21ème congrès GYNAZUR

Antibes – 20 Juin 2023

Acquired APC resistance as a marker for VTE, how does the estrogens differ?

Professor Jonathan DOUXFILS

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QUALIblood s.a., Namur, Belgium

Disclosure

- Chief Executive Officer – QUALIblood, PharmXpertisE
- Honorarium – Mithra Pharmaceuticals, Gedeon Richter, Norgine, Portola Pharmaceuticals
- Advisory board – Bayer Healthcare, DOASense, Gedeon Richter, Norgine, Portola Pharmaceutical and Roche
- Speaker fees – Bayer Healthcare, Daiichi Sankyo, Gedeon Richter, GyneBio Pharma, Instrumentation Laboratories, Roche Diagnostics, Stago Diagnostica, YHLO

Introduction

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Adapted from Morimont, L., et al. Front Endocrinol (Lausanne), 2021. 12: p. 769187.

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

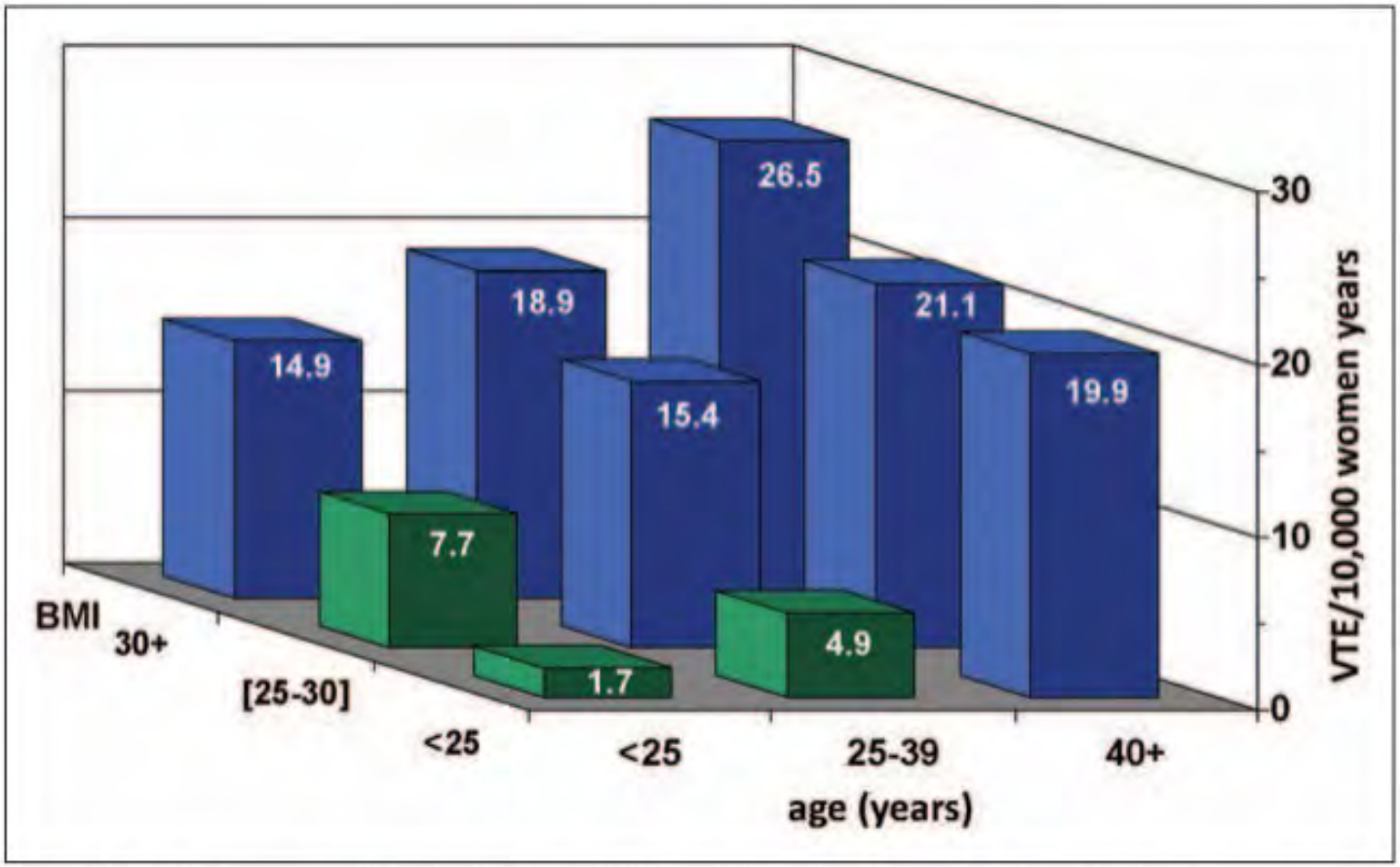
European Medicines Agency referral

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]

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

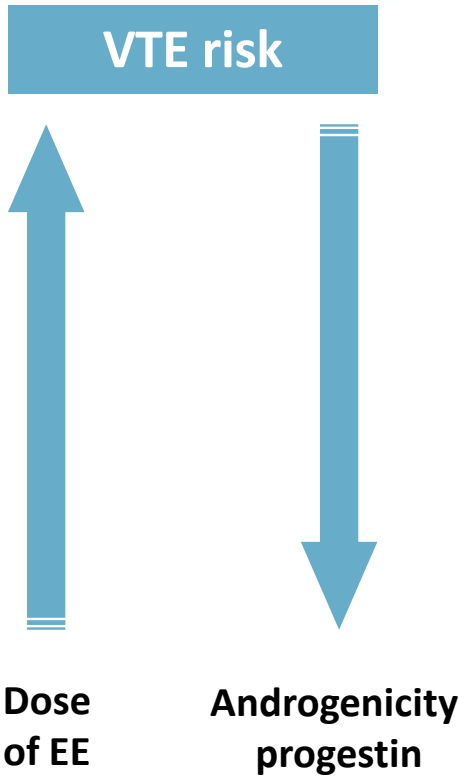
European Medicines Agency - EMA/709120/2013

VTE risk is multifactorial



Rabe, T. et al. Journal of Reproductive Medicine and Endocrinology 2011; 8 (Sonderheft 1): 178-218

Oral contraceptive and risk of VTE



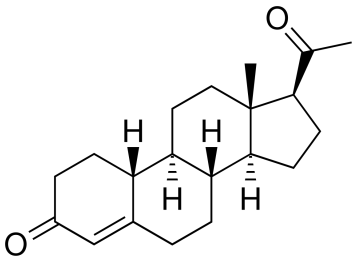
	Relative risk
No COC	1
Pregnancy	5
EE 20|30|50 µg with levonorgestrel	1,3 – 3,6 | 1,8 – 3,2 | 3,4 – 7,9
EE 20|30 µg with gestodene	1,4 – 3,2 | 2,8 – 4,9
EE 20|30 µg with desogestrel	2,5 – 4,6 | 3,3 – 5,6
EE 30 µg with drospirenone	2,7 – 5,5
EE with dienogest	3,5

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

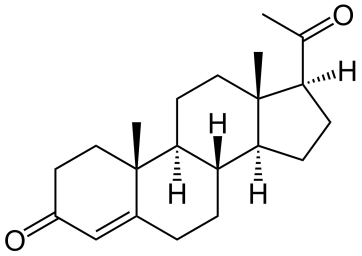
Progestin-estrogen balance

- Depends on potency and dose of estrogen compound
- Modulated by the androgenic activity of the progestin

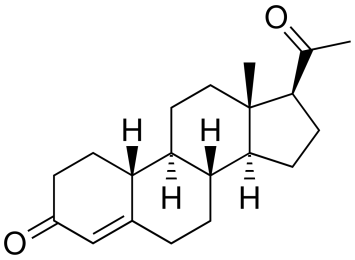
<u>4 types of orally active, synthetic progestins:</u>



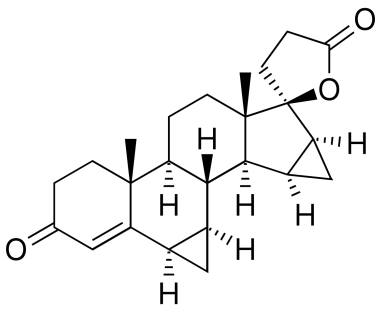
19-nortestosterone derivative
- Levonorgestrel
- Desogestrel
- Gestodene
- Dienogest



Progesterone derivative
- Chlormadinone acetate
- Cyproterone acetate



19-norprogesterone derivative
- Nomegestrol acetate



Spironolactone derivative
- Drospirenone

Kuhl H. Climacteric. 2005. 8 Suppl 1: p. 3-63

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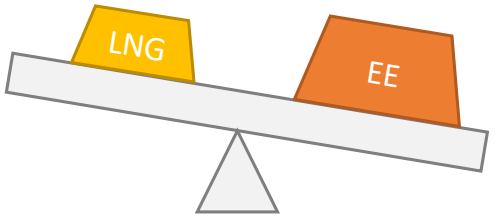
Progestin compounds	Androgenic	Anti-androgenic
Levonorgestrel (LNG)	++	
Desogestrel (DSG)	+	
Gestodene (GSD)	+	
Cyproterone acetate (CPA)		+
Drospirenone (DRSP)		+
Chlormadinone acetate (CMA)*		+
Nomegestrol acetate (NOMAC)		+
Dienogest (DNG)		+



EE : ethinylestradiol

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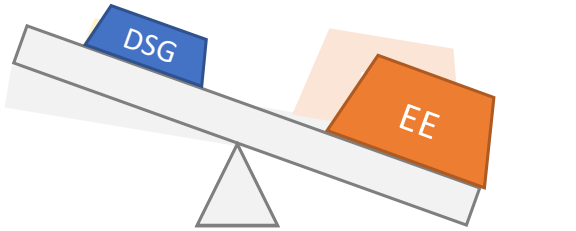

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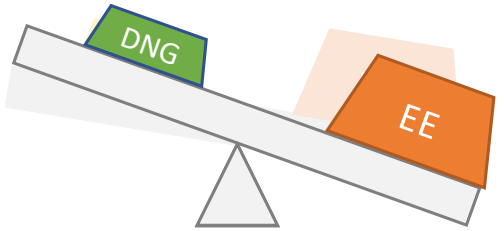

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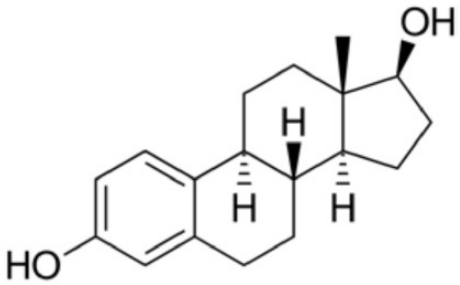
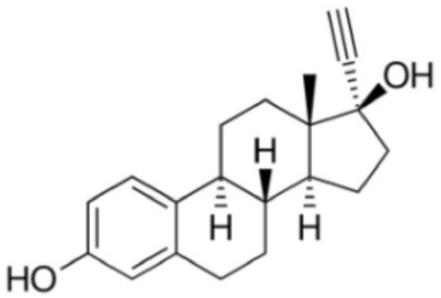
Estradiol and estradiol valerate as estrogens in COC

« 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 »



Estradiol



Ethinylestradiol

Dinger, J. et al. Front Women's Health. 2020. 5(1) | Wiegratz, I. et al. Contraception 2004. 70(2): p. 97-106.

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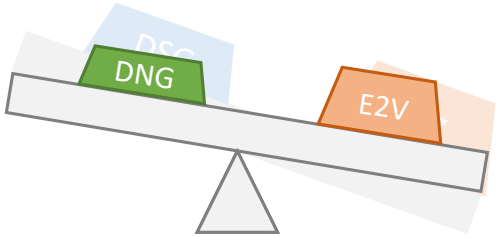

E2V: estradiol valerate

Kuhl H. Climacteric. 2005. 8 Suppl 1: p. 3-63

Data from epidemiological studies with estradiol (valerate)

Frontiers in Women's Health

oat
open access text

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, Invalidenstrass

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

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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]

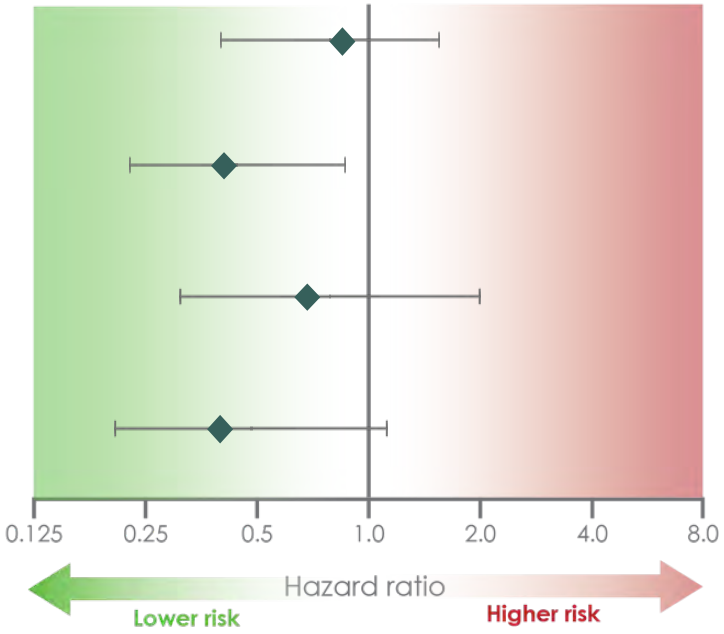
[a]Berlin Center for Epidemiology and Health Research (ZEG), Berlin, Germany; [b]Merck & Co., Inc, North Wales, PA, USA

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.

INAS–SCORE — Lower risk of confirmed VTE compared to other COC

- Primary Analysis – European study population

Comparison		Hazard ratio (95% CI)
DNG/EV vs oCOC	Crude risk	0.9 (0.4-1.7)
	Adjusted risk*	0.4 (0.2-0.9)
DNG/EV vs LNG/EE	Crude risk	0.8 (0.3-2.0)
	Adjusted risk*	0.4 (0.2-1.1)



*Adjusted for age, body mass index, current duration of use and family history of VTE.

