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PII: S2475-0379(25)00609-0

DOI: https://doi.org/10.1016/j.rpth.2025.103285

Reference: RPTH 103285

To appear in: *Research and Practice in Thrombosis and Haemostasis*

Received Date: 23 October 2025

Accepted Date: 23 November 2025

Please cite this article as: Morimont L, Creinin MD, Gaspard U, Foidart J-M, Douxfils J, Predicting venous thromboembolism risk from ETP-based nAPCsr assay: toward early assessment of combined oral contraceptives., *Research and Practice in Thrombosis and Haemostasis* (2026), doi: https://doi.org/10.1016/j.rpth.2025.103285.

Predicting venous thromboembolism risk from ETP-based nAPCsr assay: toward early assessment of combined oral contraceptives.

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Word counts: Abstract: 242 ; Text : 2643

Figures: 5

Tables: 2

Complementary material: 1 figure

Conflicts of Interest:

LM: is employee of QUALIblood s.a.

MDC: has received speaking honoraria from Gedeon Richter and Mayne, served on Advisory Boards for Estetra SRL, has stock options with Femasys, and has consulted for Gedeon Richter, Mayne, Medicines360, and Merck Sharpe Dohme. The Department of Obstetrics and Gynecology, University of California, Davis, receives contraceptive research funding for Dr. Creinin from Femasys, Organon, Sebela, and Myovant (Sumitomo Pharma).

UG: has received consultancy fees from Mithra Pharmaceuticals.

JMF: has received speaking honoraria from Gedeon Richter and Mayne, served on Advisory Boards for Estetra SRL, and has consulted for Gedeon Richter.

JD: consultancy fees from Gedeon Richter, Estetra, and Mithra Pharmaceuticals. He is also the founder of QUALIblood sa, a company involved in the development and validation of the ETP-based activated protein C resistance assay.

ABSTRACT

Background: Combined oral contraceptives (COCs) increase venous thromboembolism (VTE) risk, depending on estrogen type, dose, and the progestin. While epidemiological studies provide insight into these risks, they require years to complete. The normalized activated protein C sensitivity ratio (nAPCsr), a standardized assay of acquired APC resistance, has emerged as a potential biomarker for COC-induced VTE risk.

Objectives: To develop a population-based *in silico* model predicting VTE risk associated with various COC formulations based on their mean nAPCsr values.

Methods: We analyzed 200 plasma samples from non-COC users and 257 from users of nine different COCs. We constructed an exponential model correlating mean nAPCsr of five COCs with their available population-based VTE relative risk extracted from *a published* meta-analysis. We assessed model performance using R^2, Spearman's rank correlation, and Root Mean Square Error (RMSE) and performed a sensitivity analysis by excluding COC non-users. We then estimated population-based VTE risks for the four COCs not used in model construction.

Results: The model demonstrated high predictive accuracy (R^2=0.96, RMSE=0.21, Spearman's Rs=1) and remained robust despite group size imbalance. Predicted VTE risks for EE 30µg-dienogest 2mg, EE 20 µg-drospirenone 3mg, E2 1.5mg-nomegestrol acetate 2.5mg, and E4 15 mg-drospirenone 3mg were 4.36, 3.43, 1.50 and 1.45, respectively, consistent with or complementary to existing epidemiological evidence.

Conclusions: Our model based on mean nAPCsr provides a reliable, biomarker-based approach for predicting population-based COC-related VTE risk. This strategy could help shorten the time between product launch and population-based risk assessment.

58 **Keywords:** activated protein C resistance; combined oral contraceptives; estrogens; risk
59 assessment; venous thromboembolism

INTRODUCTION

Combined hormonal contraceptives (CHCs) containing the synthetic estrogen ethinyl estradiol (EE) are associated with an increased venous thromboembolism (VTE) risk compared to non-users. This risk varies from 2.2-6.6 times higher, depending on the EE dosage, the associated progestin and various clinical factors such as body mass index (BMI), diabetes, mellitus, hypertension, or polycystic ovary syndrome.[1-4]

Over the past decade, new combined oral contraceptives (COCs) containing body identical estrogens such as estradiol (E2) and estetrol (E4), have been introduced with the aim of significantly reducing VTE risk compared to EE-containing regimens. A meta-analysis of population-based observational studies and a pharmacovigilance analysis using the Eudravigilance database have provided data to support lower VTE risk with these body identical estrogens.[5, 6]

In current COC regulatory pathways, surrogate coagulation markers are typically evaluated during safety clinical trials.[7] To date, no surrogate markers have been clearly categorized as directly correlating with COC-related VTE risk. Consequently, our only resources for VTE risk estimations are phase IV population-based post authorization safety studies (PASS) which often take several years to complete. For example, results from the E2-nomegestrol acetate PASS were published in 2021, nearly a decade after initial marketing.[8]

COC use is associated with acquired activated protein C resistance (APCr), a dysregulation of hemostasis that occurs independent of factor V (FV) Leiden genetic mutations.[9, 10] Among the several methods developed to detect APCr, endogenous thrombin potential (ETP)-based APCr assay, introduced in 1997, has proven to be the most suitable for assessing COC-induced coagulation changes.[11-15] This method is currently

endorsed by European Medicines Agency (EMA) guidelines for the assessment of new steroidal contraceptives in women.[7] Moreover, the International Society on Thrombosis and Haemostasis (ISTH) Subcommittee on Plasma Coagulation Inhibitors declared the ETP-based APCr assay as the test of choice for assessing hormone-induced acquired APCr.[16] Prior to 2020, this assay suffered from a lack of standardization, hampering study-to-study comparison. Since 2020, when the test underwent analytical validation, it has been available as a fully harmonized measurement scale, known as the normalized activated protein C sensitivity ratio (nAPCsr).[17] Because early evidence suggests a correlation of nAPCsr with COC-associated VTE risk, [12, 18] we aimed to develop a population-based *in silico* model. This model integrates nAPCsr values with epidemiological data on VTE risk related to specific COCs, to predict the VTE risk linked to newly formulated CHC. To accomplish our study goals, we first obtained plasma samples from COC and non-COC users to measure nAPCsr using the validated ETP-based APCr assay [17], and then developed an *in silico* model incorporating the measured nAPCsr values with VTE risk based on epidemiological data.

