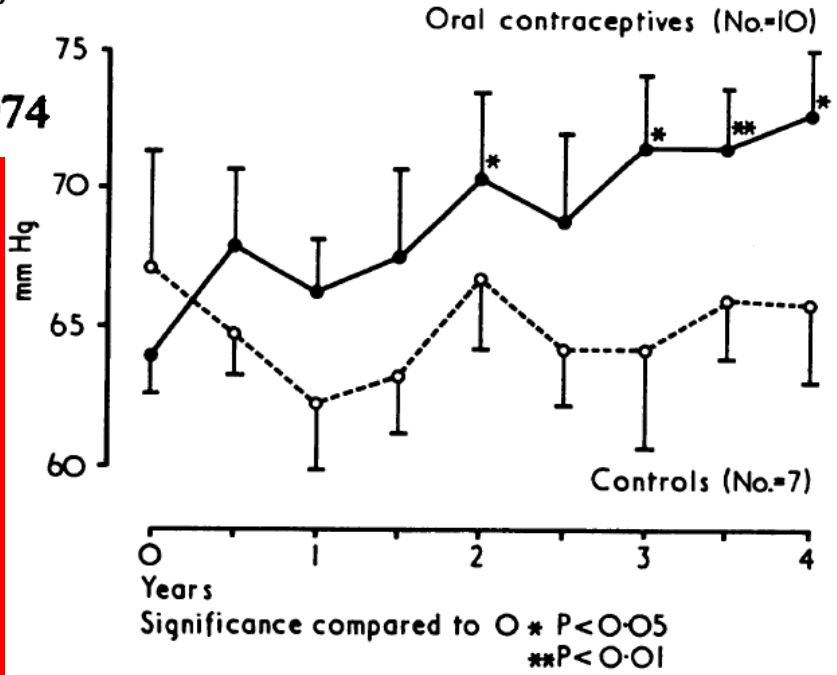


FIG. 2—Mean diastolic blood pressure (±S.E.M.) after four years in group of women taking oral contraceptives and in control group using mechanical methods of contraception.

Summary

A controlled prospective survey of women taking oestrogen-progestogen oral contraceptives showed increases in mean systolic and diastolic blood pressure of 14·2 mm Hg and 8·5 mm Hg respectively after four years. The largest increases in individual cases were 36 mm Hg systolic and 20 mm Hg diastolic. Blood pressure returned to pre-treatment levels within three months after oral contraceptives had been stopped. These changes in blood pressure were unrelated to the progestogenic potencies of the preparations being taken.

