Validation and standardization of the ETP-based activated protein C resistance test for the clinical investigation of steroid contraceptives in women

An unmet clinical and regulatory need

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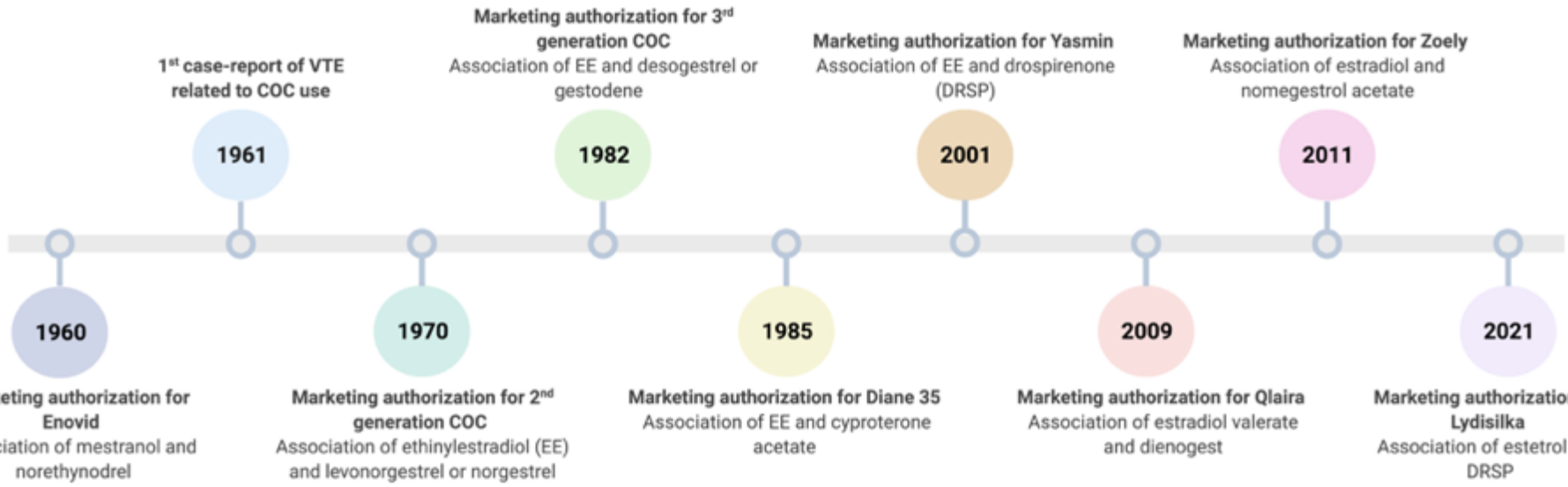
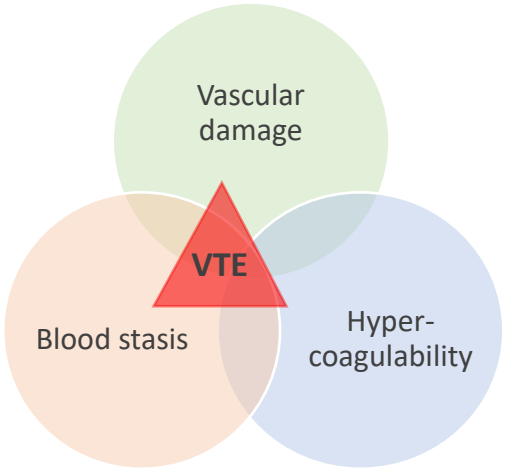
Your expert in blood testing

Introduction



Etiology of VTE under COC use



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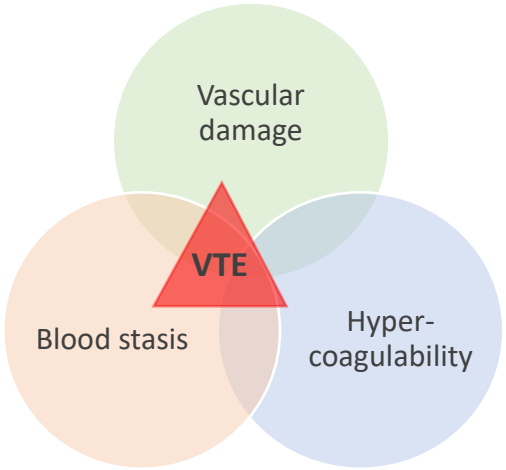

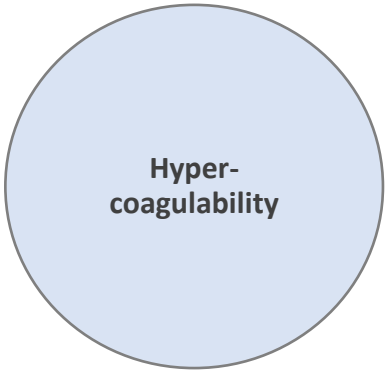

Inherited thrombophilia
- Factor V Leiden - Prothrombin G20210A mutation - Protein S deficiency - Protein C deficiency - Antithrombin deficiency

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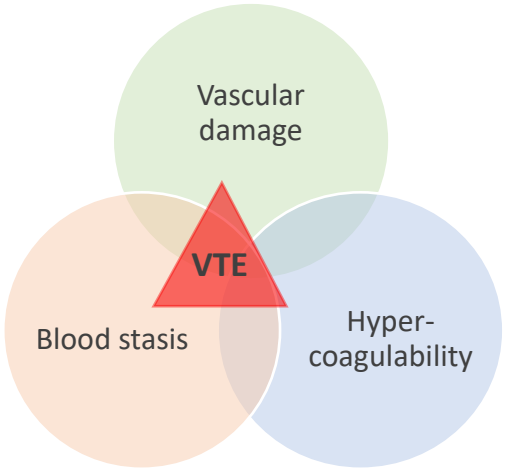
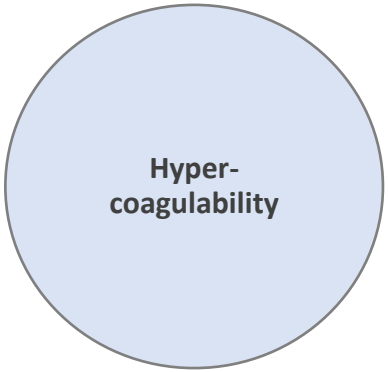


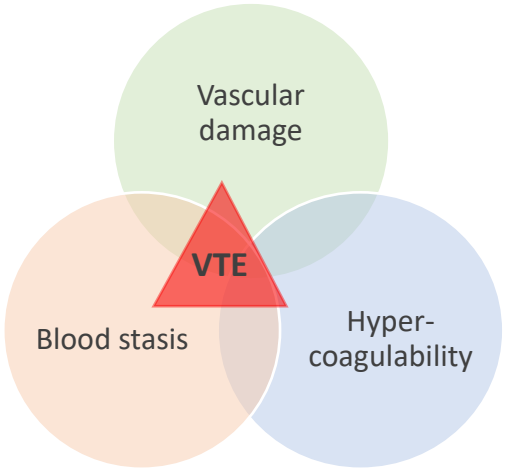


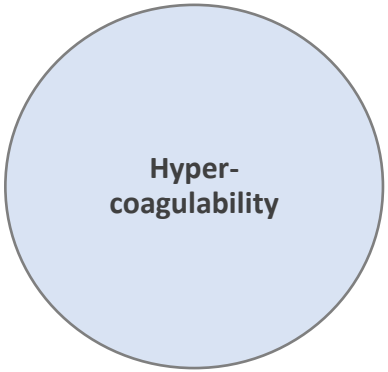
Prevalence: 2-5%
RR of VTE
- **Heterozygous:** 4-8
- **Homozygous:** 30-80

Inherited thrombophilia

- **Factor V Leiden**
- **Prothrombin G20210A mutation**
- Protein S deficiency
- Protein C deficiency
- Antithrombin deficiency

Etiology of VTE under COC use



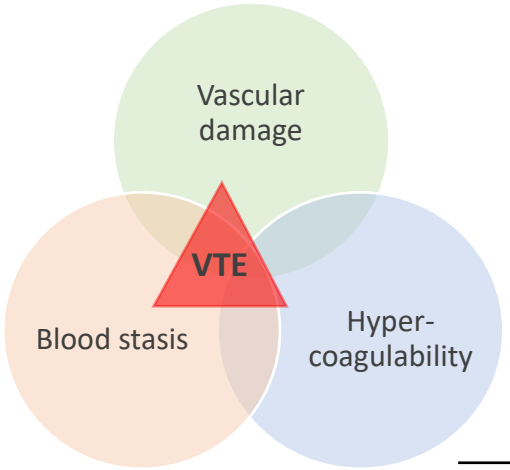


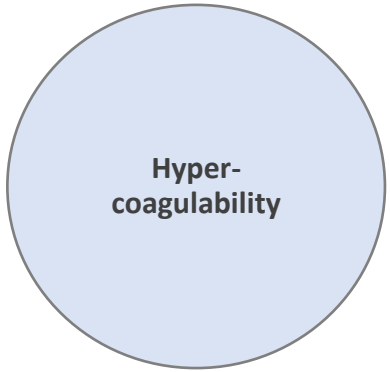
Prevalence: < 1%
RR of VTE: 10 - 50

Inherited thrombophilia

- Factor V Leiden
- Prothrombin G20210A mutation
- **Protein S deficiency**
- **Protein C deficiency**
- **Antithrombin deficiency**

Etiology of VTE under COC use





Acquired thrombophilia

- Central venous catheter
- Malignancy
- Surgery (especially orthopedic)
- Trauma
- Immobilization
- **Pregnancy**
- **Combined hormonal contraceptive**
- **Hormonal replacement therapy**
- Chemotherapy
- Heart failure
- Antiphospholipid syndrome
- ≥65 years
- Obesity
- Severe liver disease
- Inflammatory bowel disease
- Nephrotic syndrome

Inherited thrombophilia

- Factor V Leiden
- Prothrombin G20210A mutation
- **Protein S deficiency**
- **Protein C deficiency**
- **Antithrombin deficiency**

Epidemiology of VTE under COC use

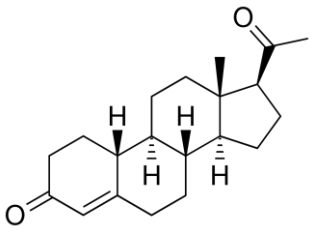
Estimated incidence of risk of VTE with COC[1]	
Non-pregnant non-user	About 2 out of 10,000 women
COC containing ethinylestradiol (EE) + levonorgestrel (LNG), norethisterone or norgestimate (NGM)	About 5-7 out of 10,000 women
COC containing EE + gestodene (GSD), desogestrel (DSG) or drospirenone (DRSP)	About 9-12 out of 10,000 women
COC containing EE + chlormadinone acetate (CMA) or dienogest (DNG)	RR of 1.28 vs EE-LNG (DNG)
COC containing estradiol valerate (E2V) + DNG	aRR of 0.4 vs EE-LNG[2]
COC containing estradiol (E2) + nomegestrol acetate (NOMAC)	aRR of 0.6 vs EE-LNG[2]
COC containing estetrol (E4) + drospirenone (DRSP)	PASS requested by the EMA and the FDA