2.0 MATERIAL & METHODS

2.1 Sample collection

We collected plasma samples from 2 different sources: a phase II clinical trial (NCT 02957630) conducted in 2016-2017 for which sample collection have been previously described [19], and the NAmur Biobank-eXchange (NAB-X), the registered biobank (notification number BB190116) affiliated with the University of Namur (Namur, Belgium). We obtained these latter specimens from 18 different blood donation campaigns organized since 2018 at the University of Namur (Namur, Belgium) that recruited volunteers to donate blood for research purposes, in accordance with approval from the Ethical Committee of the Centre

Hospitalier Universitaire, Université Catholique de Louvain (CHU UCL, Namur, Belgium) (approval number B03920096633). Eligibility criteria for blood donation excluded current pregnancy, individuals with a history of thrombotic or hemorrhagic events, and using antiplatelet or anticoagulant medication or any other drugs known to affect platelet function or coagulation. Study staff obtained written informed consent from participants prior to sample collection and recorded demographic data, medical history, and current medication use. Blood samples were collected in sodium citrate tubes. The first tube, used as a primer, was reserved for genotyping of FV Leiden and prothrombin G20210A mutations using a CE-marked in-vitro diagnostic (IVD) technique (LAMP Human FII&FVL duplex kit, Lacar, Belgium). The remaining tubes were processed to obtain plasma which was then frozen in liquid nitrogen and stored at ≤-70°C in the NAB-X biobank.

For the present study, we requested NAB-X plasma samples obtained from women of childbearing age (18-40 years), not carrying a FV Leiden or G20210A prothrombin mutation, not using any hormonal contraceptive method or had been using the same COC for at least 3 consecutive cycles, and stored for less than 3 years (to ensure plasma integrity for the ETP-based APC resistance assay, which remains stable for up to 36 months). All samples, whether originating from the clinical trial or from NAB-X, were analyzed within three years after collection. The validated, standardized, and ISO/IEC 17025-accredited method ensures well-controlled batch transitions, thereby maintaining consistent comparability between historical and recent results.

2.2 ETP-based APC resistance assay

The ETP-based APC resistance assay was performed as summarized in **Figure 1.** Briefly, this test is a variant of the thrombin generation assay, a global coagulation test, enabling a

continuous overview of clotting over time in a test cuvette. Thrombin generation is measured in the presence and absence of a defined amount of exogenous APC. This amount is batch-specific and determined using a standardized procedure calibrated to achieve 90% inhibition of ETP (i.e. area under the thrombin generation curve) in a healthy pooled plasma.[17] In the absence of APC, the resulting thrombin generation curve reflects all the pro- and anticoagulant reactions that regulate thrombin formation and inhibition. In the presence of exogenous APC, thrombin generation is significantly decreased in a normal plasma sample allowing measurement of the sample sensitivity towards APC. Results are expressed as a ratio, the nAPCsr.

2.3 Statistical analysis

We performed all statistical analyses using GraphPad Prism version 10.6.1 for macOS (GraphPad Software, San Diego, CA, USA, www.graphpad.com). We used a convenience sampling, including all available samples, and stratified them according to the COC used.

To assess subgroup homogeneity, we compared age and BMI using Kruskal-Wallis followed by Dunn's multiple comparison, given the non-normal distribution of the data. For nAPCsr values, although the data were normally distributed (with the exception of the non-user group which has a sufficiently large sample size), we used Welch's ANOVA because of unequal variance across subgroups. We identified different clusters based on previously observed phenotypic differences.[18] In this confirmatory context, we applied no correction for multiple comparisons (i.e., unpaired t with Welch's correction) to preserve statistical power and reported unadjusted p-values to reflect the *a priori*-defined comparisons of interest.

We created the model using nAPCsr values from COC non-users and COC users of products with known population-based VTE risks, as summarized in the network meta-analysis of *de Bastos et al*.[1] Because we used a convenience sampling strategy reflecting local COC prescribing patterns, we did not include all COCs reported in that meta-analysis, but focused only on those available in our cohort: EE 20µg with levonorgestrel 100µg, EE 30µg with levonorgestrel 150µg, EE 20µg with desogestrel 150µg, EE 30µg with desogestrel 150µg and EE 35µg with cyproterone acetate 2mg. Conversely, no samples were available for the following formulations: EE 50µg with levonorgestrel, EE 20µg with gestodene, EE 30µg with gestodene, EE 35µg with norgestimate and EE 30µg with drospirenone. We plotted the mean nAPCsr values on the x-axis and the corresponding VTE relative risk (RR) associated with these COCs (compared to non-users) on the y-axis.

Using these data, an exponential growth model of the form $y = Y_0 \cdot \exp(k \cdot x)$ was constructed to describe the relationship between nAPCsr values and VTE risk. Considering disparities across subgroups, the model incorporated samples size (N) through weighted fitting. We performed a sensitivity analysis to assess the potential impact of the large reference group (i.e., COC non-users), which was excluded from the curve fitting while preserving the model's anchoring at Y_0. We assessed model fit using the coefficient of determination (R^2) while the strength of association between nAPCsr and VTE risk was evaluated using Spearman's rank correlation coefficient (Rs).

