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Low Thrombin Generation in Menopausal Women Using Estetrol (E4)



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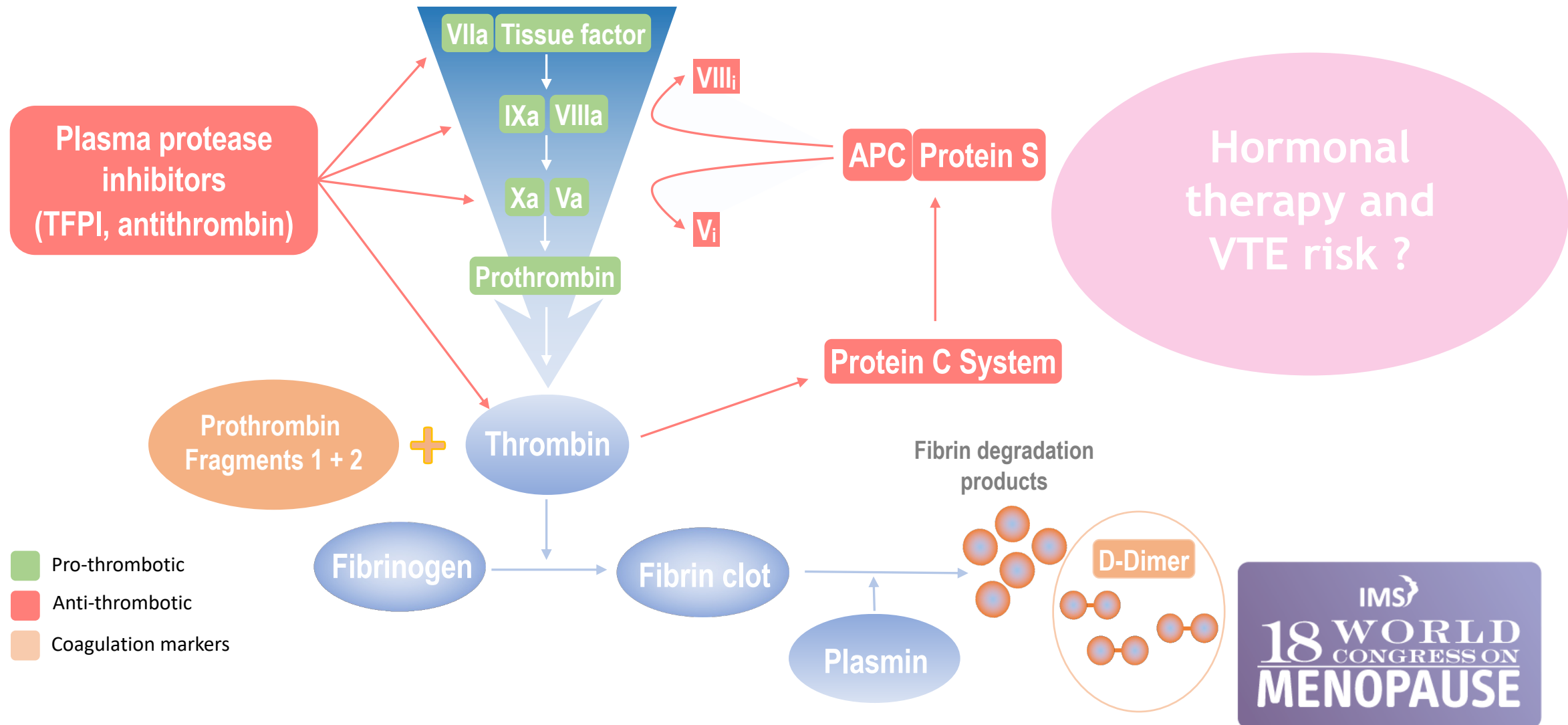
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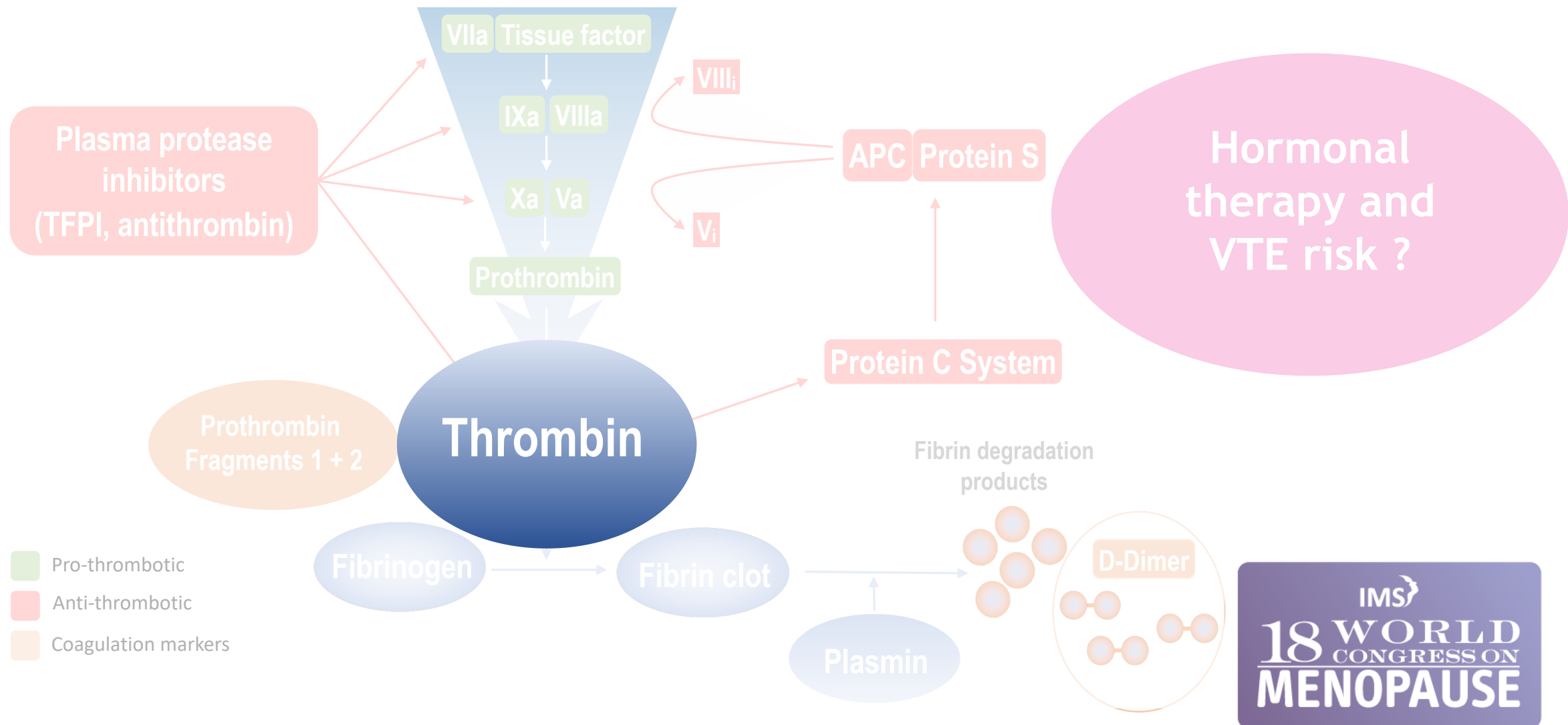
Financial relationships disclosure