Dinger, J. et al. Front Women's Health. 2020. 5(1)

PRO-E2 — E2-NOMAC not associated with a higher risk of VTE compared to COC LNG

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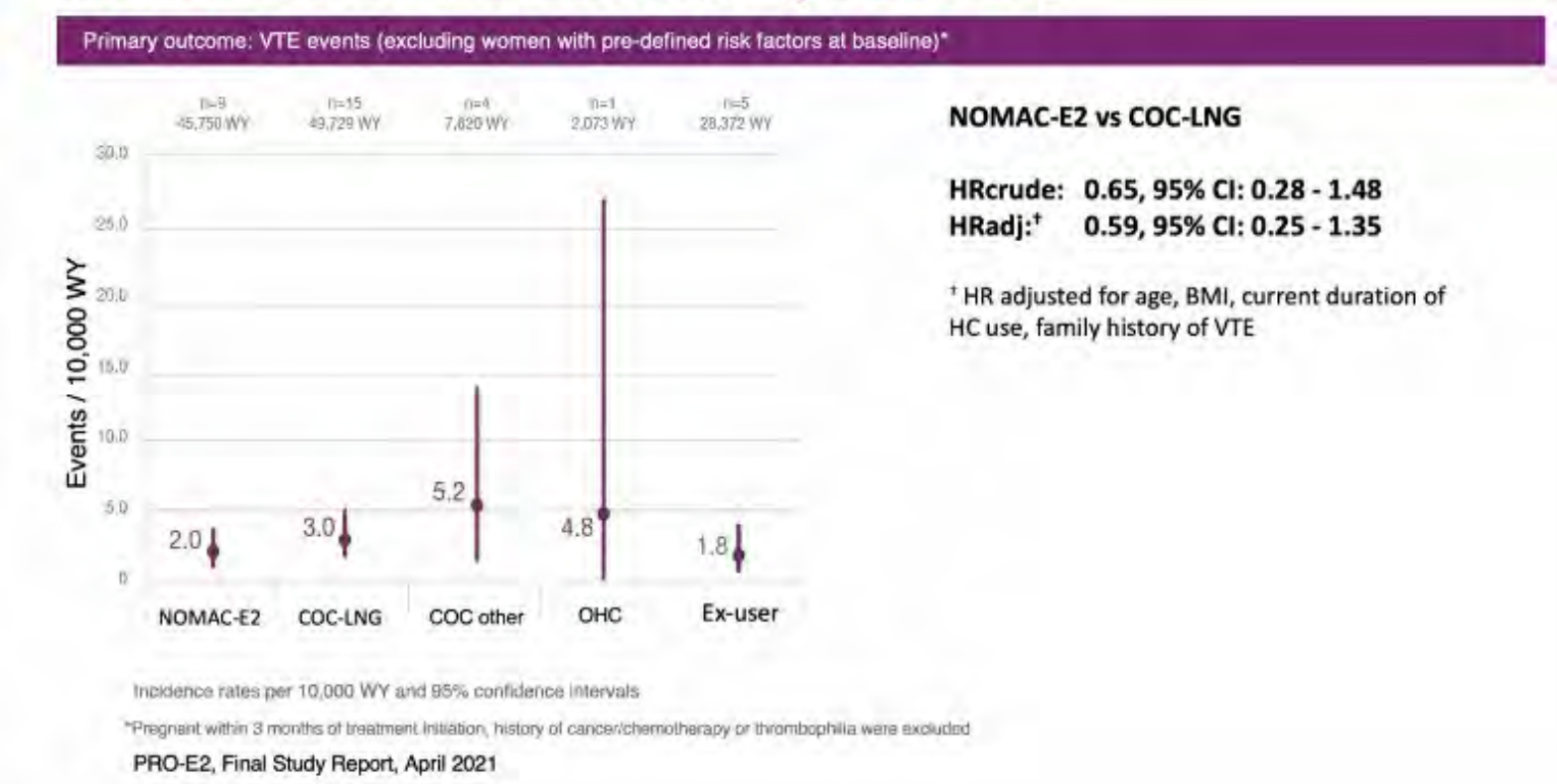


Reed, S. et al. Eur J Contracept Reprod Health Care. 2021. 26(6): p. 439-446.

Is EE/LNG still the safest COC?

Hemostasis parameters, regulatory bodies, and development of steroid contraceptives

European Medicines Agency

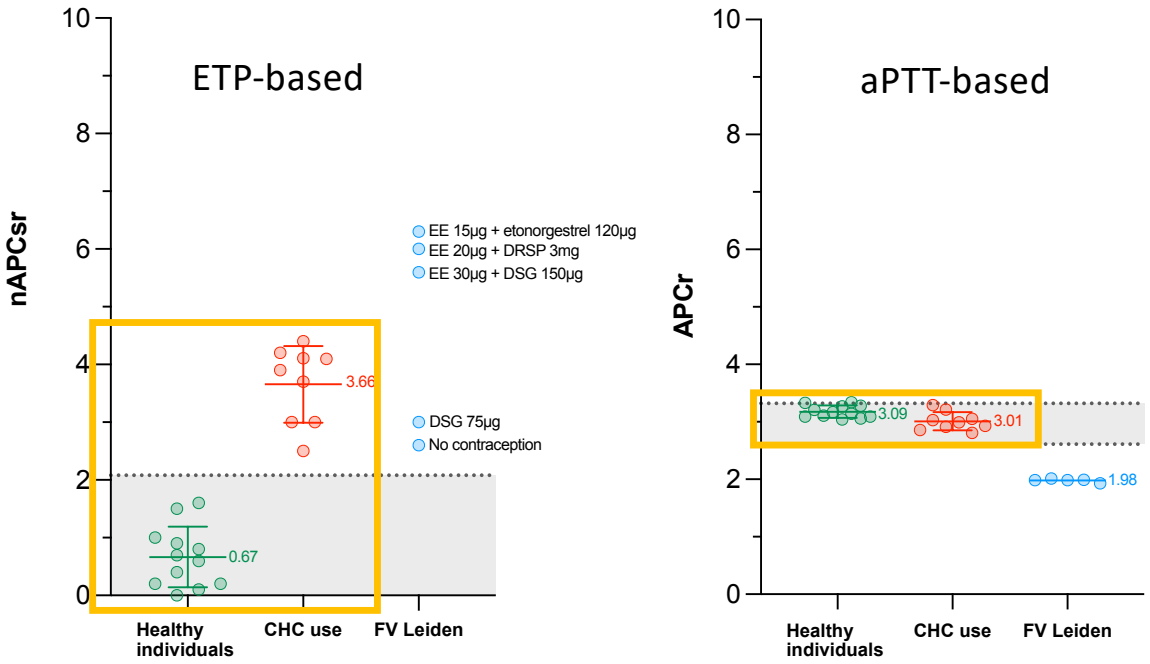
List of recommended hemostasis investigations during the development of steroid contraceptives

- 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

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

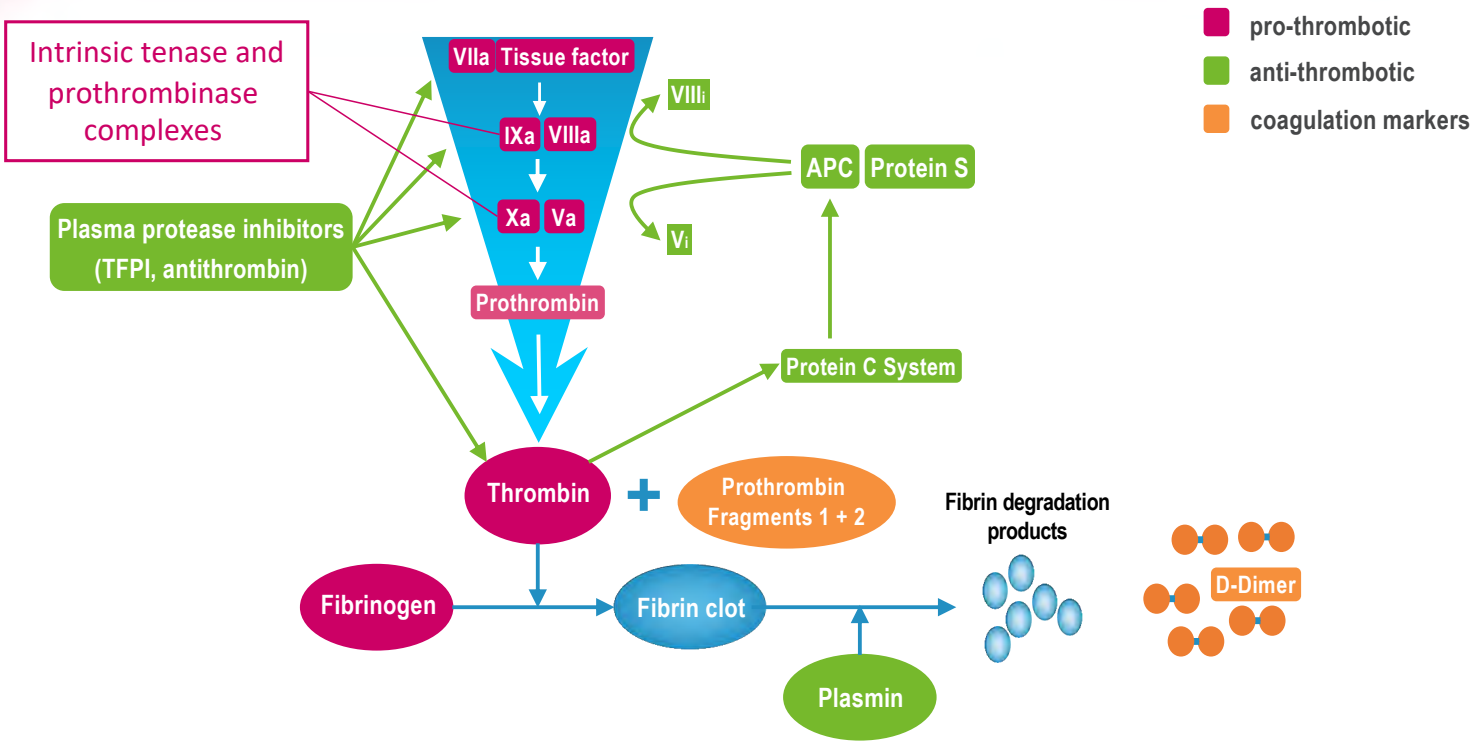
The ETP-based APC resistance is the gold standard for evaluating APC resistance induced by COC



- Current aPTT-based APC resistance assays **are not able to appreciate the impact** of COC on hemostasis
- **Only the ETP-based APC resistance assay is able** to appreciate the impact of COC on hemostasis

Morimont, L. Douxfils, J. et al. Sem Thromb Hemost. 2022.

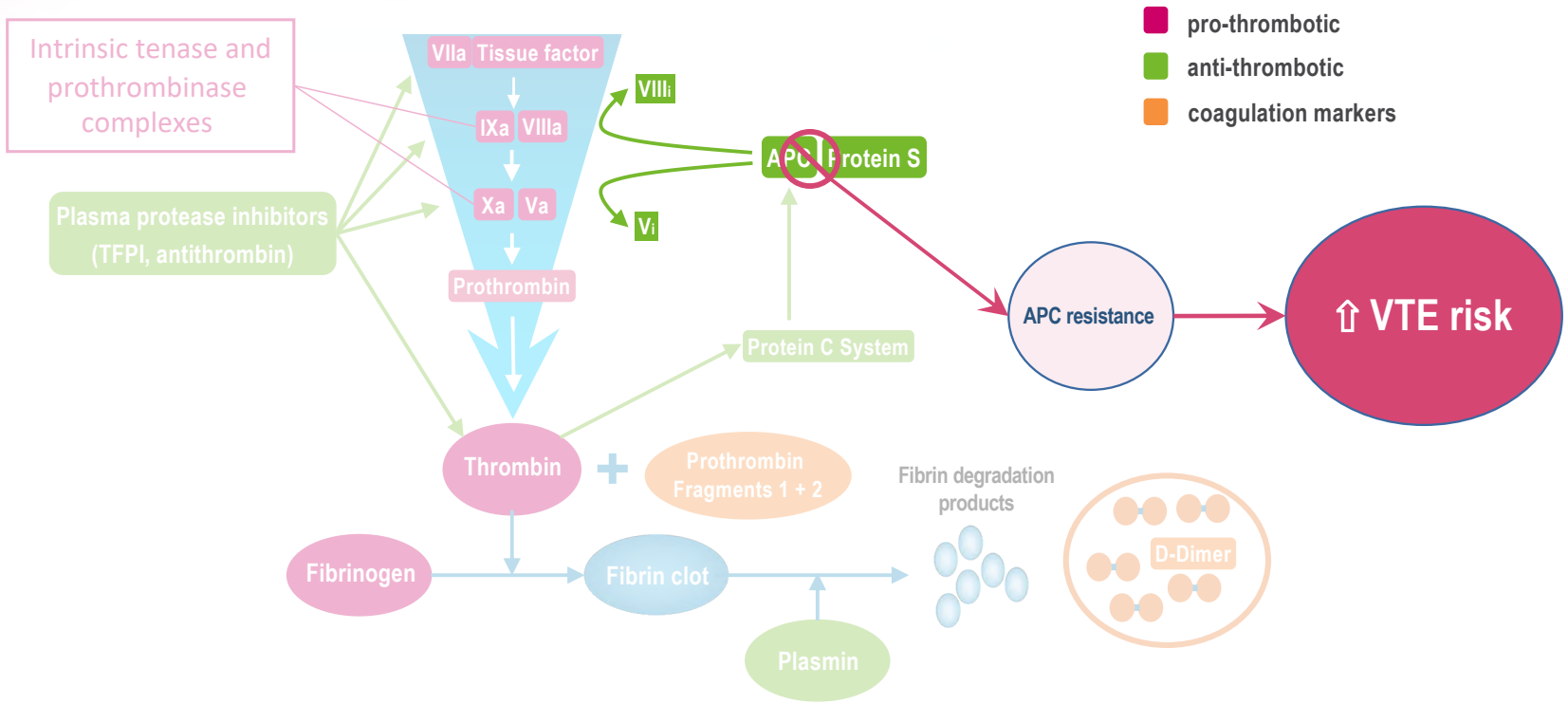
Hemostasis – coagulation cascade overview



Adapted from Douxfils et al. Contraception, 2020. 102(6): p. 396-402.

APC: activated protein C | TFPI: tissue factor pathway inhibitor

Estrogen therapies and APC resistance



- APC-protein S complex inhibits activated FV and FVIII
- Impairment in this process is linked to increased VTE risk

Adapted from Douxfils et al. Contraception, 2020. 102(6): p. 396-402.

APC: activated protein C | PAI-1: plasminogen activator inhibitor type 1 | t-PA: tissue plasminogen activator | TFPI: tissue factor pathway inhibitor | ETP: endogenous thrombin potential | VTE: venous thromboembolism

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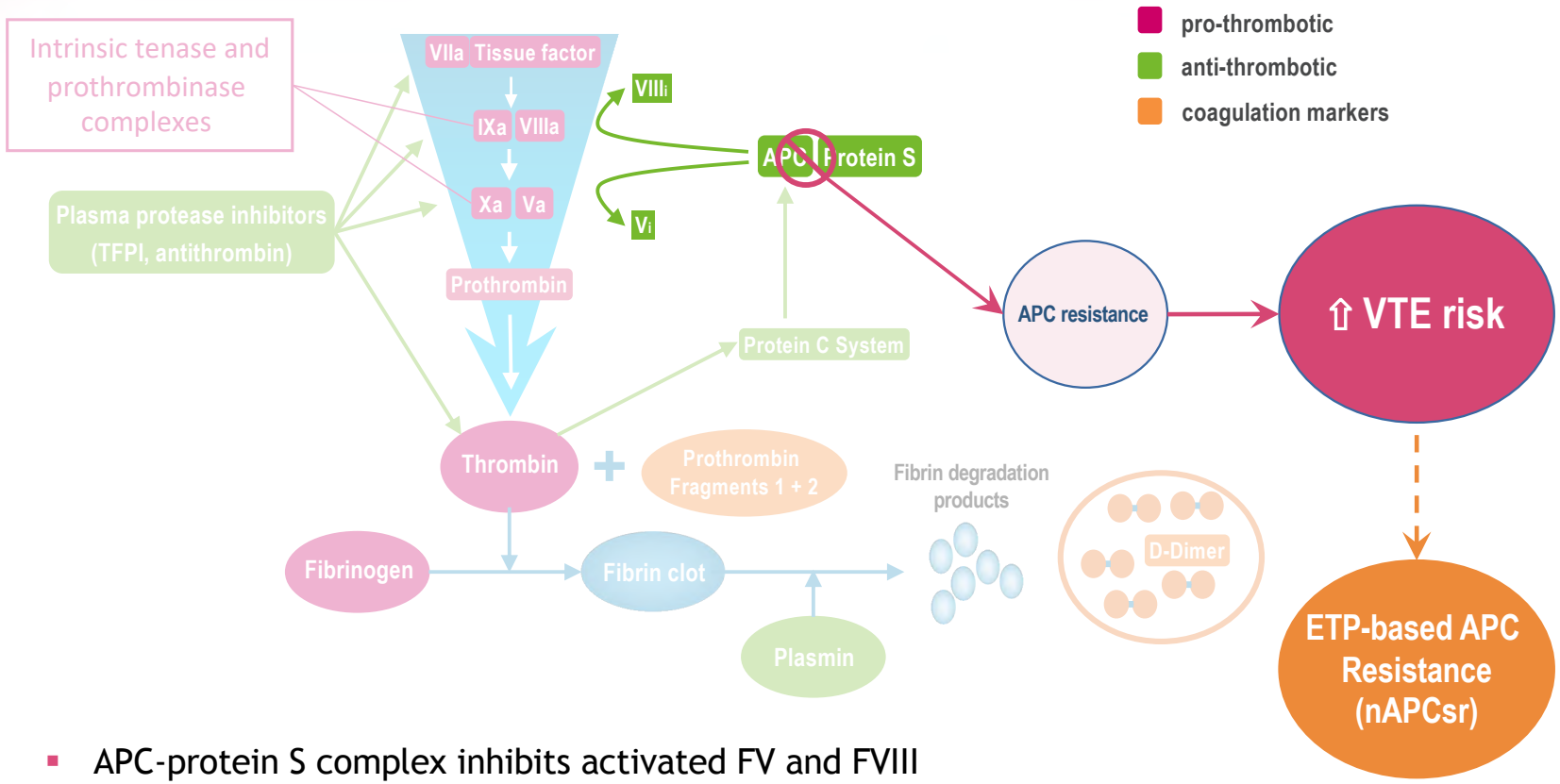

