Risque thrombotique et oestroprogestatifs
Données récentes

Données récentes sur le risque thrombotique des oestroprogestatifs

Jonathan Douxfils, Professor
Head of the Clinical Pharmacology and Toxicology Research Unit
University of Namur,
Namur, Belgium

The pill history

1960

Association of mestranol and norethynodrel

Morimont L, et al. Front Endocrinol (Lausanne). 2021;12:769187.

The pill history

1st case of thrombosis related to COC use

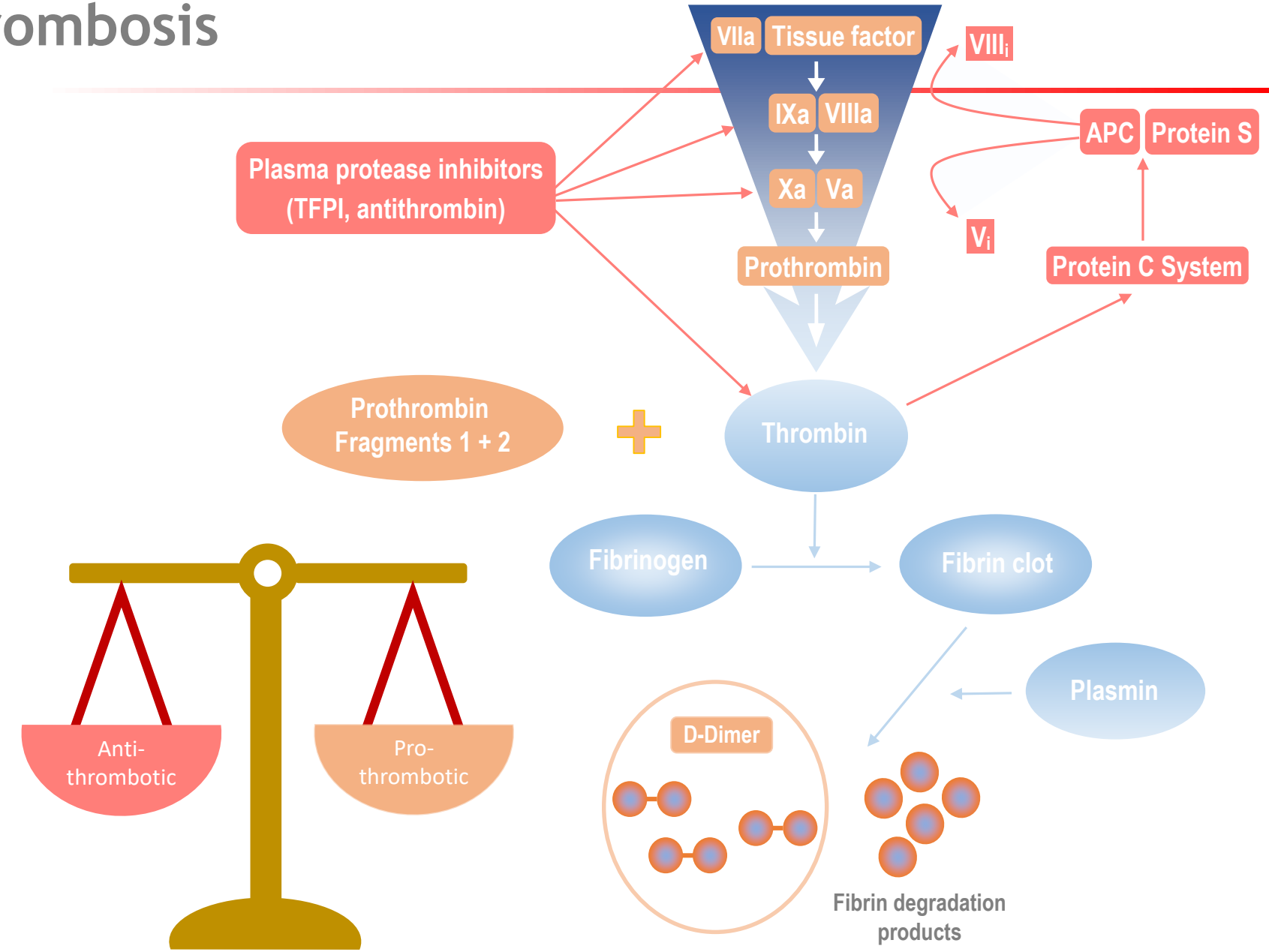
1961

1960

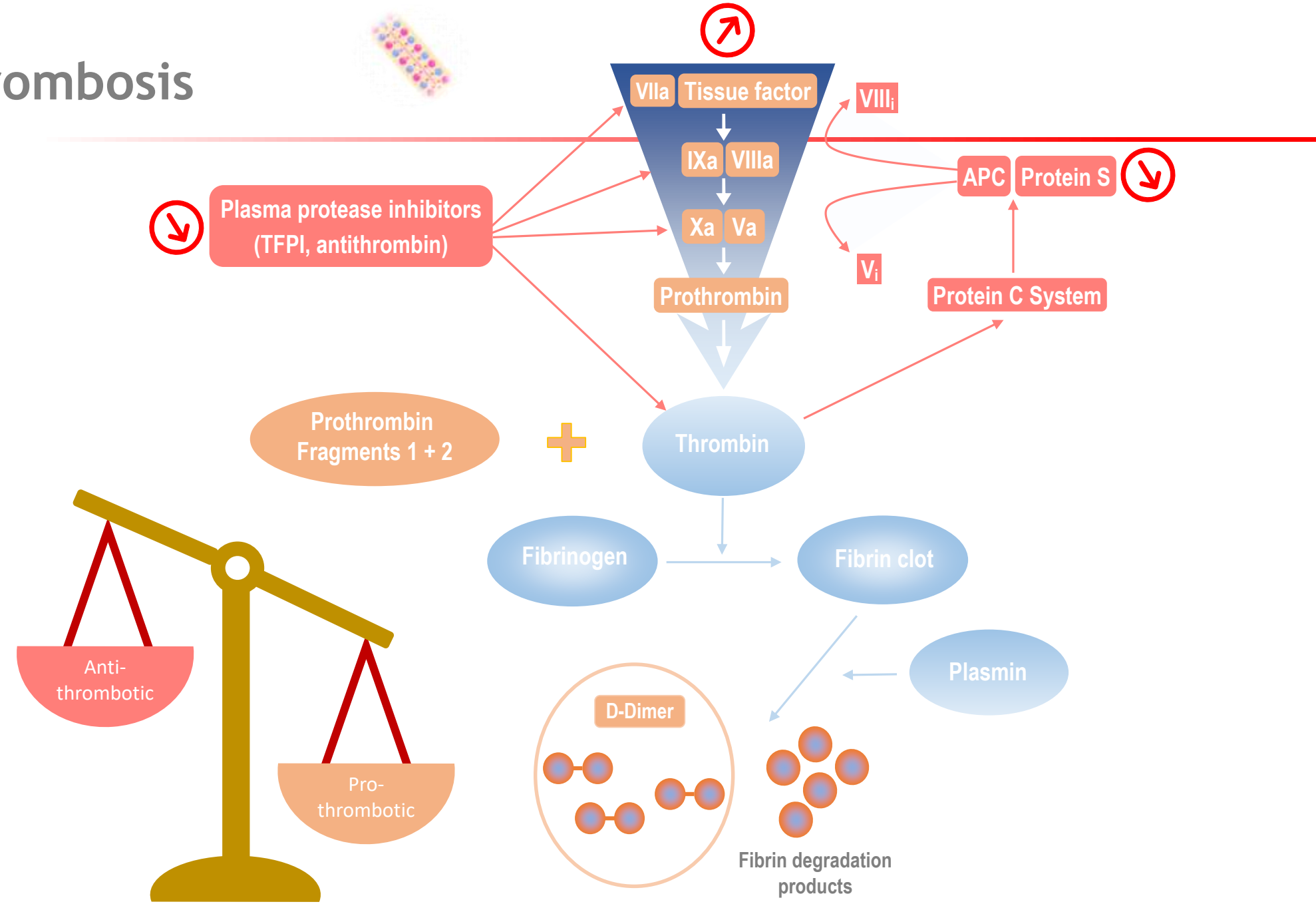
Association of mestranol and norethynodrel

Morimont L, et al. Front Endocrinol (Lausanne). 2021;12:769187.

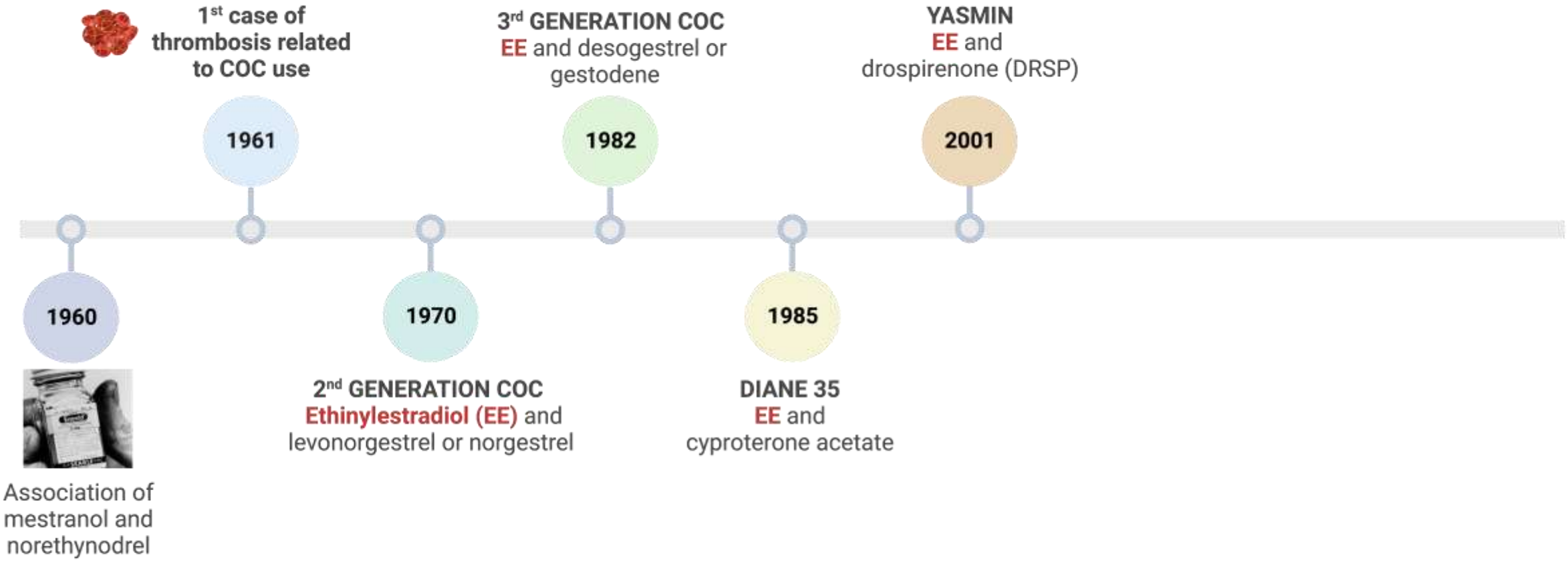
Venous thrombosis



Venous thrombosis

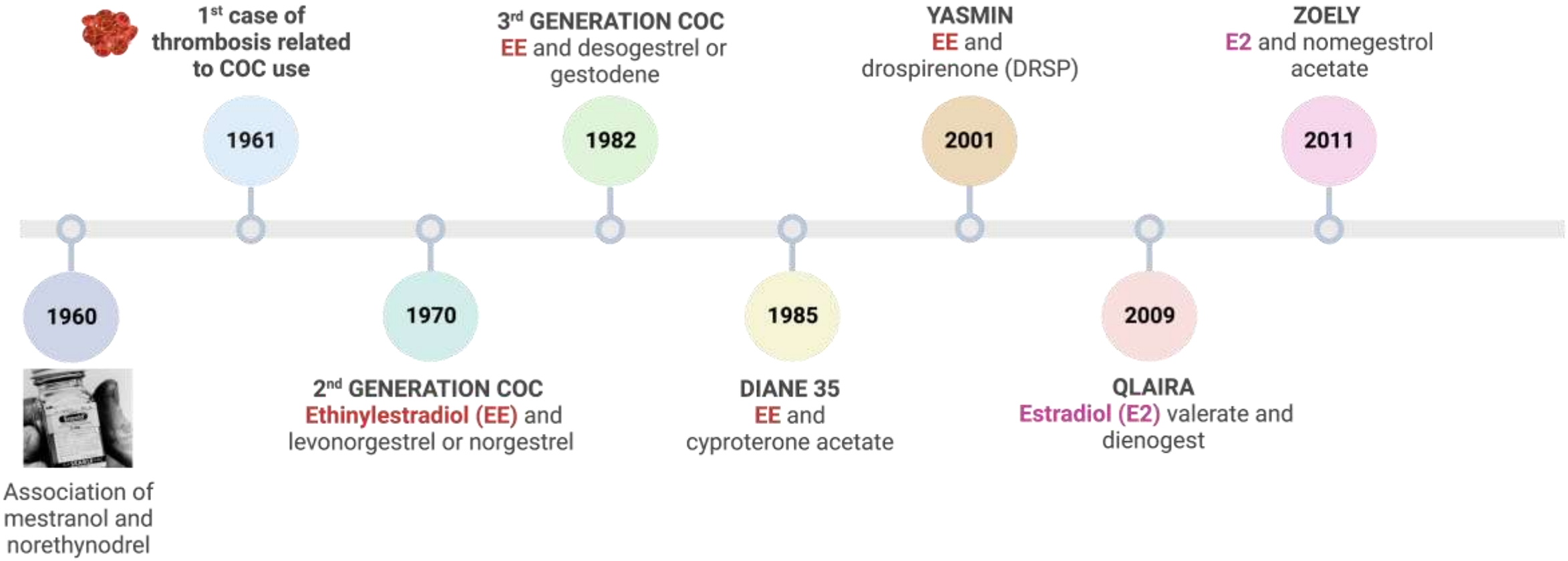


The pill history



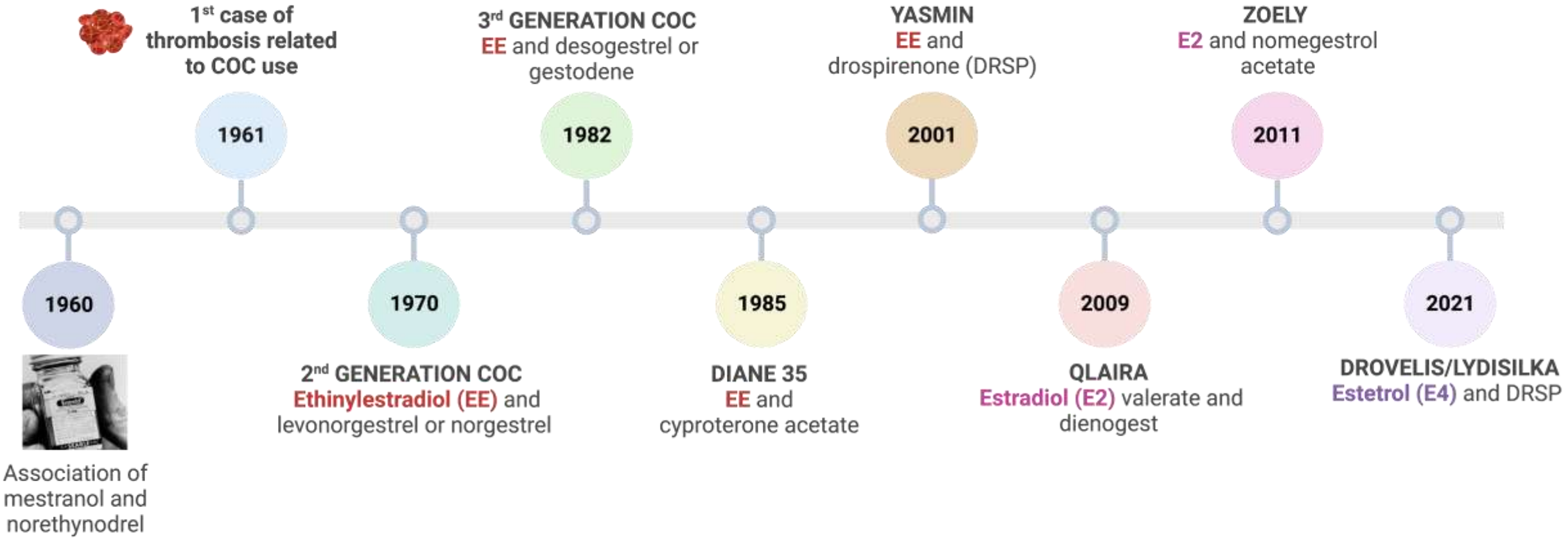
Morimont L, et al. Front Endocrinol (Lausanne). 2021;12:769187.