We validated the model using an actual versus predictive plot, in which we plotted predicted VTE risks from the *in silico* simulation against observed risks from *de Bastos* meta-analysis. We assessed quality of fit by visual alignment with the identity line (y = x) and quantified using the Root Mean Square Error (RMSE).

Finally, to further assess the model's predictive capabilities, we estimated VTE risk for COC formulations not included in the base model, using their corresponding mean nAPCsr values: EE 30µg–dienogest 2mg, EE 20µg– drospirenone 3mg, E2 1.5mg–nomegestrol acetate 2.5mg, and E4 15mg–drospirenone 3mg. For the first three products, the predictive values were compared to existing population-based estimates of VTE risk. For the fourth product, no epidemiological data were available to enable such comparison.

3.0 RESULTS

3.1 Clinical data

Our data set included 457 total samples, with 200 from COC non-users and 257 from COC users. The number of samples for each COC type and limited demographic characteristics (age, BMI, plasma collection source) for the participant populations are described in **Table 1**. Age differed between groups ($p<0.001$) but not BMI ($p=0.45$).

Figure 2A illustrates the distribution of nAPCsr values across subgroups, and corresponding mean values ± 95% confidence intervals (CI) are summarized in **Table 2**. Bioidentical estrogen COCs (i.e., E2 and E4-based COCs) and EE-levonorgestrel COCs showed the lowest nAPCsr values, with only the bioidentical estrogen COCs displaying a mean nAPCsr below 3.0. Four distinct clusters of COC-related VTE risk were considered (**Figure 2B**), ranked in ascending order of mean nAPCsr: (i) COCs containing bioidentical estrogens (ii) EE-levonorgestrel COCs (iii) EE20-desogestrel or drospirenone COCs and (iv) COC containing EE30-desogestrel, cyproterone acetate or dienogest ($p <0.005$ for all pairwise comparisons).

3.2 In-silico modeling

Figure 3 illustrates the *in silico* model developed using nAPCsr from 346 plasma samples divided into COC non-users (reference group) and five COC subgroups. The remaining

111 samples from 4 additional COC groups not included in the initial model, were used to assess predictive performance.

This approach yielded an exponential growth equation: y=*0.6108*exp (0.3886*x).* The coefficient of determination (R^2) was 0.9591 and the Spearman correlation coefficient (Rs) was 1, indicating both a strong goodness of fit and a perfect monotonic association between nAPCsr values and VTE risk. In the sensitivity analysis excluding COC non-users, the exponential curve was constrained to pass through the reference point (y_o = 0.6108) to preserve the epidemiological anchoring of the model. The resulting relationship remained virtually unchanged (**Supplementary Figure 1**), indicating the model's goodness of fit was not overly dependent on the reference group.

Model validation, as shown by the actual versus predicted plot in **Figure 4**, yielded a RMSE of 0.2029 indicating that, on average, the predicted relative risk varies by 0.2 units from the actual relative risk. The resulting *in silico* model estimated VTE risks of 4.36 (95%CI 4.29-4.43) for EE 30µg-dienogest 2mg, 3.43 (95%CI 3.39-3.47) for EE 20µg-drospirenone 3mg, 1.50 (95%CI 1.47-1.52) for E2 1.5mg-nomegestrol acetate 2.5mg and 1.45 (95%CI 1.43-1.48) for E4 15mg-drospirenone 3mg versus COC non-users (**Figure 5; Table 2**).

4.0 DISCUSSION

We successfully developed an *in silico* model to estimate VTE risk associated with new CHC formulations, using nAPCsr measurements in plasma samples. The high weighted coefficient of determination (R^2=0.96) demonstrates that the model accurately reproduces observed VTE risks trends based on mean nAPCsr values, showing strong consistency with epidemiological data. The perfect Spearman correlation (Rs=1) further supports the model's robustness, confirming that it preserves the expected hierarchy of VTE risk across COC types. The strong

agreement between predicted and observed relative risks (RMSE = 0.20; alignment with the identity line) confirms the reliability of this computational approach. Sensitivity analyses excluding non-users further demonstrated that the association between nAPCsr and VTE risk remains stable across COC groups and is not solely driven by the reference population. The concordance of the model with available population-based VTE risk estimates [2, 8, 20] and clinical data [20] suggests that our model may serve as a valuable tool to estimate the VTE relative risk of COCs for which current epidemiological data are insufficient or lacking.

When interpreting the nAPCsr values obtained in this study, several biological and methodological aspects should be considered. Although an age-related increase in thrombin generation has been reported [21], this effect is attenuated when expressed as the nAPCsr, since the latter is defined as a ratio between two thrombin generation conditions (i.e. ETP in the presence and absence of exogenous APC). Consequently, the significant age-related differences observed between subgroups are unlikely to have influenced the nAPCsr results. BMI was evenly distributed across subgroups, thereby minimizing potential bias. However, as higher BMI is known to influence coagulation factors and increase the risk of venous thrombosis [22], its impact on the nAPCsr cannot be fully excluded, even though no association was observed in our study. Finally, smoking, although a well-known cardiovascular risk factor, predominantly affects the arterial side of thrombosis [23] and is therefore not expected to influence the nAPCsr, which reflects venous hemostatic mechanisms.

Although the increased nAPCsr variability observed within COC subgroups compared with non-users may partly stem from smaller subgroup sizes, it is more likely attributable to a methodological factor. Because the relationship between APC concentration and ETP% inhibition is curvilinear, variability remains low near 90% inhibition (non-users) but increases to around 50% inhibition (COC-users) where the slope of the curve is steeper.