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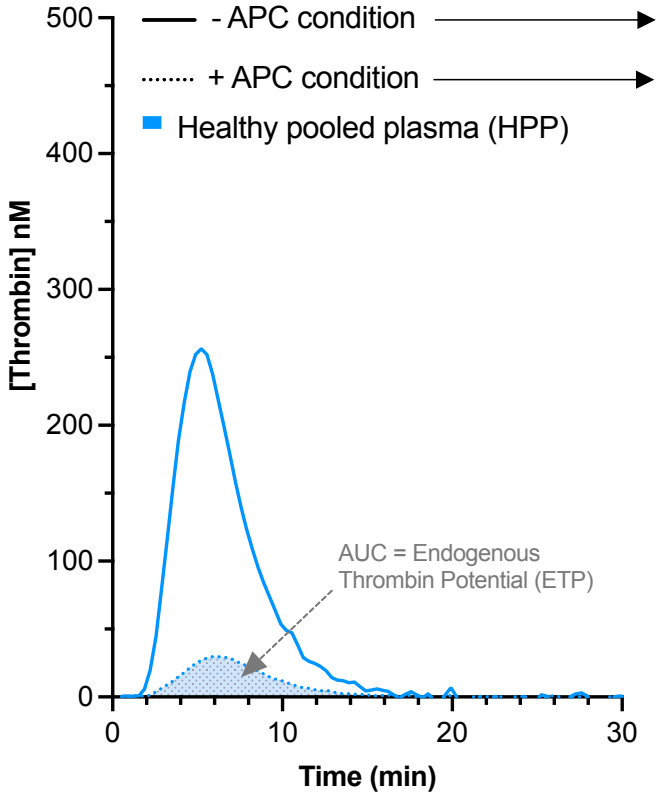
Assessment of APC resistance

The ETP-based APC resistance assay is a **global coagulation test** aiming at assessing the resistance towards APC based on the measurement of **thrombin generation over time**



ETP = 1181.39 nM.min

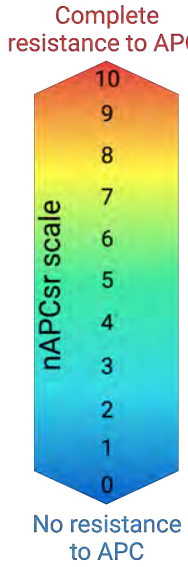
ETP = 121.26 nM.min

ETP ratio of HPP

$= \text{ETP (+APC)/ETP (-APC)}$

$= 121.26/1181.39$

$= \mathbf{0.10}$



Normalized APC sensitivity ratio (nAPCsr)

$$= \frac{Sample\ ETP\ (+APC)\ /\ Sample\ ETP\ (-APC)}{HPP\ ETP\ ratio\ (\mathbf{0.10})}$$

The nAPCsr scales from 0 to 10.

Scores which are closer to **10** show **higher resistance** to APC suggesting a **higher risk of thrombosis**

Adapted from Morimont, L. Douxfils, J. et al. Sem Thromb Hemost. 2022.

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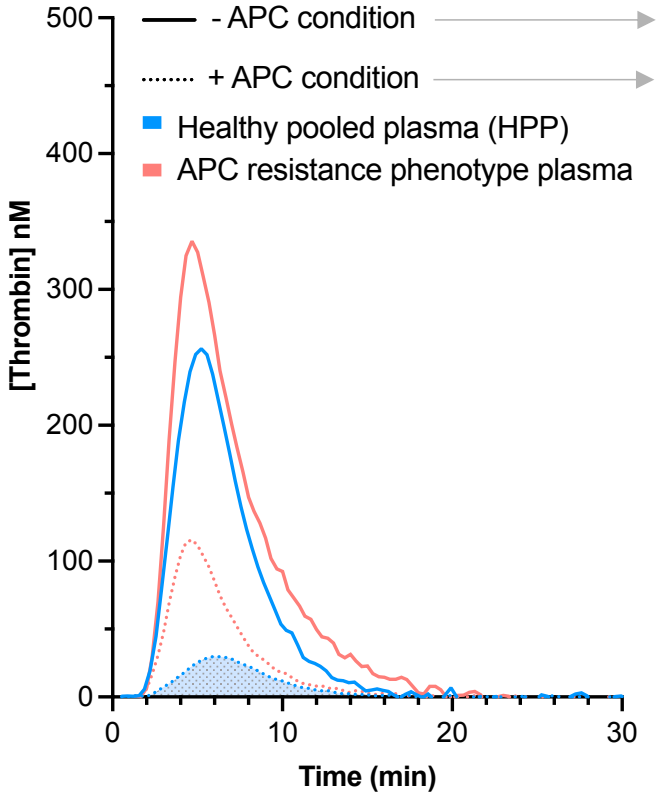

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= 121.26/1181.39

= **0.10**

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$$= \frac{623.02 / 1512.83}{\mathbf{0.10}} = \frac{0.41}{\mathbf{0.10}} = \mathbf{4.10}$$

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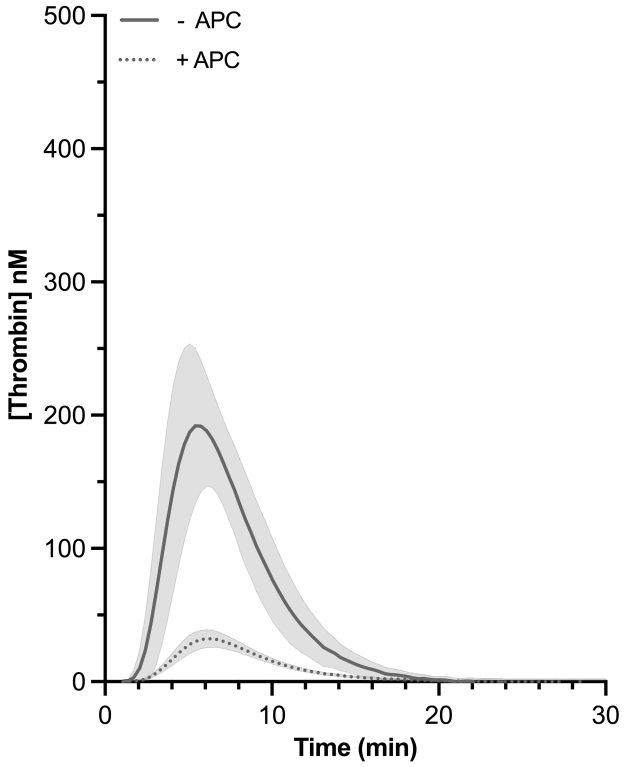
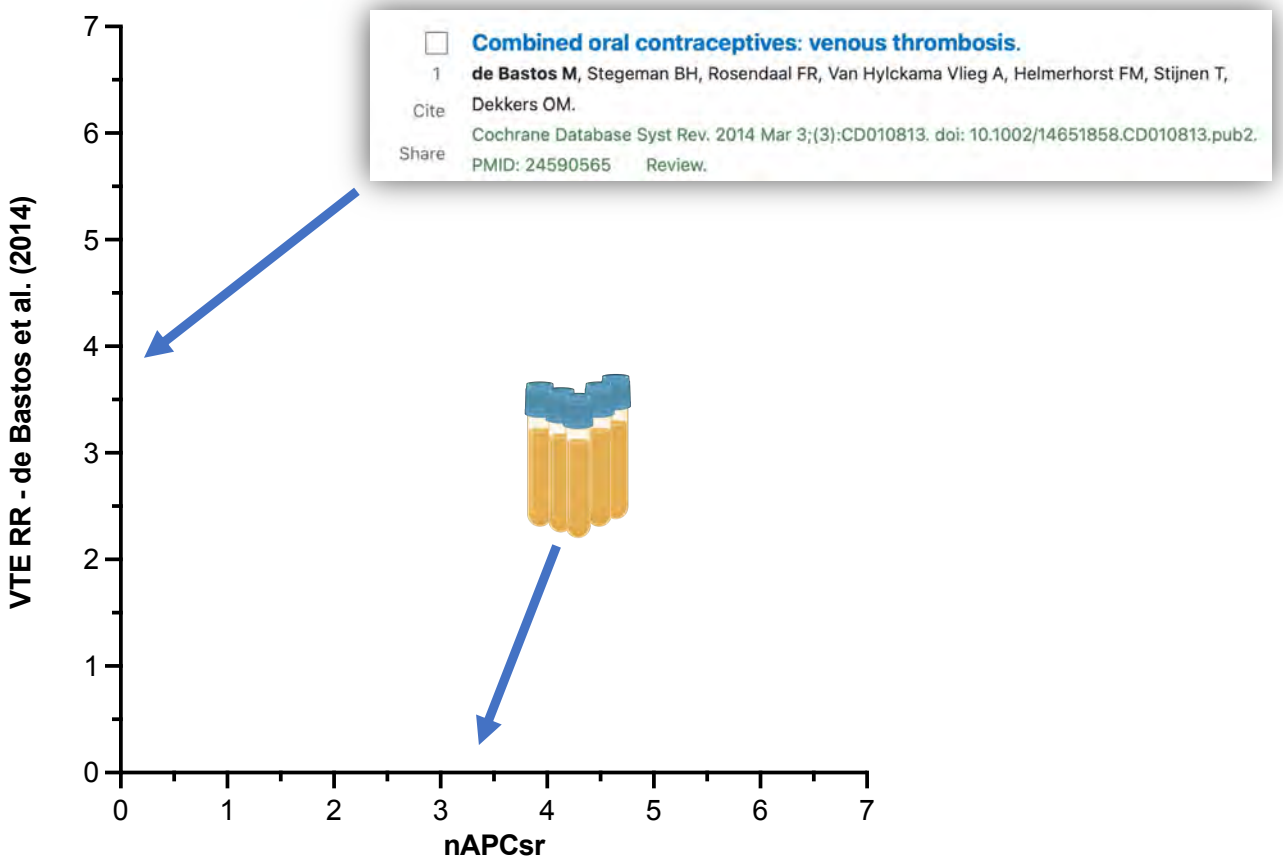
nAPCsr — a predictive tool of VTE



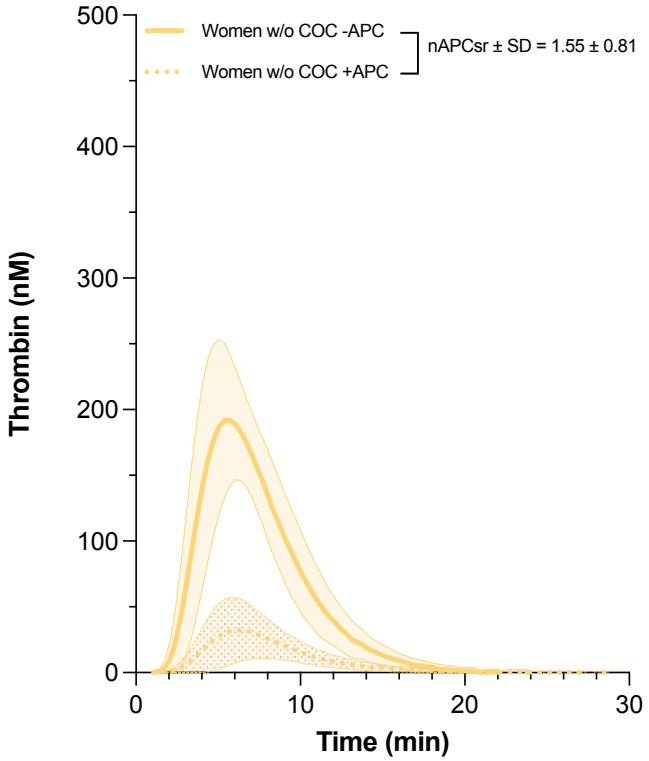


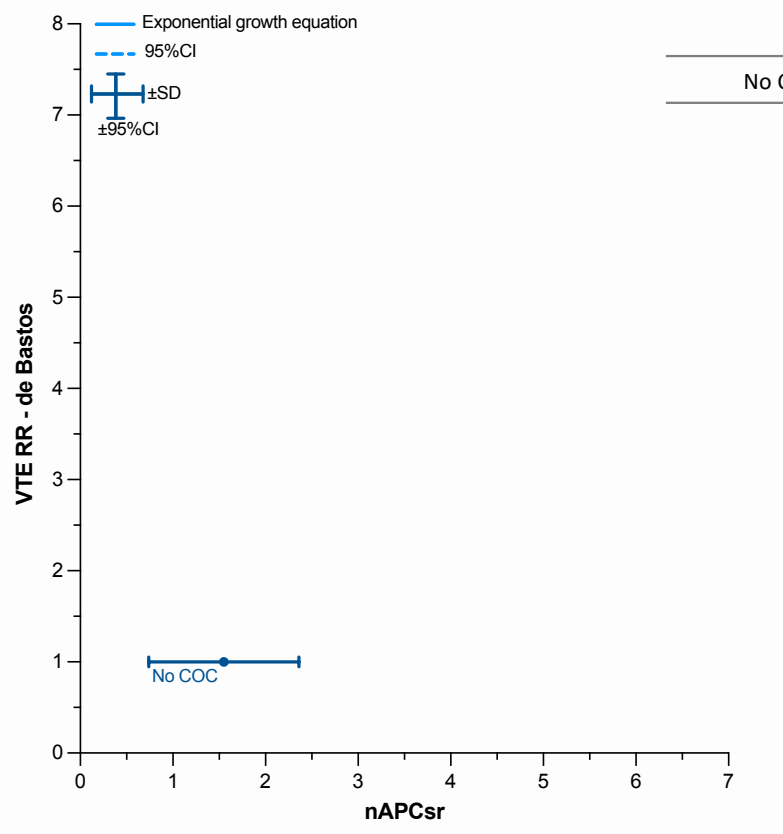
Combined oral contraceptives: venous thrombosis.
1 de Bastos M, Stegeman BH, Rosendaal FR, Van Hylckama Vlieg A, Helmerhorst FM, Stijnen T, Dekkers OM.
Cite
Cochrane Database Syst Rev. 2014 Mar 3;(3):CD010813. doi: 10.1002/14651858.CD010813.pub2.
Share
PMID: 24590565 Review.

