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Assessment of thrombomodulin resistance in women using second generation, third generation and progestin-only contraceptives

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BACKGROUND

- ❖ The identification of an APC resistance using home-made ETP-based APC resistance assay is well described but few studies consider the involvement of thrombomodulin (TM), which physiologically, promotes protein C activation.
- ❖ The addition of TM (instead of APC) to a thrombin generation test considers the whole protein C-S system and may be of interest in the identification of abnormalities in the protein C pathway.^{1,2}

AIM

To evaluate the response to TM in plasmas from male and female healthy volunteers and from women using hormonal contraceptives.

METHOD

- ❖ The resistance to TM was assessed on the Calibrated Automated Thrombogram (CAT) with the Thrombinoscope software, using commercially available CE-marked thrombin generation dedicated kit reagents from Diagnostica Stago (STG®-ThromboScreen)
- ❖ A total of 43 volunteers (FV Leiden negative) aged from 18-35 years were enrolled and stratified into several subgroups:
 - Men (n=16)
 - Women not using combined oral contraception (no COC) [n=9]
 - Women using second-generation COC (2G COC) [n=7]
 - Women using third-generation COC (3G COC) [n=5]
 - Women using progestin-only contraceptive (P) [n=6]
- ❖ These subgroups have been compared based on their TM resistance values expressed in inhibition percentage (%) of the ETP.
- ❖ Inhibition % of the ETP represents the comparison between the ETP measured without TM (-TM) and the ETP measured in the presence of TM (+TM). [► Figure 1]. This ratio (%), subtracted to 100%, gives the inhibition % :
 - $\text{Inhibition \%} = 100\% - \frac{\text{Sample ETP (+TM)}}{\text{Sample ETP (-TM)}}$