The pill history



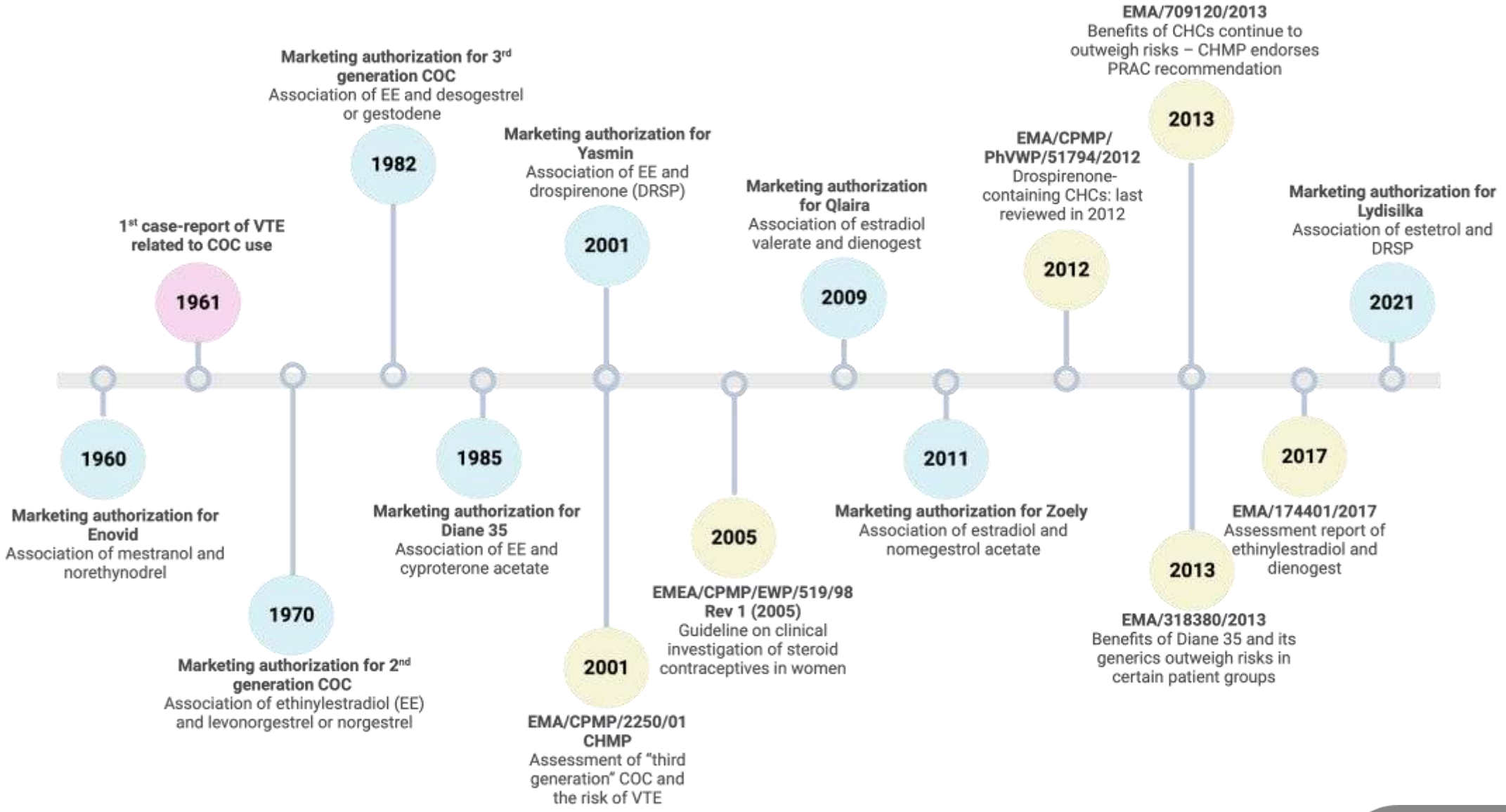
Morimont L, et al. Front Endocrinol (Lausanne). 2021;12:769187.

The pill history



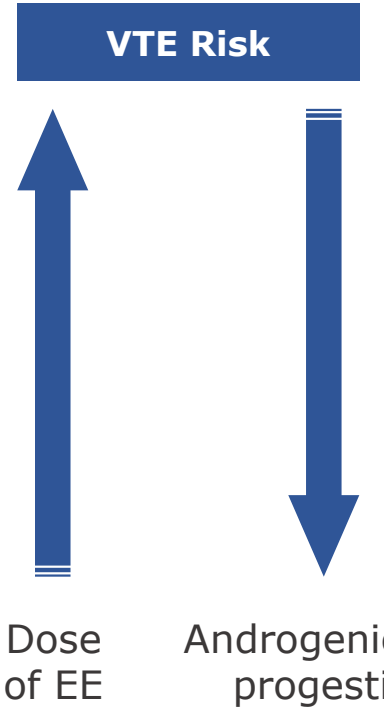
Morimont L, et al. Front Endocrinol (Lausanne). 2021;12:769187.

The « recent » regulatory pill history



Morimont L, et al. Front Endocrinol (Lausanne). 2021;12:769187.

Oral contraceptive and risk of VTE



Exposure	Relative risk
No COC	1
Pregnancy	5
EE 20|30|50 µg with levonorgestrel	1,3 – 3,6 | 1,8 – 3,2 | 3,4 – 7,9
EE 20|30 µg with gestodene	1,4 – 3,2 | 2,8 – 4,9
EE 20|30 µg with desogestrel	2,5 – 4,6 | 3,3 – 5,6
EE 30 µg with drospirenone	2,7 – 5,5
EE with dienogest	3,5

de Bastos, M., et al. Cochrane Database Syst Rev, 2014(3): p. CD010813| Dinger J et al. Contraception 2016. 94(4): p. 328-39| Heit JA et al. Ann Intern Med. 2005 . 143: p. 697-706 | Jick H et al. Lancet 1995 . 346(8990): p. 1589-93| Lidegaard Ø et al. BMJ 2009 . 339: p. b2890 | Lidegaard Ø et al. BMJ 2011. 343: p. d6423| Spitzer I et al. BMJ 1996 . 312(7023): p. 83-8 | Vlieg AVH et al. BMJ 2009. . 339: p. b2921

European Medicines Agency referral

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

22 November 2013
EMA/709120/2013

Benefits of combined hormonal contraceptives (CHCs) continue to outweigh risks – CHMP endorses PRAC recommendation

Product information to be updated to help women make informed decisions about their choice of contraception

European Medicines Agency referral

Risk of developing a blood clot (VTE) in a year	
Women **not using** a combined hormonal pill/patch/ring and are not pregnant	About 2 out of 10,000 women
Women using a CHC containing **levonorgestrel, norethisterone or norgestimate**	About 5-7 out of 10,000 women
Women using a CHC containing **etonogestrel or norelgestromin**	About 6-12 out of 10,000 women
Women using a CHC containing **drospirenone, gestodene or desogestrel**	About 9-12 out of 10,000 women
Women using a CHC containing **chlormadinone, dienogest or nomegestrol**	Not yet known[1]

WITH CHC containing EE

[1] Further studies are ongoing or planned to collect sufficient data to estimate the risk for these products.

EE-based COCs are shifting women to a prothrombotic state

- Mean incidence of VTE in non-user ±2.5/10.000 wy
- Mean incidence of VTE with EE-based COCs ±10/10.000 wy
- Mean incidence of VTE in women aged 60-69 y ±10/10.000 wy

USING EE-BASED COCs SHIFTS THE THROMBOTIC RISK OF YOUNG HEALTHY WOMEN TO A 60 YEARS WOMEN

GLOBAL BURDEN OF COC-ASSOCIATED VTE IN EUROPE

±23,000 VTE cases each year

Douxfils, J. Front Endocrinol (Lausanne). 2025;16:1559162.

- **In the US, the annual expenditures for all VTE-related healthcare is around 10 billion $ per year**

- **The average three-year societal cost attributable to VTE was between €50,000 and €100,000 per patient and could be even higher in the younger population due to indirect costs and long-term morbidity of the thrombotic event.**

Unmet (yet) medical and societal need to reduce the risk of VTE associated with COC

Gustafsson N, et al. Eur Heart J Qual Care Clin Outcomes. 2020;6:130-7. | Grosse SD et al. Thrombosis research. 2016;137:3-10. | Douxfils J. Front Endocrinol (Lausanne). 2025;16:1559162.

Is EE/LNG still the safest COC?

E2 and E2V as estrogens in COC

« Based on the **lower impact of estradiol (E2) and estradiol valerate (EV) on the hepatic system** and subsequently **on haemostatic parameters** compared to ethinylestradiol, it is assumed that E2 and E2V are associated with a similar or even **lower risk of cardiovascular events including VTE and ATE** »

Hemostatic Effects of a Novel Estradiol-Based Oral Contraceptive

An Open-Label, Randomized, Crossover Study of Estradiol Valerate/Dienogest versus Ethinylestradiol/Levonorgestrel

Christine Klipping,[1] Ingrid Duijkers,[1] Susanne Parke,[2] Uwe Mellinger,[2] Marco Serrani[2] and Wolfgang Junge[3]

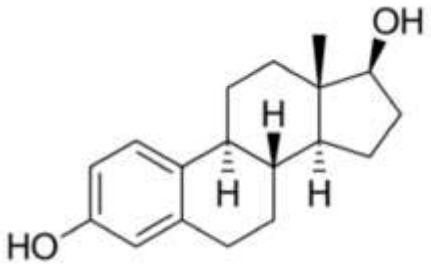
Haemostatic effects of a new combined oral contraceptive, nomegestrol acetate/17β-estradiol, compared with those of levonorgestrel/ethinyl estradiol

A double-blind, randomised study

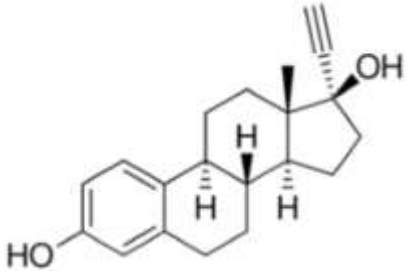
Pascale Gaussem[1–3]; Martine Alhenc-Gelas[2,3]; Jean-Louis Thomas[4]; Christilla Bachelot-Loza[3]; Veronique Remones[3]; Fouad Dali Ali[3]; Martine Aiach[1–3]; Pierre-Yves Scarabin[3]

Effects of a monophasic combined oral contraceptive containing nomegestrol acetate and 17β-oestradiol compared with one containing levonorgestrel and ethinylestradiol on haemostasis, lipids and carbohydrate metabolism

Ulla M. Ågren, Marjatta Anttila, Kristiina Mäenpää-Liukko, Maija-Liisa Rantala, Hilkka Rautiainen, Werner F. Sommer & Ellen Mommers



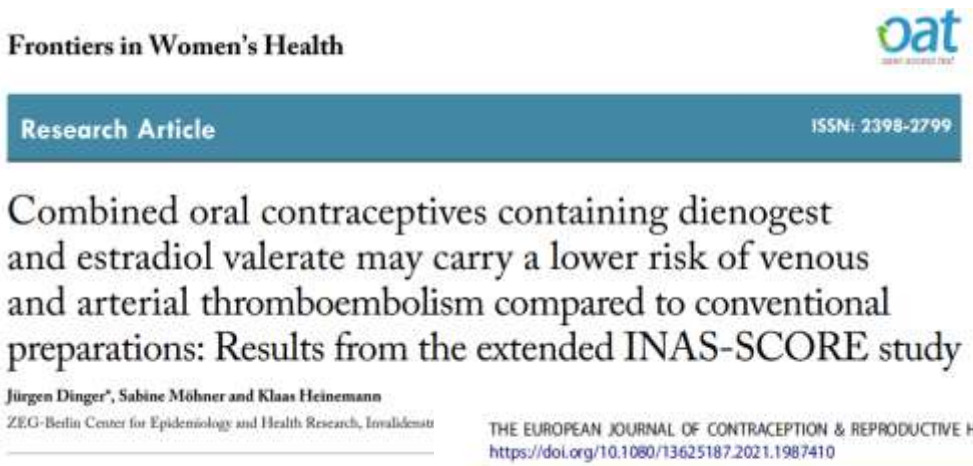
Estradiol



Ethinylestradiol

Dinger, J. et al. Front Women's Health. 2020. 5(1) | Gaussem P, et al. Thrombosis and haemostasis. 2011 Mar;105(3):560-7. | Klipping C, et al. Drugs in R&D. 2011;11(2):159-70. | Agren UM et al. Eur J Contracept Reprod Health Care. 2011;16:444-57.