[1] European Medicines Agency. Assessment report for combined hormonal contraceptives containing medicinal products — Procedure number: EMEA/H/A-31/1356. 2014
[2] Grandi et al. The European Journal of Contraception & Reproductive Health Care. 2022

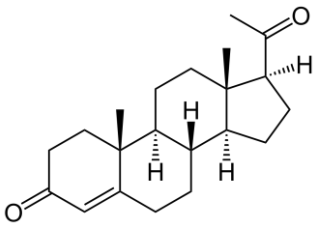
Concept of estrogenicity

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

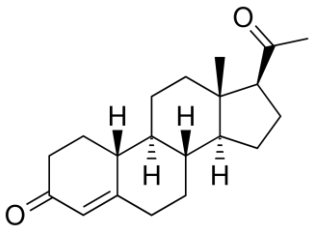
<u>4 types of orally active, synthetic progestins:</u>



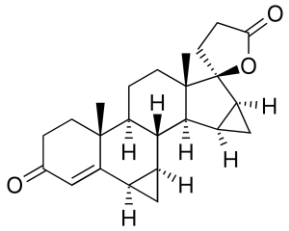
19-nortestosterone derivative
- Levonorgestrel
- Desogestrel
- Gestodene
- Dienogest



Progesterone derivative
- Chlormadinone acetate
- Cyproterone acetate



19-norprogesterone derivative
- Nomegestrol acetate

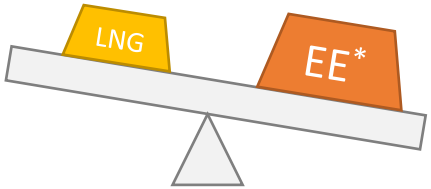


Spironolactone derivative
- Drospirenone

Concept of estrogenicity

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

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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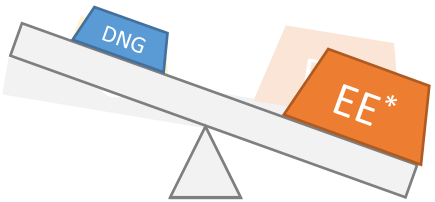
Dienogest (DNG)	-	+



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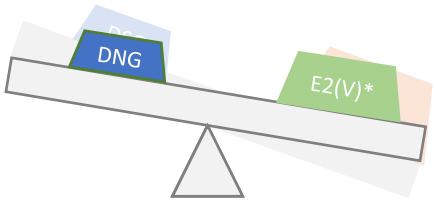
Dienogest (DNG)	-	+



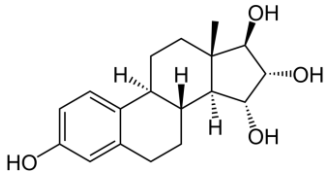
*E2(V): estradiol (valerate)

Estetrol : new estrogenic-derivative of COC

Estetrol = Natural fetal estrogenic steroid

Good oral pharmacokinetics properties:

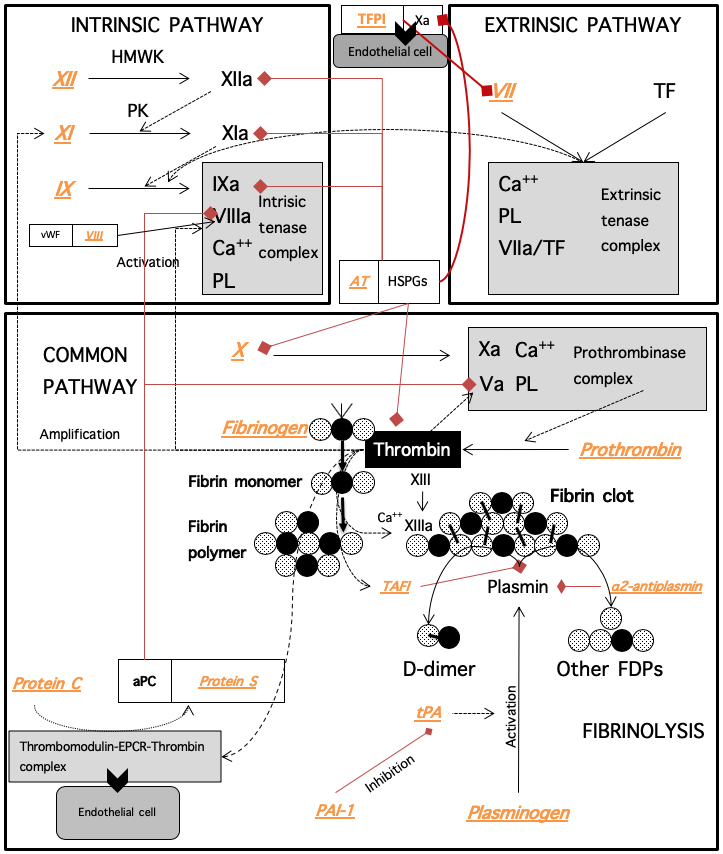
- Half-life of 20-28 hours
- Minimally, if at all, metabolized and not reconverted to E3 or E2. Mainly metabolized by glucuronidation and sulfation
- Mainly excreted in urine
- No binding to SHBG, low impact on SHBG synthesis
- High selectivity for estrogen receptors



New COC: <u>estetrol associated with drospirenone</u>

Phase I and phase II studies revealed low impact on the coagulation and fibrinolytic system (compared to EE/LNG and EE/DRSP)

Etiology of VTE under COC



Douxfils, J et al. Seminar in Thrombosis and Hemostasis, 2020

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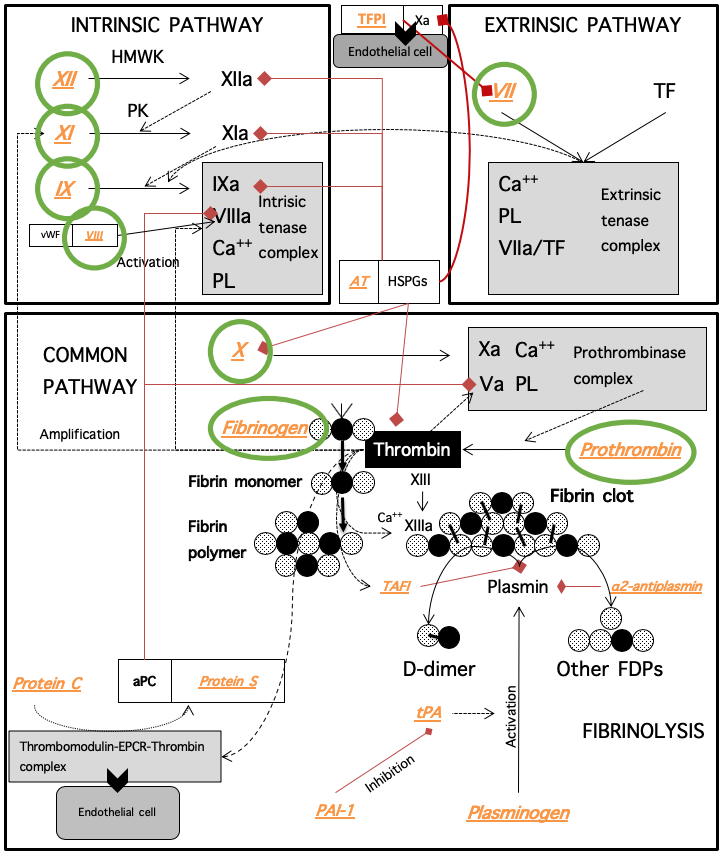

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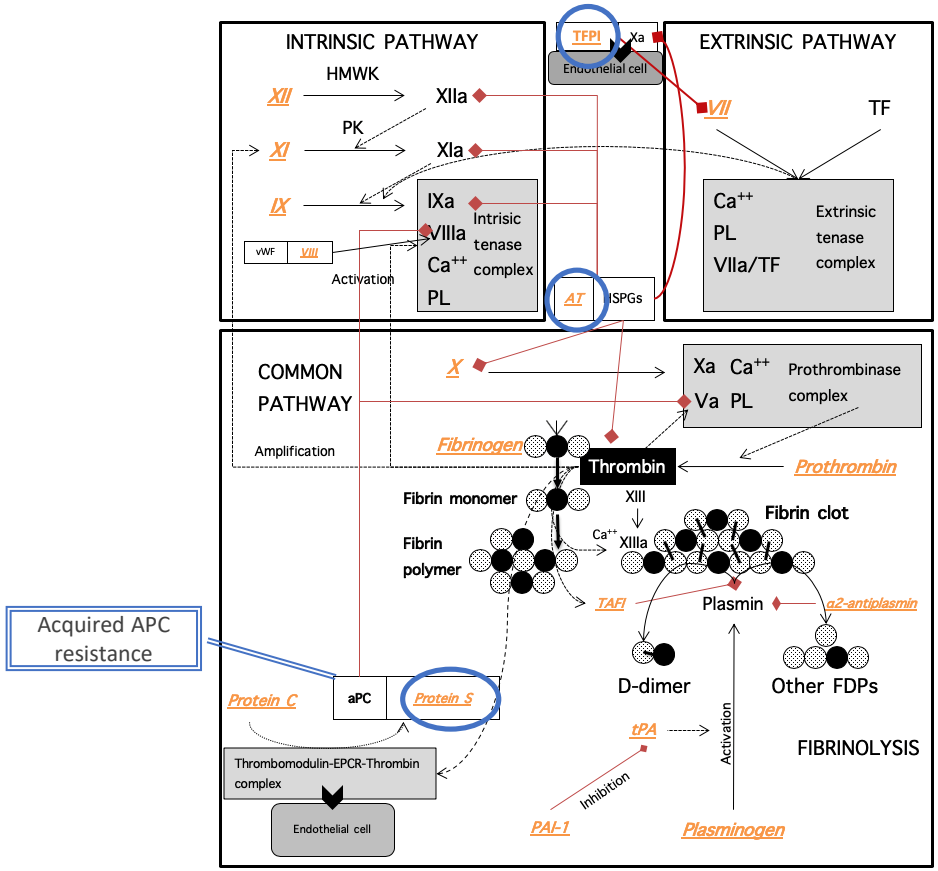

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Hemostasis investigations recommended for COC development

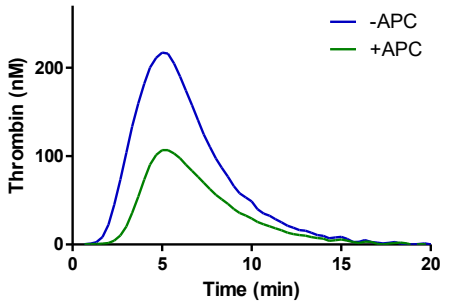
Food and Drug Administration[1]	European Medicines Agency[2]
Labelling guidance for COC (2004 ; updated in 2017)	List of recommended hemostasis investigations during the development of steroid contraceptives
Endocrine and liver function tests and blood components may be affected by OCs: - Increased FII, FVII, FVIII, FIX, FX - Decreased antithrombin - Increased norepinephrine-induced platelet aggregability - Increased SHBG	- 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

[1]Food and Drug Administration. Guidance for Industry – Labeling for Combined Oral Contraceptives. 2004.
[2]European Medicines Agency. Guideline on Clinical investigation of Steroid Contraceptives in Women — EMEA/CPMP/EWP/519/98 Rev 1. 2005.