Pressione arteriosa

Blood Pressure in Women Taking Oral Contraceptives

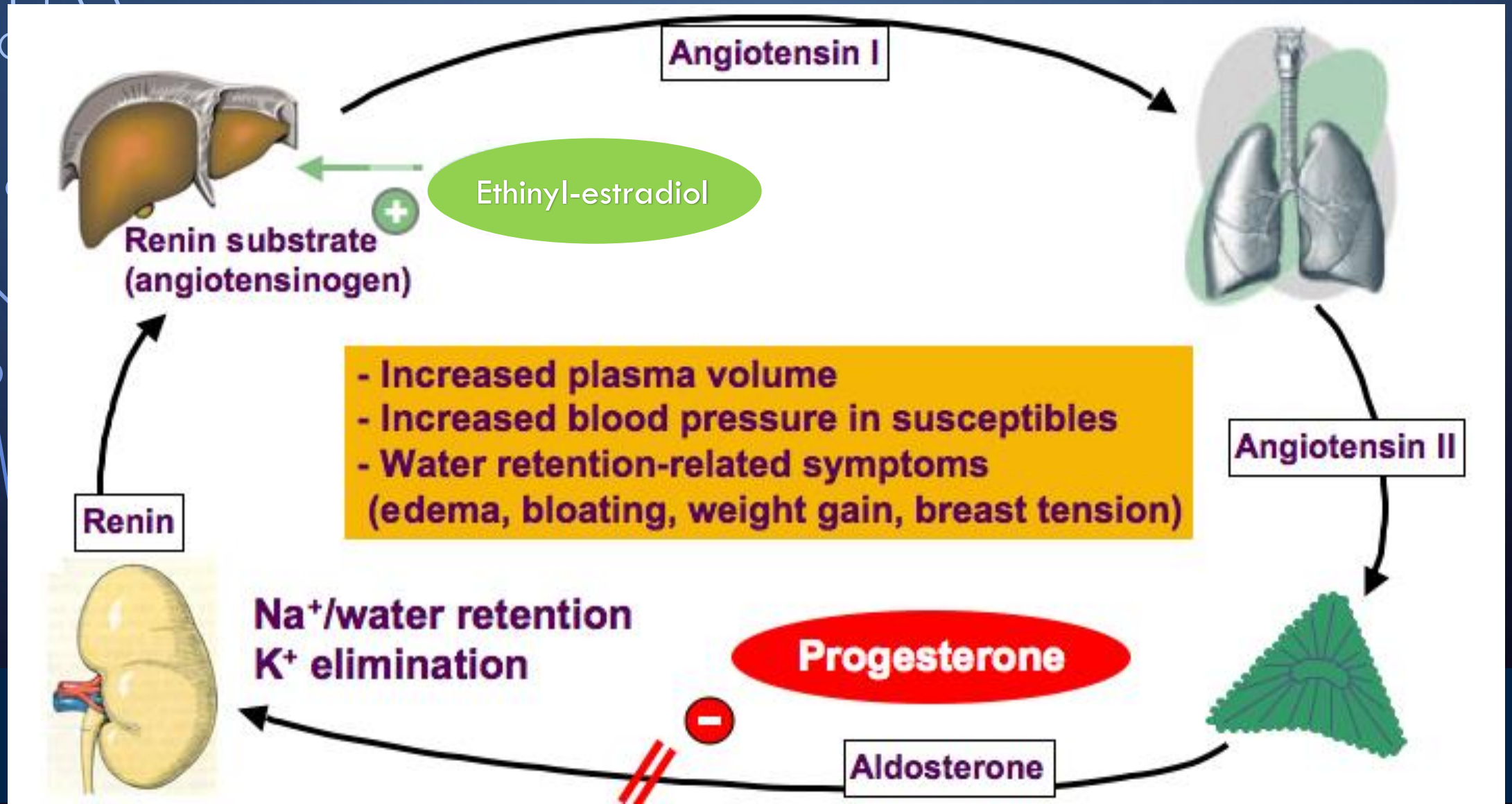
R. J. WEIR, E. BRIGGS, A. MACK, L. NAISMITH, L. TAYLOR, E. WILSON

The increases in blood pressure in this prospective survey have not so far been accompanied by clinical complications and would not generally be regarded as clinically important. Nevertheless, mortality and morbidity statistics, mostly obtained for men (Pickering, 1968; Kannel *et al.*, 1971), suggest that a relatively small increase of blood pressure within the range found in this study carries a distinct risk. Possibly, therefore, prolonged administration of oestrogen-progestogen oral contraceptives may lead to levels of blood pressure which may increase morbidity and affect life expectancy.

and 8·5 mm Hg respectively after four years. The largest increases in individual cases were 36 mm Hg systolic and 20 mm Hg diastolic. Blood pressure returned to pre-treatment levels within three months after oral contraceptives had been stopped. These changes in blood pressure were unrelated to the progestogenic potencies of the preparations being taken.

British Medical Journal

Estrogeni – Progesterone e regolazione PA

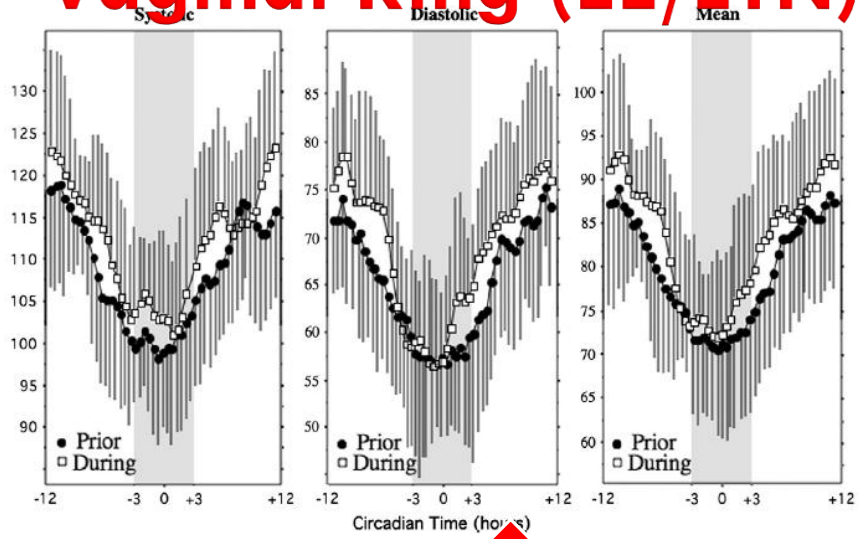


PA e anello vaginale

Cagnacci A et al,
Contraception 2013;88:539-43

Contraception
an international reproductive health journal

Vaginal Ring (EE/ETN)



24 h diastolic PA

24 h mean PA

24 h heart rate

PA e EE/DRSP COC

Contraception
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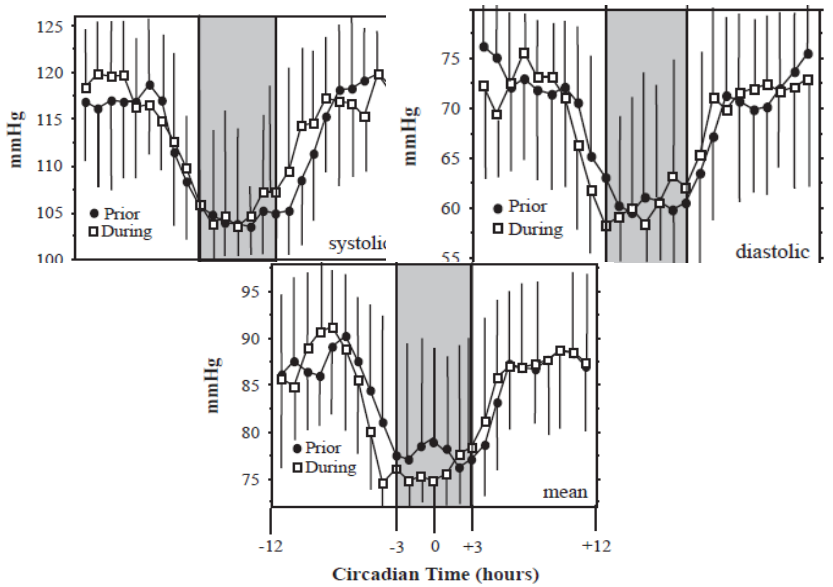
30 mcg EE/3 mg DRSP