Data from epidemiological studies with E2(V)



Frontiers in Women's Health

oat

Research Article ISSN: 2398-2799

Combined oral contraceptives containing dienogest and estradiol valerate may carry a lower risk of venous and arterial thromboembolism compared to conventional preparations: Results from the extended INAS-SCORE study

Jürgen Dinger*, Sabine Möhner and Klaas Heinemann
ZEG-Berlin Center for Epidemiology and Health Research, Invalidenstr

THE EUROPEAN JOURNAL OF CONTRACEPTION & REPRODUCTIVE HEALTH CARE
https://doi.org/10.1080/13625187.2021.1987410

Taylor & Francis
Taylor & Francis Group

RESEARCH ARTICLE

OPEN ACCESS Check for updates

Prospective controlled cohort study on the safety of a monophasic oral contraceptive containing nomegestrol acetate (2.5mg) and 17β-oestradiol (1.5mg) (PRO-E2 study): risk of venous and arterial thromboembolism

Suzanne Reed[a], Carol Koro[b], Julia DiBello[b], Kerstin Becker[a], Anja Bauerfeind[a], Christian Franke[a] and Klaas Heinemann[a]

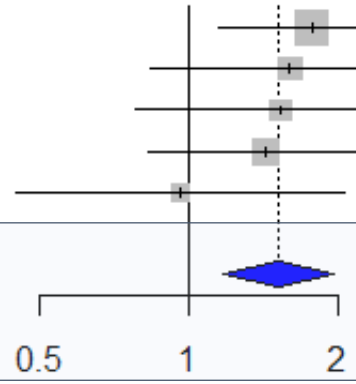
[a]Berlin Center for Epidemiology and Health Research (ZEG), Berlin, Germany; [b]Merck & Co., Inc, North Wales, PA, USA

Dinger J,. et al. Front Women's Health. 2020. 5(1) | Reed, S. et al. Eur J Contracept Reprod Health Care. 2021. 26(6): p. 439-446

Meta-analysis of EE-based versus E2-based pills

Study	EE-based Events	EE-based Total	E2-based Events	E2-based Total	OR	95%-CI	Weight
Heikinheimo, 2022	158	510	25	129	1.76	[1.15; 2.70]	35.8%
Reed, 2021	25	62337	12	48846	1.60	[0.83; 3.05]	15.5%
Schink, 2022	744	7774	6	101	1.52	[0.78; 2.97]	14.6%
Bauerfeind, 2024	99	107586	11	17932	1.42	[0.83; 2.42]	22.8%
Yonis, 2025	997	2092749	7	14135	0.96	[0.45; 2.05]	11.3%
Random effects model		**2270956**		**81143**	**1.51**	**[1.17; 1.95]**	**100.0%**

Heterogeneity: $I^2 = 0.0\%$, $\tau^2 = 0$, $p = 0.7454$

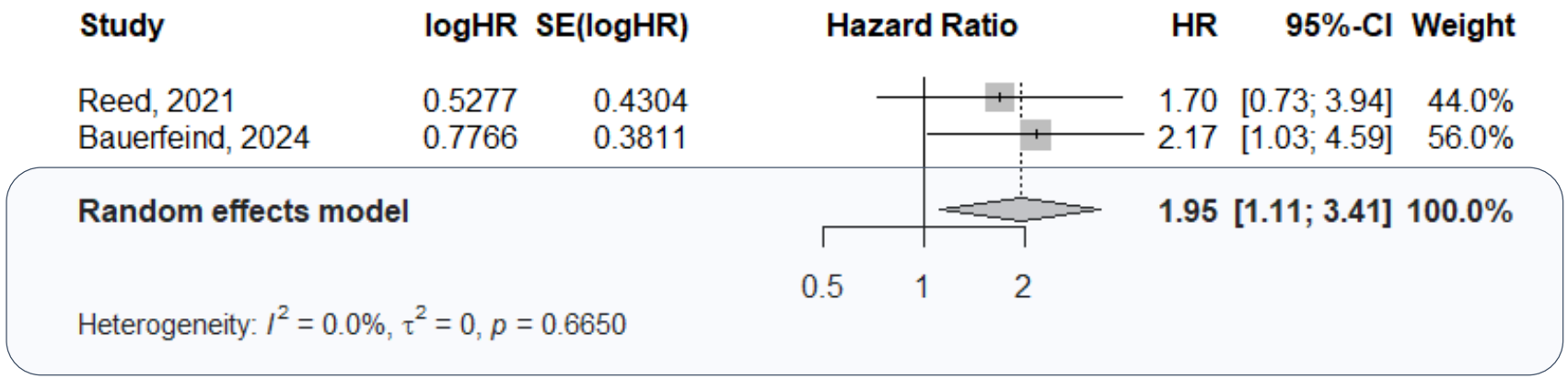


*For Bauerfeind, oCOC are extracted from Dinger et al 2020 (same study reporting different groups)

The crude* estimate reveals a 51% increase of the risk of VTE with EE-based pills

* Without adjustment for confounding factors

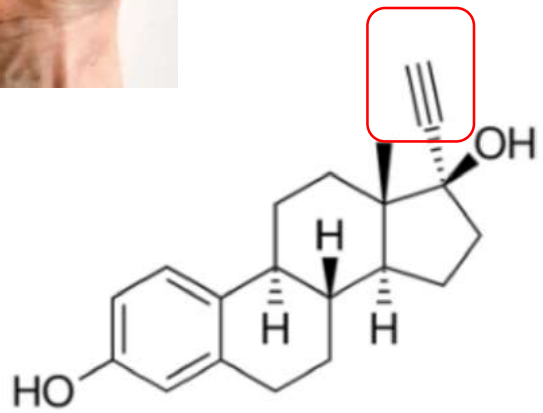
Meta-analysis of EE-based versus E2-based pills

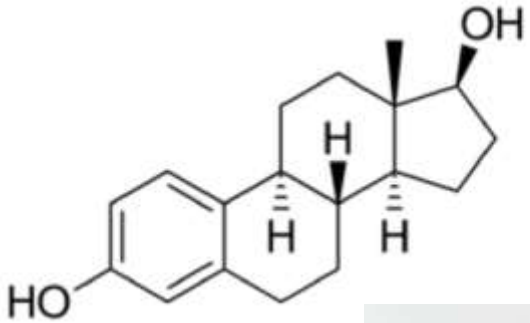


*For Bauerfeind, oCOC are extracted from Dinger et al 2020 (same study reporting different groups)

The adjusted estimate reveals a 95% increase of the risk of VTE with EE-LNG pills

Is EE/LNG still the safest COC?

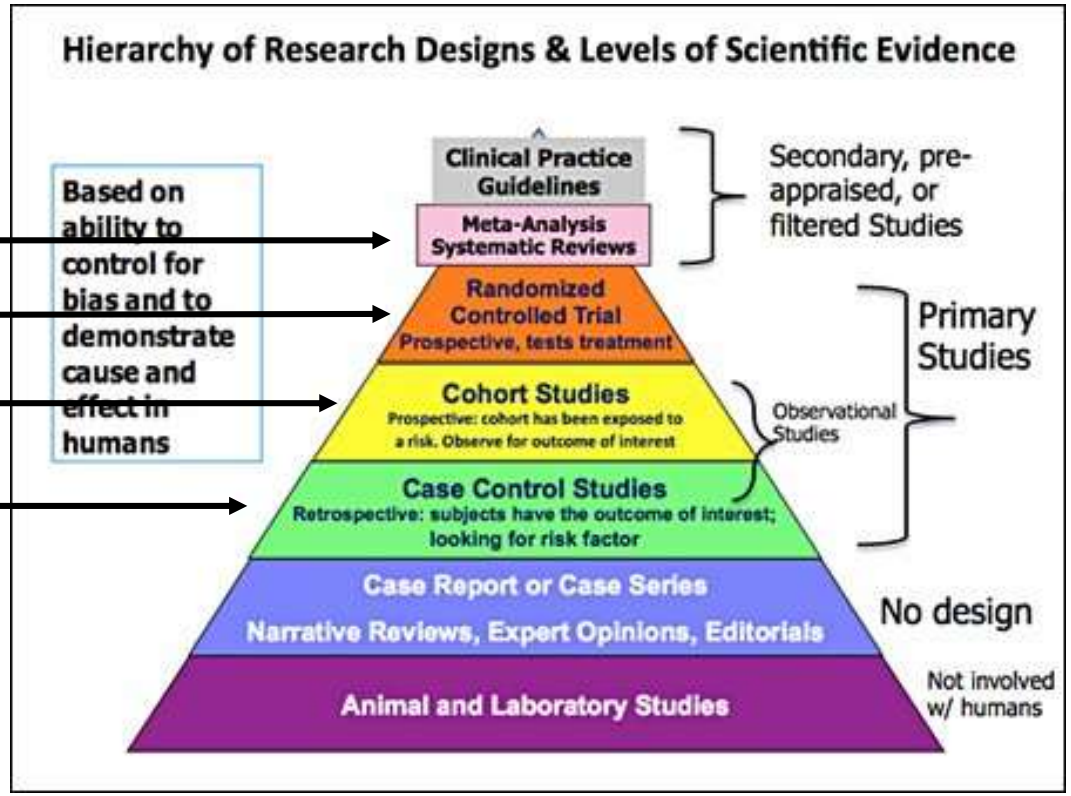




How can we state the evidence?

Conclusions from biological data, clinical and real-life experience with E4

3. Meta-analysis with natural estrogens
1. RCT with surrogate markers
2. INAS-SCORE / PRO-E2 / INAS-NEES / INAS-SEECS studies
4. Eudravigilance / FAERS data



Didembourg M et al. Contraception. 2024. doi: 10.1016/j.contraception.2024.110727. | Douxfils, J. et al. Contraception. 2020. 102(6): p. 396-402 | Morimont et al. Thromb Res. 2020. 193: p. 221-223. | Douxfils J, et al. Front Endocrinol (Lausanne). 2024;15:1428597 | Dinger J,. et al. Front Women's Health. 2020. 5(1) | Reed, S. et al. Eur J Contracept Reprod Health Care. 2021. 26(6): p. 439-446.

E4 - a Natural Estrogen with Selective action in Tissues supported by a unique mode of action

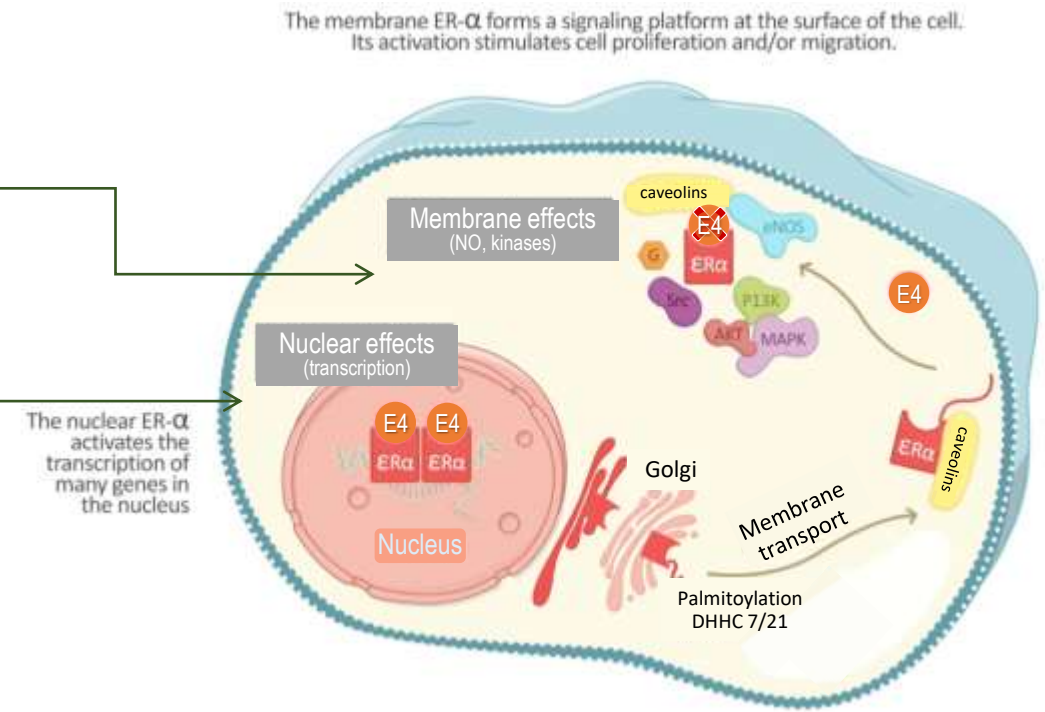
E4 acts differently depending on the tissue

Antagonist on the membrane ERα

- ✓ E4 blocks the membrane estrogen receptor[1-3]
- ✓ E4 has a neutral effect on the liver unlike other estrogens[1-3]
- ✓ E4 has a low impact on normal and malignant breast[4-7]

Agonist on the nuclear ERα

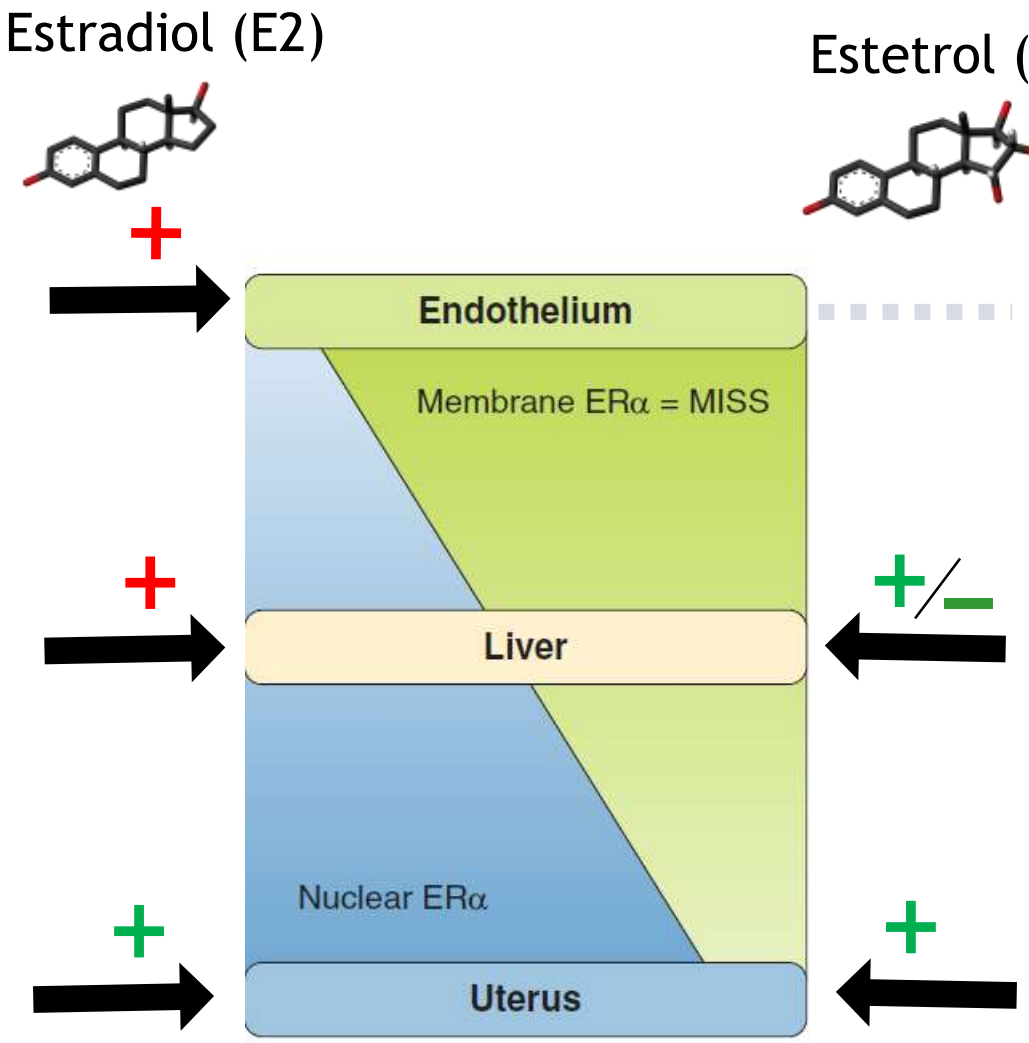
- ✓ E4 activates the nuclear estrogen receptor[1,2,3]
- ✓ E4 has important estrogenic activity on the vagina, endometrium, bone, and cardiovascular system to provide beneficial effects[1-3]