Hemostasis investigations recommended for COC development

Thrombin generation assay (TGA)

- Performed on : CAT device (soft: vers. 5.0)
- Activator reagent:
  (TS) PPL + TF / (+ or - APC)
- ETP parameter = area under the curve (nm.min)



European Medicines Agency[2]

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

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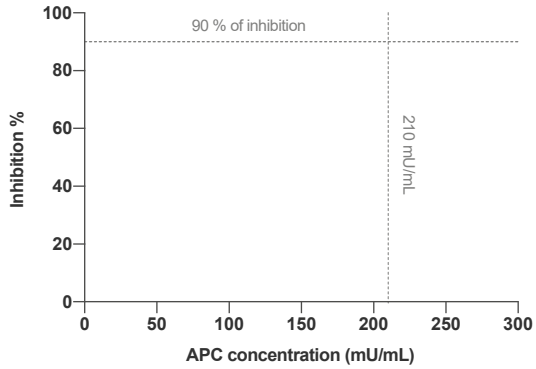
ETP-based APC resistance: principle

Dose-response curves to determine APC concentration leading to 90% of inhibition in a healthy pooled plasma (HPP)



HPP: pool of men and women not using hormonal contraception and not carrier of FV Leiden or G20210A mutation

$$Inhibition\ \% = 1 - \frac{sample\ ETP\ (+APC)}{sample\ ETP\ (-APC)}$$ expressed in %

= ETP ratio

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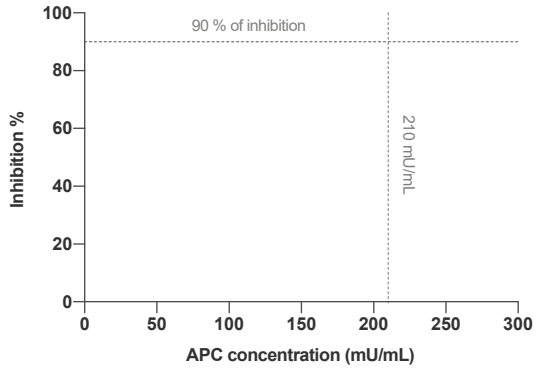
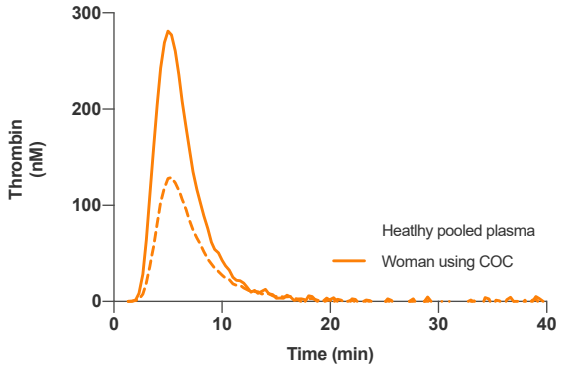
Dose-response curves to determine APC concentration leading to 90% of inhibition in a healthy pooled plasma (HPP)



Thrombin generation curves in absence (continuous line) or in presence (dotted line) of APC in HPP and woman using COC



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$$Inhibition\ \% = 1 - \frac{sample\ ETP\ (+APC)}{sample\ ETP\ (-APC)}$$ expressed in %

$\frac{sample\ ETP\ (+APC)}{sample\ ETP\ (-APC)}$ = *ETP ratio*

	Healthy pooled plasma	Woman using COC
ETP (-APC)	1181,39 nM.min	1226,83
ETP (+APC)	134,26 nM.min	623,02
Inhibition %	89%	49%
ETP ratio	0,11	0,51

ETP-based APC resistance: nAPCsr

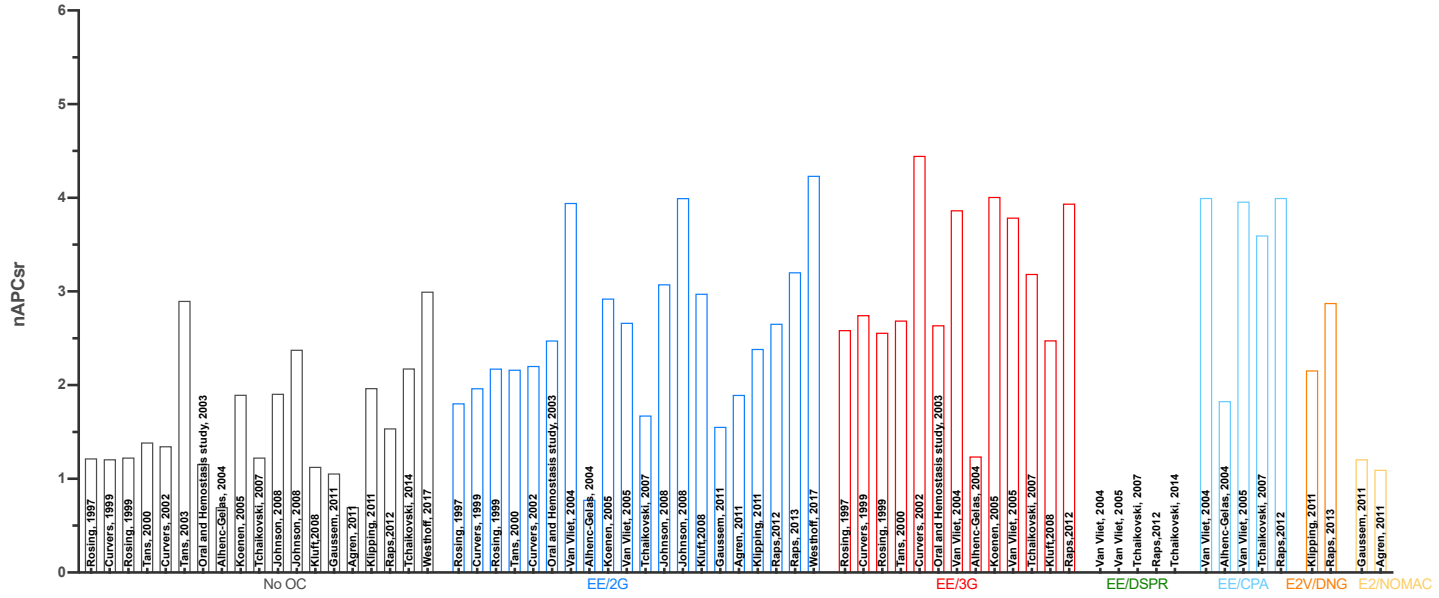
$$Inhibition\ \% = 1 - \frac{sample\ ETP\ (+APC)}{sample\ ETP\ (-APC)}$$, expressed in %

$$nAPCsr = \frac{sample\ ETP\ (+APC) / sample\ ETP\ (-APC)}{reference\ plasma\ ETP\ (+APC) / reference\ plasma\ ETP\ (-APC)}$$

	Theoretically	Practically	
Sample ETP ratio	1	1	1
Ref plasma ETP ratio	0,1	0,11	0,09
nAPCsr	10	9	11

ETP-based APC resistance: review of the literature

Synthesis of studies from 1997 to 2017 investigating the impact of oral contraceptives on the APC resistance, when expressed as nAPCsr.



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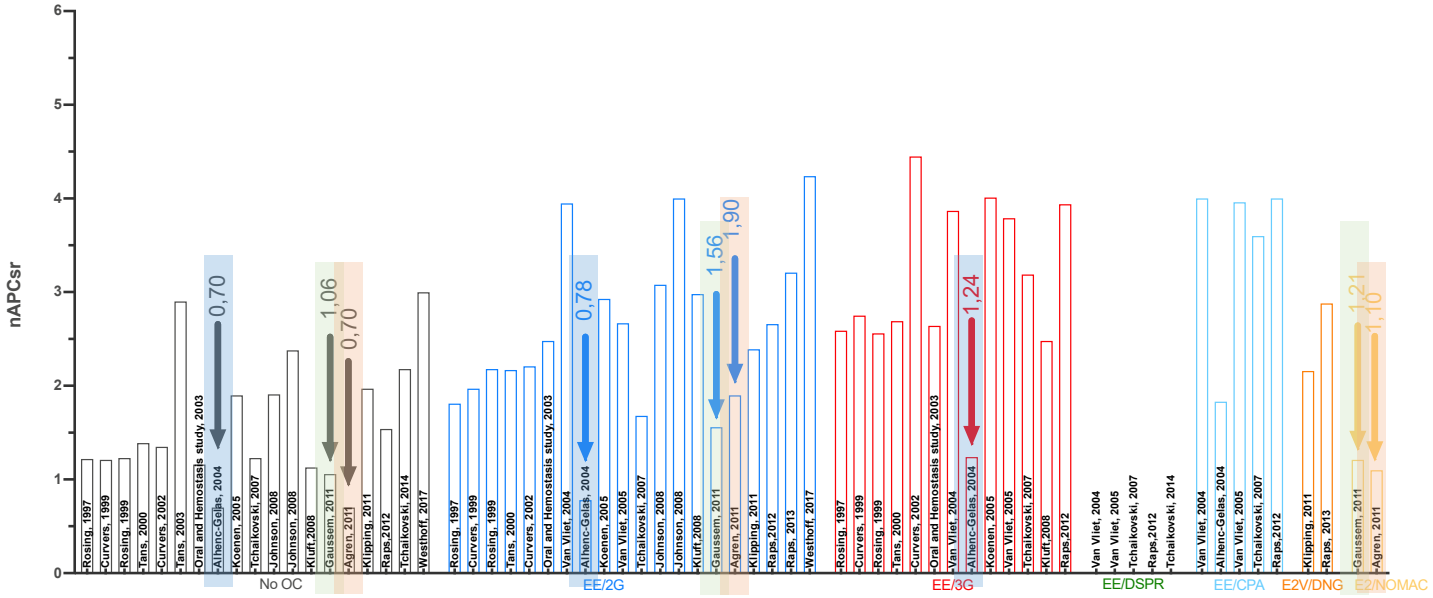
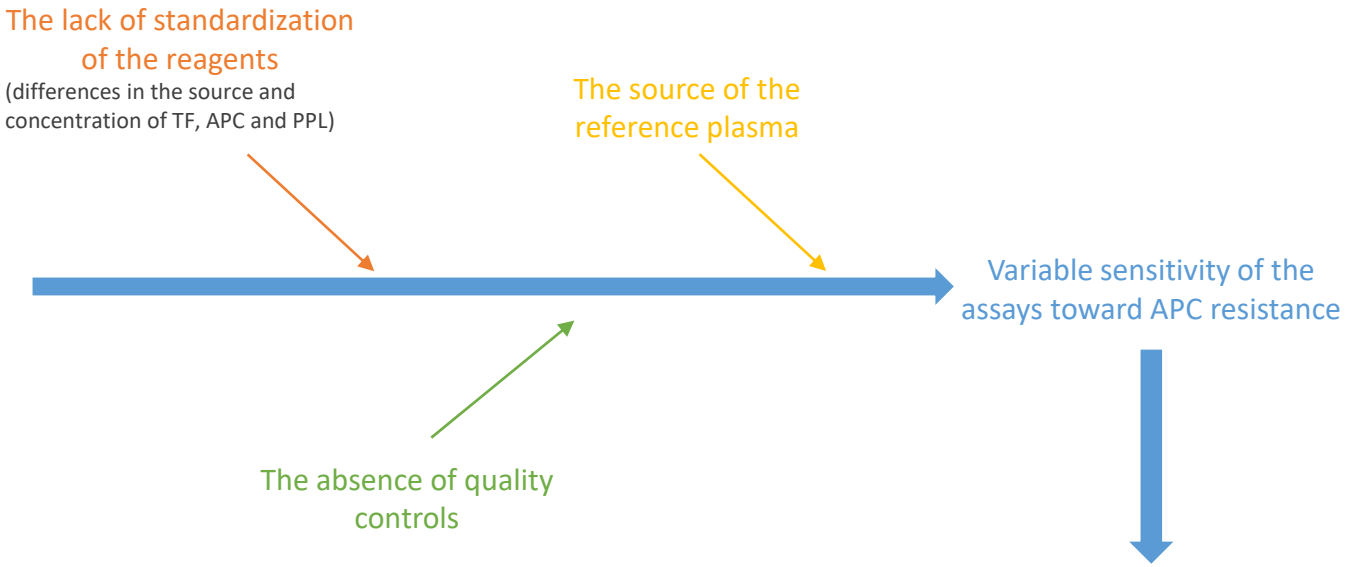