Consistent with previous findings, we confirmed that APC resistance levels depend on both the dosage and the specific nature of the estrogen and the associated progestin [13]. For EE-containing COCs, APC resistance increased with higher EE doses (30–35 µg), particularly when combined with weakly androgenic (e.g. desogestrel), or anti-androgenic progestins (e.g. dienogest and cyproterone acetate) having a neutral profile on the liver. In contrast, for EE-levonorgestrel combinations, the impact of EE dosage on APC resistance appears limited, likely due to a compensatory increase in the levonorgestrel dose, possibly mediated by its antiestrogenic activity.[13] Importantly, COCs body identical estrogens such as E2 or E4 demonstrated the lowest degree of APC resistance, with a mean nAPCsr below 3.0, the upper limit of the 95% CI for COC non-users. These results are consistent with existing evidence regarding the safest hemostatic profile of natural estrogen-containing COCs compared to conventional COCs. [19, 24]

Although more recent data on COC-associated VTE risk have been published (*Yonis et al*, JAMA 2025 [25]), we relied on the *de Bastos* meta-analysis for several reasons. First, as a network meta-analysis of multiple studies, this study offers greater external validity and a broader representation of contraceptive users. Second their risk estimates are consistent with the historical literature and regulatory benchmarks, facilitating comparison. Third, methodological differences in the recent cohort study, such as exposure definitions and population characteristics, may explain the discrepancies in rate ratios and complicate their direct integration into our modeling framework. By contrast, conducting an updated network meta-analysis integrating newly available epidemiological data for E2-based COCs represent a valuable next step.

A limitation of our analysis is the small number of women evaluated in some subgroups. However, given that the model relies on weighted subgroup means rather than

individual values, and that the sensitivity analysis demonstrated its robustness despite sample size disparities, the use of smaller groups appears acceptable for the purpose of this initial modeling approach. Continued evaluation of these outcomes with larger populations would be important to confirm these results.

To conclude, our population-based *in silico* model demonstrates reassuring robustness, supporting the reliability of this computational approach used for estimating VTE risk based on nAPCsr values. Ultimately, such modeling could serve a regulatory purpose by allowing earlier risk assessment of new CHCs, without the need to wait nearly a decade for post-marketing epidemiological data before categorizing them.

If a biomarker such as the nAPCsr can be assessed during phase II or III clinical trials, it may provide an early indication of VTE risk for new hormonal contraceptives, pending confirmation in phase IV studies. This approach has the potential to save both time and resources for regulatory authorities, pharmaceutical companies, clinicians and patients by delivering timely and reliable VTE risk data that could facilitate the early adoption of innovative hormonal therapies.

FUNDING

This study was financed by the Walloon Region, Belgium and the Federation Wallonie Bruxelles, Belgium.

AUTHOR CONTRIBUTION

LM and JD designed the study. LM and JD analyzed and interpreted the data. LM performed the statistical analyses and wrote the original draft. JD, MDC, JMF and UG provided input and critical review of the manuscript. All authors revised and approved the final version.