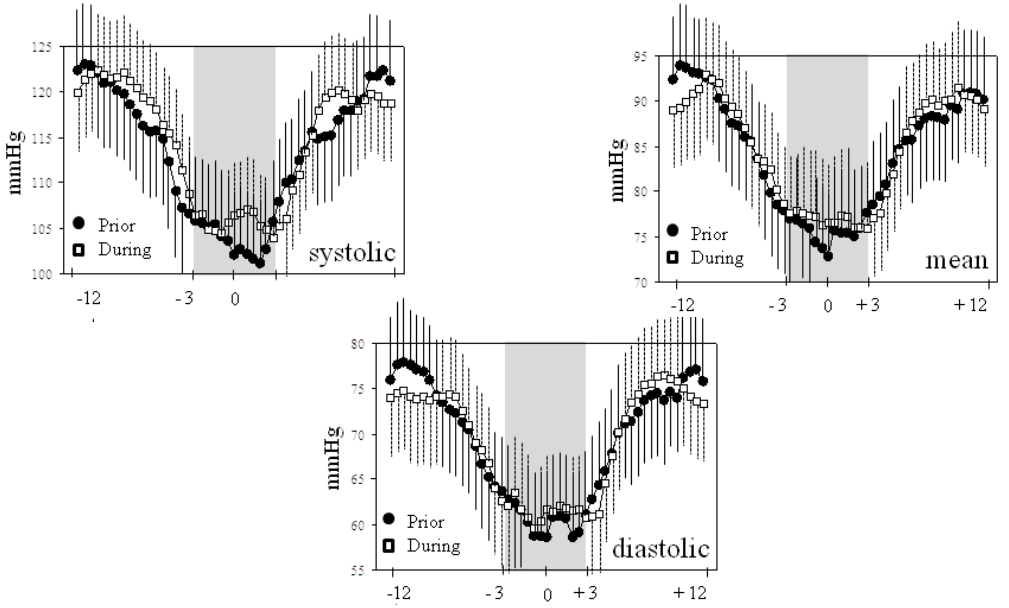
No modification of 24 h PA

24 h heart rate

Cagnacci A et al, Contraception 2013; 88:413-17

PA e E2V/E2 COC

E2V or E2 based COCs



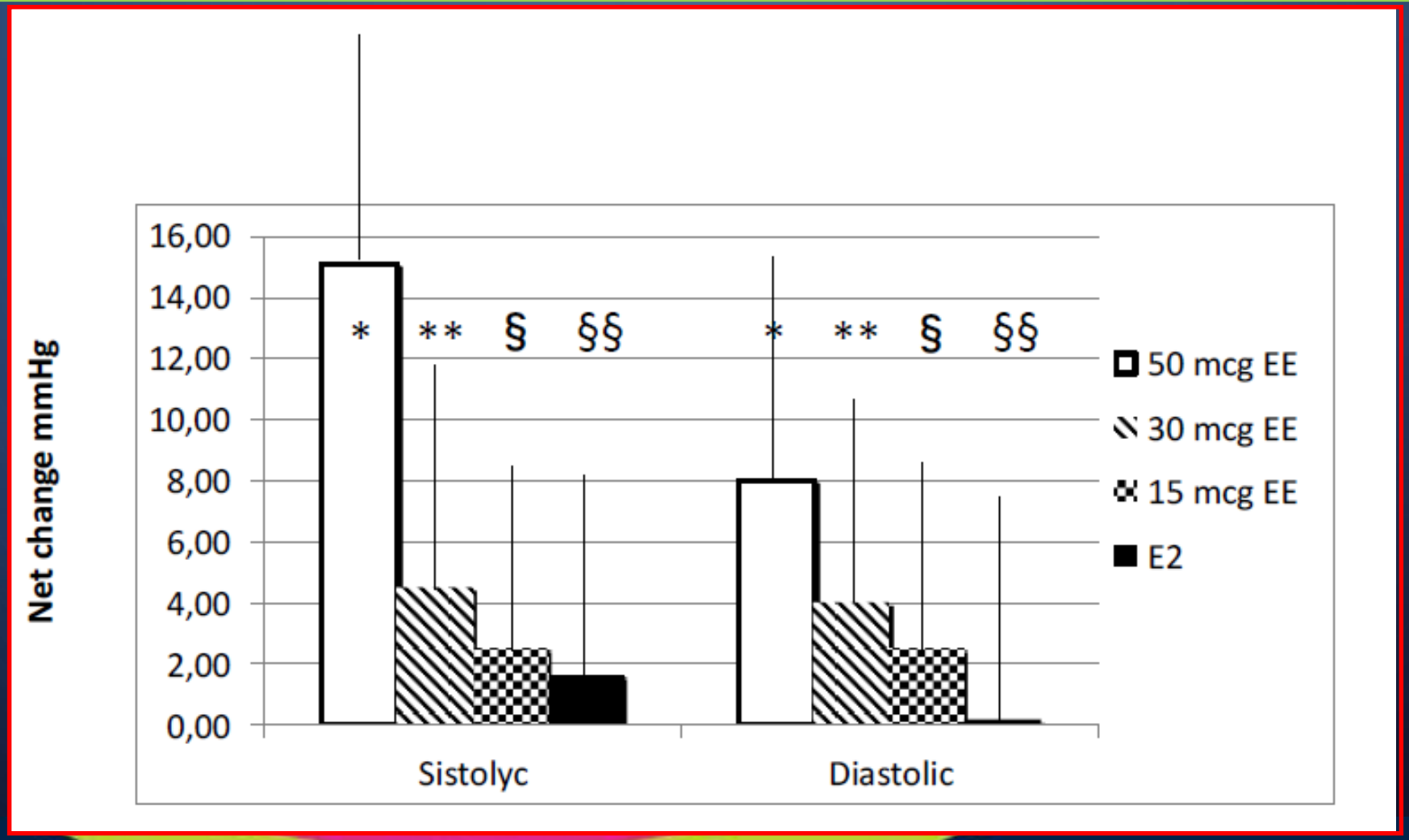
No modification of 24 h PA

No modification of 24 h heart rate

Contraception
an international reproductive health journal

Grandi G et al,
Contraception 2014;90:529-34

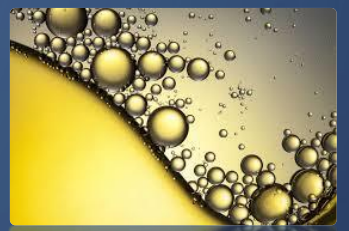
Pressione arteriosa ed evoluzione estrogenica



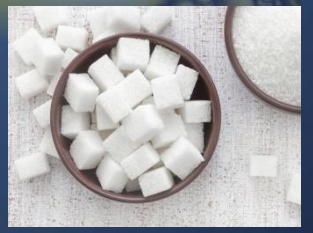
Grandi G, Napolitano A, Cagnacci A.
Exp Opinion Drug Metab Toxicol 2016

Effetti E2-COC sugli outcomes minori/secondari (2009-2016)

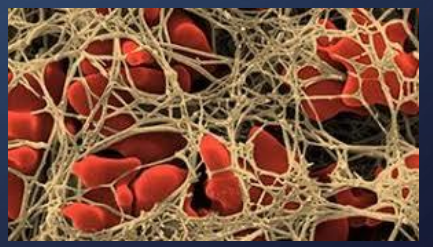
Lipidemia



Metabolismo glucidico



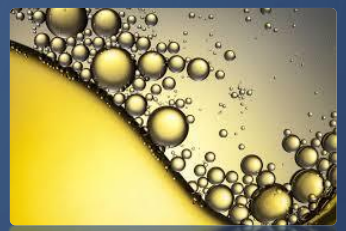
Emostasi



Pressione arteriosa

Effetti E2-COC sugli outcomes minori/secondari (2009-2016)