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

APC: activated protein C | nAPCsr: normalized APC sensitivity ratio

nAPCsr and VTE risk – Reference population



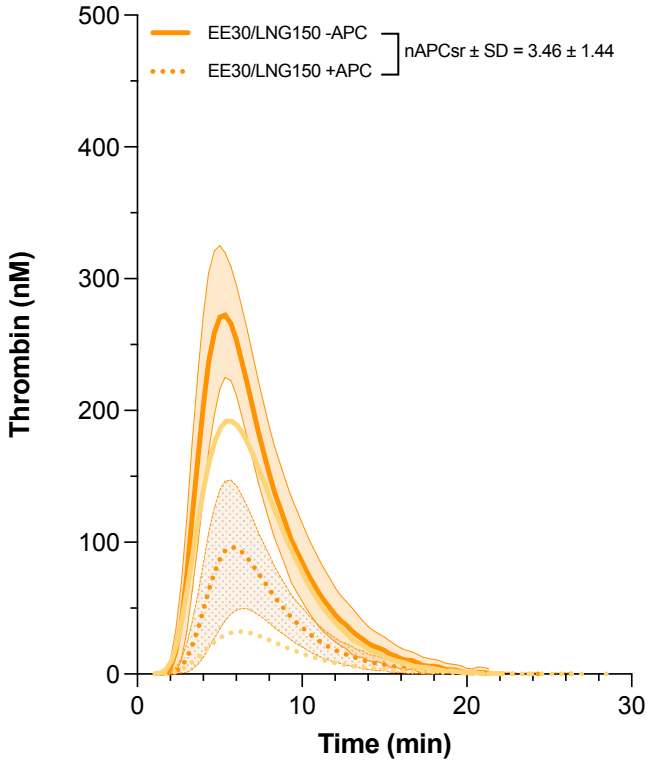


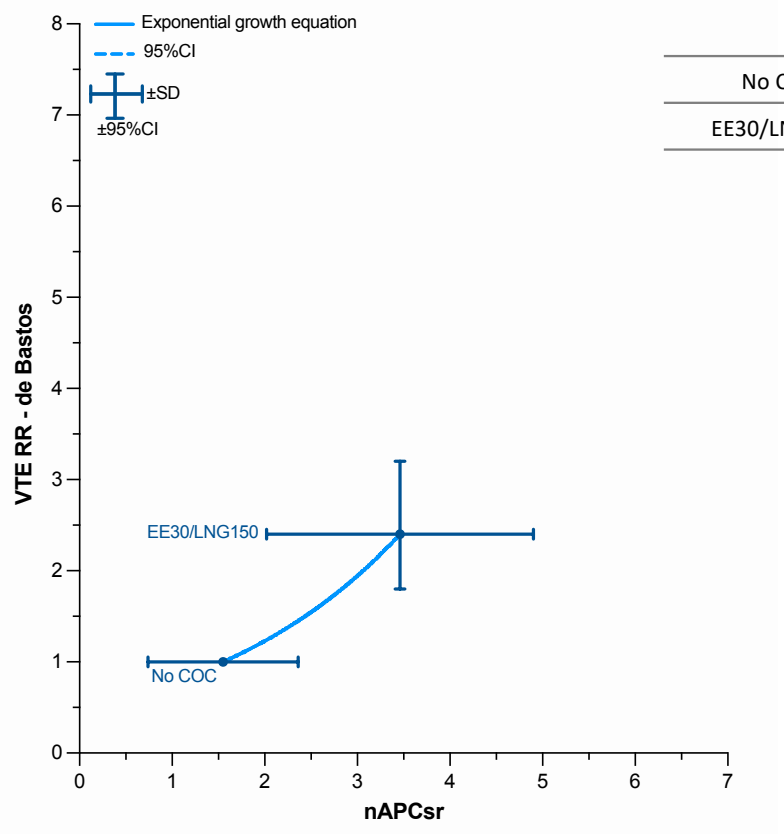
	Mean nAPCsr	VTE RR (de bastos et al. 2014)
No CHC	1.55	1.00 (ref)

APC: activated protein C | CI: confidence interval | CHC: combined hormonal contraceptives | nAPCsr: normalized APC sensitivity ratio | RR: relative risk | SD: standard deviation | VTE: venous thromboembolism

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

nAPCsr and VTE risk – EE30/LNG150



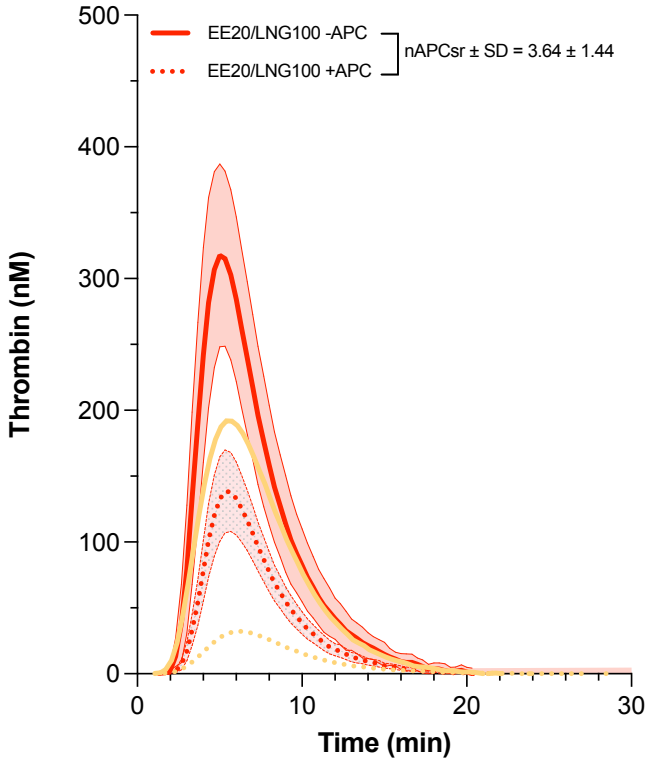


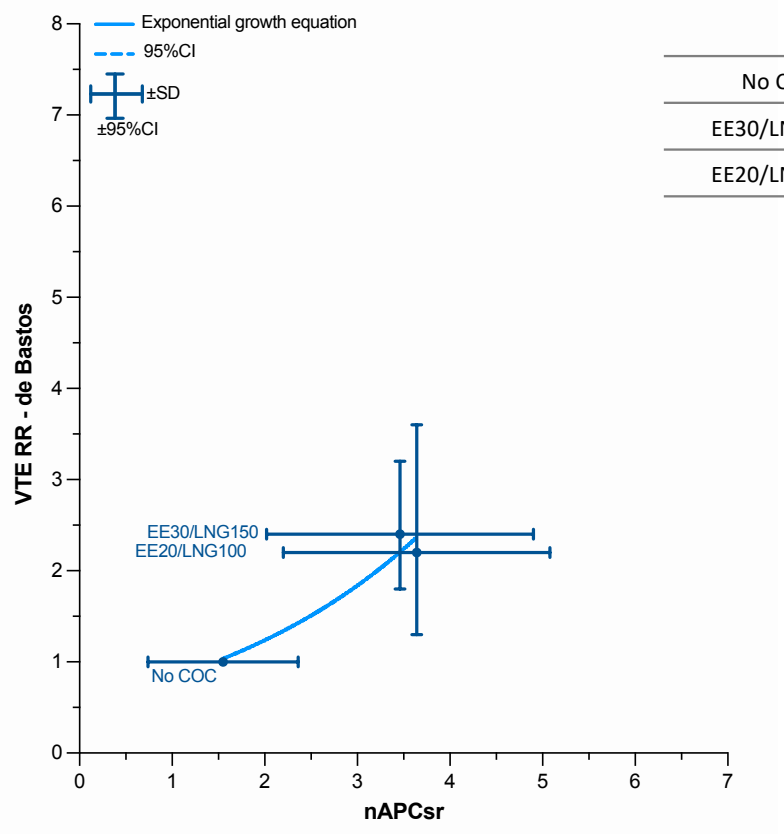
	Mean nAPCsr	VTE RR (de bastos et al. 2014)
No CHC	1.55	1.00 (ref)
EE30/LNG150	3.46	2.40

APC: activated protein C | CI: confidence interval | CHC: combined hormonal contraceptives | nAPCsr: normalized APC sensitivity ratio | RR: relative risk | SD: standard deviation | VTE: venous thromboembolism

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

nAPCsr and VTE risk – EE20/LNG100



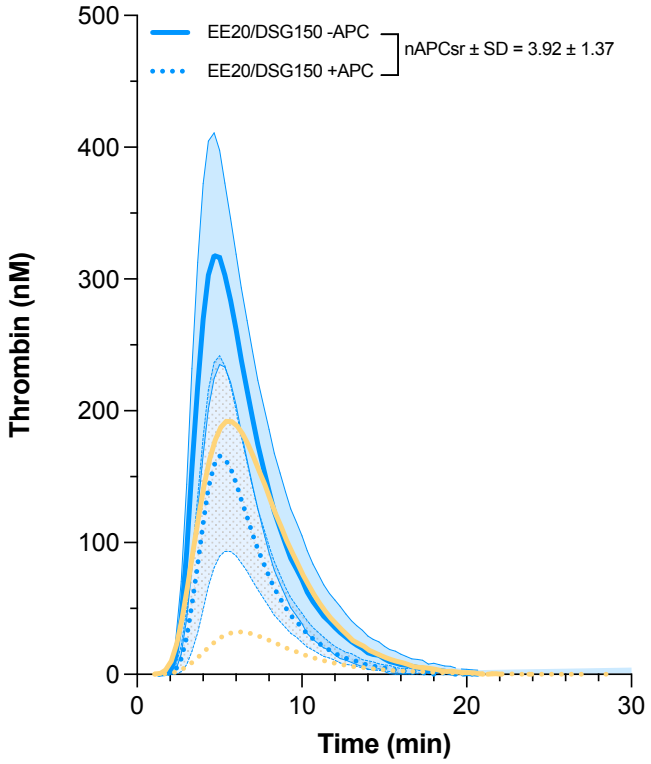


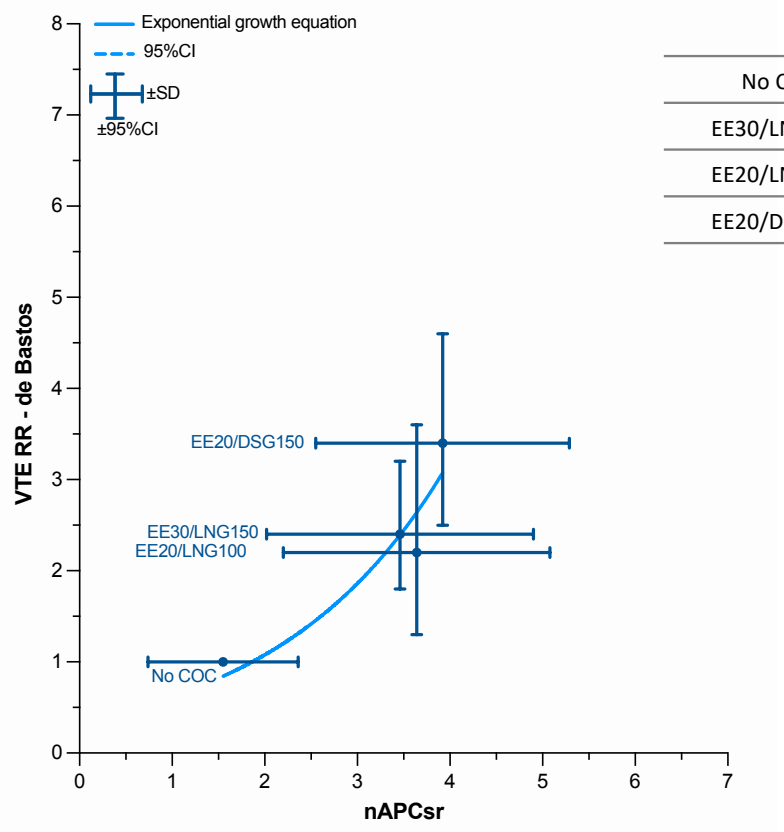
	Mean nAPCsr	VTE RR (de bastos et al. 2014)
No CHC	1.55	1.00 (ref)
EE30/LNG150	3.46	2.40
EE20/LNG100	3.64	2.20

APC: activated protein C | CI: confidence interval | CHC: combined hormonal contraceptives | nAPCsr: normalized APC sensitivity ratio | RR: relative risk | SD: standard deviation | VTE: venous thromboembolism

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

nAPCsr and VTE risk – EE20/DSG150



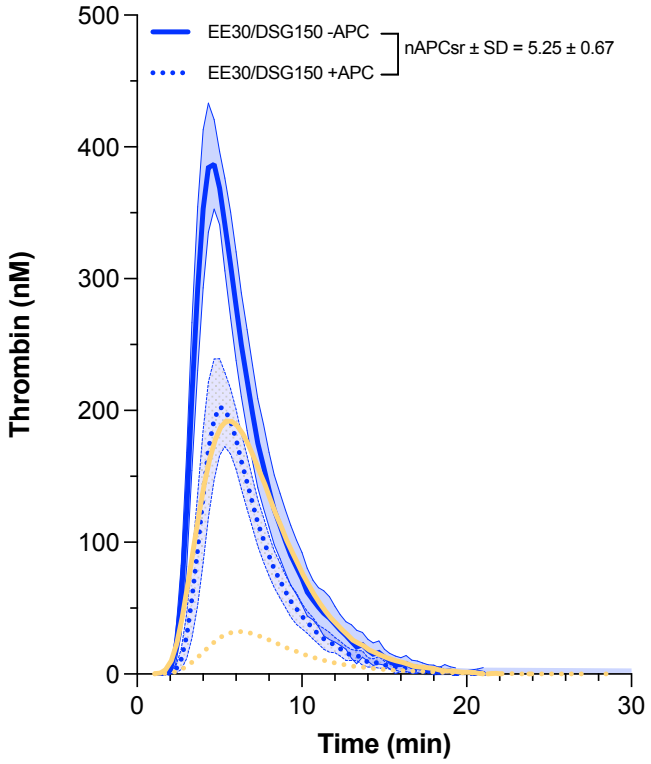


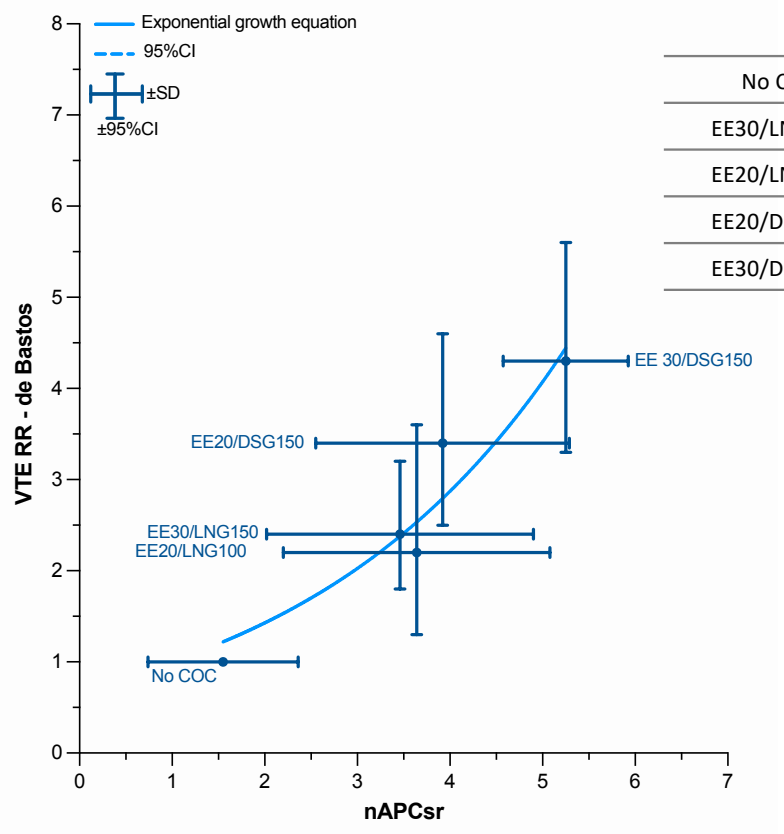
	Mean nAPCsr	VTE RR (de bastos et al. 2014)
No CHC	1.55	1.00 (ref)
EE30/LNG150	3.46	2.40
EE20/LNG100	3.64	2.20
EE20/DSG150	3.92	3.40