ER: estrogen receptor; E4: estetrol; NO: nitric oxide; G: glucose, Src: tyrosine-protein kinase; eNOS: endothelial nitric oxide synthase; PI3K: phosphatidylinositol 3-kinase; AKT: protein kinase B; MAPK: mitogen-activated protein kinase; DHHC 7/21: palmitoylacyltranferases for sex steroid receptors

[1] Abot et al. EMBO Mol Med 2014 | [2]Foidart JM et al. In: Brinton RD et al. (eds.) 2019. Sex Steroids' Effects on Brain, Heart and Vessels. ISGE Series |[3]Arnal JF et al. Physiol Rev 2017 | [4]Giretti et al. Front Endocrinol (Lausanne) 2014 | [5]Gérard et al. J Endocrinol 2015 | [6]Singer CF et al. Carcinogenesis 2014 | [7]Visser M et al. Horm Mol Biol Clin Invest 2012

Tissue-specific activity of E4



- E2 and E4 exert physiological actions in the uterus, a tissue with dominant ERα nuclear activity
- The endothelium with exclusively membrane ERα is insensitive to E4
- **The liver is more sensitive to E2 and EE, depending on both membrane and nuclear ER effects**

Arnal et al Physiol. Rev. 2017. 97; 1045-1087

Hemostasis parameters, regulatory bodies, and development of steroid contraceptives

European Medicines Agency

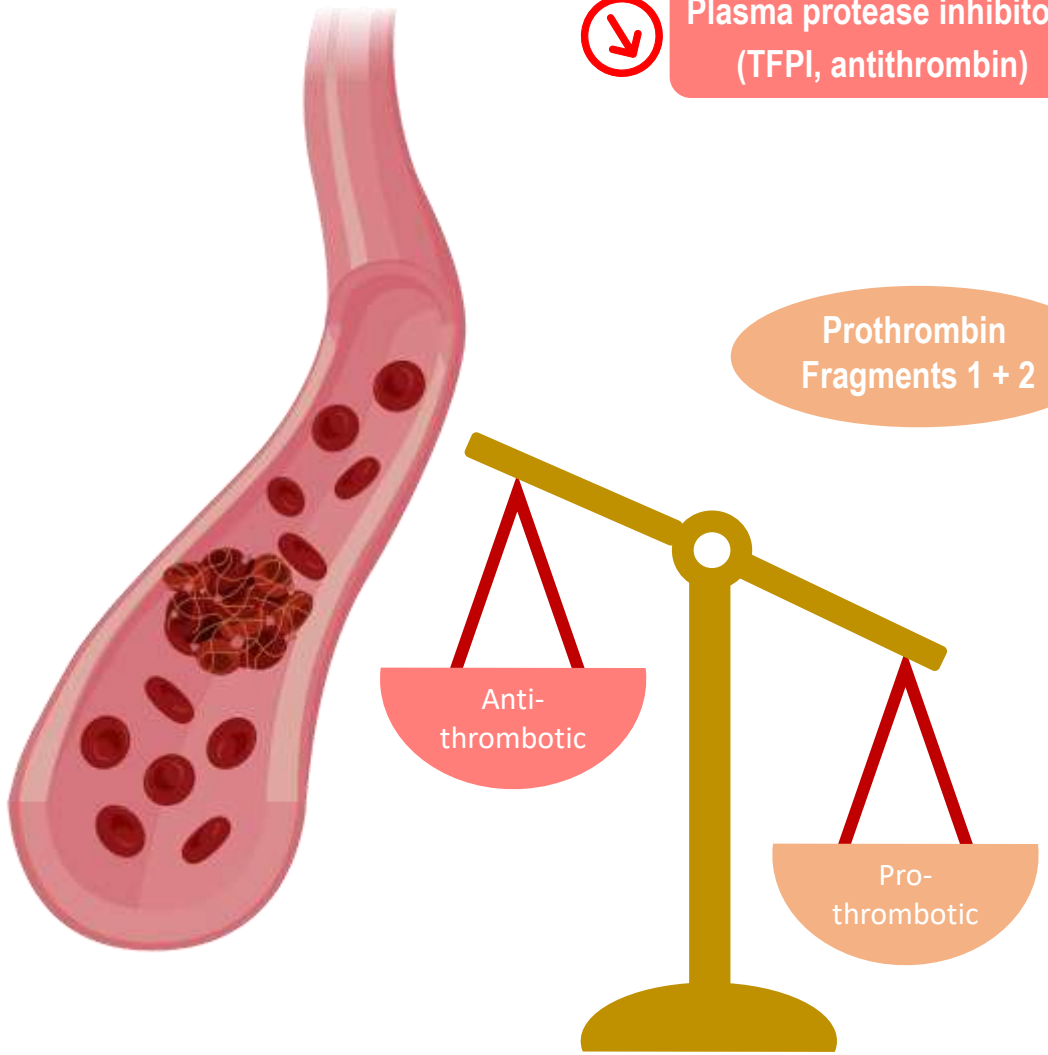
List of recommended hemostasis investigations during the development of steroid contraceptives

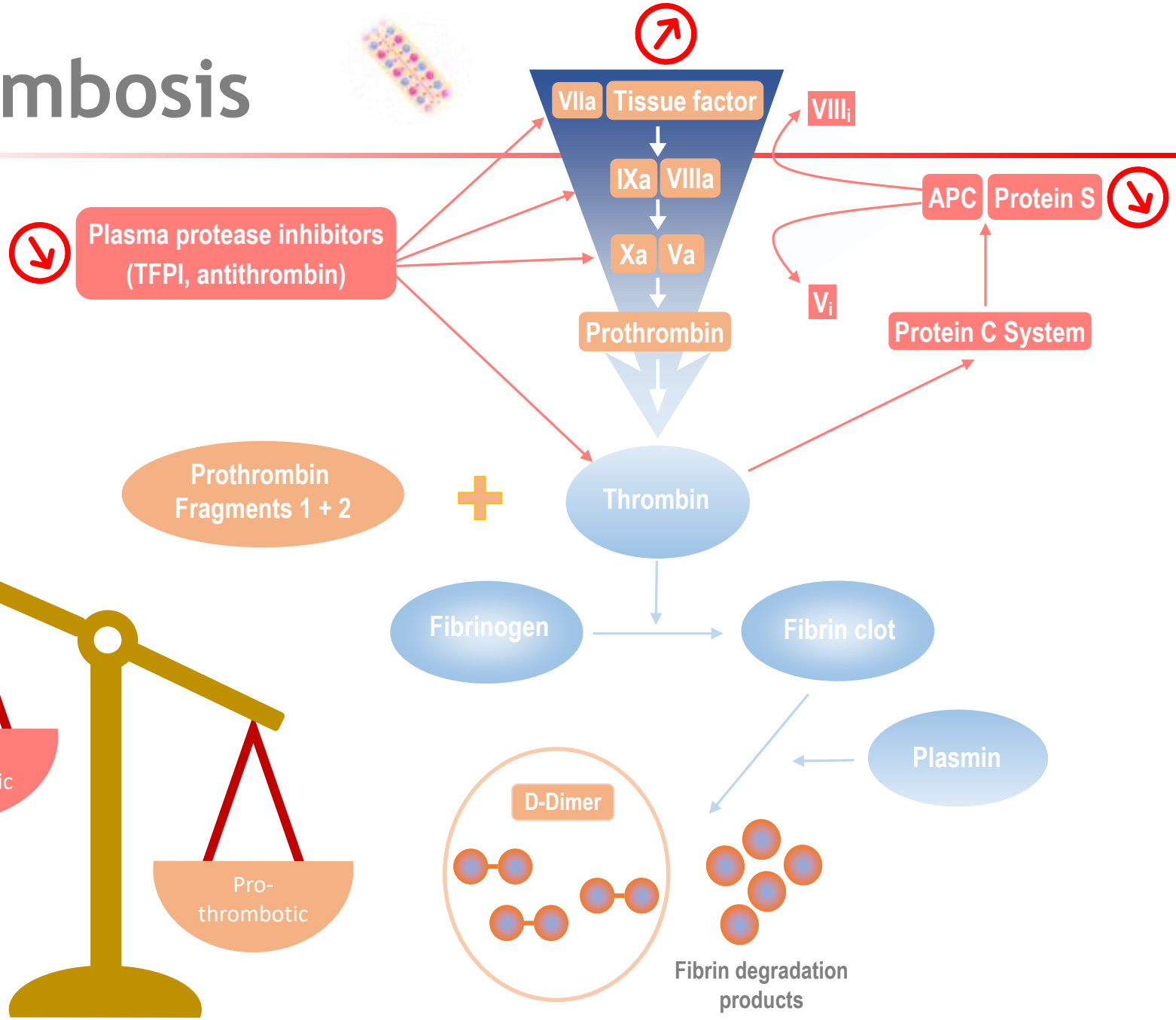
- Antithrombin
- APTT-based APC resistance
- ETP-based APC resistance
- D-Dimer
- Factor II
- Factor VII
- Factor VIII
- Protein C
- Protein S
- Prothrombin fragment 1+2
- SHBG

APC: activated protein C | APTT: activated partial thromboplastin time | COC: combined oral contraceptive | ETP: endogenous thrombin potential | SHBG: sex hormone binding globulin | VTE: venous thromboembolism

An increase or a decrease in all these factors is expected with CHC making interpretation of the global effect very difficult

Venous thrombosis





Hemostasis parameters, regulatory bodies, and development of steroid contraceptives

European Medicines Agency

List of recommended hemostasis investigations during the development of steroid contraceptives

- Antithrombin
- APTT-based APC resistance
- **ETP-based APC resistance**
- D-Dimer
- Factor II
- Factor VII
- Factor VIII
- Protein C
- Protein S
- Prothrombin fragment 1+2
- SHBG

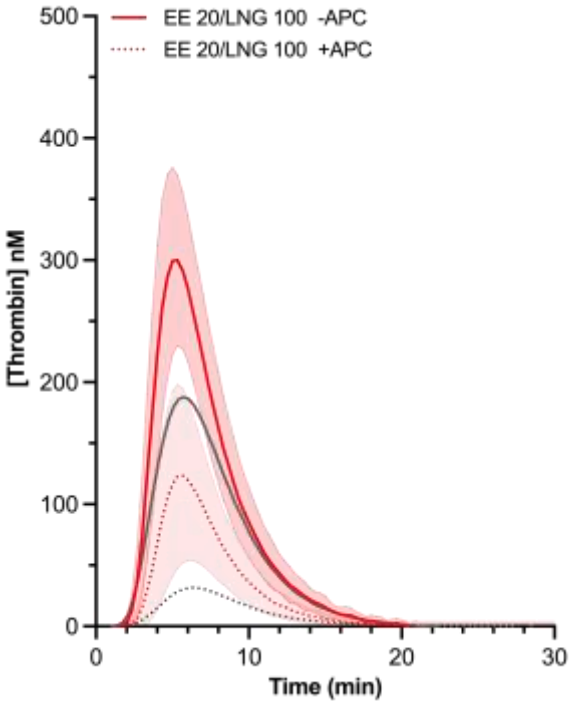
APC: activated protein C | APTT: activated partial thromboplastin time | COC: combined oral contraceptive | ETP: endogenous thrombin potential | SHBG: sex hormone binding globulin | VTE: venous thromboembolism

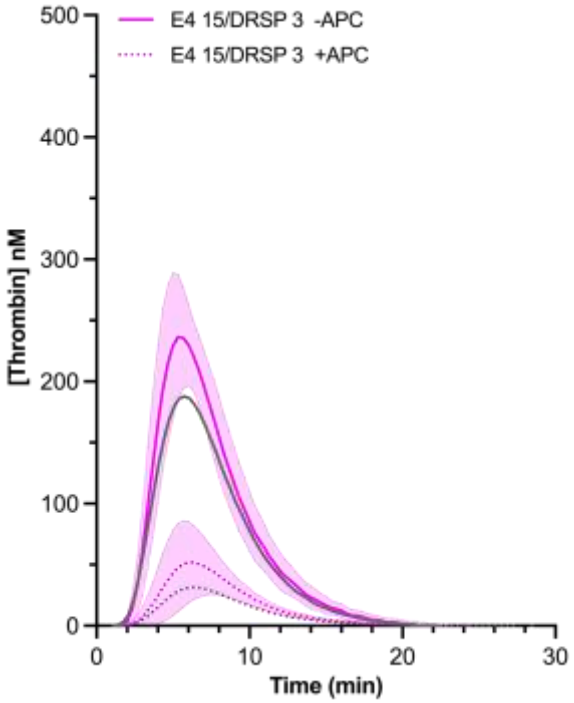
An increase or a decrease in all these factors is expected with CHC making interpretation of the global effect very difficult

Global coagulation test

European Medicines Agency. Guideline on Clinical investigation of Steroid Contraceptives in Women — EMEA/CPMP/EWP/519/98 Rev 1. 2005