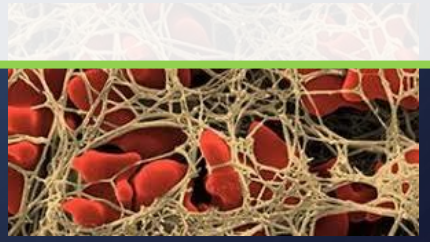
Lipidemia



Metabolismo glucidico

Effetti E2-COC sugli outcomes clinici??? 2016-

Emostasi



Pressione arteriosa

Real-World Evidence

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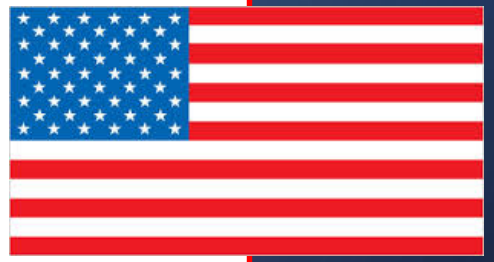
Contraception 94 (2016) 328–339

Contraception

Original research article

Impact of estrogen type on cardiovascular safety of combined oral contraceptives☆,☆☆,★



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Abstract

Objectives: The International Active Surveillance study "Safety of Contraceptives: Role of Estrogens" (INAS-SCORE) investigated the cardiovascular risks associated with the use of a combined oral contraceptive (COC) containing dienogest and estradiol valerate (DNG/EV) compared to established COCs in a routine clinical setting.

Study Design: Transatlantic, prospective, noninterventional cohort study conducted in the United States and seven European countries with two main exposure groups and one exposure subgroup: new users of DNG/EV and other COC (oCOC), particularly levonorgestrel-containing COCs (LNG). All self-reported clinical outcomes of interest (OoI) were validated via attending physicians and relevant source documents. Main OoI were serious cardiovascular events (SCE), particularly venous thromboembolic (VTEs) events. Comprehensive follow-up procedures were implemented. Statistical analyses were based on Cox regression models.

Results: A total of 50,203 new COC users were followed up for up to 5.5 years (mean value, 2.1 years). Overall 20.3% and 79.7% of these women used DNG/EV and oCOC (including 11.5% LNG users), respectively. A low loss to follow-up of 3.1% was achieved. Based on 47 (VTE) and 233 (SCE) events, the primary analysis (European data set) yielded adjusted hazard ratios for DNG/EV vs. oCOC of 0.4 and 0.5, respectively. The upper bounds of the 95% confidence intervals were 0.98 (VTE) and 0.96 (SCE). The corresponding hazard ratios for DNG/EV vs. LNG showed similar point estimates but the confidence intervals included unity.

Conclusion: DNG/EV is associated with similar or even lower cardiovascular risk compared to oCOC and LNG.

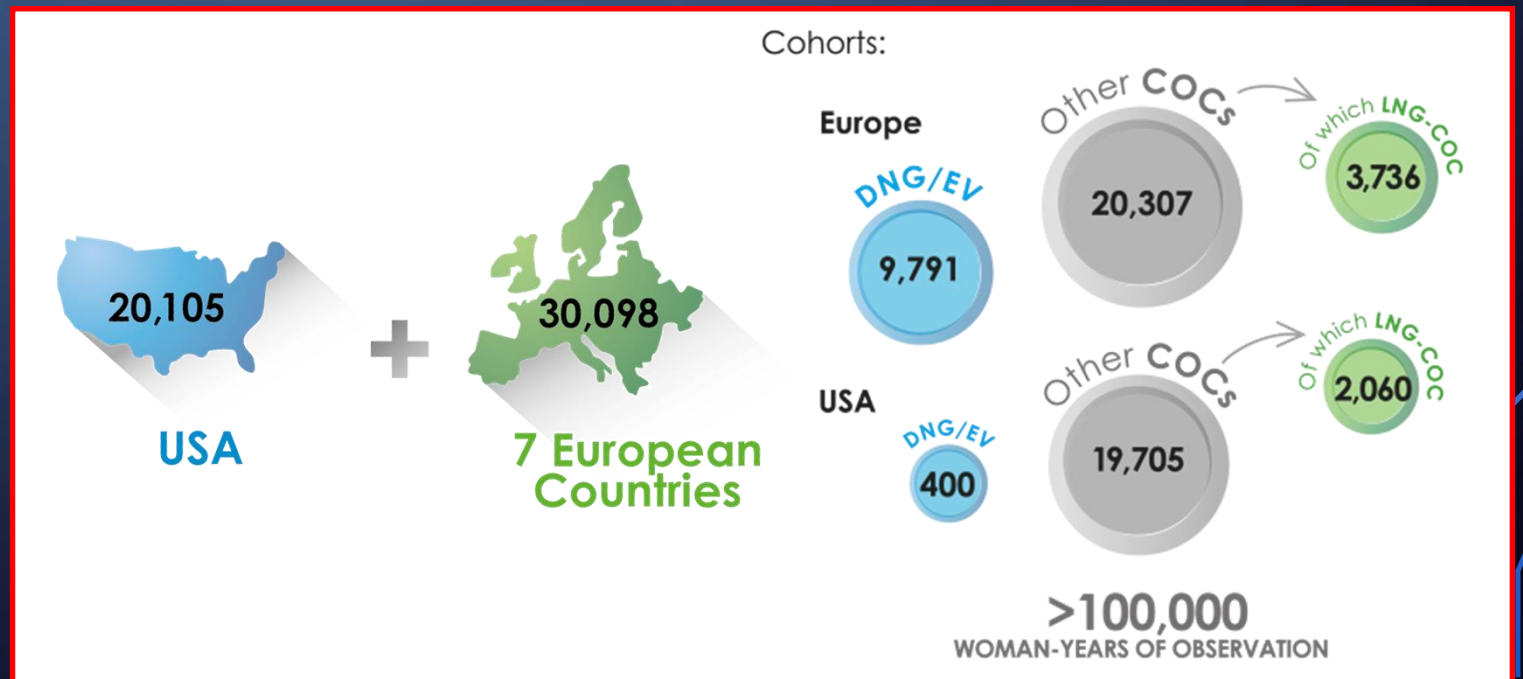
Implication Statement: A COC containing DNG and EV is associated with similar or even lower cardiovascular risk compared to COCs containing levonorgestrel or other progestogens.