ETP-based APC resistance: validation process



The validation of this assay was a requirement for the proper assessment of ETP-based APC resistance in clinical studies

Performed according to the best industry standards including FDA "Guidance for Industry: Bioanalytical Method Validation" and ICHQ2(R1) "Validation of Analytical Procedures: Text and Methodology"

ETP-based APC resistance: validation process

Method

- **Three QCs** representing plasmas with different levels of coagulation and one reference plasma (ref plasma) were used.
- The method **targets a 90% inhibition of the ETP in HPP** (10 men and 10 women not using hormonal contraception, with no coagulation abnormalities) in presence of APC compared to the same condition in absence of APC.
- As the HPP is not produced at large scale, **specific algorithms were applied to the commercial ref plasma to correlate with HPP.**

$$Correction\ factor\ (CF) = \frac{Ref\ plasma\ ETP\ (+APC) \,/\, Ref\ plasma\ ETP\ (-APC)}{HPP\ ETP\ (+APC) \,/\, HPP\ ETP\ (-APC)}$$

$$nAPCsr = \frac{Sample\ ETP\ ratio}{Ref\ plasma\ ETP\ ratio \,/\, CF}$$

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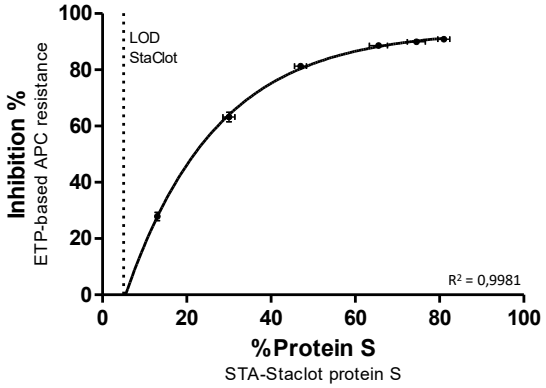
ETP-based APC resistance: validation process

Results

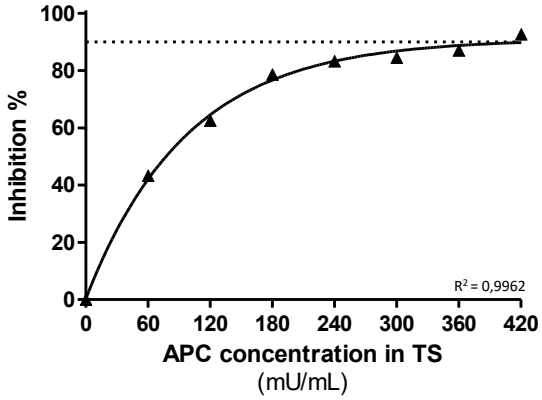
Inhibition percentage depending on a protein S deficiency.

Vertical dotted line represents the limit of detection of the STA®-Staclot® protein S kit



Inhibition percentage depending on concentration of spiked APC.

Horizontal dotted line represents 90% inhibition.



Acceptance criteria : R^2 >0,99

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ETP-based APC resistance: validation process

Results

	Intra-run variability (SD)	**Inter-run variability** (SD)	**Intermediate precision** (p-value)
QC low (hypocoagulable)	0%	0%	0,8503
QC intermediate (inter. coagulable)	1%	7%	0,6969
QC high (hypercoagulable)	3%	4%	0,8253
Ref plasma	0%	3%	0,9459

- Intra-run repeatability: 5 measurements
- Inter-run repeatability: 10 runs
- Intermediate precision: 3 operators ; 3 runs/operator

Acceptance criteria : SD <10% and no significant difference between operators

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ETP-based APC resistance: validation process

Results

Inhibition percentage of healthy individuals and women using COC

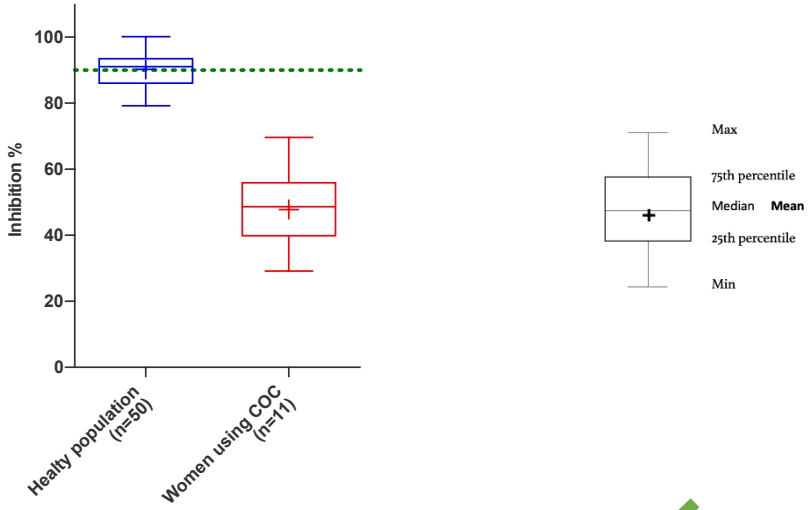
The dotted green line represents 90% inhibition.

Reference ranges (n=47) :

- Mean inh % = 90,2%
- Mean nAPCsr = 1.04

COC users (n=11) :

- Mean inh % = 47,8%
- Mean nAPCsr = 4,8



Acceptance criteria (reference ranges) **: Mean inh. % = 90% ± 2,5%**

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ETP-based APC resistance: validation process

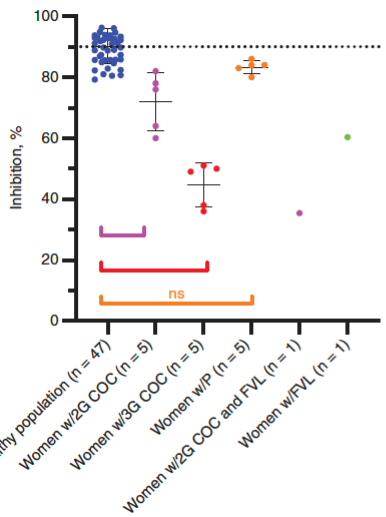
Results

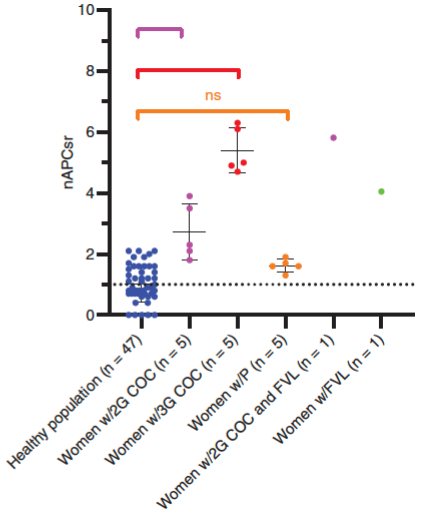
Inhibition percentage of healthy individuals and women using COC

The dotted green line represents 90% inhibition.

	Percentage of inhibition				nAPCsr				p-Value[a]
	Mean	95% CI	SD	10th–90th percentile	Mean	95% CI	SD	10th–90th percentile	
Healthy subjects (n = 47)	90%	89%–92%	6%	82%–100%	1.04	0.87–1.21	0.59	0.00–1.92	
Women on second-generation COC (n = 5)	72%	60%–84%	9%	60%–82%	2.72	1.57–3.87	0.92	1.80–3.90	0.0036
Women on third-generation COC (n = 5)	45%	36%–54%	7%	36%–51%	5.40	4.48–6.32	0.74	4.70–6.30	0.0002
Women on progestin-only contraceptive (n = 5)	83%	81%–86%	2%	80%–86%	1.62	1.35–1.89	0.22	1.30–1.90	0.1948
Woman on 2nd generation COC and Factor V Leiden heterozygous mutation (n = 1)	35%	N.A.	N.A.	N.A.	5.82	N.A.	N.A.	N.A.	N.A.
Woman with Factor V Leiden heterozygous mutation (n = 1)	60%	N.A.	N.A.	N.A.	4.05	N.A.	N.A.	N.A.	N.A.

Differences between the groups are statistically significant for the women on second- and third-generation compared to healthy subjects. No difference was observed for women with progestin-only therapy. Results were similar whether expressed as percentage of inhibition or nAPCsr. [a]p-Value was assessed using the Kruskal-Wallis test with Dunn's test multiple comparison and compared healthy subjects with the other three groups individually. COC, combined oral contraceptive; N.A., not applicable; nAPCsr, normalized activated protein C sensitivity ratio.





Douxfils, J., et al. Clin Chem Lab Med, 2020..