APC: activated protein C | CI: confidence interval | CHC: combined hormonal contraceptives | nAPCsr: normalized APC sensitivity ratio | RR: relative risk | SD: standard deviation | VTE: venous thromboembolism

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

nAPCsr and VTE risk – EE30/DSG150



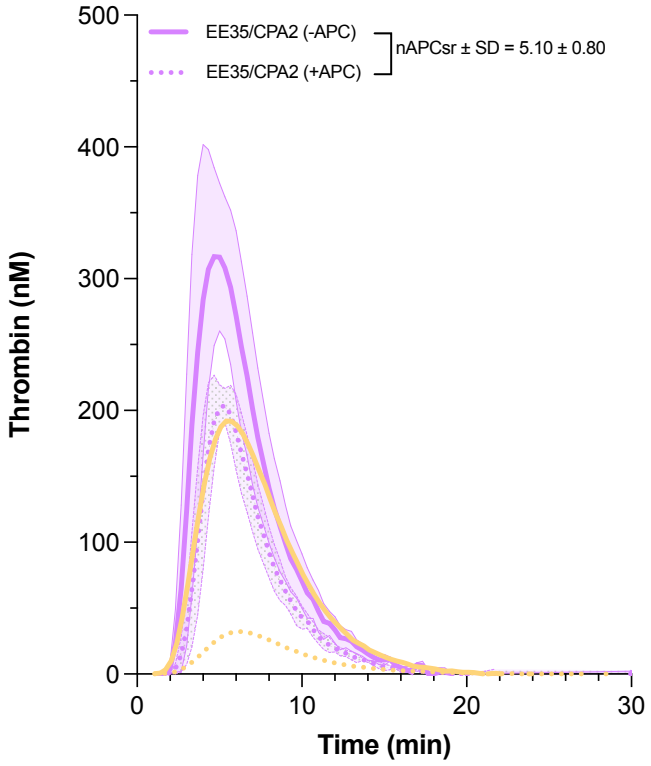


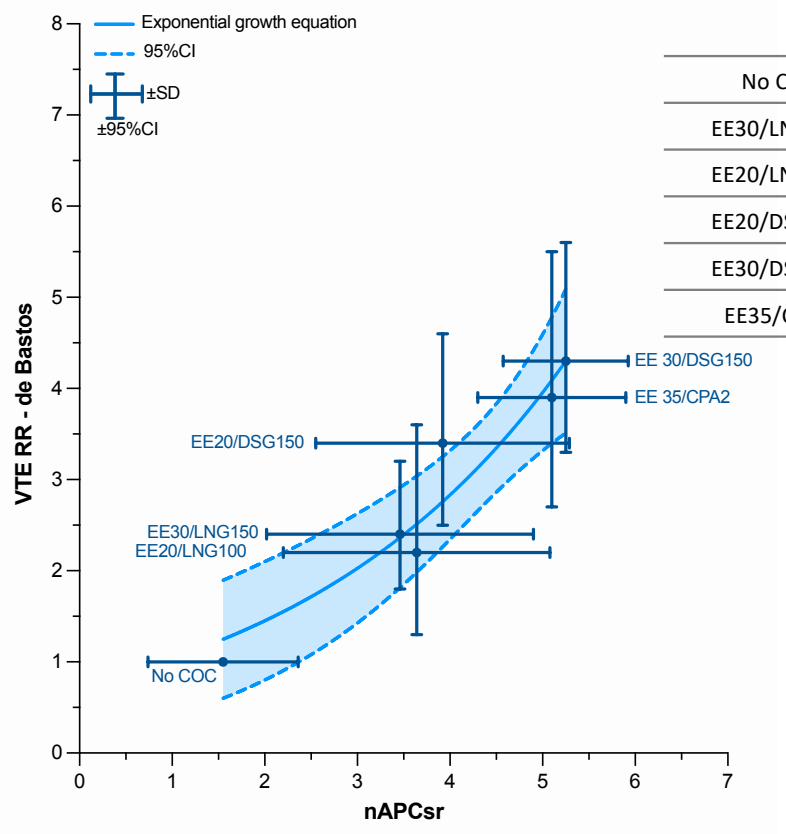
	Mean nAPCsr	VTE RR (de bastos et al. 2014)
No CHC	1.55	1.00 (ref)
EE30/LNG150	3.46	2.40
EE20/LNG100	3.64	2.20
EE20/DSG150	3.92	3.40
EE30/DSG150	5.25	4.30

APC: activated protein C | CI: confidence interval | CHC: combined hormonal contraceptives | nAPCsr: normalized APC sensitivity ratio | RR: relative risk | SD: standard deviation | VTE: venous thromboembolism

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

nAPCsr and VTE risk – EE35/CPA2





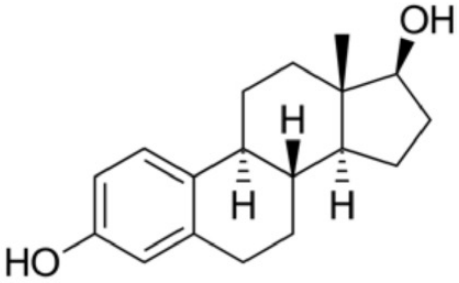
	Mean nAPCsr	VTE RR (de bastos et al. 2014)
No CHC	1.55	1.00 (ref)
EE30/LNG150	3.46	2.40
EE20/LNG100	3.64	2.20
EE20/DSG150	3.92	3.40
EE30/DSG150	5.25	4.30
EE35/CPA2	5.10	3.90

APC: activated protein C | CI: confidence interval | CHC: combined hormonal contraceptives | nAPCsr: normalized APC sensitivity ratio | RR: relative risk | SD: standard deviation | VTE: venous thromboembolism

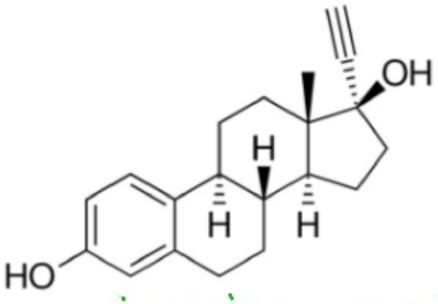
de Bastos, M., et al. Cochrane Database Syst Rev, 2014(3): p. CD010813| Morimont et al. Thromb Res. 2020. 193: p. 221-223.

Estetrol (E4) – The first Native Estrogen with Selective Tissue activity (NEST)

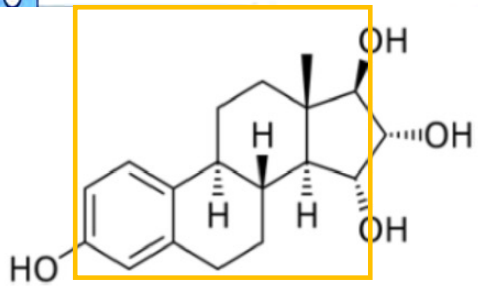
- First NEST approved for oral contraception…
- …with a different mechanism of action than E2 and other E2-derivatives…



Estradiol



Ethinylestradiol



Estetrol

Gerard C, et al. Expert Rev Clin Pharmacol. 2022. 15(2): p. 121-137 | Morimont, L., et al. Front Endocrin (Lausanne), 2021. 12: p. 769187.

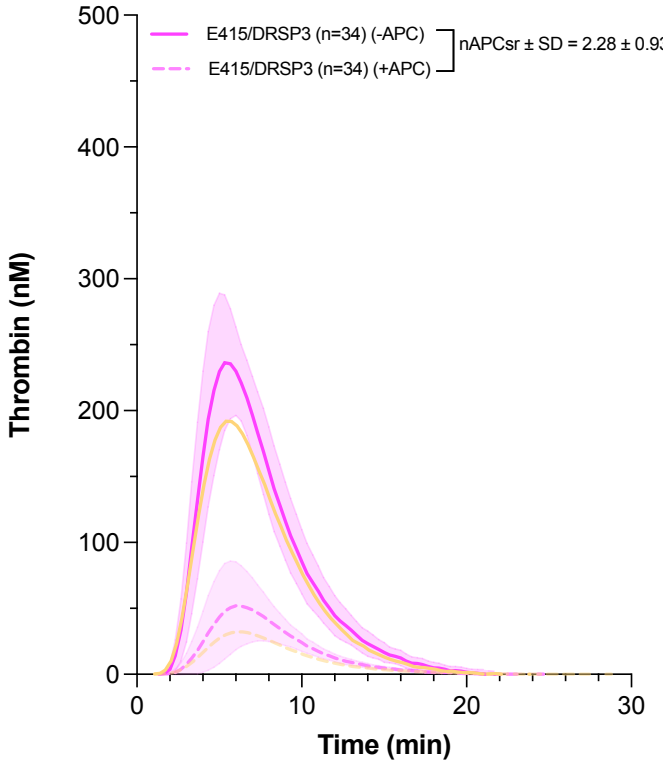
Estetrol (E4) – The first Native Estrogen with a Selective action on Tissue (NEST)

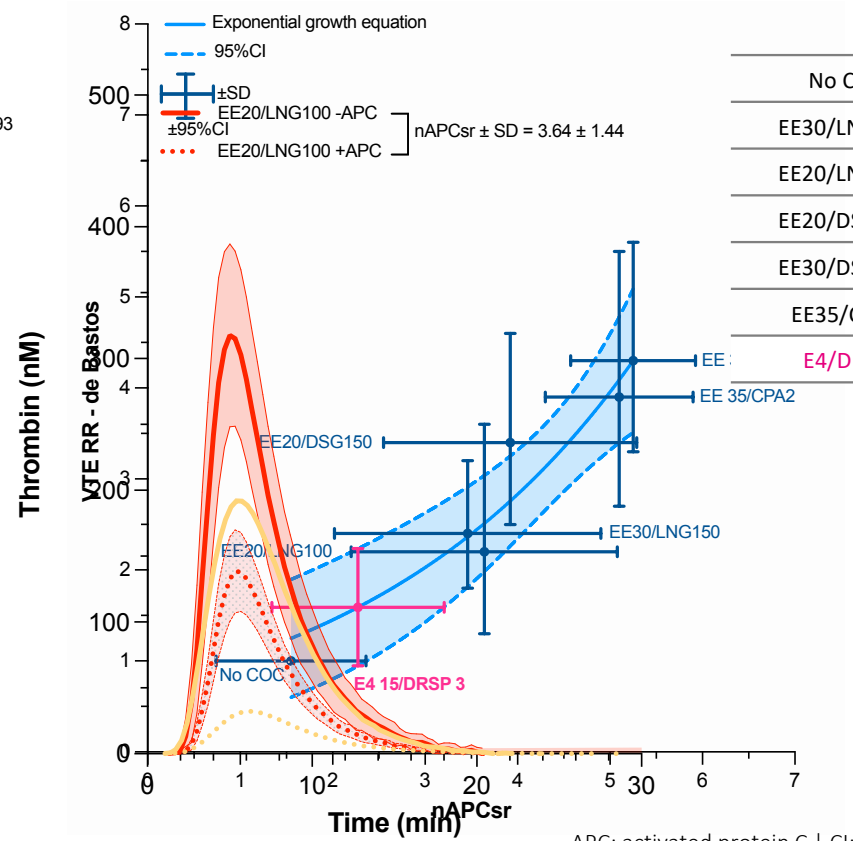
- … which is translated into less impact on the liver

	Nuclear dependent	Membrane dependent
Breast stimulate growth	No	Yes
Vascular system prevents plaque	Yes	No
Liver impacts liver metabolism	**Yes**	**Yes**
Bone maintains bones mineral density	Yes	Yes
Uterus supports tissue maintenance	Yes	No
Vagina supports tissue maintenance	Yes	No

Arnal JF, et al. Physiol Rev. 2017. 97(3): p. 1045-1087 | Abot A, et al. EMBO Mol Med. 2014. 6(10): p. 1328-46 | Coelingh Bennink HJT, et al. Climacteric. 2008. 11 Suppl 1: p. 2-14. | Benoit T, et al. Am J Pathol. 2017. 187(11): p. 2499-2507.

nAPCsr and VTE risk – E4/DRSP





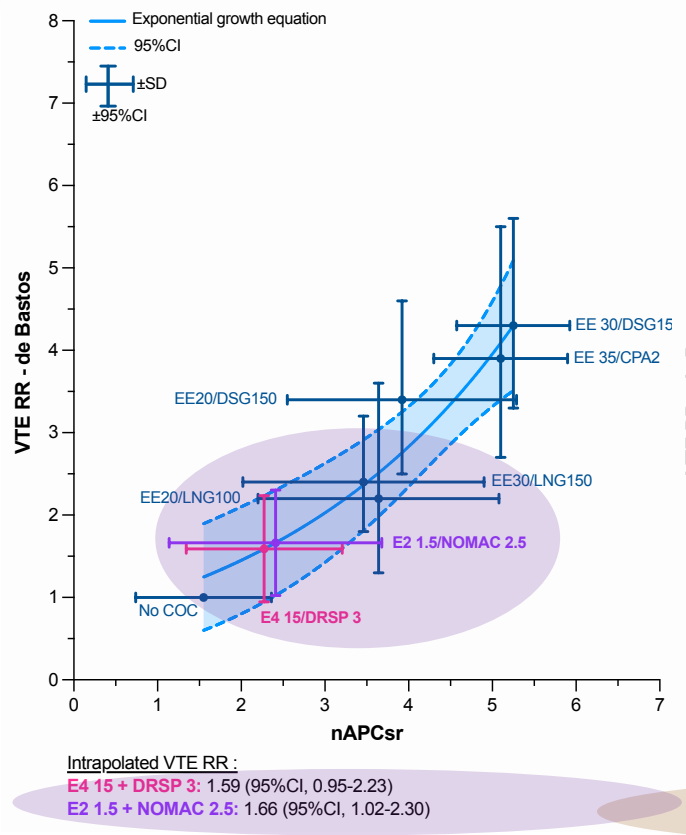
	Mean nAPCsr	VTE RR (de bastos et al. 2014)
No CHC	1.55	1.00 (ref)
EE30/LNG150	3.46	2.40
EE20/LNG100	3.64	2.20
EE20/DSG150	3.92	3.40
EE30/DSG150	5.25	4.30
EE35/CPA2	5.10	3.90
E4/DRSP	2.28	1.59*

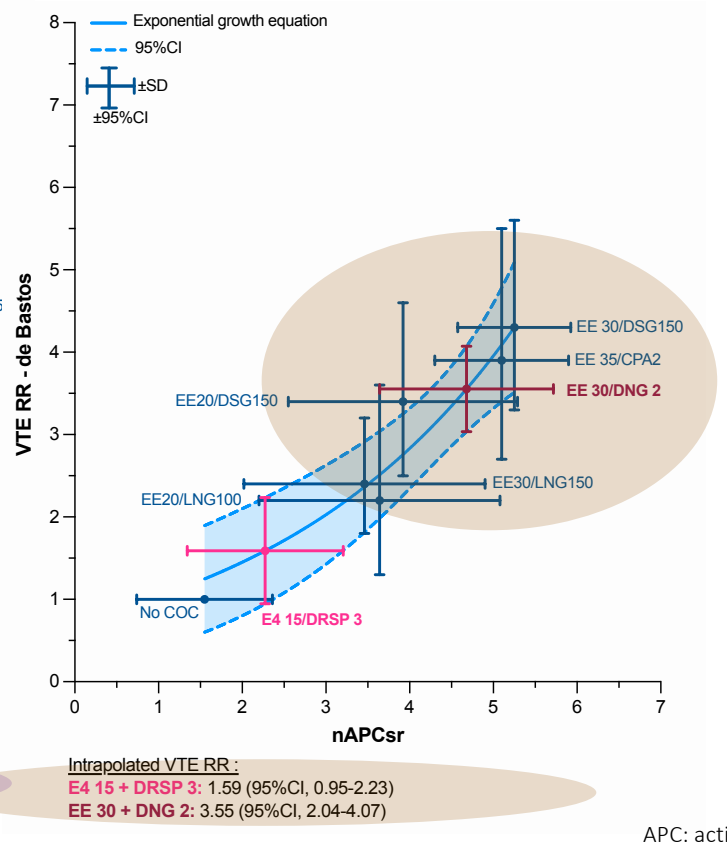
* Intrapolated from the model

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

APC: activated protein C | CI: confidence interval | CHC: combined hormonal contraceptives | nAPCsr: normalized APC sensitivity ratio | RR: relative risk | SD: standard deviation | VTE: venous thromboembolism

nAPCsr and VTE risk – Proofs of robustness





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EE20/LNG100	3.64	2.20
EE20/DSG150	3.92	3.40
EE30/DSG150	5.25	4.30
EE35/CPA2	5.10	3.90
E4/DRSP	2.28	1.59*
E2/NOMAC	2.41	1.63
EE30/DNG2	4.68	3.52 ‡