Disegno dello studio – INAS SCORE

- **Studio di coorte prospettico, controllato, non-interventistico, a lungo termine condotto in USA e EU (Austria, Francia, Germania, Italia, Polonia, Svezia e UK)**

  N=50,203

  É stato richiesto ai medici partecipanti (N=1,307) di reclutare donne con una nuova prescrizione di COCs.



Conferma degli eventi vascolari

- Al termine dello studio la classificazione di VTE e ATE come 'confermata' e 'non confermata' è stata verificata mediante un giudizio indipendente in cieco:
- Condotto da tre medici esperti indipendenti specializzati in radiologia e medicina nucleare, cardiologia, medicina interna e patologie vascolari
- Per l'analisi finale è stato mantenuto un approccio conservativo
- I casi sono stati considerati 'confermati' se erano confermati da almeno uno dei valutatori, indipendentemente dagli altri (i.e. prima di qualunque discussione sul caso)

Aggiustamento del rischio

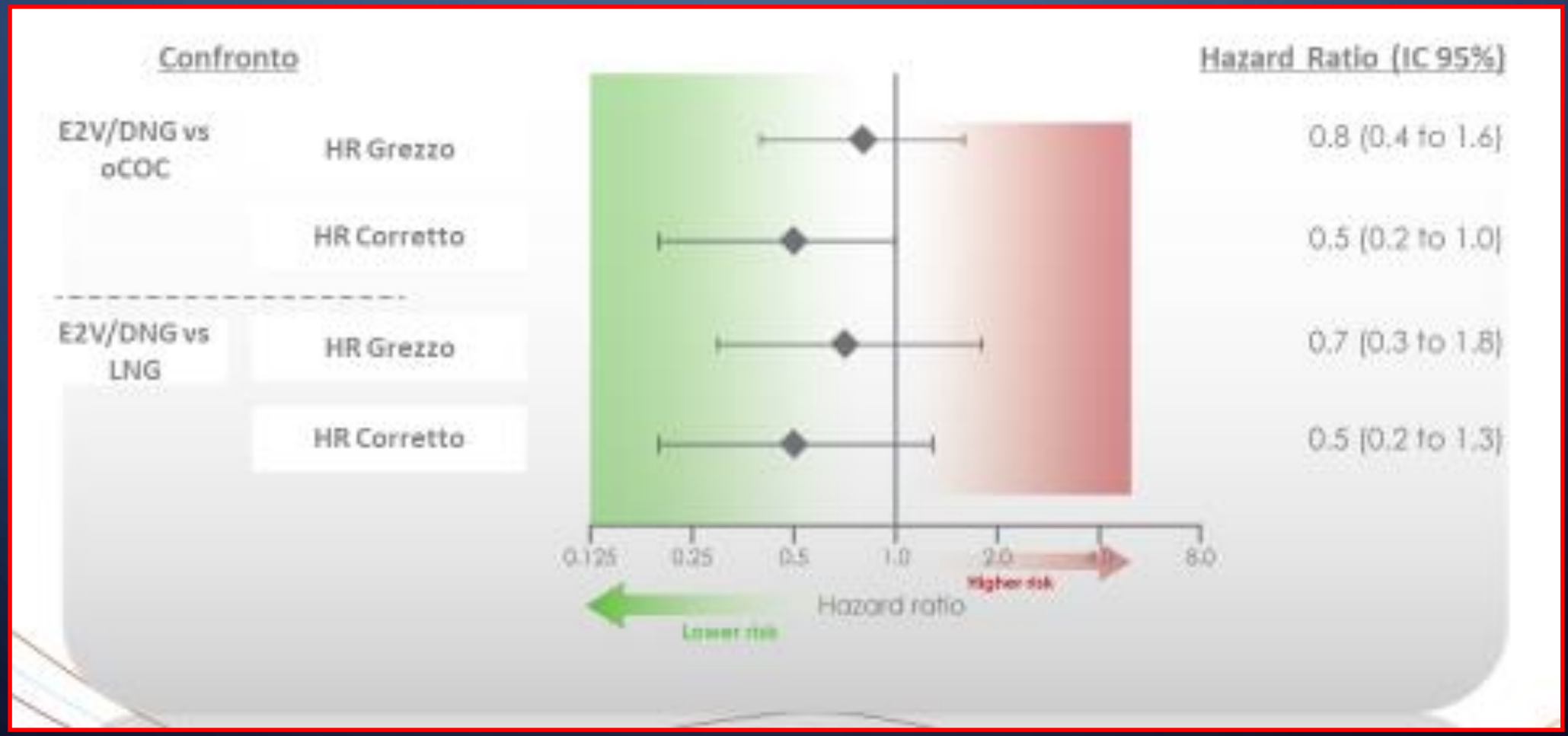
Negli studi nella vita reale generalmente le coorti risultano non confrontabili per prescrizioni selezionate sulla base delle caratteristiche delle pazienti

Un esempio relativo allo studio INAS-SCORE: alcune caratteristiche al basale che rappresentano fattori di rischio per TEV (età, peso e BMI delle donne) erano differenti tra le coorti*

	DNG/EV	oCOC	
		All	LNG
n (%)	N=10,191 (20.3)	N=40,012 (79.7)	N=5796 (11.5)
Età, media (SD)	31.7 (10.0)	26.0 (7.9)	26.0 (8.4)
Peso, media (SD)	62.7 (12.2)	66.6 (16.4)	66.1 (15.2)
BMI, media (SD)	23.0 (4.2)	24.5 (5.9)	24.2 (5.4)

