Correlation between activated protein C resistance and the relative risk of venous thromboembolism in women using hormonal therapy

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INTRODUCTION & AIM

- The frequent use of estrogens, alone or associated with progestins, throughout a woman's life, exposes to an **increased risk of venous thromboembolism** (VTE).
- Identifying one or several biomarkers to dress the "**coagulability status**" of patients before and during the course of hormonal therapy would be important to minimize the thrombotic risk.
- The **endogenous thrombin potential (ETP)-based activated protein C (APC) resistance assay** could be a potential candidate as it is significantly impacted by the use of combined oral contraceptives (COCs) and hormone replacement therapies.

The aim of this study was to assess the VTE risk prediction capacities of the normalized APC sensitivity ratio (nAPCsr), the score frequently used to express APC resistance.

MATERIALS & METHODS

- Two in silico-modeling were computed by combining both the nAPCsr for specific COC preparations with their respective VTE relative risk (RR) issued from the Danish cohort study of **Lidegaard (2011)** and the Cochrane network meta-analysis of **de Bastos (2014).**
- nAPCsr values were obtained retrospectively from 147 women's samples.
- The different COC subgroups, their respective nAPCsr values and the associated RR of VTE are reported in **Table 1**.

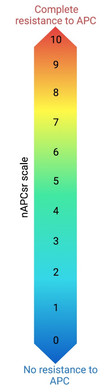
RESULTS

Table 1: Mean normalized APC sensitivity ratio (nAPCsr) and standard deviations (SD) depending on the type of combined oral contraceptives (COC) and their respective relative risk (RR) [95%CI] of venous thromboembolism (VTE) issued from the study of Lidegaard and from the meta-analysis of de Bastos.

Subgroups	nAPCsr		VTE risk (Lidegaard)		VTE risk (de Bastos)	
	Mean	SD	RR	95%CI	RR	95%CI
Women w/o COC (n=41)	1.68	0.88	1.00	-	1.00	-
EE 30 µg + LNG 150 µg (n=33)	3.75	1.43	2.19	1.74 to 2.75	2.40	1.80 to 3.20
EE 20 µg + LNG 100 µg (n=15)	4.09	1.53	-	-	2.20	1.30 to 3.60
EE 20 µg + DSG 150µg (n=11)	4.45	1.38	3.26	2.88 to 3.69	3.40	2.50 to 4.60
EE 30 µg + DSG 150 µg (n=5)	5.40	0.63	4.21	3.63 to 4.87	4.30	3.30 to 5.60
EE 20 µg + GSD 75 µg (n=5)	4.60	0.87	3.50	3.09 to 3.97	-	-
EE 35 µg + CPA 2 mg (n=3)	5.10	0.80	4.10	3.37 to 4.99	3.90	2.70 to 5.50
E4 15 mg + DRSP 3 mg (n=34)	2.28	0.93	1.37*	0.86 to 1,89*	1.29*	0.61 to 1.96*

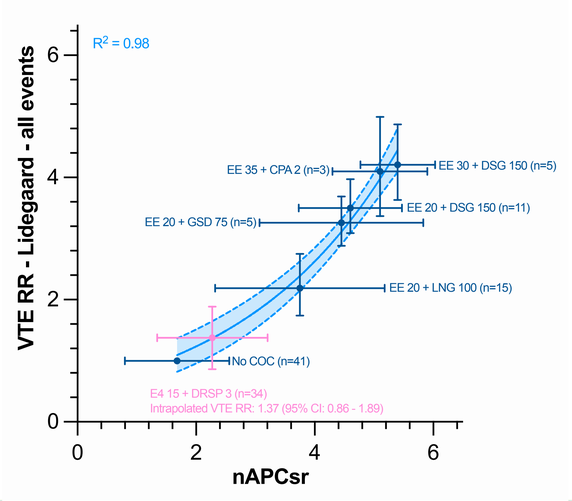
Acronyms: CPA, cyproterone acetate ; DRSP, drospirenone ; DSG, desogestrel ; EE, ethinylestradiol ; E4, estetrol ; GSD, gestodene ; LNG, levonorgestrel

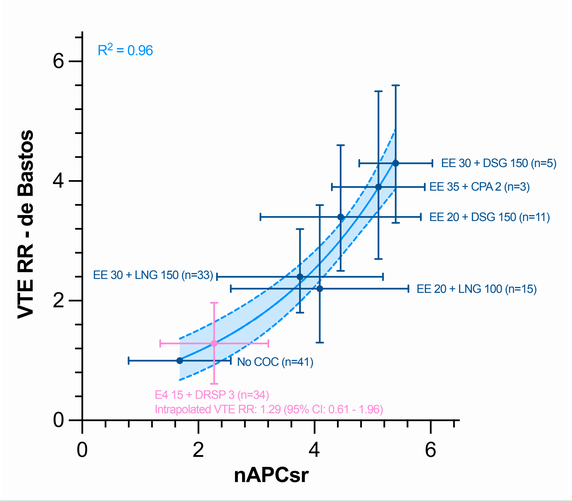
** Intrapolated VTE risk*



- As shown in **Figure 1**, exponential growth equations best fit the correlations between nAPCsr and the RR of VTE depending on the type of COC (either based on the study of Lidegaard or the meta-analysis of de Bastos).
- R squared of both correlations were above **0.95**.
- Out of 34 women using the new combination estetrol/drospirenone, the mean **nAPCsr** was **2.28**.
- By intrapolation, this new association might express a **RR of 1.37 (0.86-1.89)** based on the study of Lidegaard or a **RR (95% CI) of 1.29 (0.61-1.96)** based on the meta-analysis of de Bastos.
- This is in line with data obtained so far in which estetrol 15 mg, associated with drospirenone 3 mg, shows a **promising hemostatic profile** compared to the other COCs.

Figure 1: Correlation between nAPCsr values and the relative risk (RR) of VTE (Lidegaard, 2011 on the left and de Bastos, 2014 on the right) for different combined oral contraceptives





SUMMARY / CONCLUSION

These prediction models are only exploratory and further investigations and validation are needed. However, these data support the concept that the nAPCsr could become a universal test to assess the hormone-induced risk of VTE in women on hormonal contraception

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COI

- J-M Foidart is a member of the board at Mithra Pharmaceuticals.
- J. Douxfils is CEO and founder of QUALIblood and reports personal fees from Daiichi-Sankyo, Diagnostica Stago, DOASense, Gedeon Richter, Mithra Pharmaceuticals, Norgine, Portola.

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