* Intrapolated from the mode
† Adjusted from PRO-E2
‡ Adjusted from Dinger et al. 2020

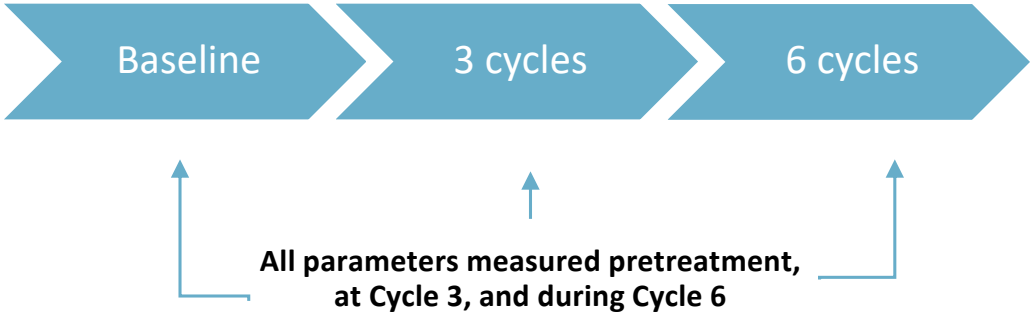
de Bastos, M., et al. Cochrane Database Syst Rev, 2014(3): p. CD010813| Morimont et al. Thromb Res. 2020. 193: p. 221-223.

APC: activated protein C | CI: confidence interval | CHC: combined hormonal contraceptives | nAPCsr: normalized APC sensitivity ratio | RR: relative risk | SD: standard deviation | VTE: venous thromboembolism

Phase 2 programs of E4 – Comparison of APC resistance data

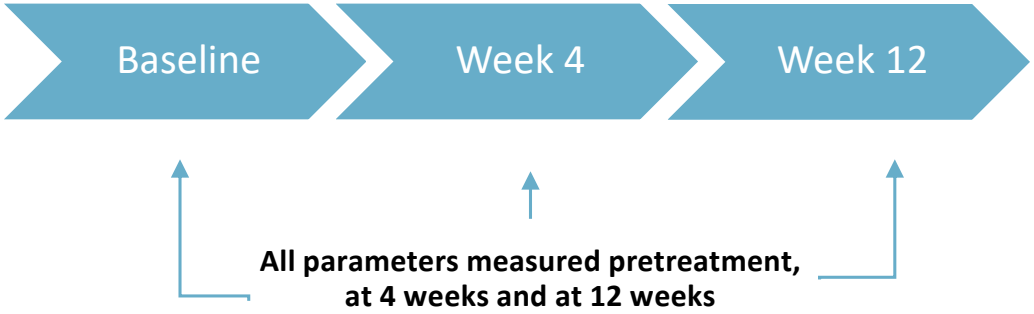
- Estelle Phase 2 Trial

Treatments	Analysis set
E4 15 mg + DRSP 3 mg	34
EE 30 µg + LNG 150 µg (Melleva®)	27
EE 20 µg + DRSP 3 mg (Yaz®)	30



- E4Relief Phase 2b Trial - Menopause

Treatments	Analysis set
E4 15 mg*	35
E4 10 mg*	35
E4 5 mg*	32
E4 2.5 mg*	44
Placebo	34

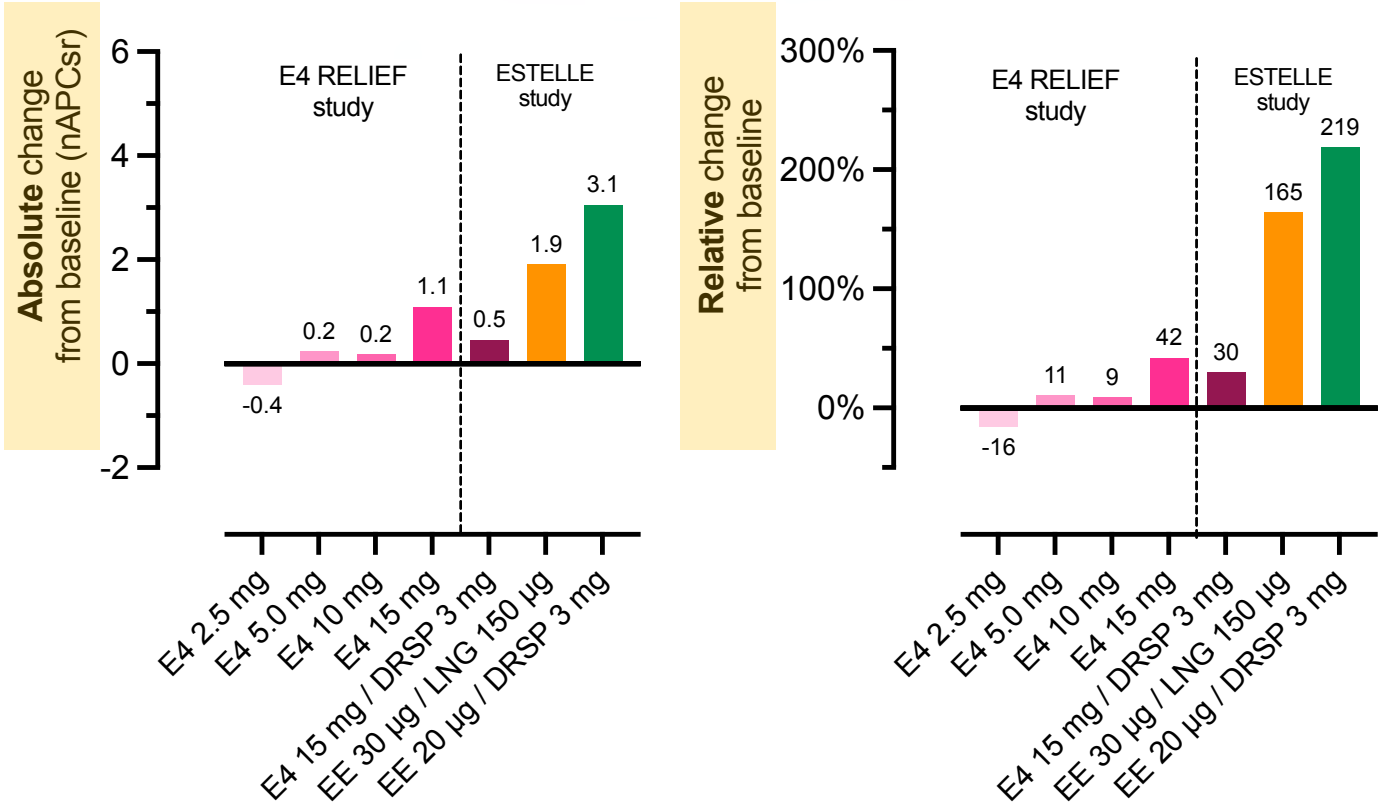


*not marketed in Denmark.

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

Low impact of E4* on APC resistance

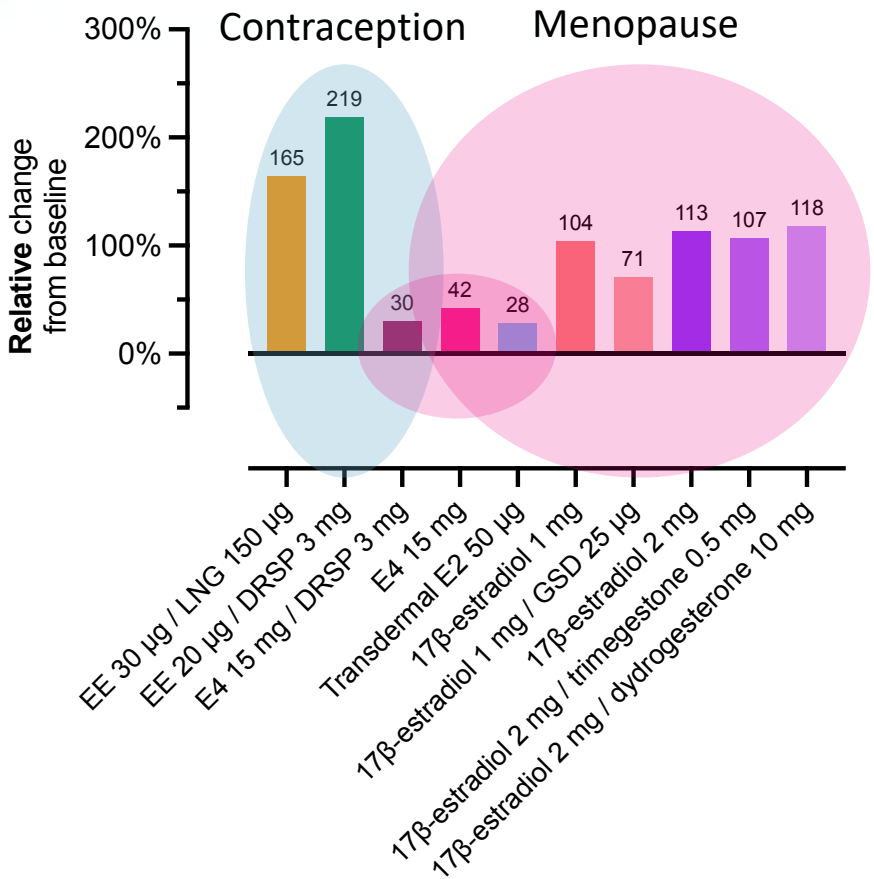
As nAPCsr scales from 0 to 10, the **absolute increase values observed for EE-containing products were close and even higher than the upper limit of the normal range**†



†normal range in healthy population not on COC: 0.00 to 2.08
*E4 2,5/5,0/10/15 mg are not available on the Danish market

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

Low impact of E4 on APC resistance



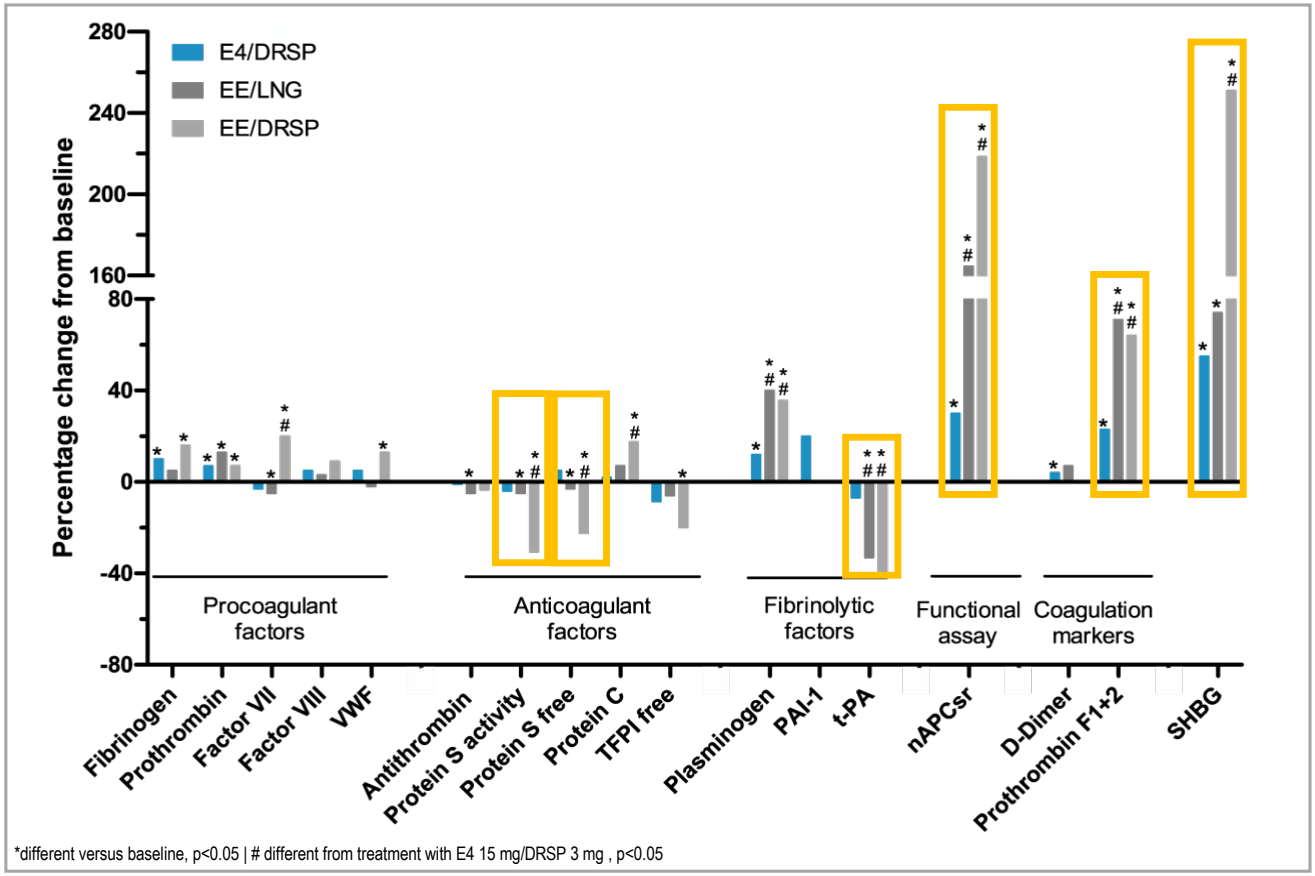
Compared to **oral EE or E2** the relative increase in nAPCsr is lower with E4 15 mg

The relative increase in nAPCsr with E4 15 mg is **similar to transdermal E2 50 µg**

Post et al. Br J Haematol. 2002. 119(4): p. 1017-23 | Post et al. Arterioscler Thromb Vasc Biol 2003. 23(6): p. 1116-21 | Douxfils, J. et al. Contraception. 2020. 102(6): p. 396-402 | Douxfils, J. et al. Climacteric. 2023. 26(1): p. 55-63

Effect of E4+DRSP on other hemostasis factors

- Lower or similar hemostatic changes with E4+DRSP versus EE+LNG
- Less pronounced hemostatic changes with E4+DRSP versus EE+DRSP
- **The choice of the estrogens modulates the impact on hemostasis**