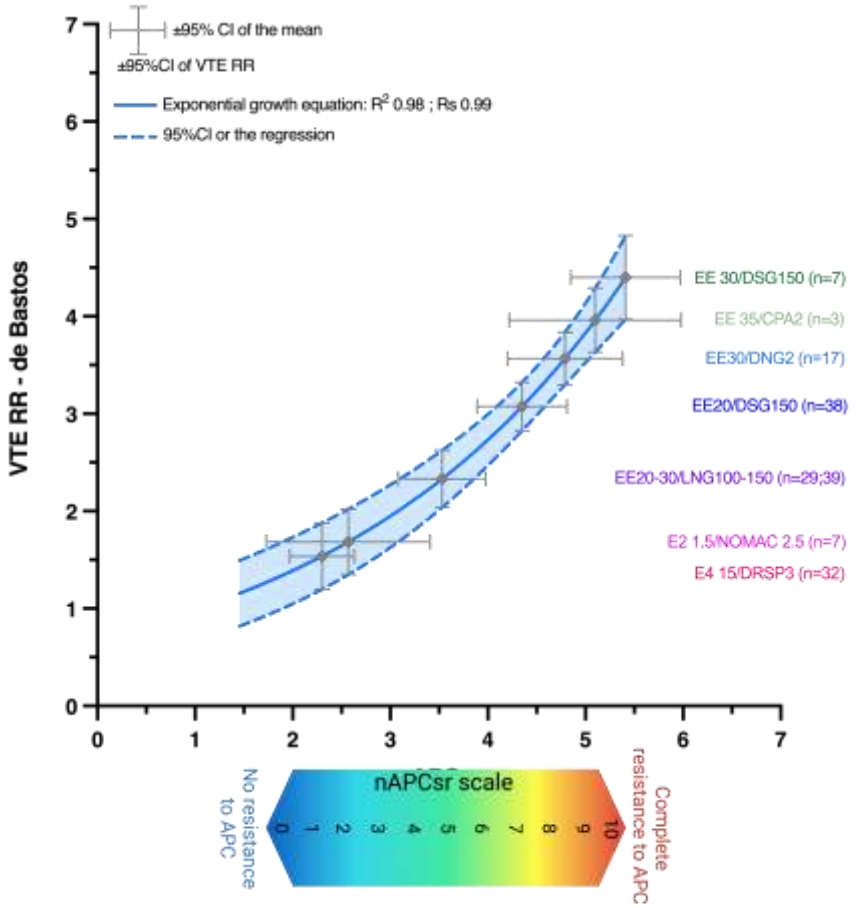
ETP-based APC resistance and VTE risk – E4/DRSP



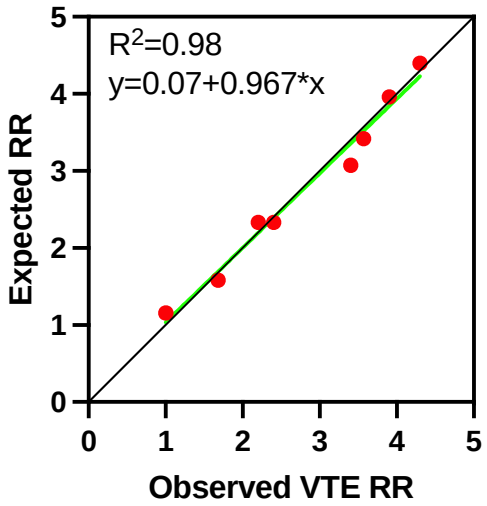


Douxfils, J. et al. Contraception. 2020. 102(6): p. 396-402 | Douxfils, J. et al. Climacteric. 2023. 26(1): p. 55-63

Thrombosis prediction model – EMA Qualification advise discussions



Subgroups	Observed VTE risk (model)	Expected VTE risk (literature)
EE 30 + DSG 150	4.40 (3.97-4.83)	4.30 (3.30-5.60)[1]
EE 35 + CPA 2	3.96 (3.63-4.29)	3.90 (2.70-5.50)[1]
EE 30 + DNG 2	3.57 (3.30-3.84)	3.42 (1.51-7.29)[2,*]
EE 20 + DSG 150	3.07 (2.83-3.32)	3.40 (2.50-4.60)[1]
EE 30 + LNG 150	2.33 (2.04-2.62)	2.40 (1.80-3.20)[1]
EE 20 + LNG 100	2.33 (2.04-2.62)	2.20 (1.30-3.60)[1]
E2 1.5/NOMAC 2.5	1.68 (1.35-2.02)	1.58 (0.61-4.08)[2,**]
E4 15/DRSP 3	1.54 (1.20-1.88)	Not known



de Bastos, M., et al. Cochrane Database Syst Rev, 2014(3): p. CD010813| Morimont et al. Thromb Res. 2020. 193: p. 221-223.

Clinical experience with E4+DRSP

Data from phase 3 studies supports these assumptions

One single VTE event over 3,417 participants in the US/CANADA and EU/RUS studies

This represents an estimated incidence of 3.7/10,000 women-year

The estimated incidence using the nAPCsr model is 3.8/10,000 women-year*

Comparison:

- 3 VTE events over 1,683 participants in EE 10 µg /NETA 1 mg trial (COC)
- 4 VTE events over 1,188 participants in EE 13 µg / segesterone 150 µg trial (vaginal ring)
- 4 VTE events over 2,031 participants in EE 30 µg / LNG 120 µg trial (patch)

* Considering the baseline incidence as being 2.4/10,000 women-year according to the data from the PRO-E2 study (excl. Russian data and woman with VTE risk factors like VTE without pre-defined risk factors like Pregnant within 3 months of treatment initiation, history of cancer/chemotherapy or an increased genetic risk of VTE (e.g., Factor V Leiden, Protein S or C deficiency).

Archer et al. Obstet Gynecol. 2013. 122(3): p. 601-7 | Gemzell-Danielsson K. et al. Contraception. 2019. 99(6): p. 323-328. | Nelson AL. et al. Contraception. 2021. 103(3): p. 137-143.

Eudravigilance database

- EudraVigilance is a **data and information system developed by the EMA** for the collection, management, and analysis of reports of suspected side effects of medicines that are authorized or being studied in clinical trials in the **European Economic Area**

Didembourg M et al. Contraception. 2024. doi: 10.1016/j.contraception.2024.110727.

Disproportionnality analysis

- **(Dis)proportionality analysis** is a set of **statistical signal detection techniques based on comparing reporting proportions** between the study drug and all drugs of a particular class in the spontaneous reporting database combined

European Medicines Agency
Evaluation of Medicines for Human Use

London, 16 November 2006
Doc. Ref. EMEA/106464/2006

EUDRAVIGILANCE EXPERT WORKING GROUP (EV-EWG)

GUIDELINE ON THE USE OF STATISTICAL SIGNAL DETECTION METHODS IN THE EUDRAVIGILANCE DATA ANALYSIS SYSTEM

Didembourg M et al. Contraception. 2024. doi: 10.1016/j.contraception.2024.110727.

Disproportionnality analysis

- This statistical method relies on the principle that when **a signal detection report identifies a specific AE linked to a medicinal product**, **this AE is reported more frequently in connection with this product**, compared to other medications.

- This **(D)PRR is like a relative risk (RR)** except that the denominator is not the patient-exposure but the total number of AEs reported for the product or the entire therapeutic class (COCs) in the database.

$$PRR = \frac{A/(A+B)}{C/(C+D)}$$

Where:

- (A) represents the number of individual cases reporting the venous thrombotic event associated with the study drug.
- (B) represents the number of individual cases reporting other events associated with the study drug.
- (C) represents the number of individual cases reporting the venous thrombotic event associated with all other medicinal products of the therapeutic class.
- (D) represents the number of individual cases reporting other events associated with all other medicinal products of the therapeutic class.

Didembourg M et al. Contraception. 2024. doi: 10.1016/j.contraception.2024.110727.

Adverse events reported in EudraVigilance

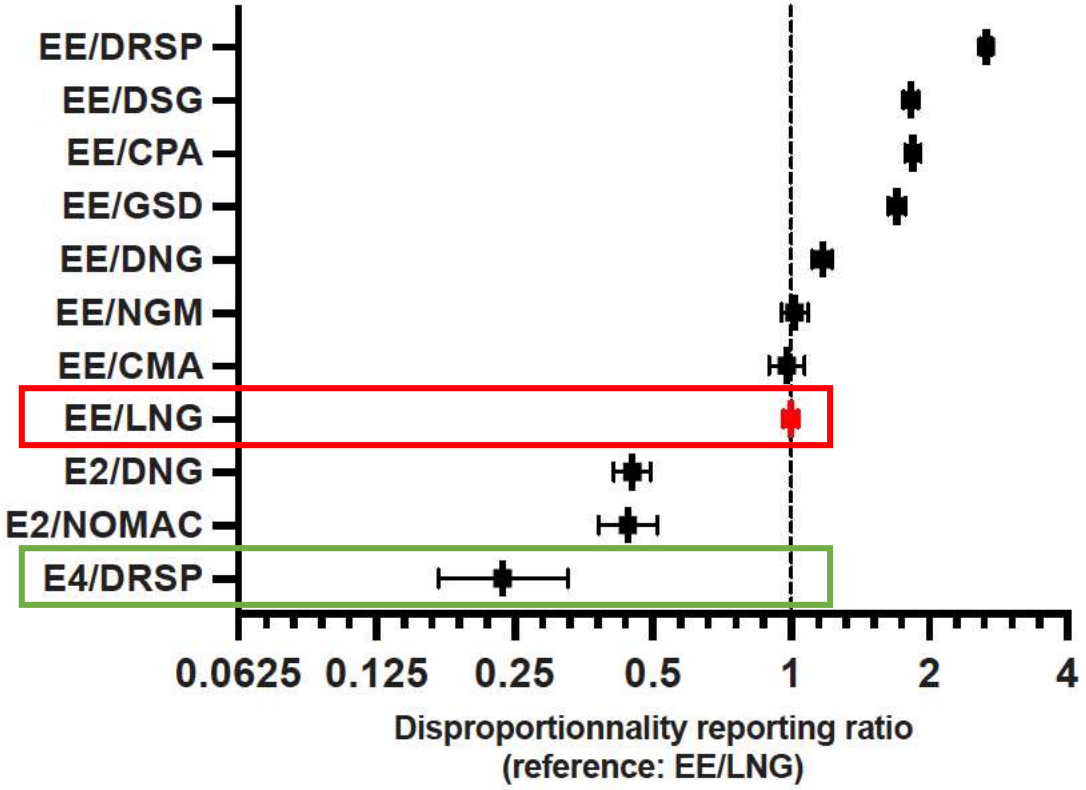
Table 1
Number of extracted thrombotic and other adverse events from the EudraVigilance database for all combined oral contraceptives (COC) or drospirenone at the dose of 4 mg alone

Estroprogestative association	Number of "thrombotic" events reported[a]	Number of adverse events reported	Reporting ratio
E2/DNG	428	3330	0.13
E2/NOMAC	158	1256	0.13
E4/DRSP	34	507	0.07
EE/CMA	396	1419	0.28
EE/CPA	2391	4552	0.52 (5)
EE/DNG	1286	3852	0.33
EE/DRSP	30,022	39,578	0.76
EE/DSG	2275	4374	0.52
EE/GSD	1616	3335	0.48 (5)
EE/LNG (gold standard)	3869	13,583	0.28 (5)
EE/NGM	722	2489	0.29
All COC	**43,197**	**78,275**	0.55
DSRP[b]	92	1361	0.07

Didembourg M et al. Contraception. 2024. doi: 10.1016/j.contraception.2024.110727.

EE/LNG as reference

Reporting ratio all COCs = 0.55
Reporting ratio EE/LNG = 0.28
Reporting ratio E4/DRSP = 0.07



When **compared to EE/LNG**:

- **Natural estrogen are ”safer” than EE/LNG**
- **Among natural estrogens, E4+DRSP shows the safest profile**
- **These results support the observed effect of:**
  - **The meta-analysis**
  - **Coagulation data**

Didembourg M et al. Contraception. 2024. doi: 10.1016/j.contraception.2024.110727. | Douxfils J, et al. Front Endocrinol (Lausanne). 2024;15:1428597 | de Bastos, M., et al. Cochrane Database Syst Rev, 2014(3): p. CD010813| Morimont et al. Thromb Res. 2020. 193: p. 221-223.

E4/DRSP has similar PRR as DRSP alone

Table 2
Summary of proportionality reporting rate estimates and significance of all COC compared to the therapeutic class and compared to the gold standard EE-LNG

Estrogen/progestin combination	Proportionality reporting rate [95% CI] vs the therapeutic class	*p*-value	Proportionality reporting rate [95% CI] vs the gold standard EE-LNG	*p*-value
E2/DNG	0.23 [0.21–0.25]	< 0.001	0.45 [0.41–0.49]	< 0.001
E2/NOMAC	0.23 [0.19–0.26]	< 0.001	0.44 [0.38–0.51]	< 0.001
E4/DRSP	0.12 [0.09–0.17]	< 0.001	0.24 [0.17–0.33]	< 0.001
EE/CMA	0.50 [0.46–0.54]	< 0.001	0.98 [0.90–1.07]	0.65
EE/CPA	0.95 [0.92–0.98]	< 0.001	1.84 [1.77–1.92]	< 0.001
EE/DNG	0.59 [0.57–0.62]	< 0.001	1.17 [1.11–1.23]	< 0.001
EE/DRSP	2.23 [2.19–2.26]	< 0.001	2.66 [2.59–2.74]	< 0.001
EE/DSG	0.94 [0.91–0.97]	< 0.001	1.83 [1.76–1.90]	< 0.001
EE/GSD	0.87 [0.84–0.90]	< 0.001	1.70 [1.63–1.78]	< 0.001
EE/LNG (gold standard)	0.47 [0.46–0.48]	< 0.001	1.00 [0.96–1.04]	-
EE/NGM	0.52 [0.49–0.55]	< 0.001	1.02 [0.95–1.09]	0.59
DSRP[a]	0.12 [0.10–0.15]	< 0.001	0.24 [0.19–0.29]	< 0.001

Didembourg M et al. Contraception. 2024. doi: 10.1016/j.contraception.2024.110727.

Data from the FAERS database

COC	Reporting rate in EUDRAVIGILANCE	DPRR [95%CI] in EUDRAVIGILANCE	Reporting rate in FAERS	DPRR [95%CI] in FAERS
EE/LNG (reference)	0.28	1.00	0.12	1.00
EE/NETA	/	/	0.14	1.16 [1.09-1.23]
EE/DRSP	0.76	2.66 [2.59–2.74]	0.62	5.21 [4.98-5.45]
E2/DNG	0.13	0.45 [0.41–0.49]	0.09	0.80 [0.66-0.97]
E4/DRSP	0.07	0.24 [0.17–0.33]	0.06	0.54 [0.30-0.99]
DRSP	0.07	0.24 [0.19–0.29]	0.08	0.64 [0.55-0.74]

Raskin L et al. AJOG. Under Review.