ETP-based APC resistance: validation process

Conclusion

Validation steps	Acceptance criteria	Results
Linearity		
– Activated protein C dose response	– $R^2 > 0.99$ (non-linear regression accepted)	– $R^2 = 0.996$ (for in-house reference plasma)
– Protein S deficiency dose response	– $R^2 > 0.99$ (non-linear regression accepted)	– $R^2 = 0.998$
Stability of reagents	– All points (three levels of QCs and the commercial reference plasma) must be within the acceptance range calculated as the mean inhibition of the four manipulations expressed in % ±5% for each level of control	– All QCs were within 5% of deviations of the mean percentage of inhibition during the 4-h period
Precision – repeatability		
– Intra-run repeatability	– SD < 10%	– SD were 0%, 1%, 3% and 0% for the QC low, intermediate, high and the commercial reference plasma
– Inter-run repeatability	– SD < 10%	– SD were 0%, 7%, 4% and 3% for the QC low, intermediate, high and the commercial reference plasma
Precision – intermediate precision	– SD < 10% and no significant difference between operator (evaluated by ANOVA with Tukey's multiple comparison test). A p-value below 0.05 considers the difference between operators as significant	– The SD of the three different operators range from 0% to 0%, 2% to 5%, 0% to 4% and 1% to 2% for the QC low, intermediate, high and the reference plasma, respectively. The p-values were 0.8503, 0.6969, 0.8253 and 0.9459 for the QC low, intermediate, high and the reference plasma, respectively
Reference range	– Mean percentage of inhibition of the 47 healthy donors[a] = 90% ± 2.5%	– Mean percentage of inhibition in the 47 healthy donors is 90% (SD = 6%; 95% confidence interval of the mean = 89% to 92%; 10th–90th percentile = 82%–100%)

[a]Three donors were excluded due to incomplete information provided on the informed consent. QC, quality control; SD, standard deviation.

Douxfils, J., et al. Clin Chem Lab Med, 2020.

ETP-based APC resistance: Inter-laboratory transferability

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ORIGINAL ARTICLE

Interlaboratory variability of activated protein C resistance using the ETP-based APC resistance assay

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Morimont, L. et al. RPTH, 2022.

ETP-based APC resistance: Inter-laboratory transferability

Step 3

Interlaboratory variability - 60 plasma samples analyzed at each site

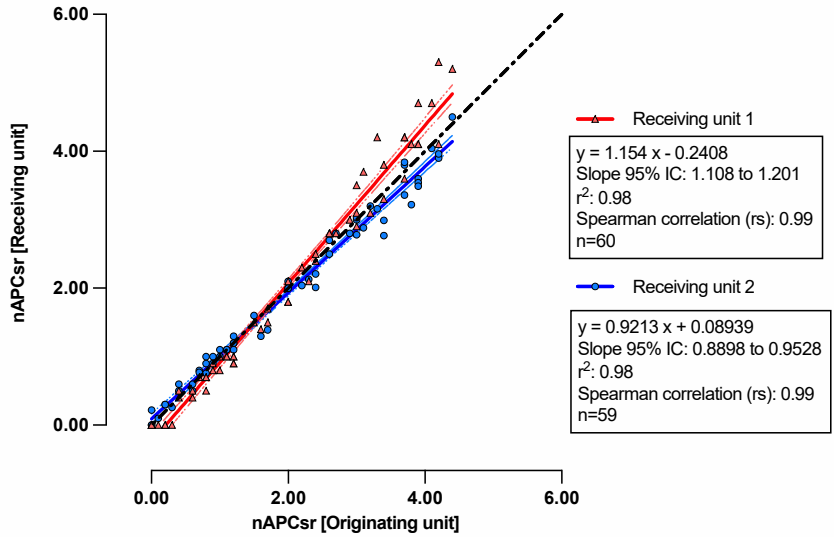
Receiving unit 1 UNIVERSITÉ DE NAMUR

Receiving unit 2 CHU CLERMONT-FERRAND

Reference unit QUALIblood

- **60** plasma samples tested in each unit
  - Pairwise multiple comparison **Friedman test** to compare nAPCsr values from each donor between units

Correlation between nAPCsr obtained at the receiving units and nAPCsr obtained at the originating unit



2G : 2nd generation| 3G: 3rd generation| COC: combined oral contraceptives | nAPCsr: normalized activated protein C sensitivity ratio

ETP-based APC resistance: Inter-laboratory transferability

Step 3

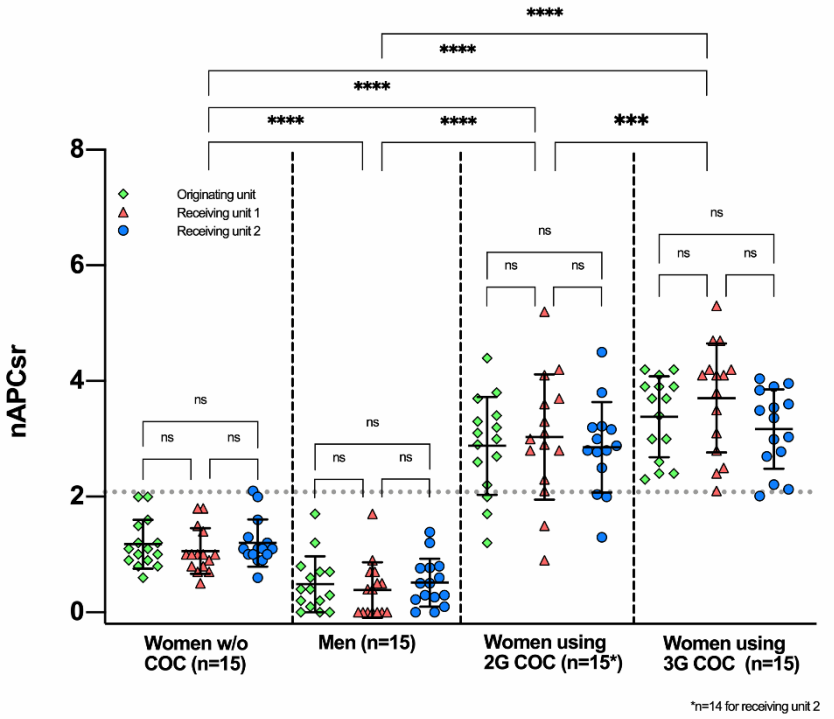
Interlaboratory variability - 60 plasma samples analyzed at each site

Receiving unit 1 UNIVERSITÉ DE NAMUR

Receiving unit 2 CHU CLERMONT-FERRAND

Reference unit QUALIblood

- **60** plasma samples tested in each unit
  - Pairwise multiple comparison **Friedman test** to compare nAPCsr values from each donor between units
- Comparison between **4 subgroups**:
  - **Men**
  - Women **not using hormonal therapy**
  - Women using **2G COC** (containing ethinylestradiol + levonorgestrel)
  - Women using **3G COC** (containing ethinylestradiol + desogestrel or gestodene)
- Results expressed as **nAPCsr values**



2G : 2nd generation| 3G: 3rd generation| COC: combined oral contraceptives | nAPCsr: normalized activated protein C sensitivity ratio

In silico-modeling based on the Cochrane network meta-analysis of de Bastos, in 2014.

VTE RR was based on the Cochrane network meta-analysis :

- Including 14 studies providing data per type of COC + comparison with non-user

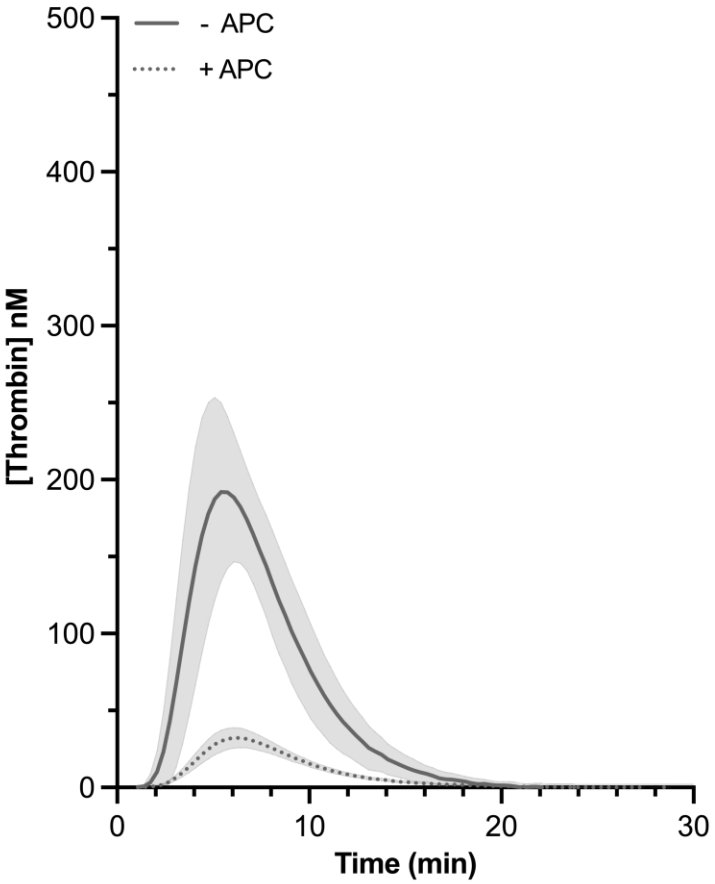
Van Hylckama Vlieg, 2009	Lidegaard, 2011	Parkin, 2000	Lidegaard, 2002	Bloemenkamp, 1999	Bloemenkamp, 1995	Farmer, 2000
Todd, 1999	Farmer, 1996	Jick, 2006	Bird, 2013	Jick, 2011	Parkin, 2011	Lewis, 1996

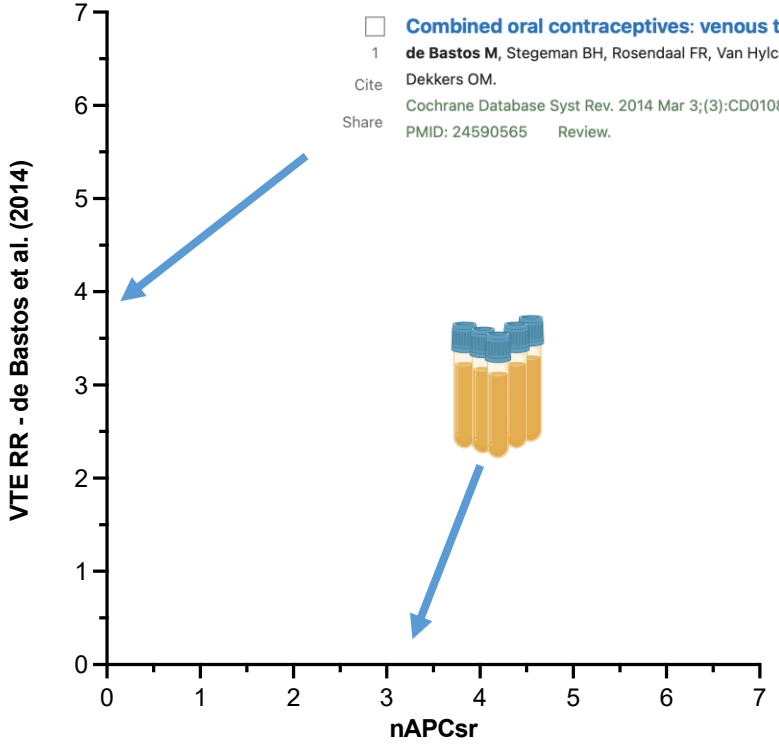
nAPCsr values were obtained from samples issued:

- From one phase-2 clinical trial
- From blood campaigns organized at UNamur (NAB-X biobank)