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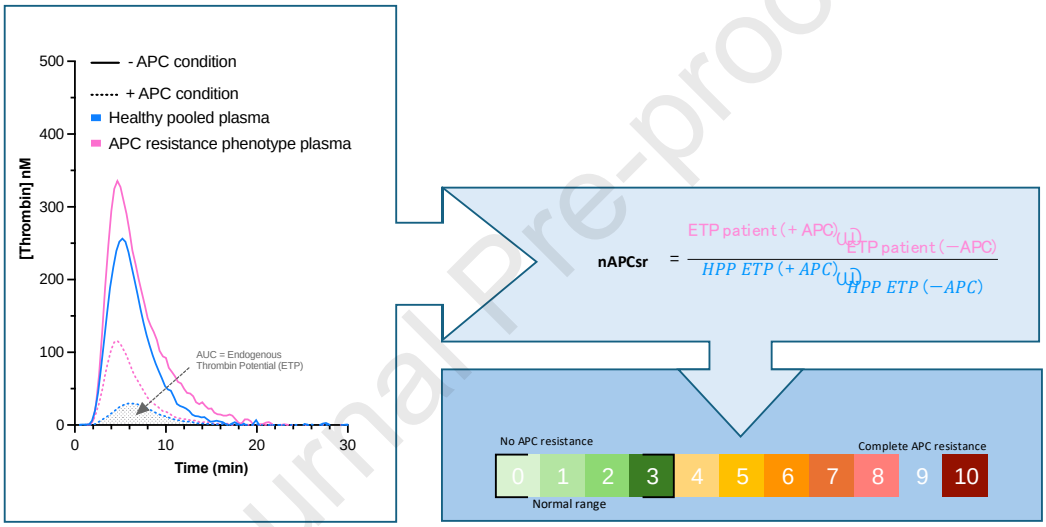
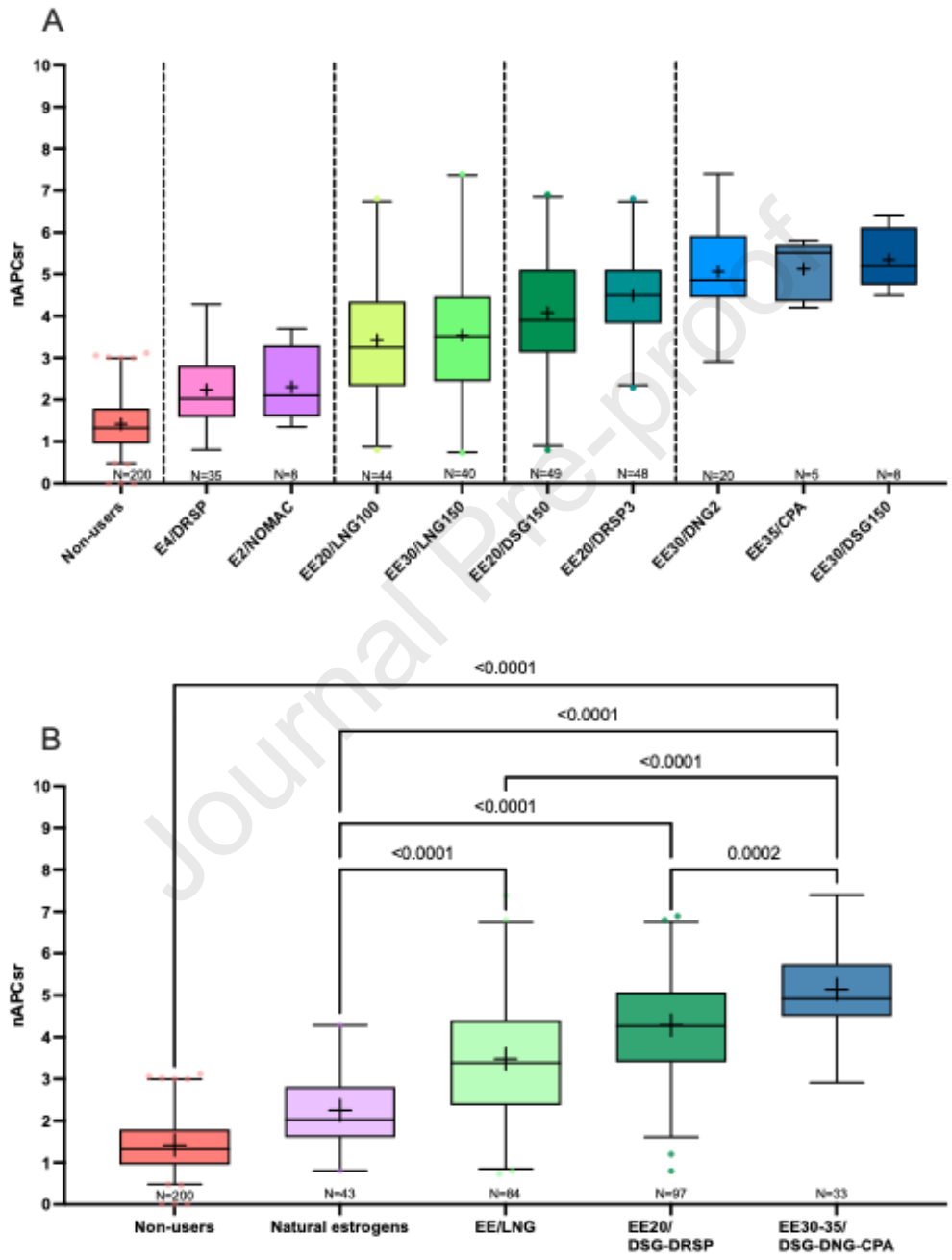
Figure 1: Thrombin generation curves in absence (continuous line) and in presence of activated protein C (APC) (dotted lines) of a healthy pooled plasma (blue) and an APC resistant phenotype plasma (pink) along with the normalized APC sensitivity ratio (nAPCsr) scale. The reference plasma used to calculate nAPCsr values is derived from pooled plasma of healthy individuals (men and women (in a 1:1 ratio) not using hormonal contraception, not carrier of FV Leiden or prothrombin G20210A mutations). In presence of APC, the ETP (i.e., area under the curve) decreases by 90%, corresponding to a nAPCsr value of 1. In contrast, the APC resistant phenotype plasma, typically seen in women using ethinylestradiol-containing products, shows increased thrombin generation both with and without APC, when compared to the reference plasma. On the nAPCsr scale, this results in a value above the upper limit of the normal range.



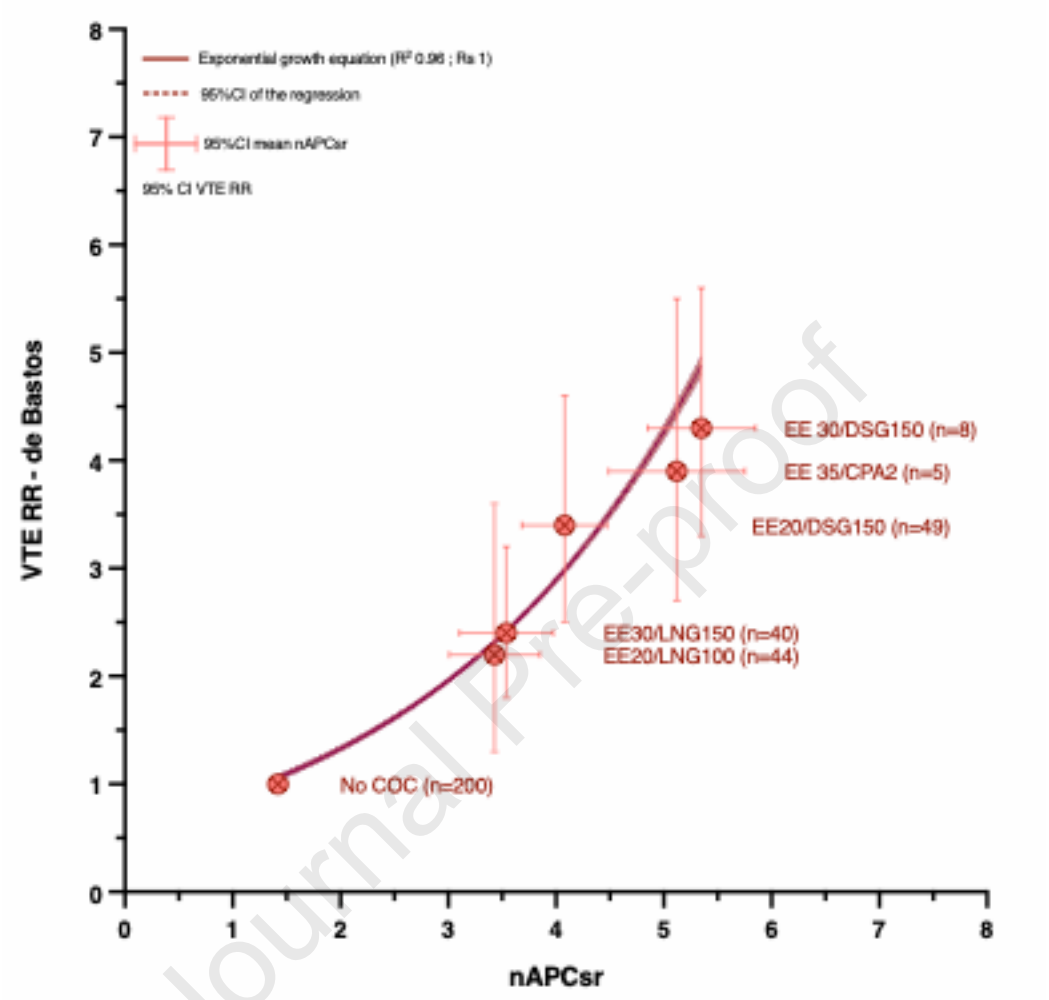
Abbreviations: APC, activated protein C; AUC, area under the curve; ETP, endogenous thrombin potential; HPP, healthy pooled plasma; nAPCsr, normalized activated protein C sensitivity ratio