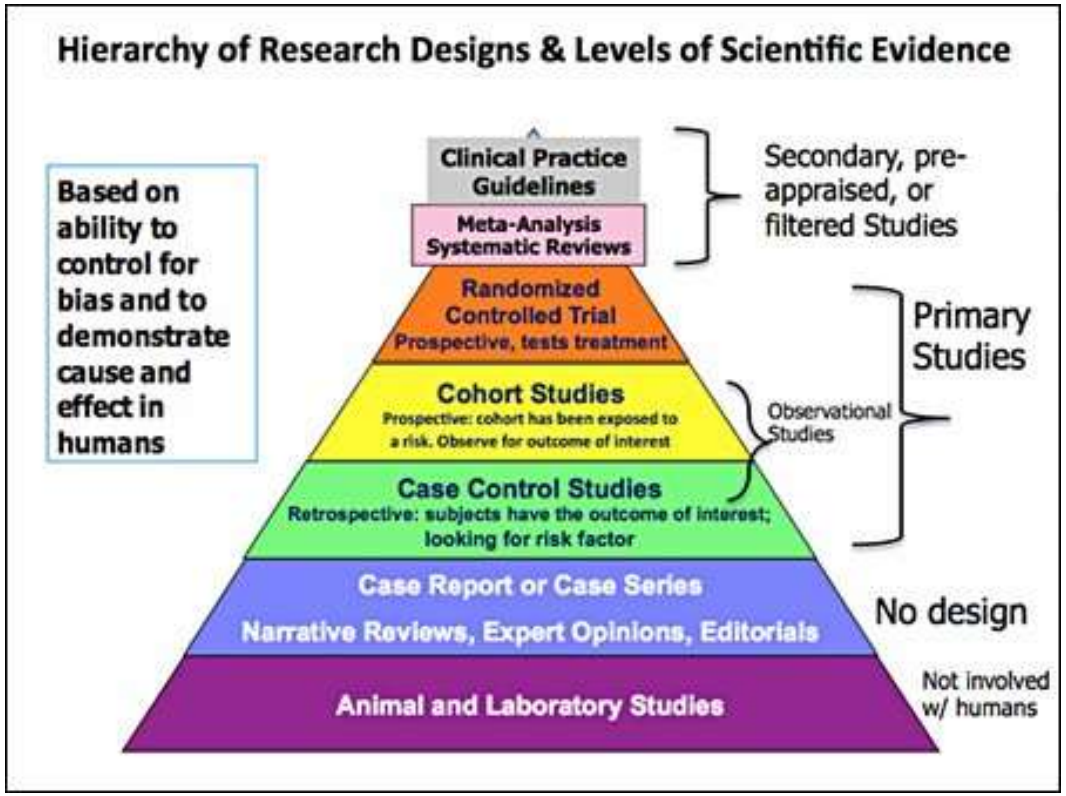
Do we need epidemiological studies?

Conclusions from biological data, clinical and real-life experience with E4

Hemostasis biological data, the current clinical and the real-life experience are very reassuring

E4 is a safer compound in contraception and probably in menopause

Data from large epidemiological studies will only be there to further confirm these observations **NOT to characterize the risk**



Gemzell-Danielsson K. et al. Contraception. 2019. 99(6): p. 323-328. | Morimont, L. et al. J Clin Endocrinol Metab. 2022. 108(1): p. 135-143 | Douxfils, J. et al. Contraception. 2020. 102(6): p. 396-402 | Douxfils, J. et al. Climacteric. 2023. 26(1): p. 55-63

Do we need epidemiological studies?

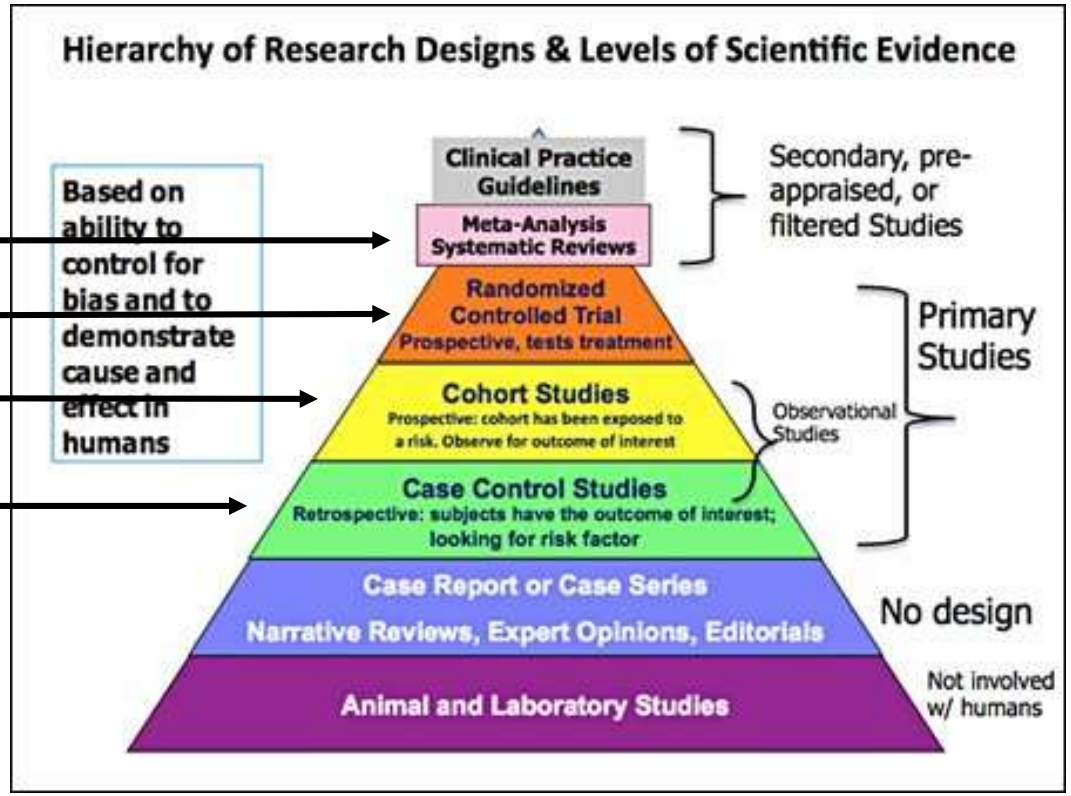
Conclusions from biological data, clinical and real-life experience with E4

Meta-analysis with natural estrogens

RCT with surrogate markers*

INAS-SCORE / PRO-E2 studies

Eudravigilance / FAERS data



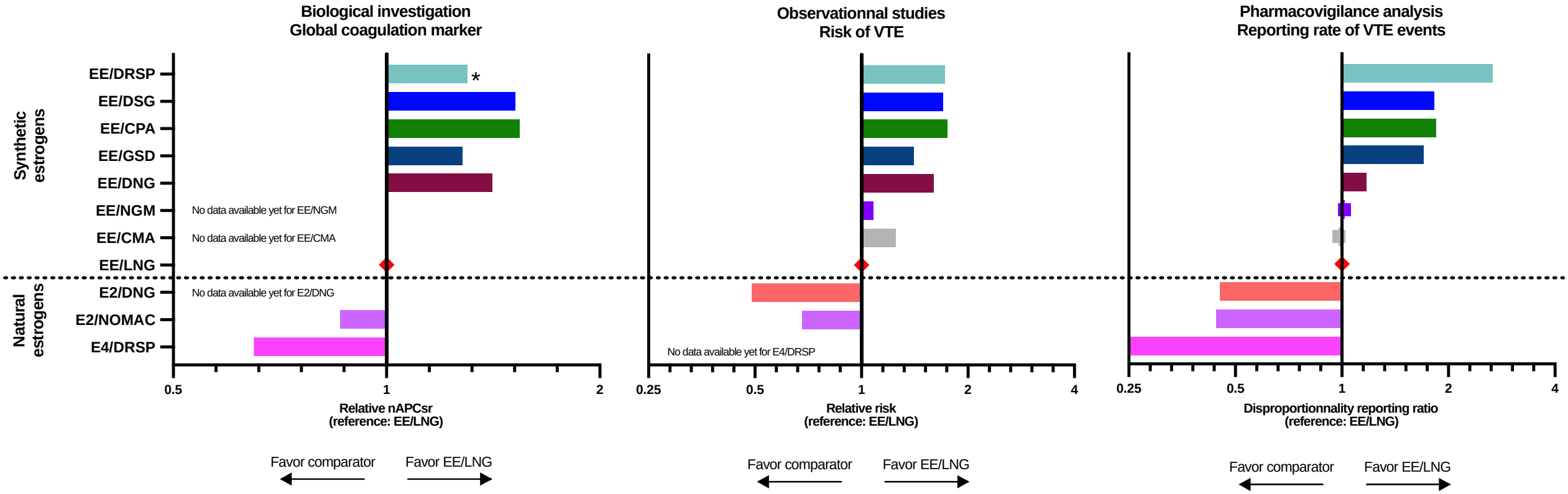
* The level of evidence depends on the validity of the surrogate markers

Note that the ETP-based APC resistance is listed as recommended investigation by the EMA but not yet validated as a predictive biomarker by regulatory bodies.

Gemzell-Danielsson K. et al. Contraception. 2019. 99(6): p. 323-328. | Morimont, L. et al. J Clin Endocrinol Metab. 2022. 108(1): p. 135-143 | Douxfils, J. et al. Contraception. 2020. 102(6): p. 396-402 | Douxfils, J. et al. Climacteric. 2023. 26(1): p. 55-63

Multiple level of evidence suppport lower risk of VTE with natural estrogens

- Current evidence robustly supports the safety of natural estrogens like E2 and E4 over EE, in reducing thrombotic risks.



Epidemiological studies

Large epidemiological studies (like INAS-SCORE, e.g.) will take **more than 7 years** to be issued

These epidemiological studies are requested due to **regulatory standards** following the risk observed with EE-containing pills (i.e. now all new COC needs to conduct a post authorization safety epidemiological study)

Thrombosis is a multifactorial disease and non-interventional **studies are not always able to capture all these risk factors** and adjust for that, they are providing rough estimates and cannot be translated into individuals' strategies

A simple tool characterizes **the impact of a particular COC on hemostasis** which is linked to the risk of VTE from very large epidemiological studies

Multilevel of evidence is essential and provides consistent information

Idea for a task force? Things are moving!

The choice of the oestrogen matters when considering the risk of VTE and classification of COC should be reappraised considering the latest scientific evidence

Received: 28 May 2025 | Revised: 30 June 2025 | Accepted: 4 July 2025

DOI: 10.1002/ijgo.70393

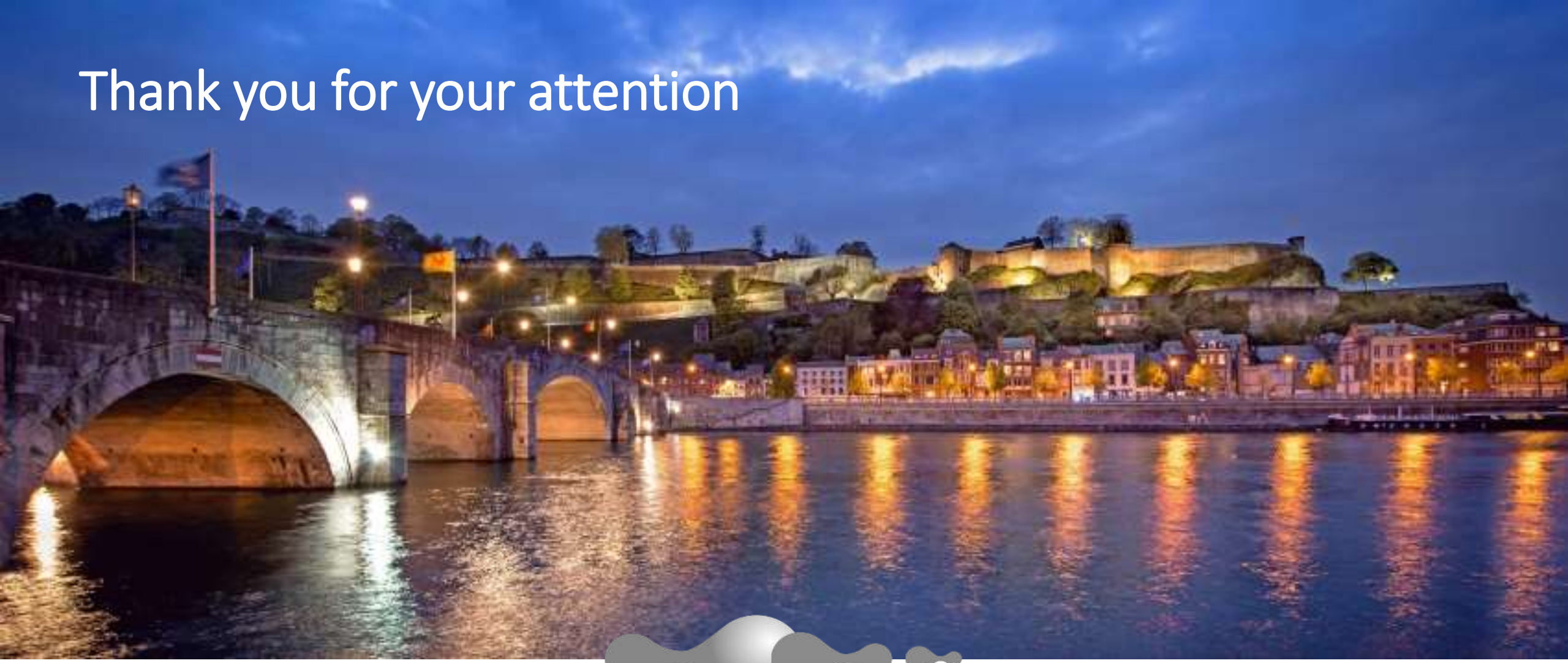
BRIEF COMMUNICATION

Obstetrics

Body-identical estrogens in combined hormonal contraceptives: A safer path forward

Nathalie Chabbert-Buffet[1] | Ivonne J. Diaz Yamal[2] | Jonathan Douxfils[3] | Jean-Michel Foidart[4] | Franca Fruzzetti[5] | Kristina Gemzell-Danielsson[6] | Rossella E. Nappi[7,8] | Yutaka Osuga[9] | Philippe Descamps[10]