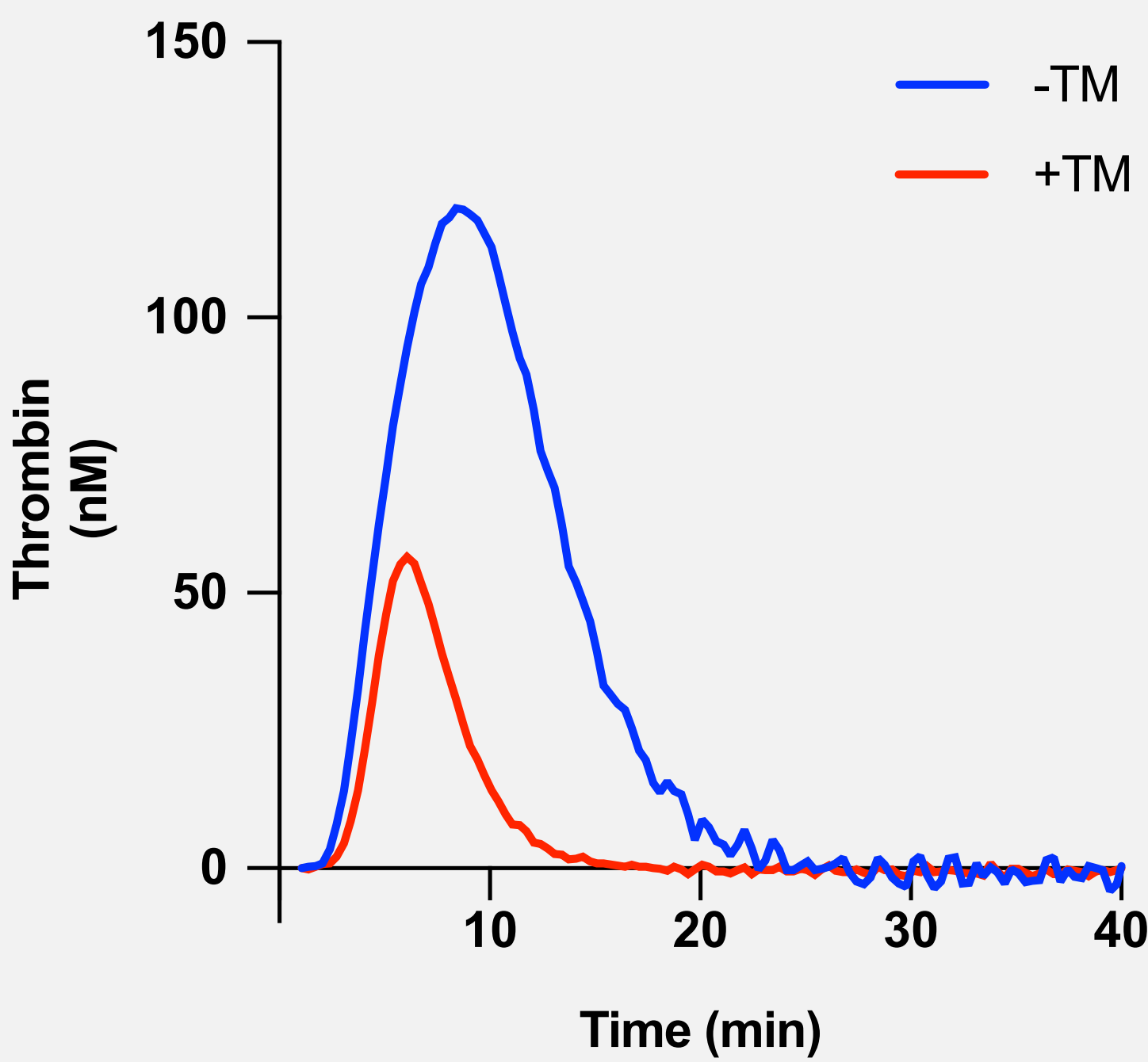


Figure 1 : Thrombin generation in absence of TM (blue curve) and in presence of TM (red curve).

RESULTS

- ❖ The mean inhibition % [± SD] of each subgroup [► Figure 2] were :
 - 67 % [± 16%] for men
 - 50 % [± 16%] for women not using hormonal contraception
 - 28% [± 13%] for women using 2G COC
 - 20 % [± 7%] for women using 3G COC
 - 46% [± 14%] for women using P
- ❖ Men were significantly more sensitive to TM than women, whether or not they were taking hormonal contraceptive (p-value < 0.05)
- ❖ For women, it depended on the type of contraceptive:
 - Significant differences were observed between women using 2nd and 3rd generation COC with women not using hormonal contraception (p-value <0.05).
 - The use of progestin-only contraceptive, on the other hand, did not affect the sensitivity to TM and showed similar inhibition % (46%) compared to women not using hormonal contraception (50%).
 - The difference between 2nd and 3rd generation COC users was not significant, probably because the insufficient power. [► Table 1]