- Per questo motivo le coorti devono essere corrette per potenziali fattori di rischio al basale per permettere un confronto valido
- Il rapporto di rischio (HR) senza correzione viene chiamato 'hazard ratio grezzo', quello considerando tali correzioni, 'hazard ratio corretto'

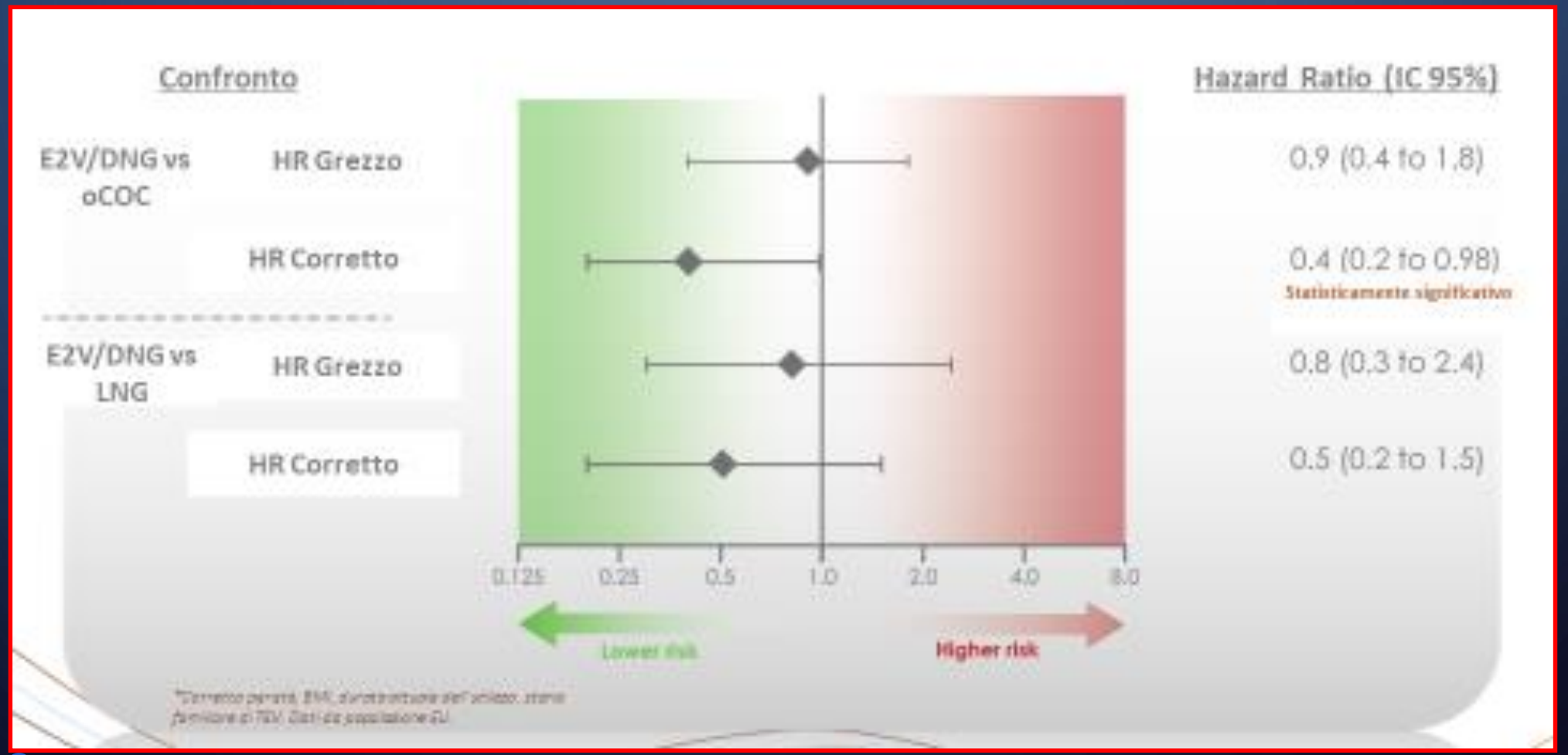
Rischio VTE generale



Contraception
an international reproductive health journal

Dinger JC et al Contraception 2016;94:328-339

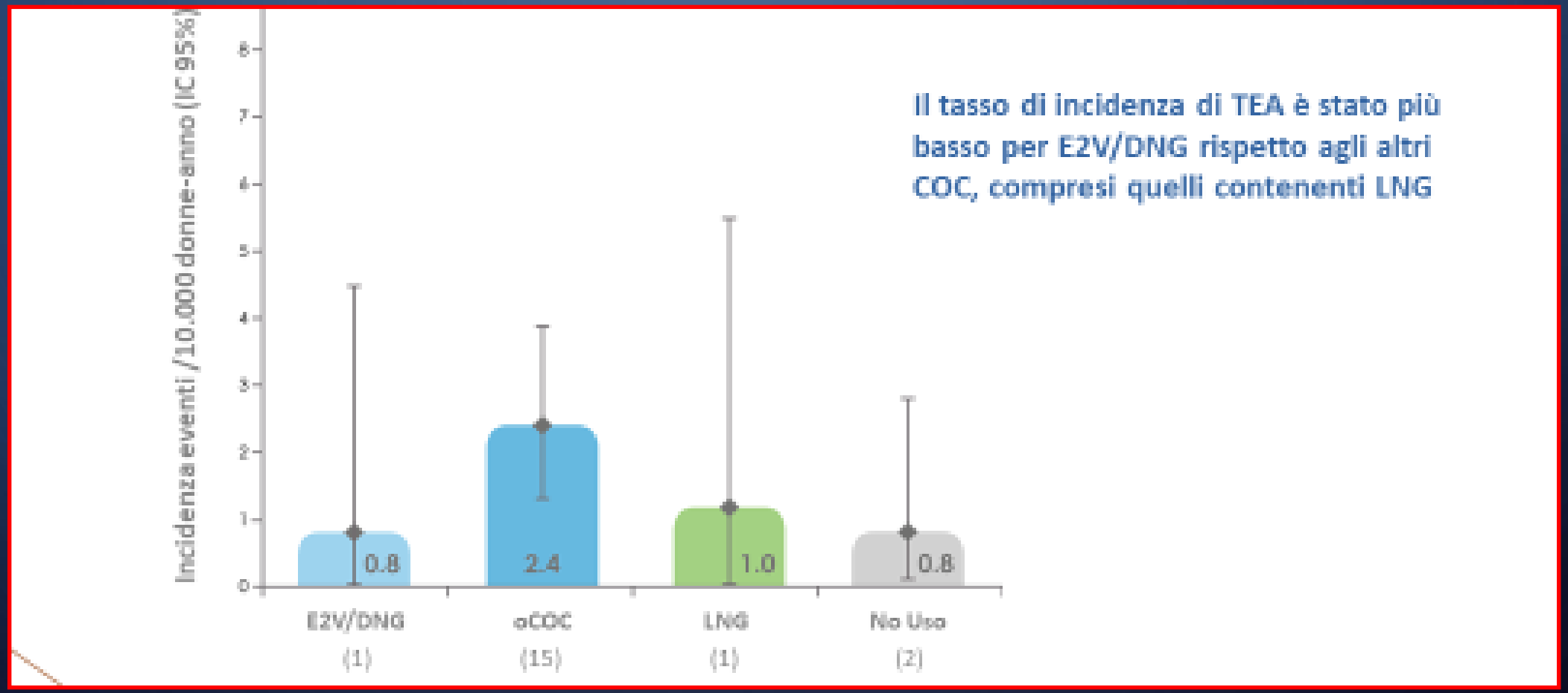
Rischio VTE europeo



Contraception
an international reproductive health journal

Dinger JC et al Contraception 2016;94:328-339

Rischio arterioso



Contraception
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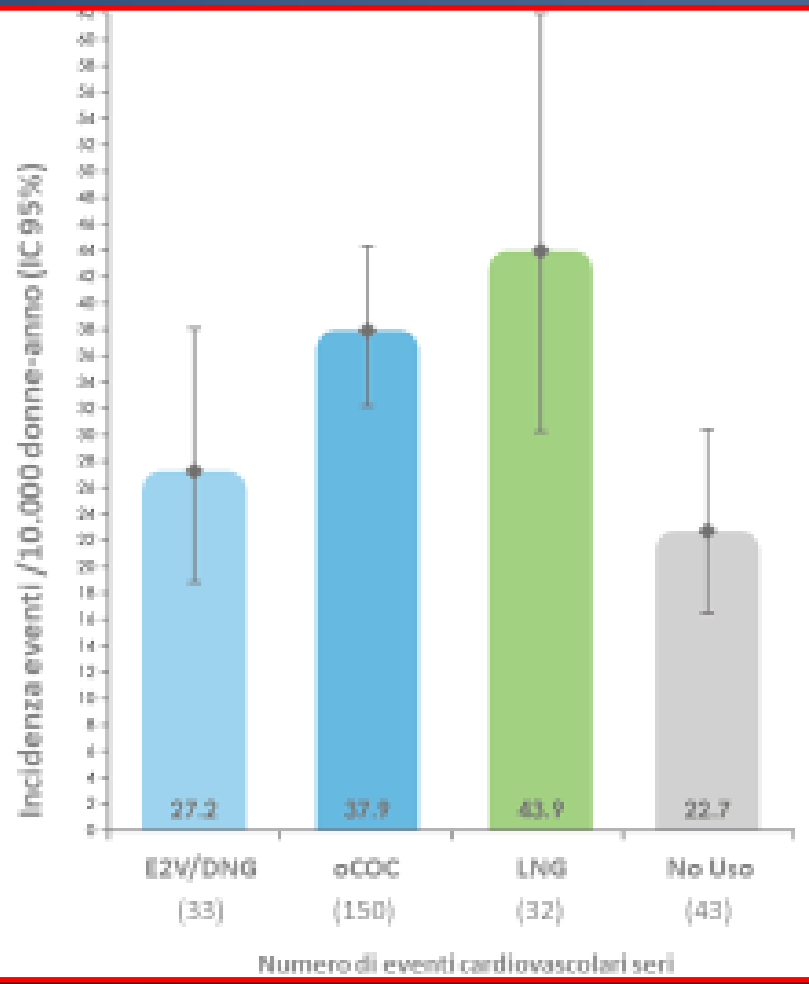
Dinger JC et al Contraception 2016;94:328-339

Eventi cardiovascolari seri



Sono compresi anche gli eventi TEV e TEA.
Il tasso di incidenza di eventi cardiovascolari seri è stato più basso per E2V/DNG rispetto agli altri COC, compresi quelli contenenti LNG

- La stima puntuale del HR corretto per il confronto tra E2V/DNG vs oCOC è stata di 0.6 con un limite di confidenza superiore al 95% di 0.96 (**statisticamente significativo**)
- La stima puntuale del HR corretto per il confronto tra E2V/DNG vs LNG è stata di 0.6 con limiti di confidenza al 95% di (0.4 - 1.1)

Contraception
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Dinger JC et al Contraception 2016;94:328-339