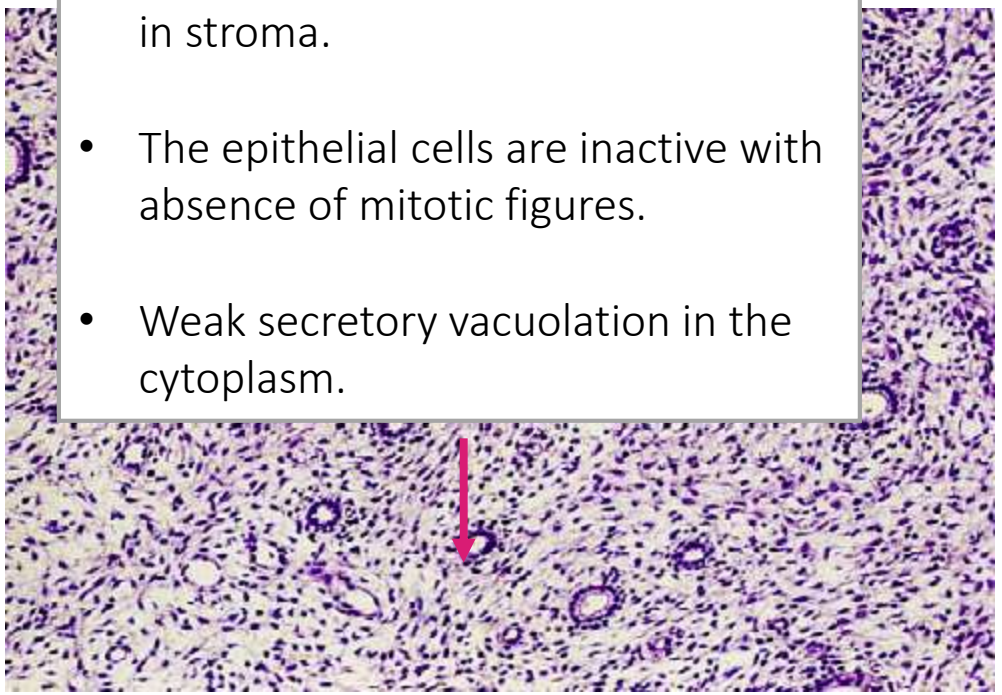
Thank you for your attention



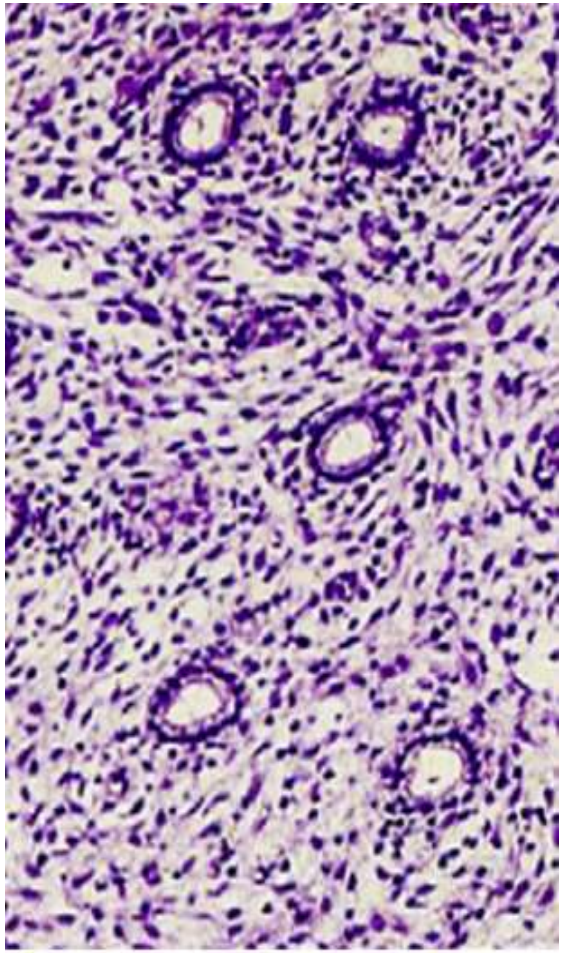
UNIVERSITÉ DE NAMUR

The estrogen in COC stabilizes the endometrium

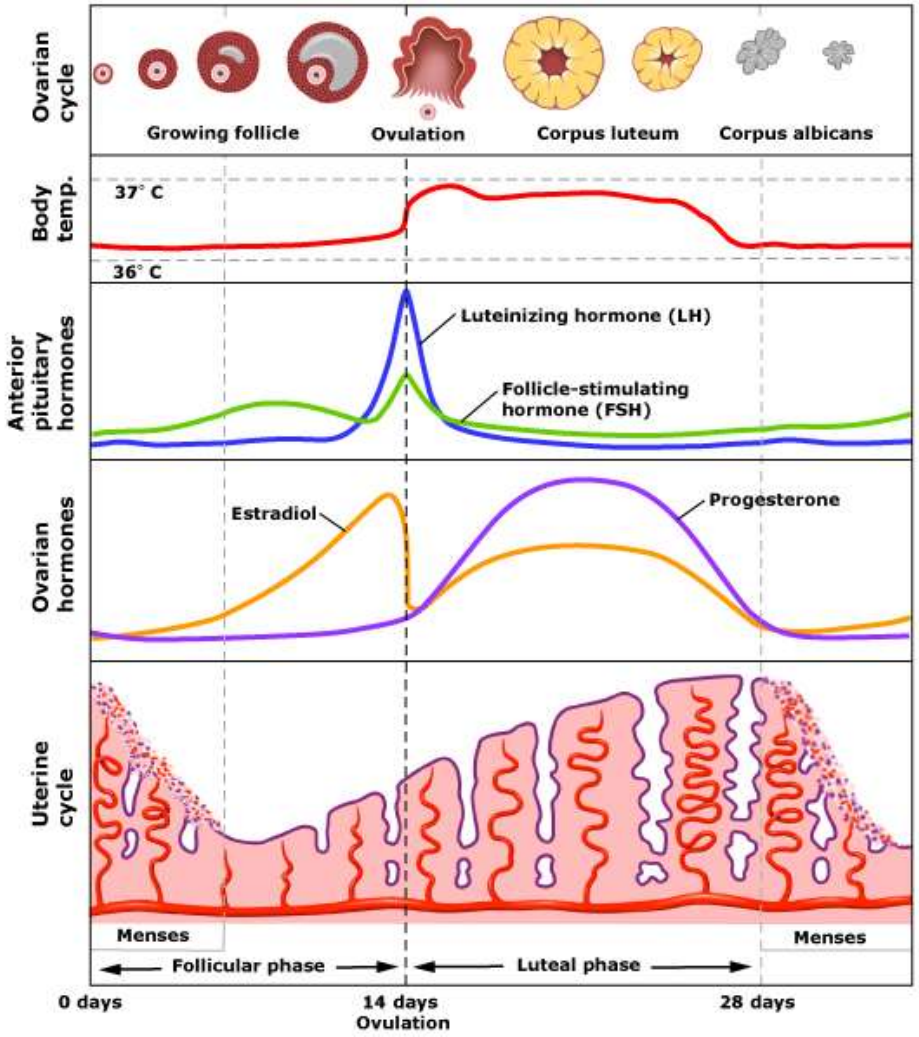
- Endometrial glands show a tubular structure. Glands are widely spaced in stroma.
- The epithelial cells are inactive with absence of mitotic figures.
- Weak secretory vacuolation in the cytoplasm.



Limited unscheduled bleeding



The key role of progestins: blockade of ovulation



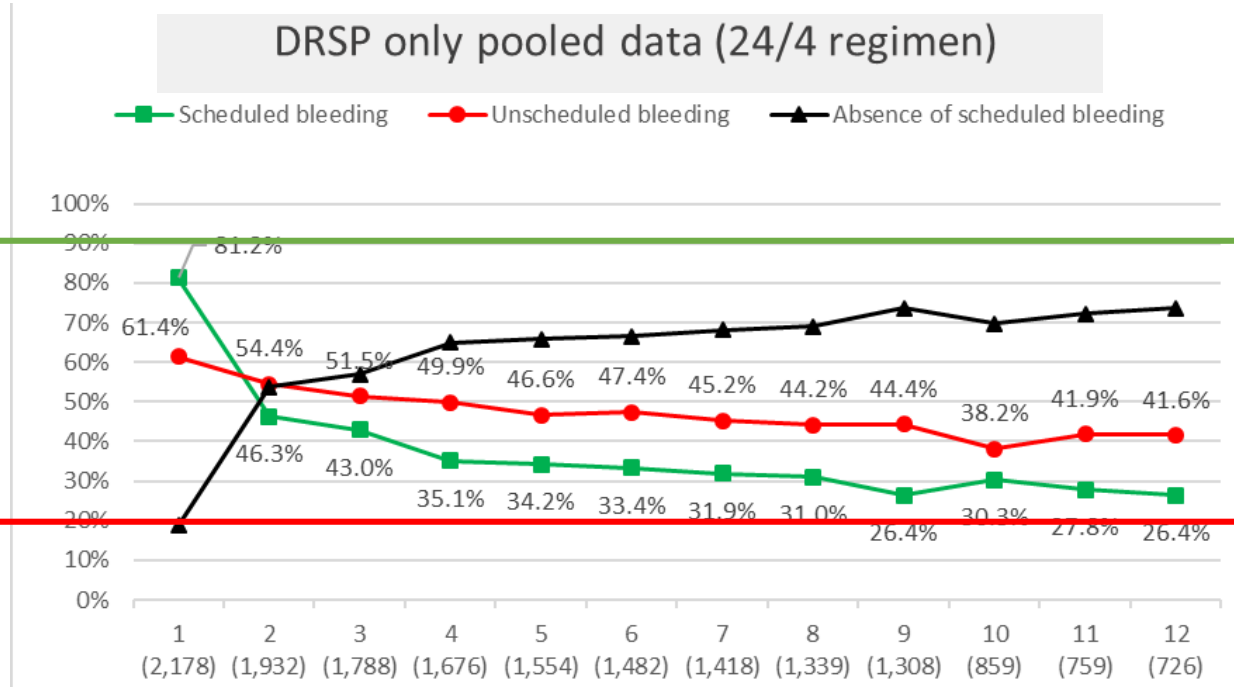
Norethisterone,	(Estrane)
Levonorgestrel, Norgestimate,	(Gonane)
Desogestrel, Gestodene,	(Gonane)
Dienogest,	(Gonane)
Chlormadinone,	(Pregnane)
Cyproterone acetate,	(Pregnane)
Nomegestrol acetate,	(Norpregnane)
Drospirenone	**(Spirolactone)**

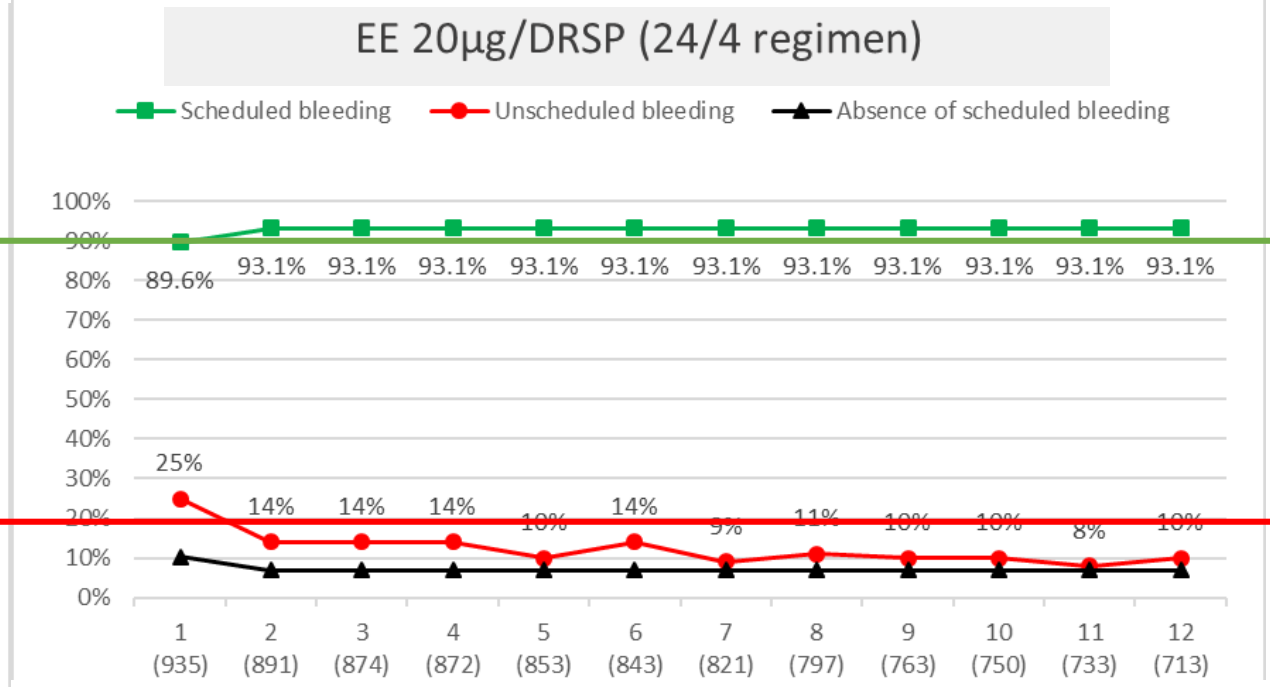
Why to add an estrogen to the progestin?

1. To **improve** the **menstrual bleeding pattern** by stabilizing the endometrium,
2. To **assist the progestin in inhibiting ovulation** and **suppressing FSH**,
3. To **prevent estrogen deficiency** causing vaginal dryness,
4. To **maintain or improve well-being / quality of life**.

Cooper DB and Mahdy H. StatPearls 2021; Baird DT and Glasier AF. N Engl J Med 1993; FSHR Guidelines Combined Hormonal Contraception 2019; Merchenthaler I. Encyclopedia of Reproduction (2nd Ed.) 2018; IARC 2012

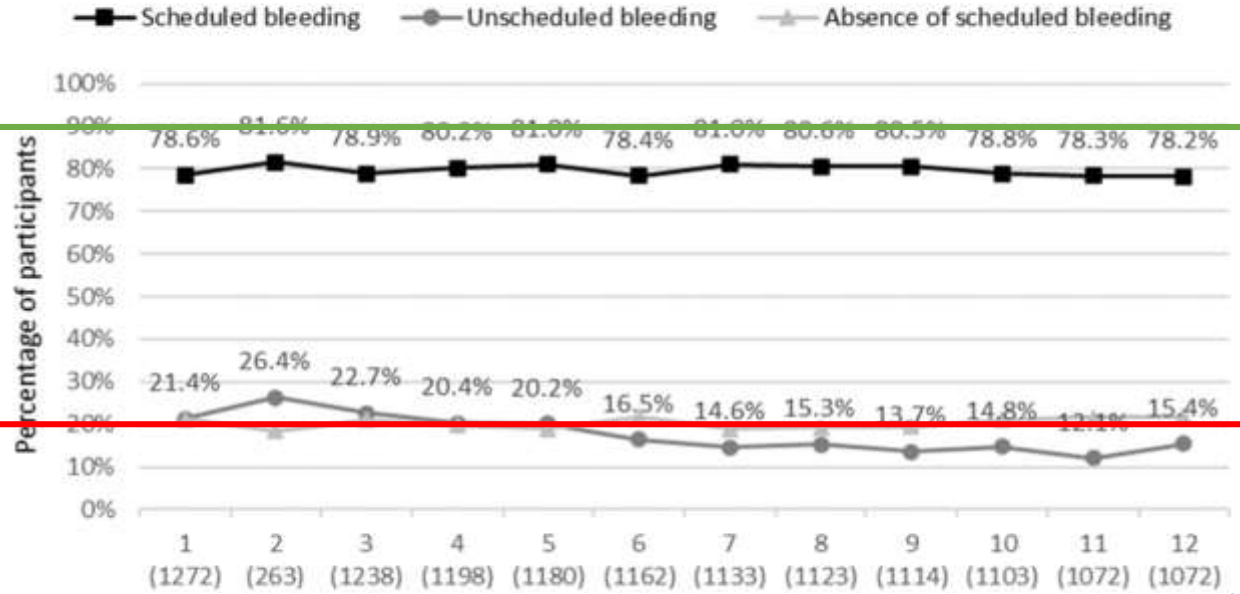
Cycle control is better under E+P versus P only