Morimont et al. Thromb Res. 2020

nAPCsr - a predictive tool of VTE

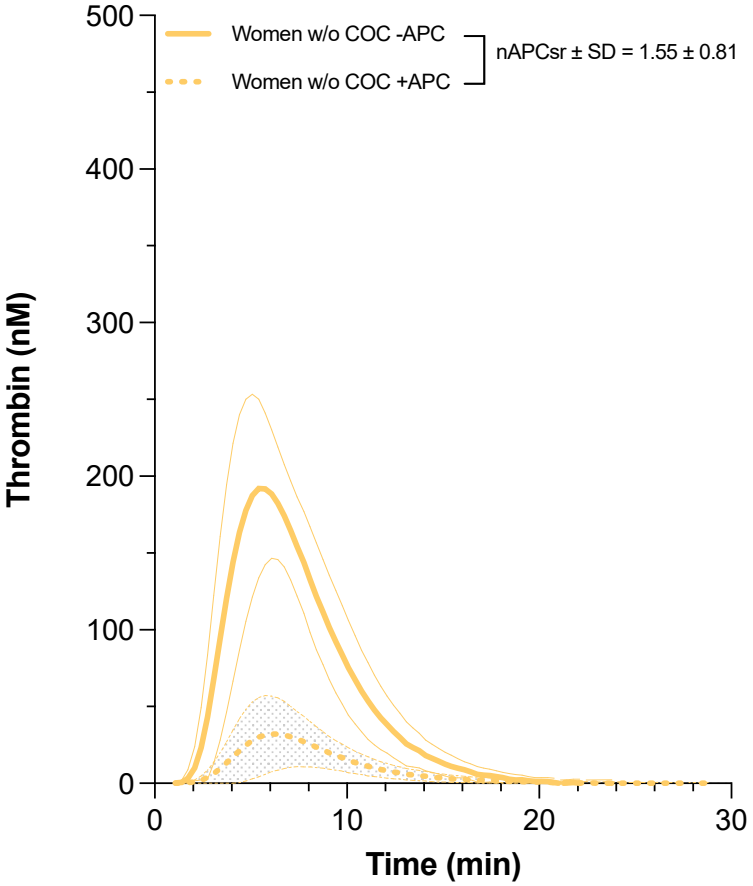


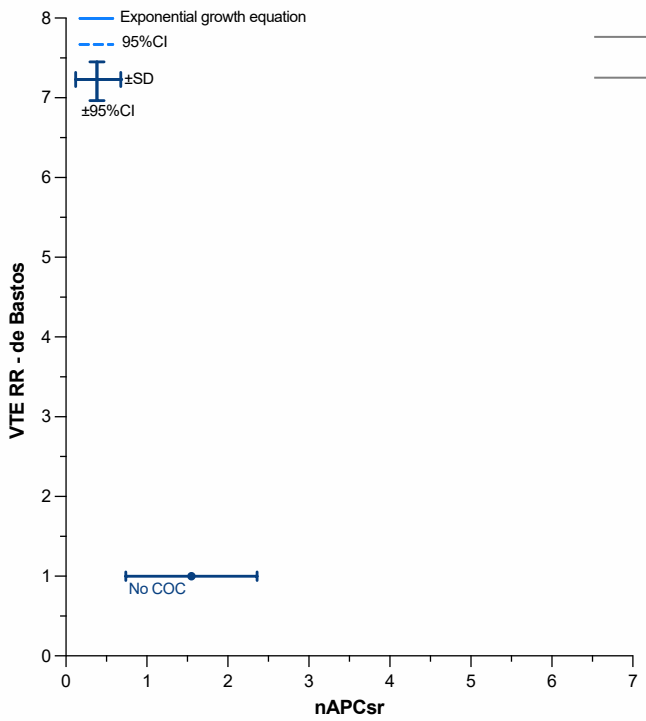


Combined oral contraceptives: venous thrombosis.
1 de Bastos M, Stegeman BH, Rosendaal FR, Van Hylckama Vlieg A, Helmerhorst FM, Stijnen T, Dekkers OM.
Cite
Share
Cochrane Database Syst Rev. 2014 Mar 3;(3):CD010813. doi: 10.1002/14651858.CD010813.pub2.
PMID: 24590565 Review.

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

nAPCsr and VTE risk – Reference population

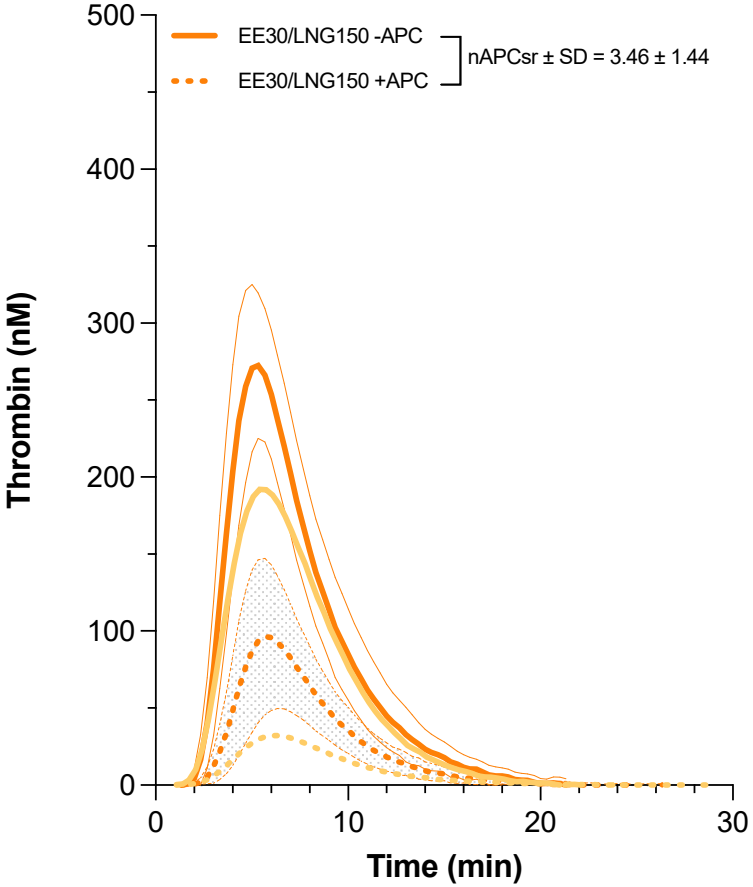


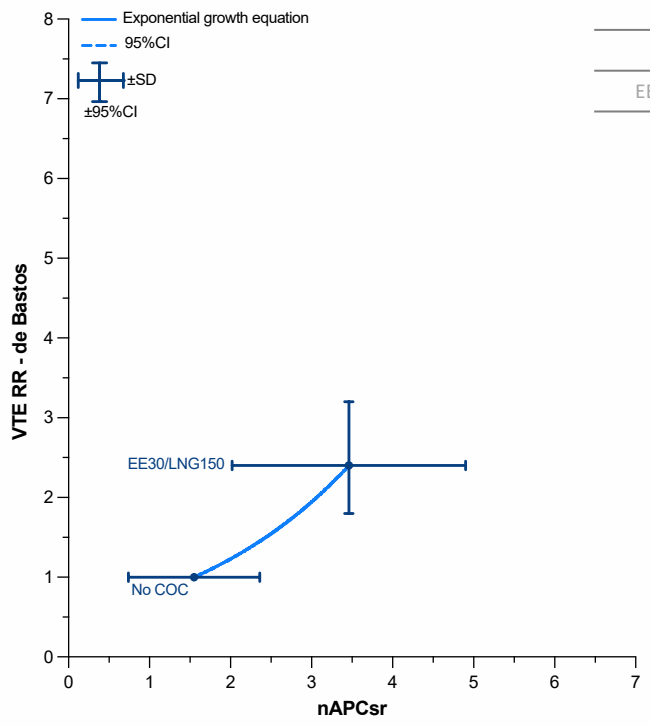


	Mean nAPCsr	VTE RR (de bastos et al. 2014)
No CHC	1.55	1.00 (ref)

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

nAPCsr and VTE risk – EE30/LNG150

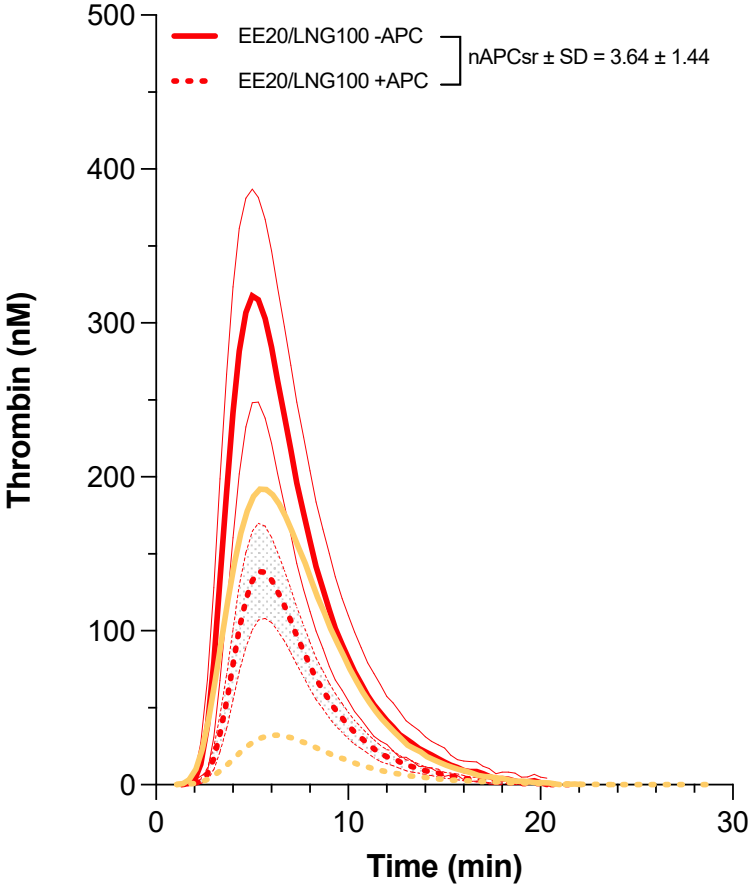


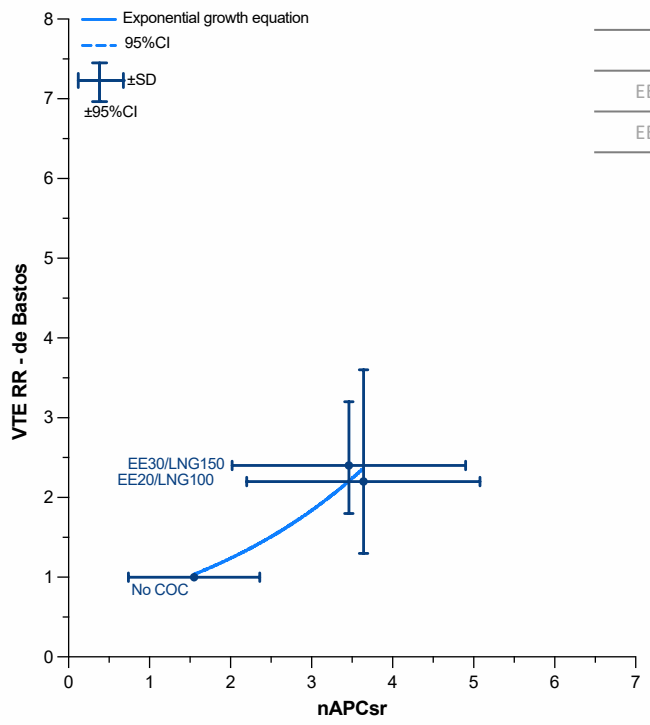


	Mean nAPCsr	VTE RR (de bastos et al. 2014)
No CHC	1.55	1.00 (ref)
EE30/LNG150	3.46	2.40