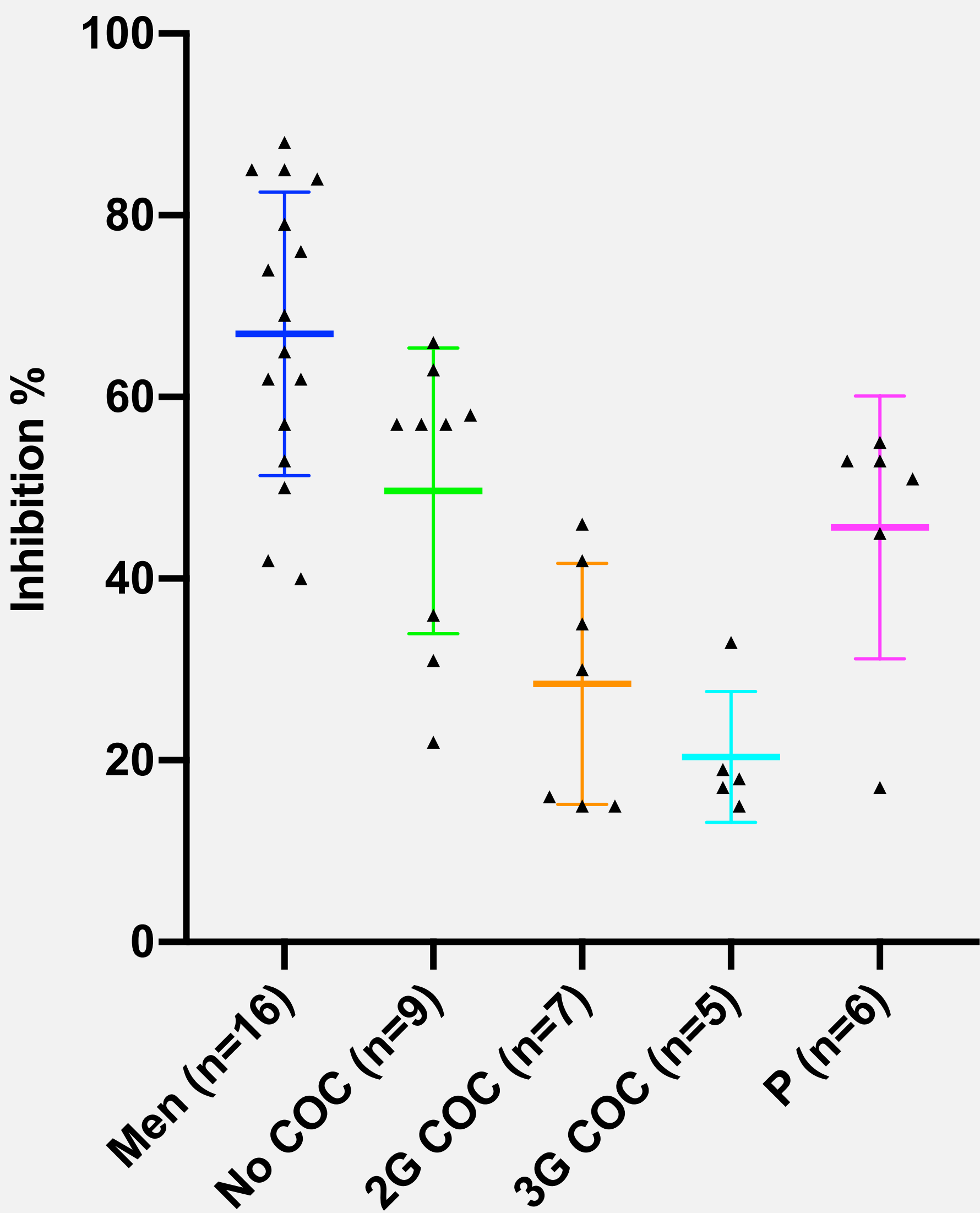


Figure 2 : Inhibition % of the ETP [± SD] of men, women not using hormonal contraception (no COC), women using 2nd generation COC (2G COC), women using 3rd generation COC (3G COC) and women using progestin-only contraceptive (P).

Mann-Whitney tests	Significantly different ? (p<0.05)	Summary	p-value
Men (n=16) vs. No COC (n=9)	Yes	*	0.0278
Men (n=16) vs. 2G COC (n=7)	Yes	****	<0.0001
Men (n=16) vs. 3G COC (n=5)	Yes	****	<0.0001
Men (n=16) vs. P (n=6)	Yes	*	0.0159
No COC (n=9) vs. 2G COC (n=7)	Yes	*	0.0160
No COC (n=9) vs. 3G COC (n=5)	Yes	**	0.0035
No COC (n=9) vs. P (n=6)	No	ns	0.1700
2G COC (n=7) vs. 3G COC (n=5)	No	ns	0.6364
2G COC (n=7) vs. P (n=6)	Yes	*	0.0204
3G COC (n=5) vs. P (n=6)	Yes	*	0.0346

Table 1: Comparison of TM sensitivity between subgroups by using Mann-Whitney t-test.

- ❖ Nonetheless, the negative point of this method results in the large variability within subgroups [► Table 2]. Indeed, coefficient of variation (CV) goes up to more than 30% in women subgroups.

Subgroups	CV
Men (n=16)	23,30%
No COC (n=5)	31,6%
2G COC (n=7)	46,62%
3G COC (n=5)	35,28%
P (n=6)	31,66%

Table 2: Coefficient of variation (CV) of the different subgroups

CONCLUSION

The thrombomodulin resistance is an interesting pathway to assess, being able to discriminate women depending on the type of oral contraceptive. However, the high variability observed in specific subgroups warrants further investigation on the possible confounding variables. An improvement of the method is mandatory in order to address the issue of the important inter-individual variation observed and to provide more reliable tools for risk stratification.

Conflict of Interest :
Jonathan Douxflis reports personal fees from Daiichi Sankyo, Diagnostica Stago, Roche and Roche Diagnostics outside the submitted work. Jonathan Douxflis is the CEO and founder of QUALIBlood s.a.

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