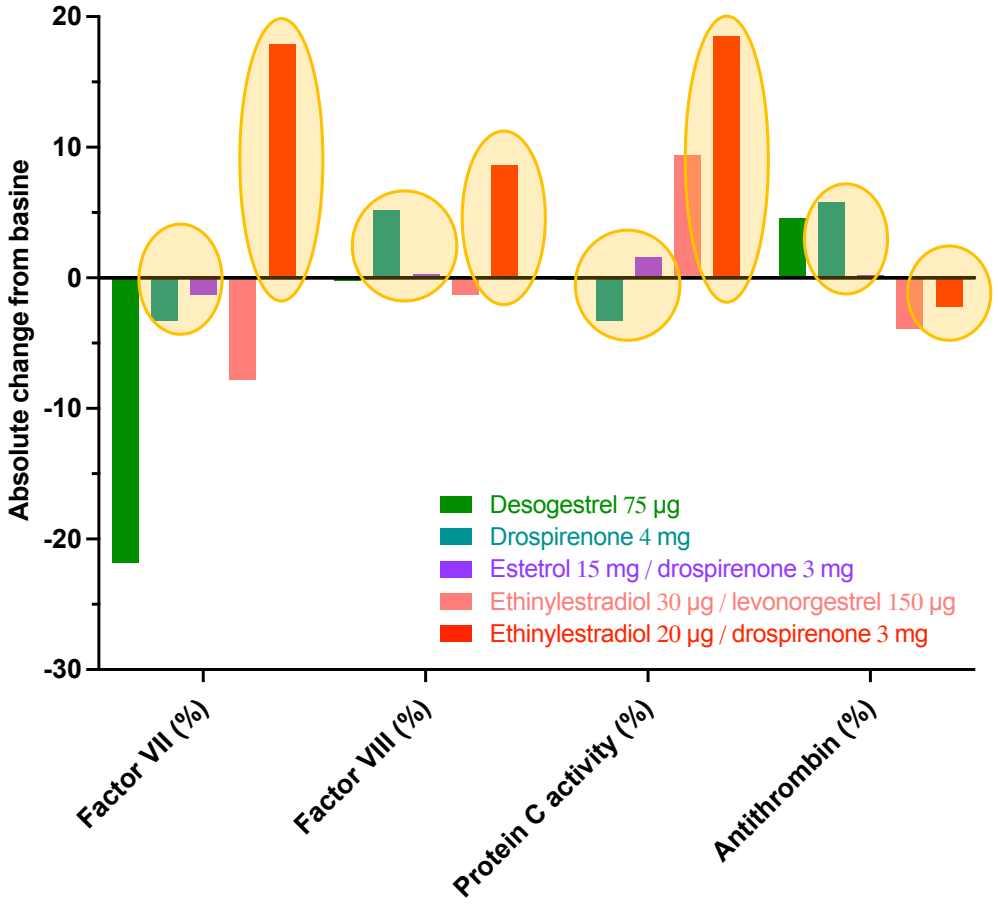


E4/DRSP: Estetrol 15 mg/drospirenone 3 mg | EE/LNG: ethinylestradiol 30 µg/ levonorgestrel 150 µg | EE/DRSP: ethinylestradiol 20 µg/ DRSP 3 mg | nAPCsr: normalized activated protein C sensitivity ratio | PAI-1: plasminogen activator inhibitor type 1 | SHBG: sex hormone binding protein | t-PA: tissue plasminogen activator | TFPI: tissue factor pathway inhibitor | VWF: von Willebrand factor

Douxfils, J. et al. Contraception. 2020. 102(6): p. 396-402

Effect of DRSP or E4+DRSP on comparable hemostasis factors

- DRSP, as a progestin-only contraceptive at a dose of 4mg, has not been categorized by regulatory bodies as having a different risk of VTE from other progestin-only contraceptives.
- Hemostatic investigations of individual coagulation factors did not reveal the clinically relevant impact of this DRSP at 4 mg
- E4, in combination with DRSP, **has a coagulation profile similar to DRSP alone**, whereas a clear difference is observed with the EE/DRSP combination.



E4/DRSP: Estetrol 15 mg/drospirenone 3 mg | EE/LNG: ethinylestradiol 30 µg/ levonorgestrel 150 µg | EE/DRSP: ethinylestradiol 20 µg/ DRSP 3 mg | nAPCsr: normalized activated protein C sensitivity ratio | PAI-1: plasminogen activator inhibitor type 1 | SHBG: sex hormone binding protein | t-PA: tissue plasminogen activator | TFPI: tissue factor pathway inhibitor | VWF: von Willebrand factor

Douxfils, J. et al. Res Pract Thromb Haemost **7**(4): 100155.

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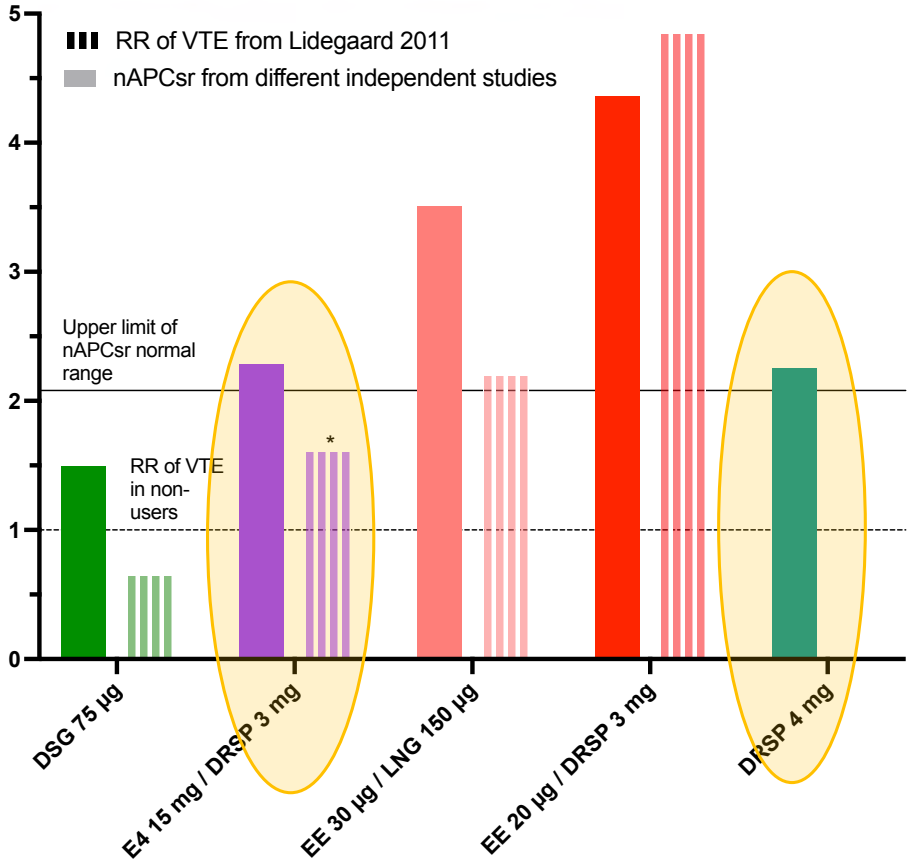
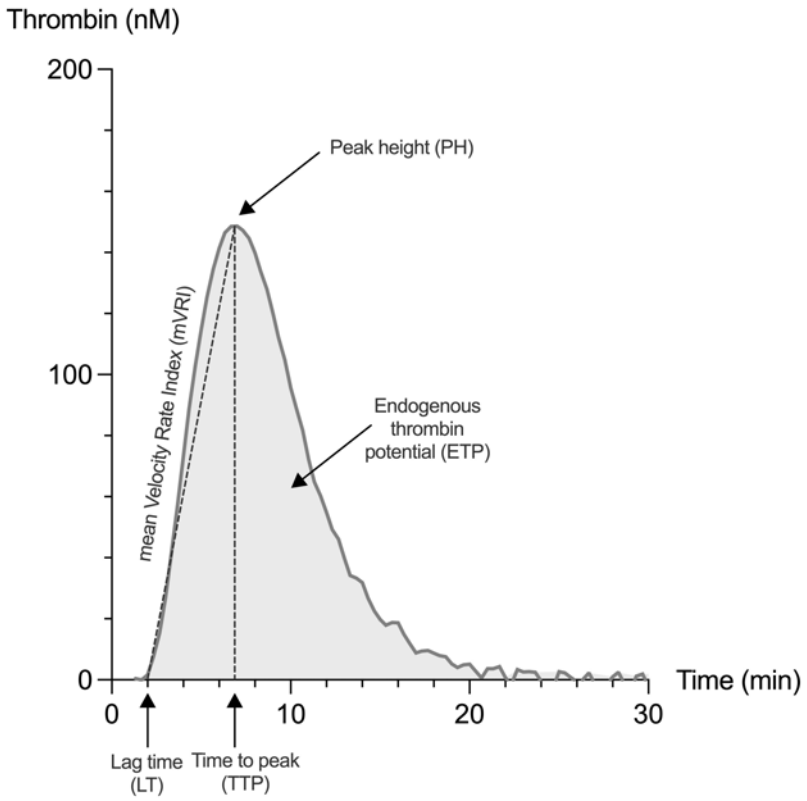
- E4, in combination with DRSP, **has a coagulation profile similar to DRSP alone**, whereas a clear difference is observed with the EE/DRSP combination.



* VTE risk not extracted from Lidegaard 2011 but extracted from in silico modeling according to Morimont et al. and adapted to the Lidegaard's data.[65]

E4/DRSP: Estetrol 15 mg/drospirenone 3 mg | EE/LNG: ethinylestradiol 30 µg/ levonorgestrel 150 µg | EE/DRSP: ethinylestradiol 20 µg/ DRSP 3 mg | nAPCsr: normalized activated protein C sensitivity ratio | PAI-1: plasminogen activator inhibitor type 1 | SHBG: sex hormone binding protein | t-PA: tissue plasminogen activator | TFPI: tissue factor pathway inhibitor | VWF: von Willebrand factor

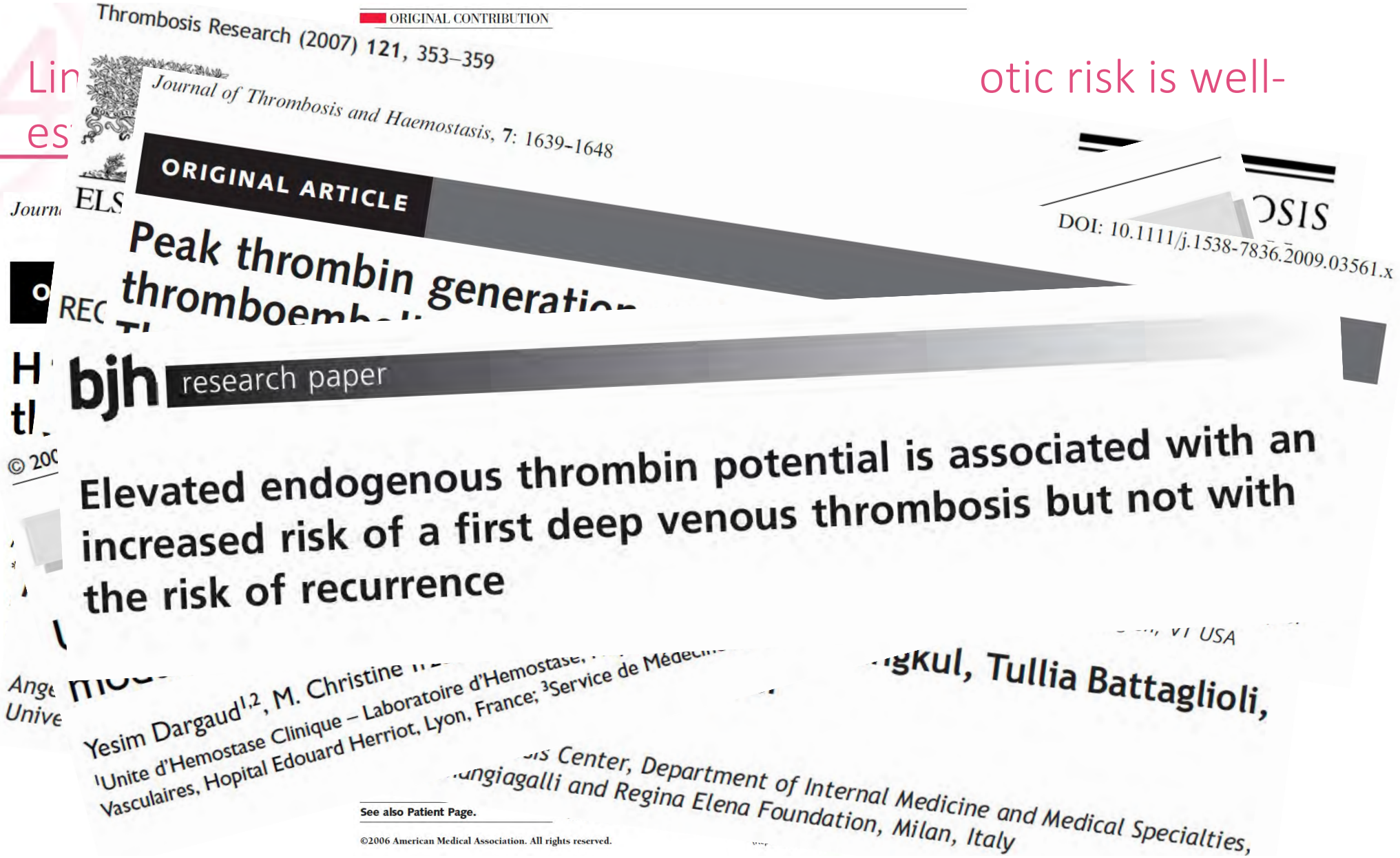
The need to assess hemostasis globally



- Synergistic effect cannot be captured by singular measurements of coagulation parameters
- Global test capable of capturing all pro- and anticoagulants factors levels changes (except APC)
- **Thrombin generation test/assay** permits to assess the coagulation process in its entirety
- **TGA** has been shown to be sensitive to the synergistic hemostatic alterations induced by CHCs

Hemker, KH. et al. Pathophysiol Haemost Thromb. 2003. 33(1): p. 4-15.

Lin… …otic risk is well-
es…



Thrombosis Research (2007) 121, 353–359

ORIGINAL CONTRIBUTION

Journal of Thrombosis and Haemostasis, 7: 1639–1648

ORIGINAL ARTICLE

Peak thrombin generation… thromboemb…

DOI: 10.1111/j.1538-7836.2009.03561.x

bjh research paper

Elevated endogenous thrombin potential is associated with an increased risk of a first deep venous thrombosis but not with the risk of recurrence

…VT USA

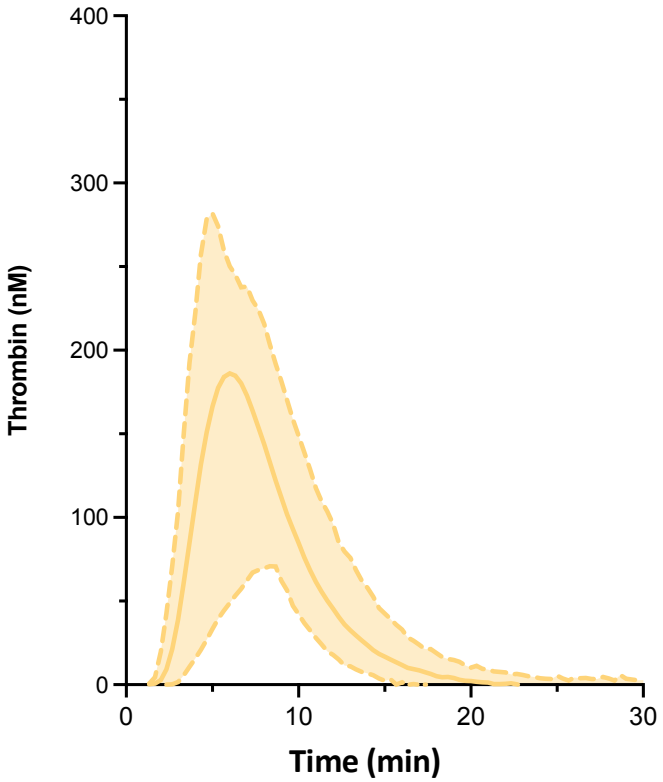
Yesim Dargaud[1,2], M. Christine …, …gkul, Tullia Battaglioli,

[1]Unite d'Hemostase Clinique – Laboratoire d'Hemostase, … Vasculaires, Hopital Edouard Herriot, Lyon, France; [3]Service de Médeci…

…is Center, Department of Internal Medicine and Medical Specialties, …ngiagalli and Regina Elena Foundation, Milan, Italy

See also Patient Page.