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

nAPCsr and VTE risk – EE20/LNG100

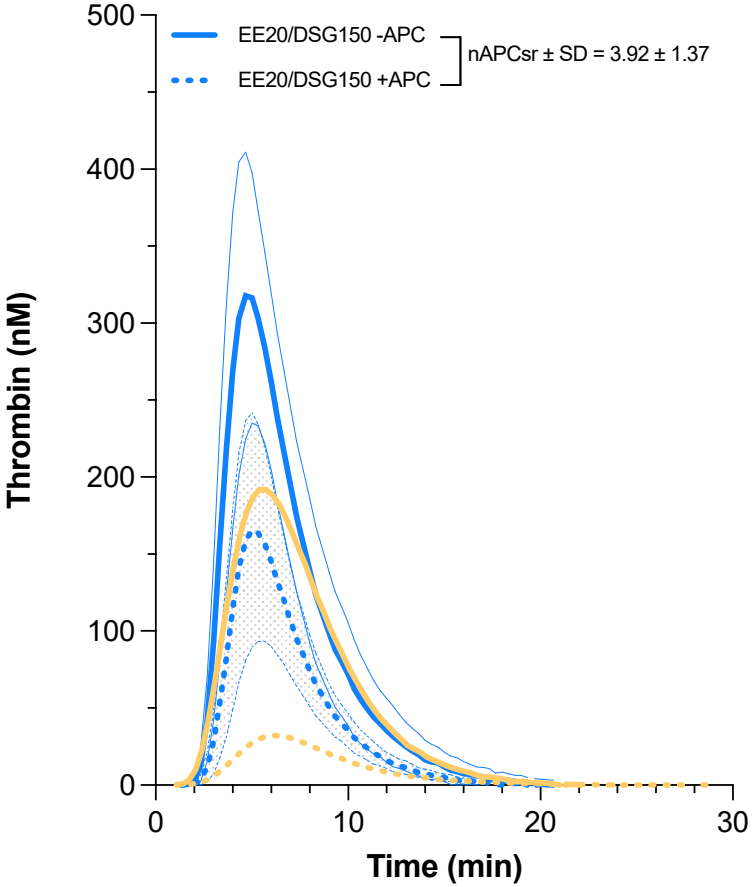


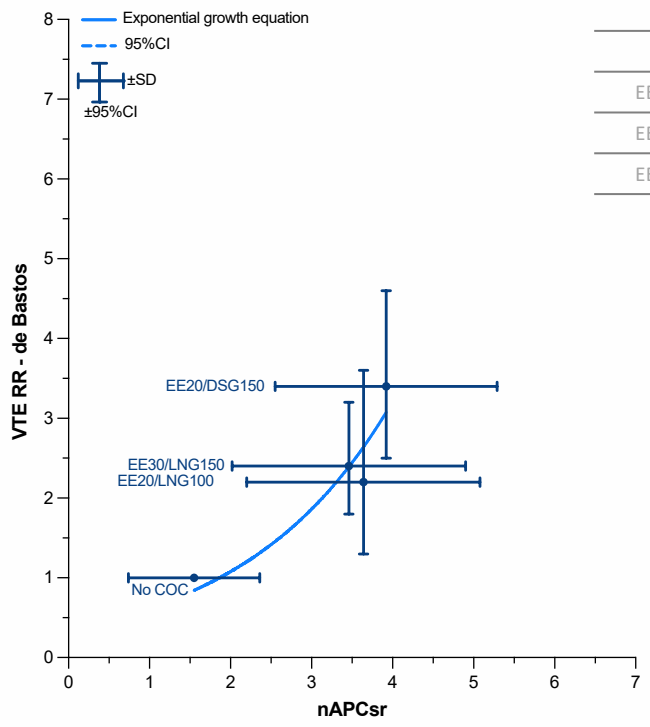


	Mean nAPCsr	VTE RR (de bastos et al. 2014)
No CHC	1.55	1.00 (ref)
EE30/LNG150	3.46	2.40
EE20/LNG100	3.64	2.20

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

nAPCsr and VTE risk – EE20/DSG150

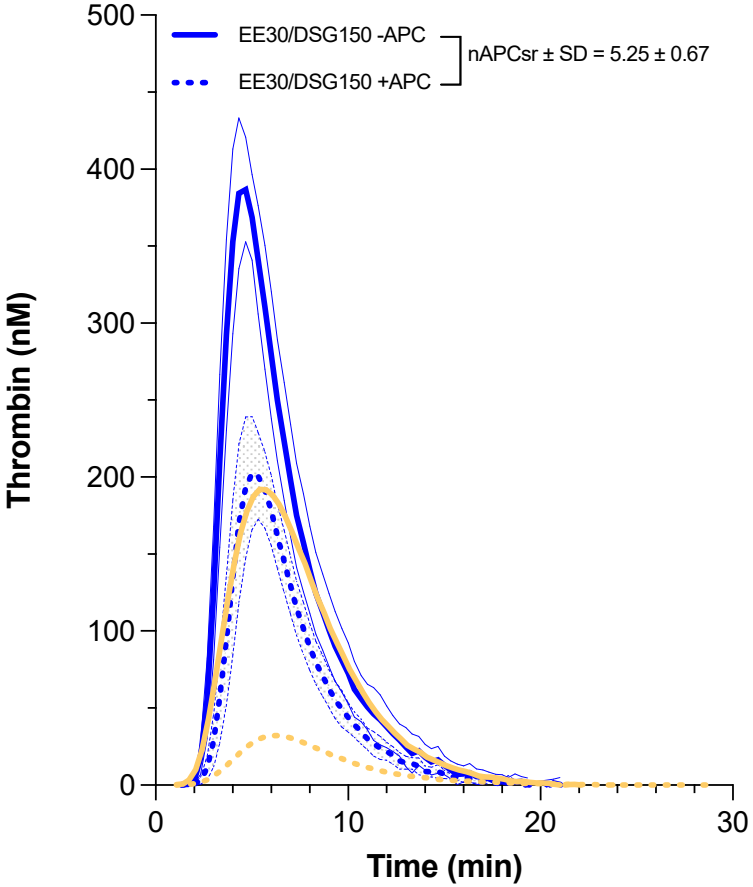


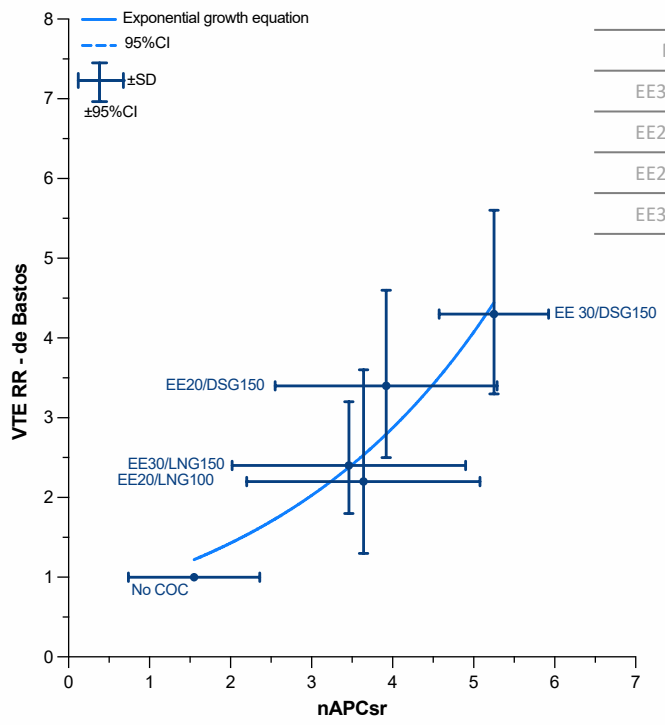


	Mean nAPCsr	VTE RR (de bastos et al. 2014)
No CHC	1.55	1.00 (ref)
EE30/LNG150	3.46	2.40
EE20/LNG100	3.64	2.20
EE20/DSG150	3.92	3.40

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

nAPCsr and VTE risk – EE30/DSG150

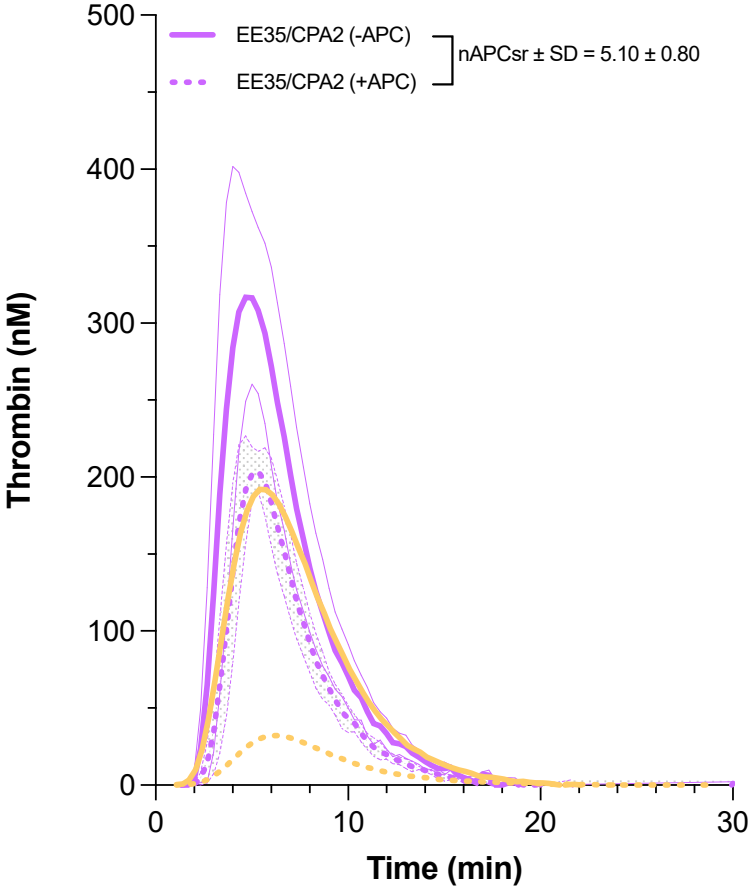


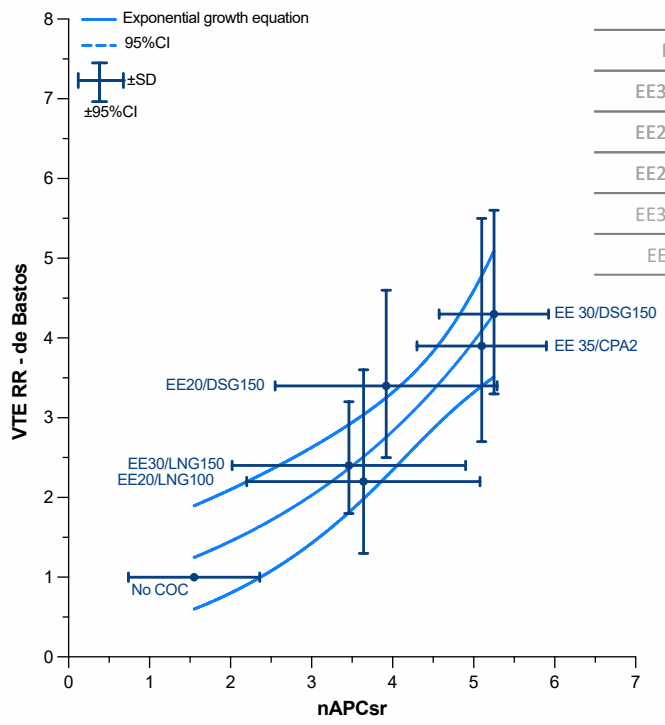


	Mean nAPCsr	VTE RR (de bastos et al. 2014)
No CHC	1.55	1.00 (ref)
EE30/LNG150	3.46	2.40
EE20/LNG100	3.64	2.20
EE20/DSG150	3.92	3.40
EE30/DSG150	5.25	4.30