Figure 2: Box-and-Whisker plot of nAPCsr across each study subgroups (A) and identified clusters (B). The box represents the central 50% of the data, with the lower edge indicating the 1st quartile and the upper edge the 3rd quartile. The line inside the box corresponds to the median while the cross indicates the mean. The whiskers extend to the 2.5th and 97.5th percentiles. Differences between clusters were assessed by an analysis of variance with unpaired t test with Welch's correction. Threshold for significance was set at 0.05.



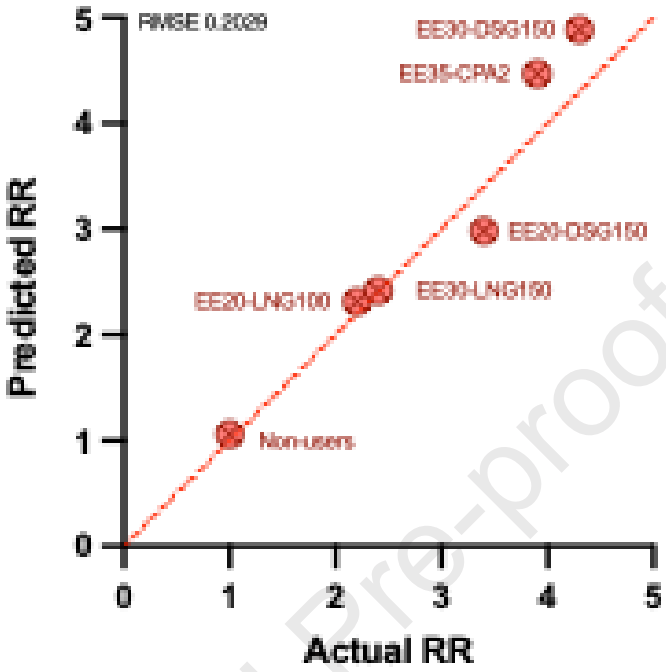
Abbreviations: COC, combined oral contraceptive; CPA, cyproterone acetate; DNG, dienogest; DRSP, drospirenone; DSG, desogestrel; EE, ethinylestradiol; E2, estradiol; E4, estetrol; LNG, levonorgestrel; nAPCsr, normalized activated protein C sensitivity ratio; NOMAC, nomegestrol acetate.

Figure 3: *In silico* modeling based on nAPCsr data and venous thromboembolism relative risk estimates as reported in the meta-analysis of *de Bastos et al.*



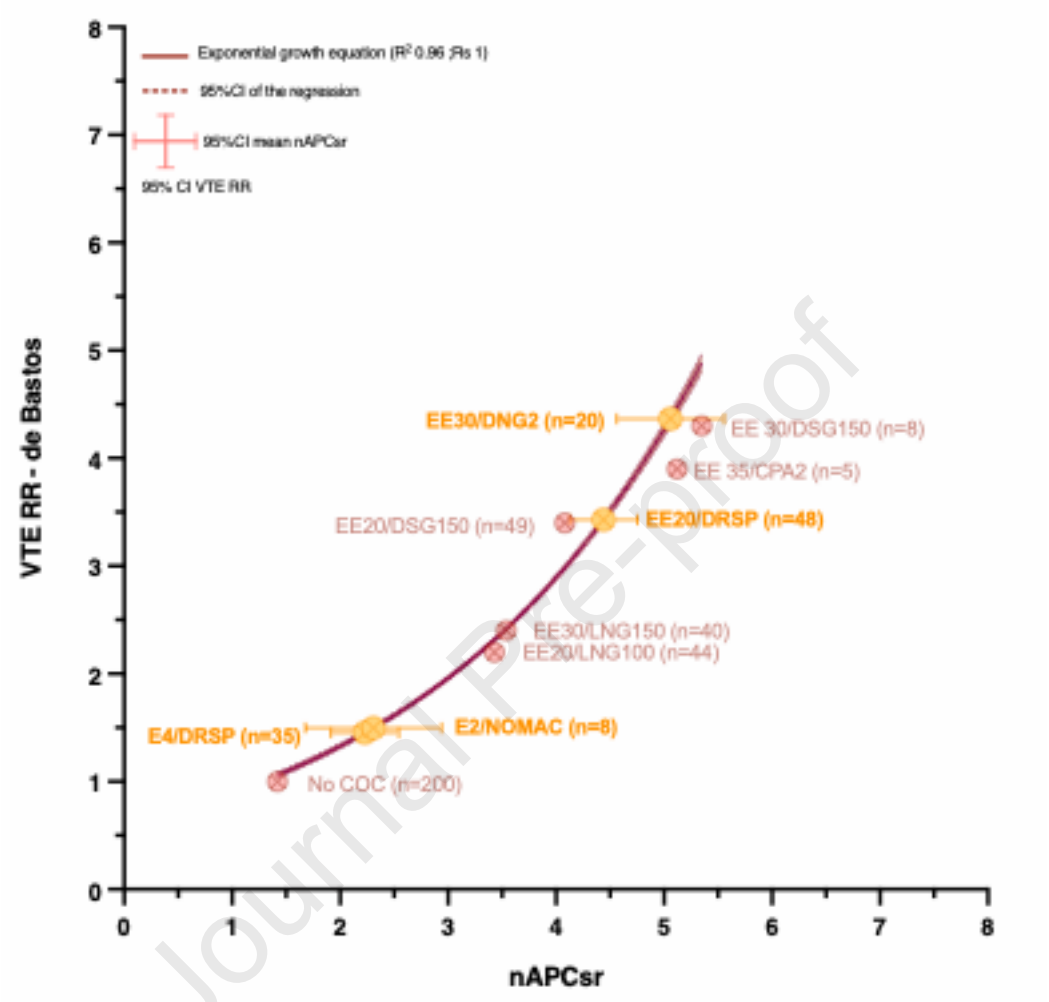
Abbreviations: CI, confidence interval; COC, combined oral contraceptive; CPA, cyproterone acetate; DRSP, drospirenone; DSG, desogestrel; EE, ethinylestradiol; LNG, levonorgestrel; nAPCsr, normalized activated protein C sensitivity ratio; RR, relative risk; SD, standard deviation; VTE, venous thromboembolism