Impact of E4 on thrombin generation - Contraception

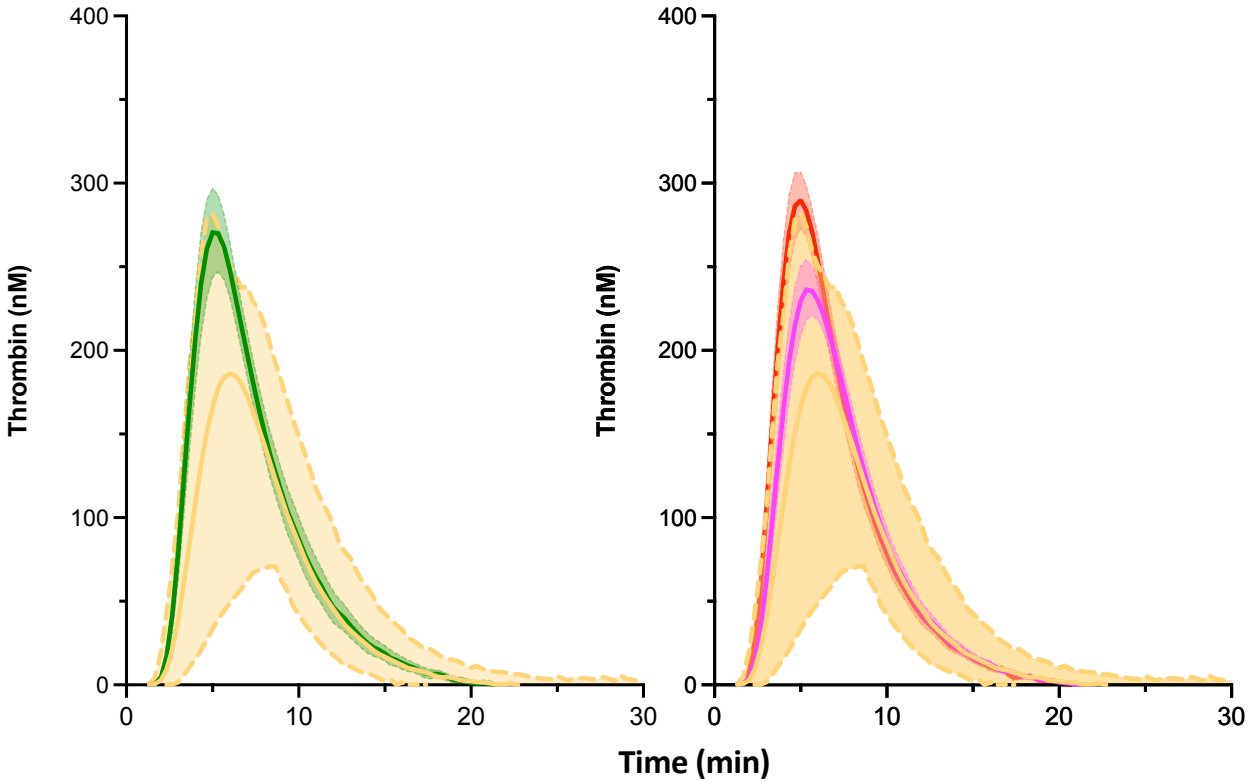


Reference ranges for thrombin generation and associated parameters are reported as the 2.5th – 97.5th percentile of the entire baseline cohort (n=86), in accordance with the definition of the reference intervals as reported in the Clinical & Laboratory Standards Institute (CLSI) EP-28-A3C[1]

1. Clinical and Laboratory Standards Institute. Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline — Third Edition. *CLSI document EP28-A3C. Wayne, PA*: Clinical and Laboratory Standards Institute; 2010.

Morimont, L. et al. J Clin Endocrinol Metab. 2022. 108(1): p. 135-143

Impact of E4 on thrombin generation - Contraception

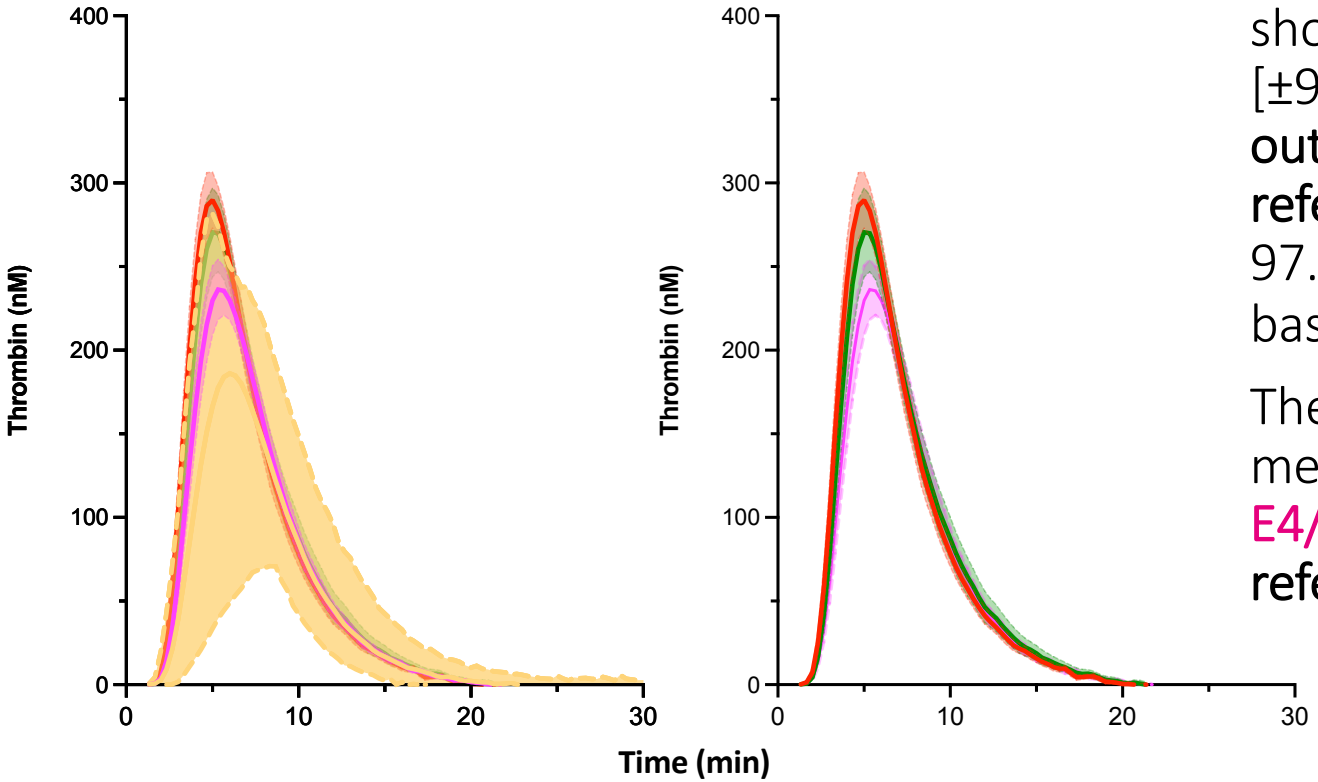


EE/LNG and EE/DRSP groups show a mean thrombogram [±95%CI of the mean] **outside the upper limit of the reference range**, i.e., the 97.5th percentile of all baseline thrombograms

The mean [±95%CI of the mean] thrombogram of E4/DRSP is **within this reference interval**

Morimont, L. et al. J Clin Endocrinol Metab. 2022. 108(1): p. 135-143

Impact of E4 on thrombin generation - Contraception

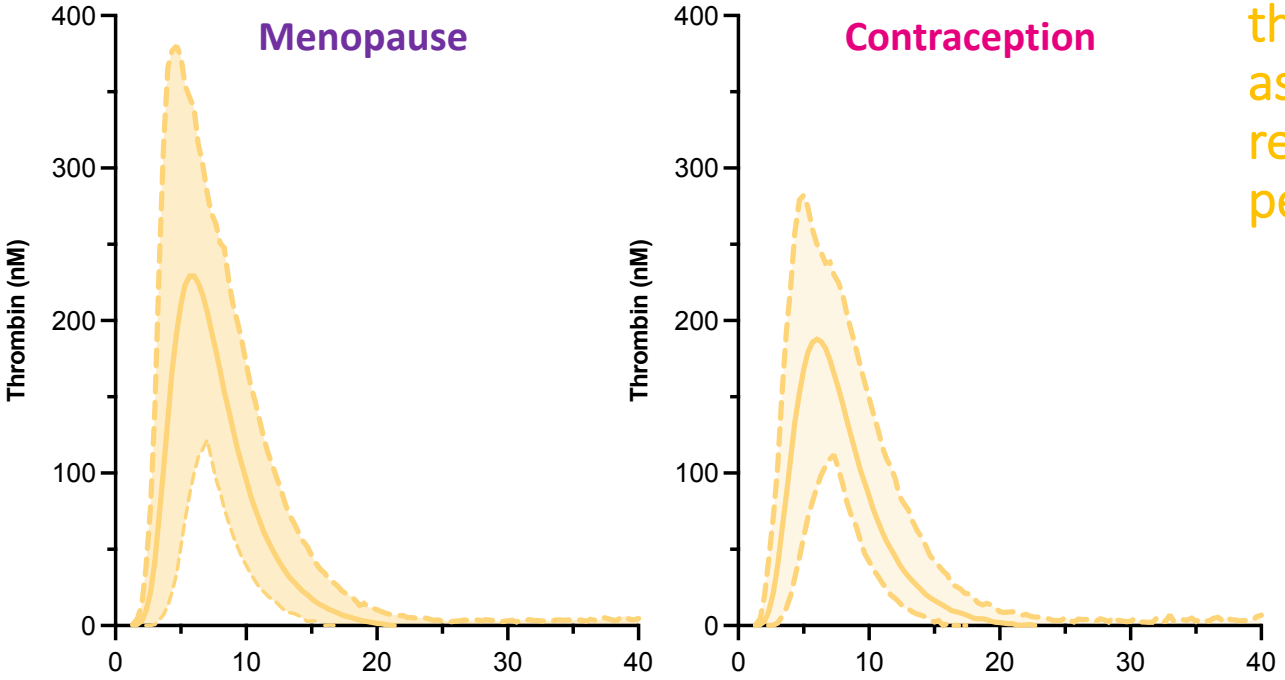


EE/LNG and EE/DRSP groups show a mean thrombogram [±95%CI of the mean] **outside the upper limit of the reference range**, i.e., the 97.5th percentile of all baseline thrombograms

The mean [±95%CI of the mean] thrombogram of E4/DRSP is **within this reference interval**

Morimont, L. et al. J Clin Endocrinol Metab. 2022. 108(1): p. 135-143

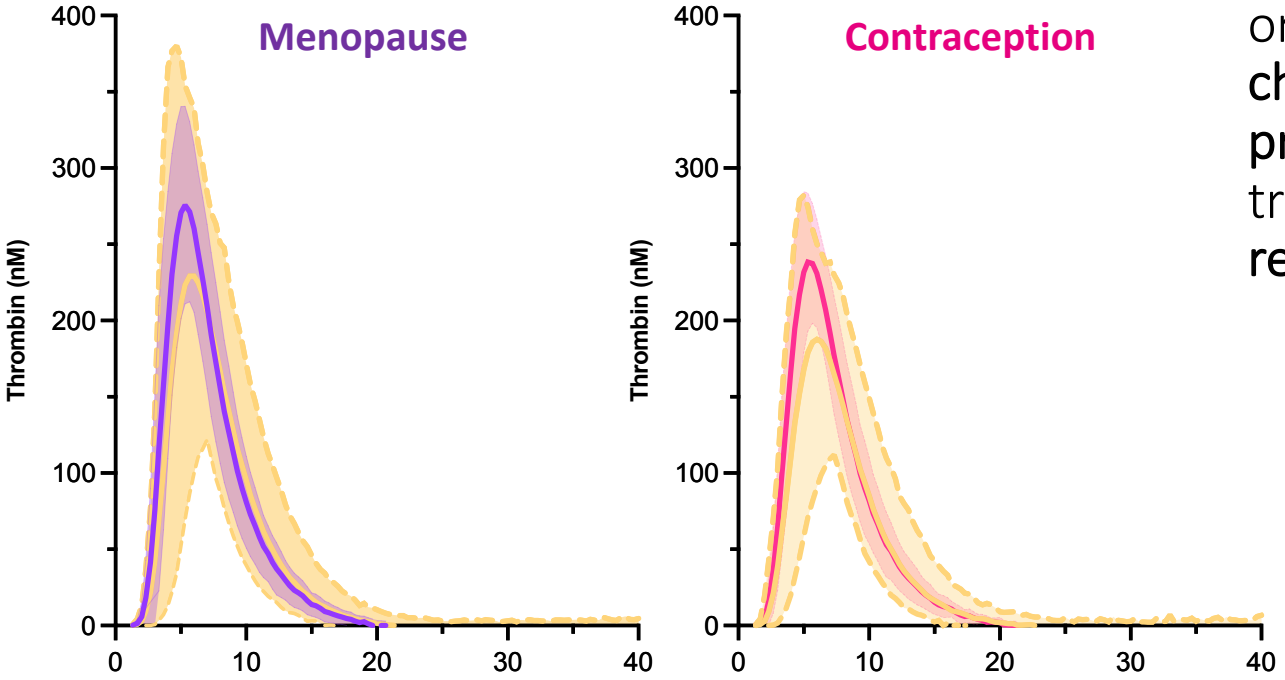
Impact of E4 on thrombin generation
HRT vs contraception



Reference ranges for thrombin generation and associated parameters are reported as the 2.5th – 97.5th percentile

Douxfils, J. et al. Thromb Res. 2022

Impact of E4 on thrombin generation
HRT vs contraception



E4, either in contraception or in HRT, **does not induce changes in the coagulation process** which are translated into **clinically relevant changes**

Douxfils, J. et al. Thromb Res. 2022

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 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.

Conclusions from biological data and early clinical experience with E4

- Hemostasis biological data and the early clinical experience are very reassuring
- Safer compound in contraception
- Data from PASS studies to support and provide real-life estimate **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

Conclusions

- E4 alone or in combination with DRSP exhibits a safer hemostatic profile compared to EE containing products.
- The choice of the estrogen modulates the impact on hemostasis.
- **E4 alone is the only oral estrogen having a similar impact on APC resitance as transdermal E2 50 µg in menopausal women.**
- The ETP-based APC resistance seems to be a suitable biomarker to estimate the risk of VTE of COC.

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 | de Bastos, M., et al. Cochrane Database Syst Rev, 2014(3): p. CD010813| Morimont et al. Thromb Res. 2020. 193: p. 221-223 | Reed, S. et al. Eur J Contracept Reprod Health Care. 2021. 26(6): p. 439-446 | Morimont, L., et al. Front Endocrinol (Lausanne), 2021. 12: p. 769187 | Dinger, J. et al. Front Women's Health. 2020. 5(1)

Conclusions

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

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 | de Bastos, M., et al. Cochrane Database Syst Rev, 2014(3): p. CD010813| Morimont et al. Thromb Res. 2020. 193: p. 221-223 | Reed, S. et al. Eur J Contracept Reprod Health Care. 2021. 26(6): p. 439-446 | Morimont, L., et al. Front Endocrinol (Lausanne), 2021. 12: p. 769187 | Dinger, J. et al. Front Women's Health. 2020. 5(1)

Thank you for your attention

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Picture taken from the cable car overhanging the city of Namur and allowing to link the city center to our Citadel

Correlation between SHBG and ETP-based APC resistance