Estensione Gennaio 2017

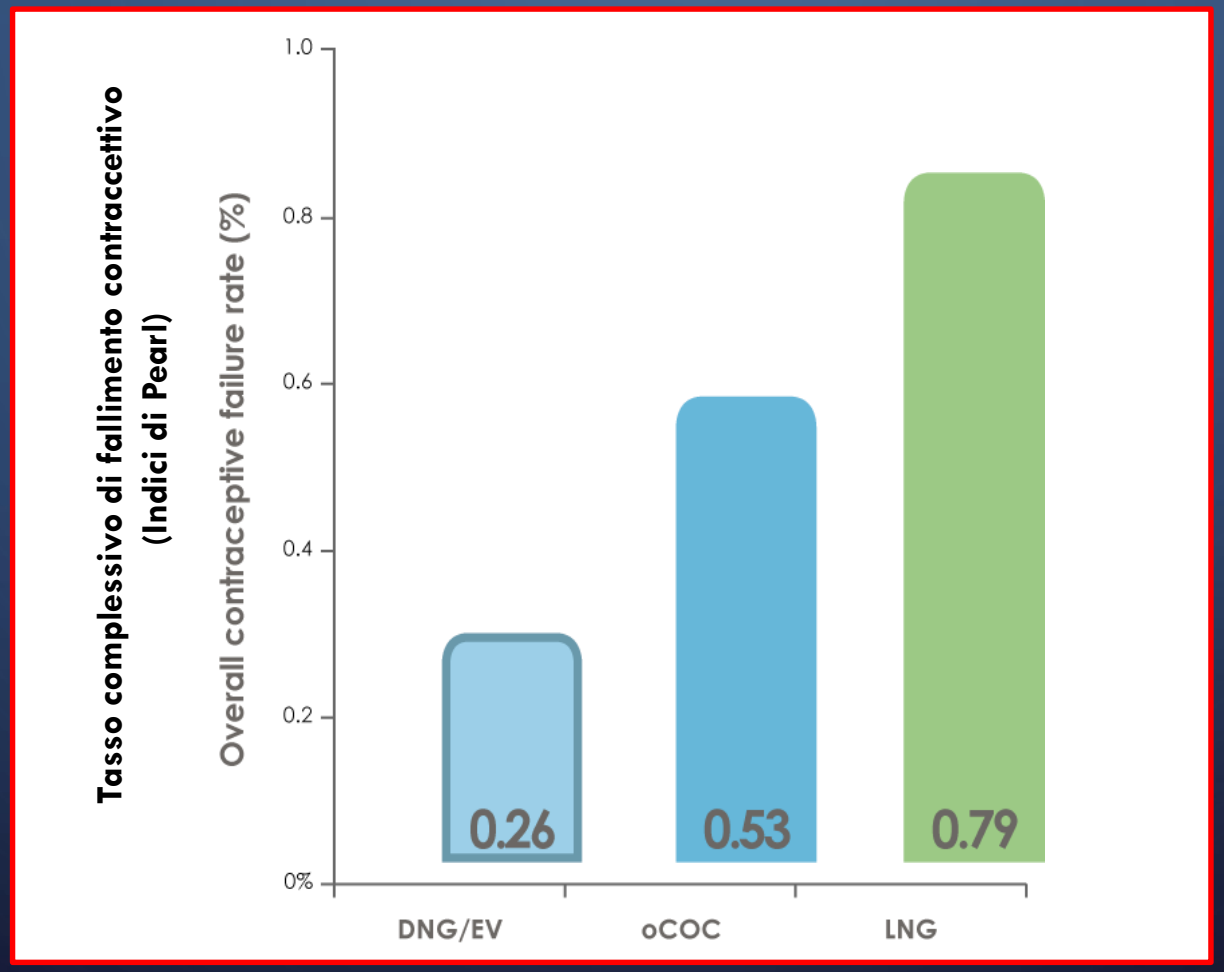
THE EUROPEAN SOCIETY OF CONTRACEPTION AND REPRODUCTIVE HEALTH

VTE: Adjustment for age, BMI, duration of current OC use and family history of VTE lead to HRs of 0.4 (95% CI: 0.2–0.9) vs. Other COCs and 0.4 (95% CI: 0.2–1.1) vs. LNG-COCs.

ATE incidences were very low with 0.7 ATE/10,000 WY for Qlaira and 3.5 ATE/10,000 WY for Other COCs. The adjusted hazard ratios (HRadj) for DNG/EV vs. Other COCs and vs. LNG-COCs subcohort were:
0.1 (95% CI 0.0–0.6) and 0.1 (95% CI 0.0–1.2)

Heinemann K et al. Eur J Contracept Reprod HealthCare 2018;FC03:40

INAS-SCORE Efficacia contraccettiva



Barnett C et al. Eur J Contracept Reprod HealthCare 2017;22:17-23

Prossimi steps

ELSEVIER

CrossMark

Contraception
an international reproductive health journal

Contraception

Contraception 92 (2015) 289–297

Original research article

A dose-finding, cross-over study to evaluate the effect of a Nestorone®/Estradiol transdermal gel delivery on ovulation suppression in normal ovulating women☆

Vivian Brache[a,*], Ruth Merkatz[b], Narender Kumar[b], Cristian Jesam[c], Heather Sussman[b], Elena Hoskin[b], Kevin Roberts[b], Mohcine Alami[b], Deshawn Taylor[d], Aidelis Jorge[a], Horacio Croxatto[c], Ellen Lorange[e], Daniel R. Mishell[d], Regine Sitruk-Ware[b]

With most CHCs that combine EE with a progestin, the small amount of EE contributes to the antiovulatory effect. E2, on the other hand, may not be sufficient to add any antigonadotropic effect to that of the progestin; thus, it is important to select a potent progestin to ensure ovulation suppression when using E2 rather than EE.

Nestorone® (NES) is a 19-nor-progesterone derivative that has the highest antiovulatory activity among synthetic progestins. NES has a neutral metabolic profile, no androgenic or estrogenic activity and therefore is an attractive option for use with E2 [11]. NES is not active orally but is rapidly absorbed through the skin. A prior 3-month dose-finding study

Estradiol (E2) is much less potent than EE and its impact on liver proteins and coagulation factors has been shown to be minimal when administered transdermally [9]. It was also shown in postmenopausal women that transdermal E2 is safer than oral estrogen in terms of VTE risk [10].

Scarabin PY et al,
Lancet 2003;362:428-32

THE LANCET

EDITORIAL

Estradiol in hormonal contraception: real evolution or just same old wine in a new bottle?

Hormonal contraceptives were originally designed to avoid unintended pregnancies giving the least possible side effects: with the important limitations of this observational study [16,17], its promising results indicate that the most serious and feared side effects during CHCs use (such as VTEs and other cardiovascular events) could be at least halved with the use of E2V/DNG, being associated with an almost doubled contraceptive efficacy. These results should be theoretically similar or even better for E2 and NOMAc [14], although population data are still lacking. If these results will be confirmed, these preparations could sign a real evolution in CHC technology over the next few years. This is especially true if combinations with E2 could be developed for transdermal or transvaginal applications thus theoretically lowering cardiovascular risk even more.

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