Figure 4: Predicted versus actual relative risk of venous thromboembolism based on nAPCsr data. Actual relative risk values are taken from the meta-analysis of *de Bastos et al.* The dashed line represents the identity line, indicating perfect agreement between predicted and observed values.



Abbreviations: CPA, cyproterone acetate; DRSP, drospirenone; DSG, desogestrel; EE, ethinylestradiol; LNG, levonorgestrel; nAPCsr, normalized activated protein C sensitivity ratio; RR, relative risk; RMSE, Root Mean Square Error.

Figure 5: Venous thromboembolism risk estimates for four combined oral contraceptives based on our *in silico* modeling: estetrol (E4) 15mg with drospirenone 3mg, estradiol (E2) 1.5mg with nomegestrol acetate 2.5mg, ethinylestradiol (EE) 20µg with drospirenone 3mg, and ethinylestradiol (EE) 30µg with dienogest 2mg.



Abbreviations: CI, confidence interval; COC, combined oral contraceptive; CPA, cyproterone acetate; DRSP, drospirenone; DSG, desogestrel; EE, ethinylestradiol; E2, estradiol; E4, estetrol; GSD, gestodene; LNG, levonorgestrel; nAPCsr, normalized activated protein C sensitivity ratio; NOMAC, nomegestrol acetate; RR, relative risk; SD, standard deviation; VTE, venous thromboembolism

Table 1. Demographic data of participants that provided samples for endogenous thrombin potential-based nAPCr assay

	TOTAL	Non-COC users	EE 20µg - LNG 100µg	EE 30µg - LNG 150µg	EE 20µg - DSG 150µg	EE 30µg - DSG 150µg	EE 35µg - CPA 2mg	E4 15mg - DRSP 3mg	E2 1.5mg - NomAc 2.5mg	EE 20µg - DRSP 3mg	EE 30µg - DNG 2mg	P-value*
Number	409	200	44	40	49	8	5	35	8	48	20	
Age (years)												
Mean (±SD)	23 (±5)	24 (±6)	21 (±2)	24 (±5)	21 (±3)	22 (±2)	20 (±2)	26 (±6)	22 (±2)	24 (±5)	22 (±2)	***<0.001***
Range	18-47	18-47	18-28	18-44	18-29	19-26	18-22	19-43	20-25	18-40	19-27	
BMI (kg/m^2)												
Mean (±SD)	22.6 (±3.2)	22.7 (±3.4)	22.3 (±3.2)	22.4 (±3.2)	22.3 (±2.6)	21.6 (±2.2)	22.3 (±2.2)	23.3 (±2.9)	23.1 (±3.6)	21.8 (±2.4)	21.6 (±2.7)	0.45
Range	16.9-38.9	16.9-38.9	17.6-28.7	17.4-29.8	17.7-31.3	18.3-24.8	20.2-25.8	19.0-30.0	19.5-30.0	18.4-28.7	18.5-29.8	
Collection Source												
Biobank	251(62%)	104(52%)	44(100%)	12(30%)	49(100%)	8(100%)	5(100%)	1(3%)	8(100%)	17(35%)	20(100%)	
Clinical Trial	158(38%)	96(48%)	0(0%)	28 (70%)	0(0%)	0(0%)	0(0%)	34(97%)	0(0%)	32(65%)	0(0%)	

* Kruskal-Wallis test

Abbreviations: BMI, body mass index; EE, ethinylestradiol, E2, estradiol; E4, estetrol; nAPCsr, normalized activated protein C sensitivity ratio; SD, standard deviation