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

nAPCsr and VTE risk – EE35/CPA2

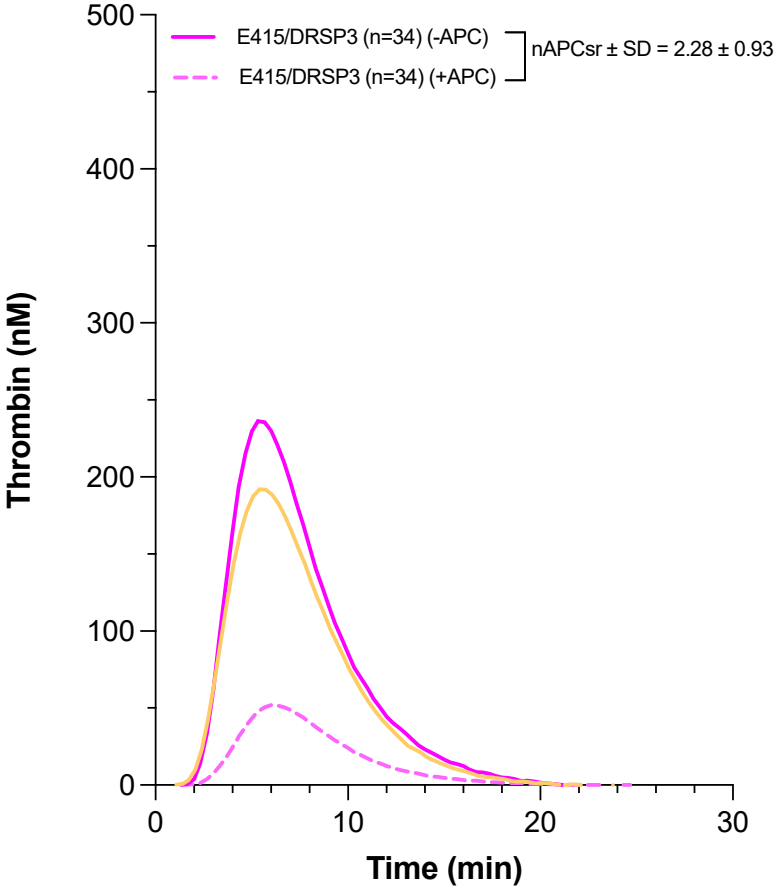


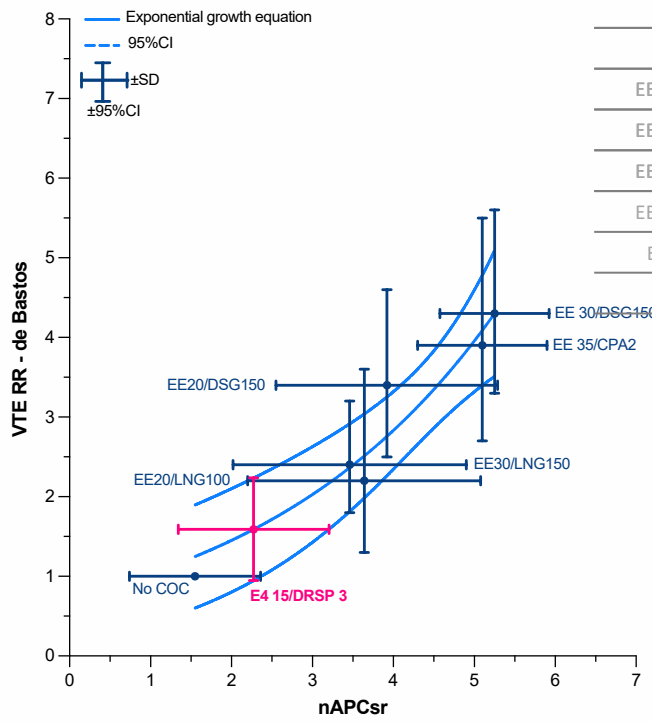


	Mean nAPCsr	VTE RR (de bastos et al. 2014)
No CHC	1.55	1.00 (ref)
EE30/LNG150	3.46	2.40
EE20/LNG100	3.64	2.20
EE20/DSG150	3.92	3.40
EE30/DSG150	5.25	4.30
EE35/CPA2	5.10	3.90

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

nAPCsr and VTE risk – E4/DRSP



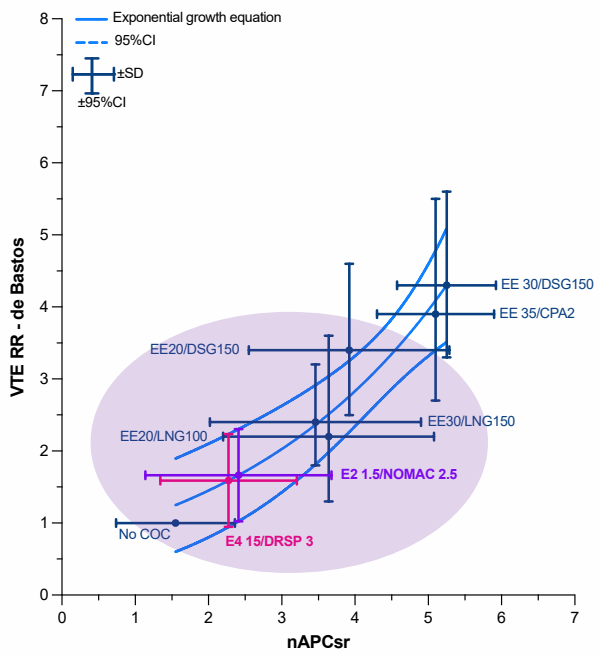


	Mean nAPCsr	VTE RR (de bastos et al. 2014)
No CHC	1.55	1.00 (ref)
EE30/LNG150	3.46	2.40
EE20/LNG100	3.64	2.20
EE20/DSG150	3.92	3.40
EE30/DSG150	5.25	4.30
EE35/CPA2	5.10	3.90
E4/DRSP	2.28	1.59*

* Intrapolated from the model

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

nAPCsr and VTE risk – External validation



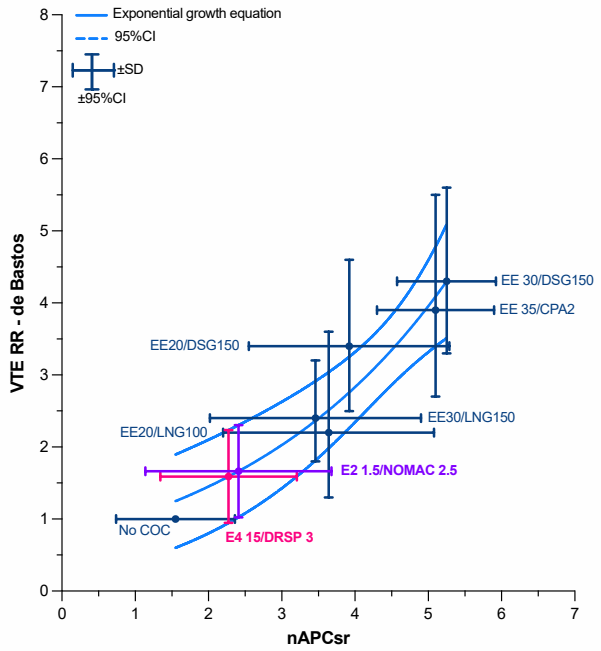
Intrapolated VTE RR :
E4 15 + DRSP 3: 1.59 (95%CI, 0.95-2.23)
E2 1.5 + NOMAC 2.5: 1.66 (95%CI, 1.02-2.30)

	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*
E2/NOMAC	2.41	1.63†

* Intrapolated from the mode
† Adjusted from the PRO-E2 study

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

nAPCsr and VTE risk – External validation



Intrapolated VTE RR :
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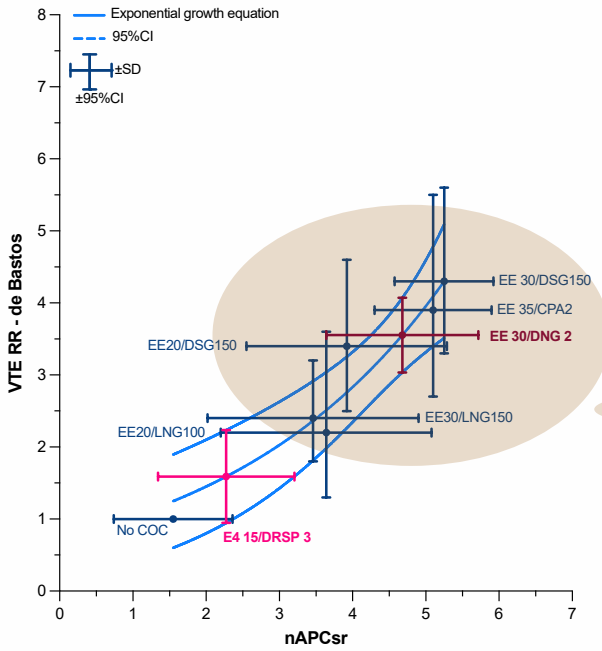

Intrapolated VTE RR :
E4 15 + DRSP 3: 1.59 (95%CI, 0.95-2.23)
EE 30 + DNG 2: 3.55 (95%CI, 2.04-4.07)

	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*
E2/NOMAC	2.41	1.63†
EE30/DNG2	4.68	3.52 ‡

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

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

In silico-modeling based on the Cochrane network meta-analysis of de Bastos, in 2014.

Limitations

- The number of studies included is limited (n = 14) and not all of these studies compared each COC group versus non-user (i.e. EE 30/DRSP 3)

- The sample size is small (n = 237 samples) , ideally 120 samples per group

Thank you for your attention

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