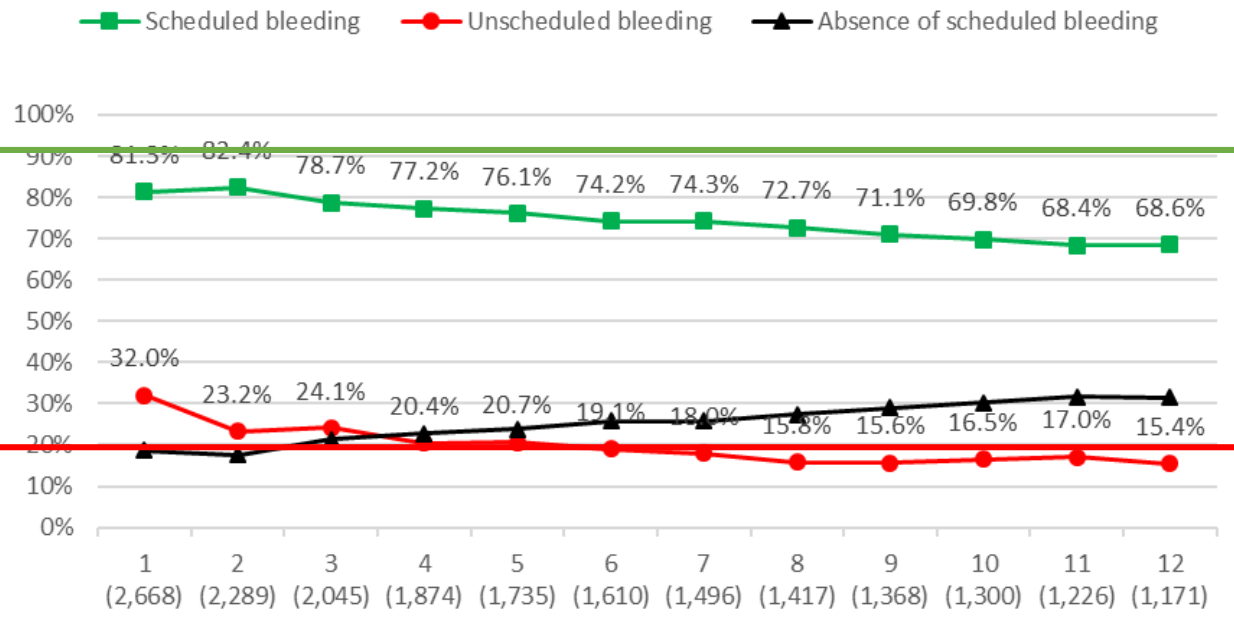


Archer D et al. 2022, Journal of Clinical Medicine. 2022;11(15):4634.

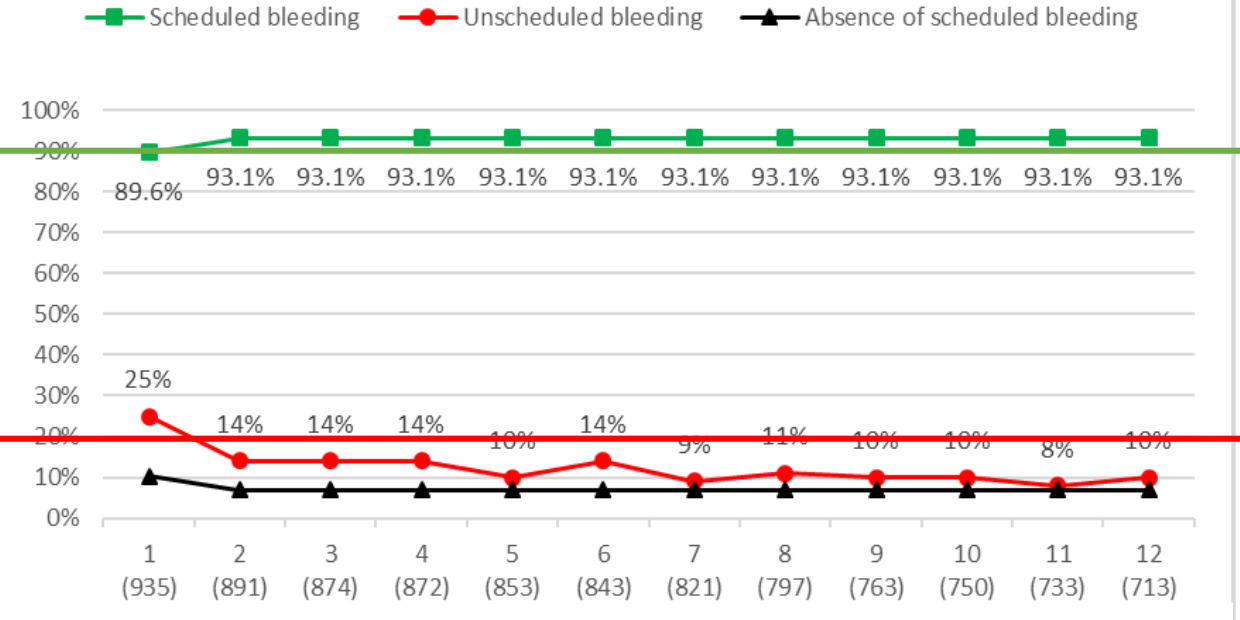
E2V/DNG Phase 3 trial EU (2/22/2/2 regimen)



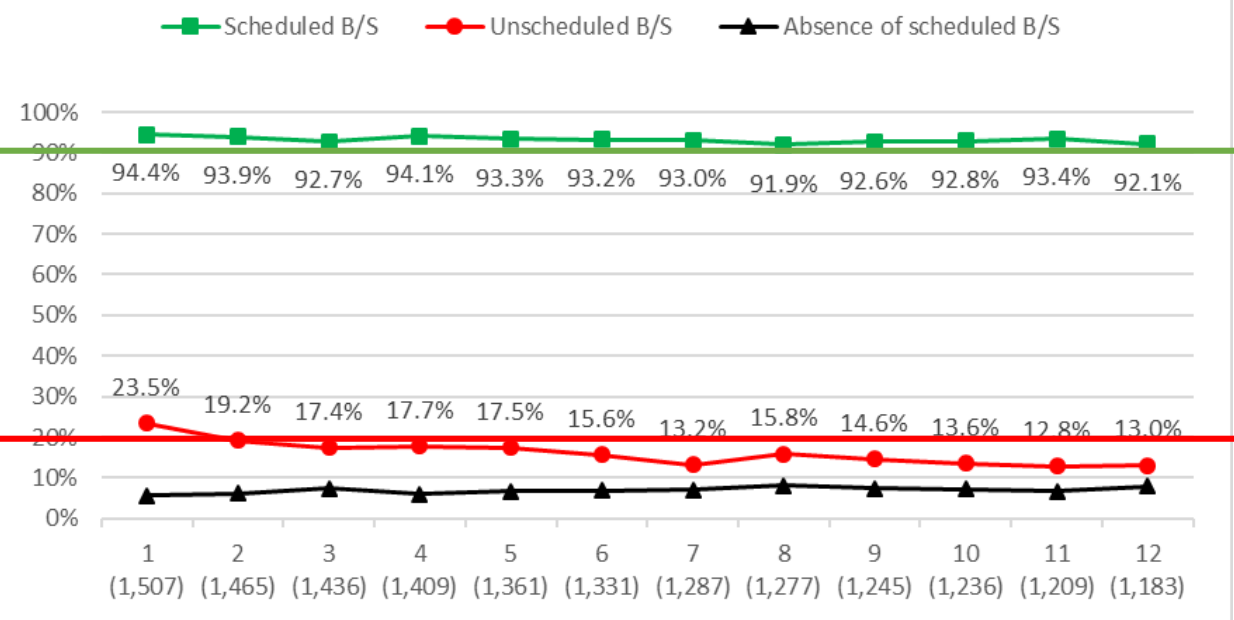
E2/NOMAC pooled phase 3 data (24/4 regimen)



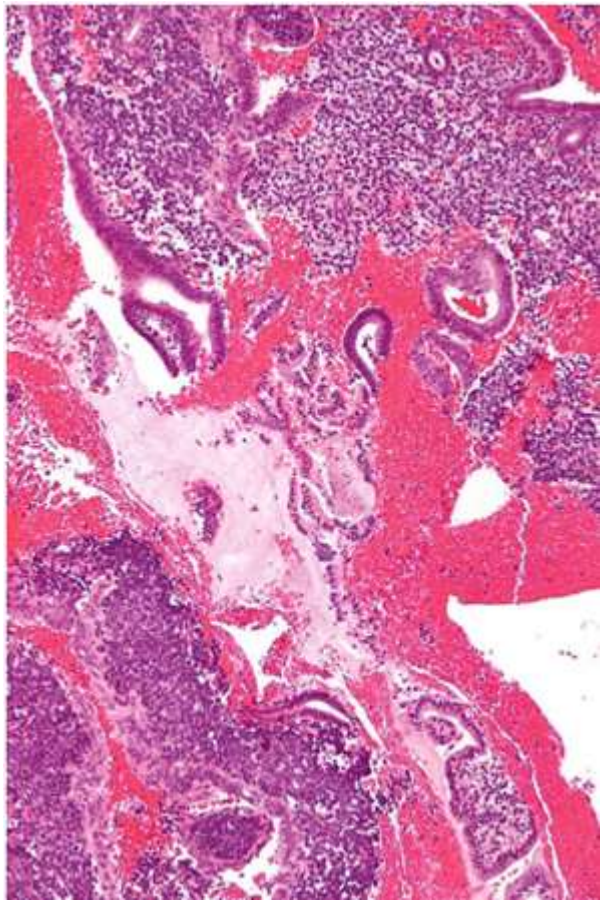
EE 20µg/DRSP (24/4 regimen)

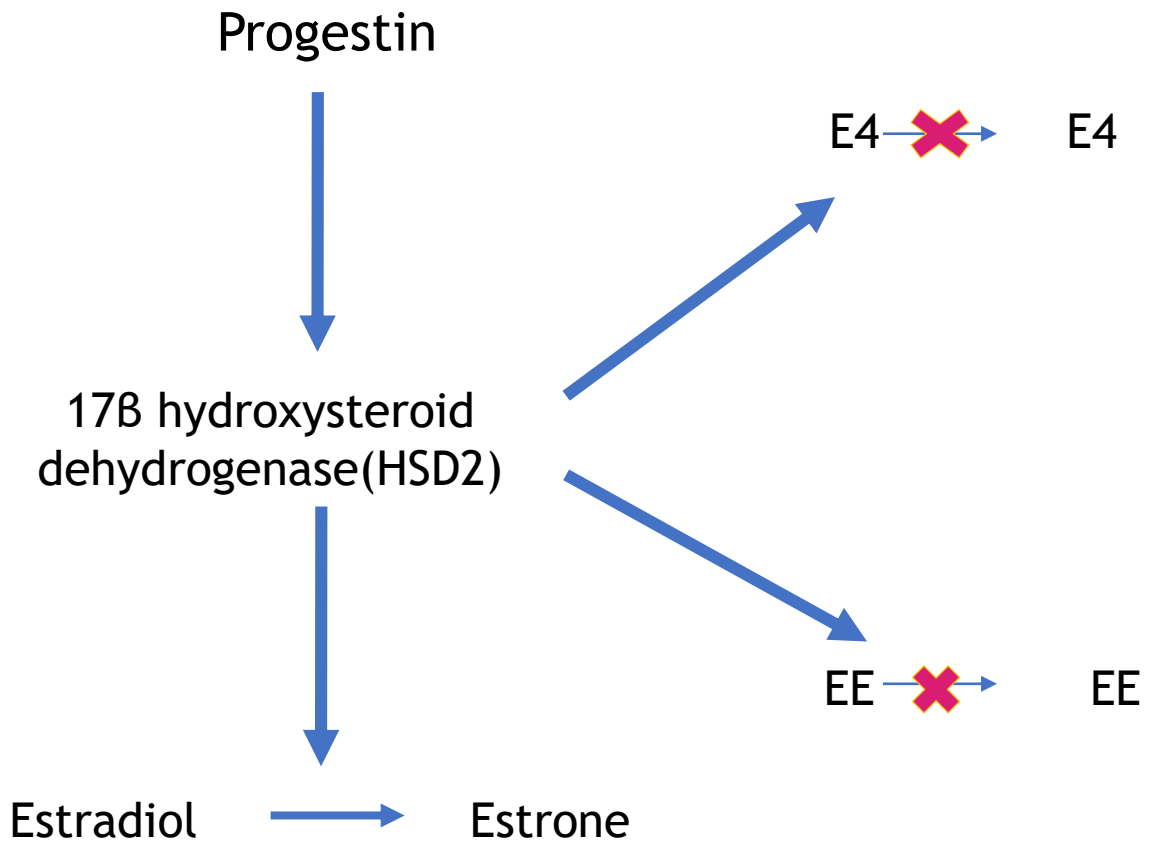


E4/DRSP phase 3 EU/RUS (24/4 regimen)



Estradiol and endometrial control





E4, estetrol; EE, ethinylestradiol

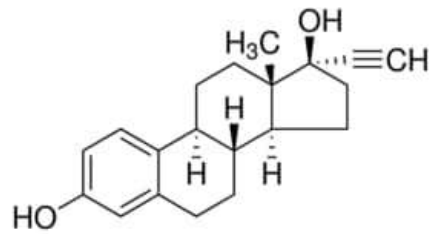
Maentausta et al J.Clin. Endocrinol.Metab. 1993;77;913-918 | Burton et al. Hum.Reprod. 2003;18 ;2610-2617

Ethinylestradiol predominant position

EE has been the predominant estrogen used in COCs. Although EE is overall safe at doses of 50 µg or less, concerns regarding some of its adverse and side effects persist.

- Hypertension
- Myocardial infarction
- Stroke

- Deep vein thrombosis and pulmonary embolism



- Moderately increased relative risk of breast cancer (RR :1.2).
- Absolute risk low 13/ 100,000 person-years

- Plasma triglycerides increase
- Unwanted drug-drug interaction

Even very low doses of EE in COCs that cause poor cycle control have been shown to adversely affect hemostatic parameters.

Stanczyk et al contraception 130 2024 ; Sitruk-Ware R. Fertil Steril 2016;106:1289–94; Cameron NA, et al.Hypertension. 2023 80:924-935; Cohen MA et al. Cochrane Database Syst Rev. 2023 9; CD014908; Morch et al N Engl J Med 2017 377 2228-2239.