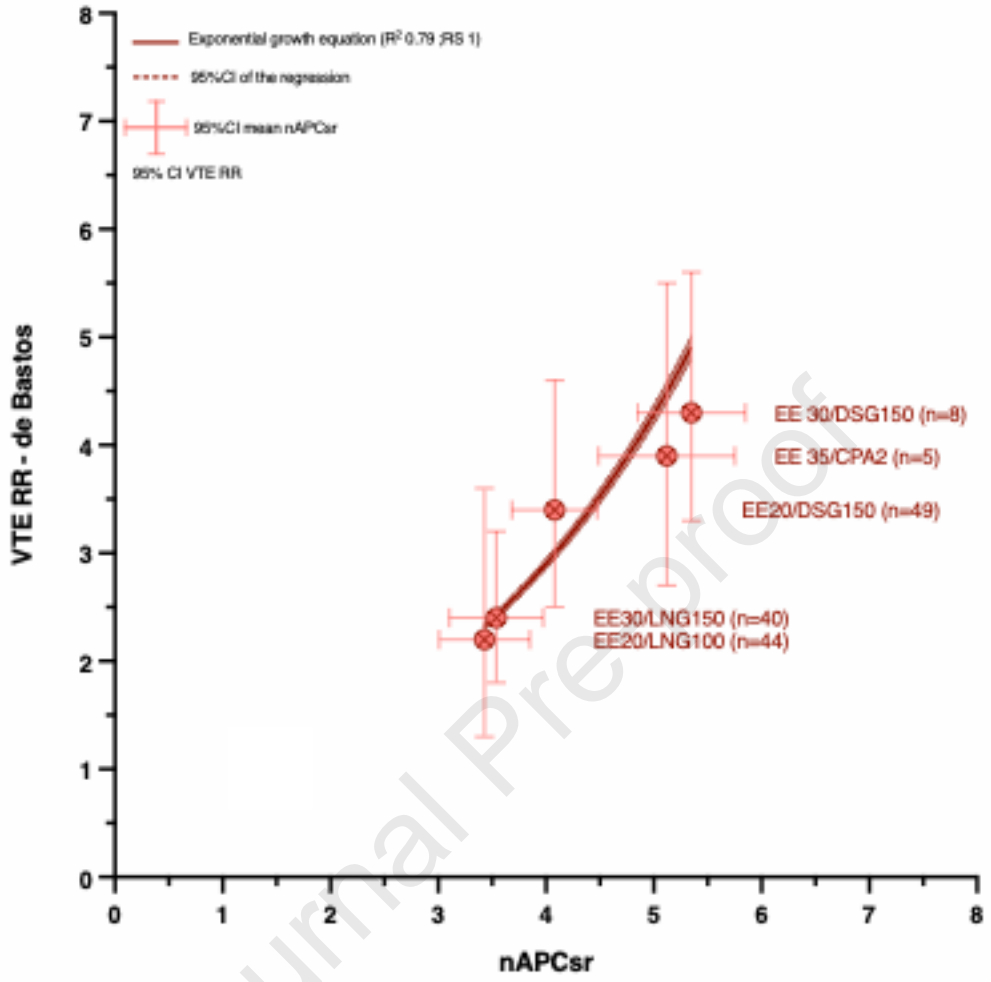
Table 2. Mean nAPCsr values (±SD), epidemiologically derived venous thromboembolism (VTE) risk (95%CI), and model-based estimated VTE risks (95%CI)

	COC non-users	EE 20µg - LNG 100µg	EE 30µg - LNG 150µg	EE 20µg - DSG 150µg	EE 30µg - DSG 150µg	EE 35µg - CPA 2mg	E4 15mg - DRSP 3mg	E2 1.5mg - NomAc 2.5mg	EE 20µg – DRSP 3mg	EE 30µg - DNG 2mg
nAPCsr										
Mean ±SD	1.42 ± 0.09	3.43 ± 0.42	3.54 ± 0.44	4.08 ± 0.40	5.35 ± 0.50	5.12 ± 0.63	2.23 ± 0.31	2.31 ± 0.63	4.50 ± 1.05	5.06 ± 0.50
Epidemiologically derived VTE risk										
n (95%CI)	1	2.2 (1.3-3.6) [1]	2.4 (1.8-3.2) [1]	3.4 (2.5-4.6) [1]	4.3 (3.3-5.6) [1]	3.9 (2.7-5.5) [1]	-	1.6 (0.6-4.1) [*2]	4.84 (3.2-7.3) [3]	3.4 (1.5-7.3) [*4]
Model-based estimated VTE risk [5]										
n (95%CI)	1.06 (1.04-1.09)	2.32 (2.29-2.34)	2.42 (2.39-2.44)	2.98 (2.95-3.02)	4.89 (4.80-4.97)	4.47 (4.39-4.54)	1.45 (1.43-1.48	1.50 (1.47-1.52)	3.43 (3.39-3.47)	4.36 (4.29-4.43)

[1] population-based risk from *de Bastos et al.* Cochrane Database Syst Rev. 2014: CD010813.
[2] population-based risk from *Reed et al.* Eur J Contracept Reprod Health Care. 2021; 26: 439-46.
[3] population-based risk from Lidegaard et al. BMJ. 2011; 343
[4] population-based risk from *Dinger et al*. Frontiers in Women's Health. 2020; 5.
[5] Estimated using *in silico* model

Abbreviations: CI, confidence interval; COC, combined oral contraceptive; CPA, cyproterone acetate; DNG, dienogest; DSG, Desogestrel; EE, ethinylestradiol; E2, estradiol; E4, estetrol; LNG, levonorgestrel; nAPCsr, normalized activated protein C sensitivity ratio; NomAc, nomegestrol acetate; SD, standard deviation; VTE, venous thromboembolism

Supplementary Figure 1: Sensitivity analysis - model robustness after exclusion of the reference group



Abbreviations: CI, confidence interval; CPA, cyproterone acetate; DRSP, drospirenone; DSG, desogestrel; EE, ethinylestradiol; LNG, levonorgestrel; nAPCsr, normalized activated protein C sensitivity ratio; RR, relative risk; SD, standard deviation; VTE, venous thromboembolism