I have no financial relationships to disclose

Context - Coagulation cascade overview



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Trial design, population and treatments

❖ E4Relief phase 2b Trial

- ❑ Multicenter, randomized, double-blind, placebo-controlled, dose-finding study in postmenopausal women
- ❑ 168 postmenopausal women (40-65 years of age) included for TGA analysis
- ❑ Intervention:
 - Placebo (N=31)
 - E4 2.5 mg (N=42)
 - E4 5 mg (N=29)
 - E4 10 mg (N=34)
 - E4 15mg (N=32)
- ❑ Daily administration for 12 weeks

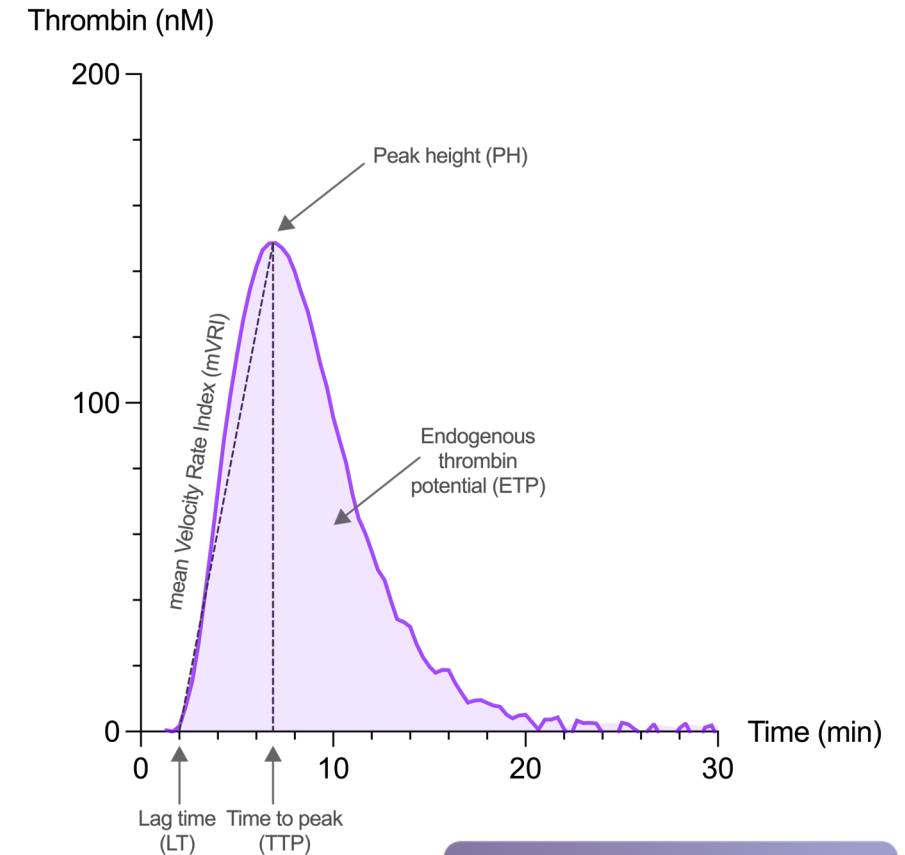
Main Outcome Measures

❖ Thrombograms and TGA parameters

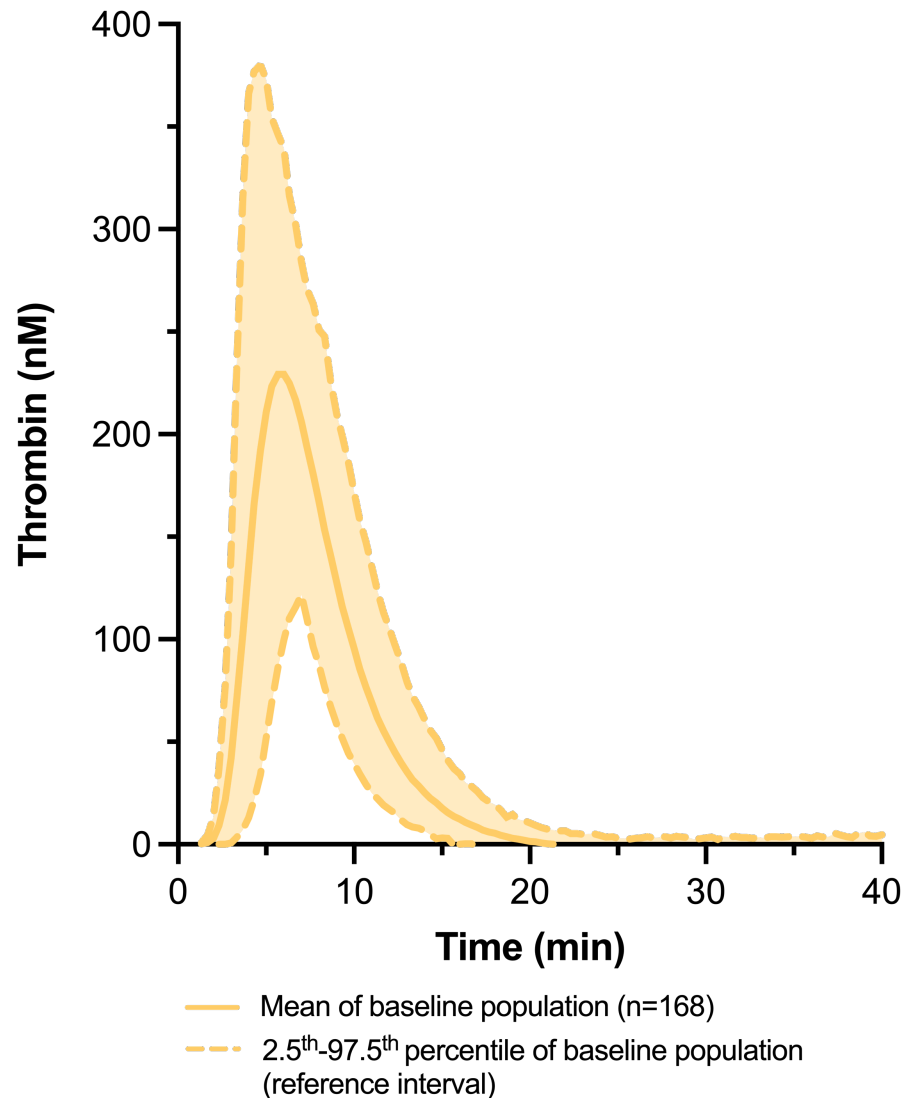
- ❑ Lag time – start of thrombin generation
- ❑ Peak height – maximal [thrombin]
- ❑ Time-to-peak – time to reach the peak
- ❑ Endogenous thrombin potential – AUC
- ❑ Mean velocity rate index – maximal rate of TG

❖ Timepoints

- ❑ At baseline
- ❑ After 12 weeks of treatment



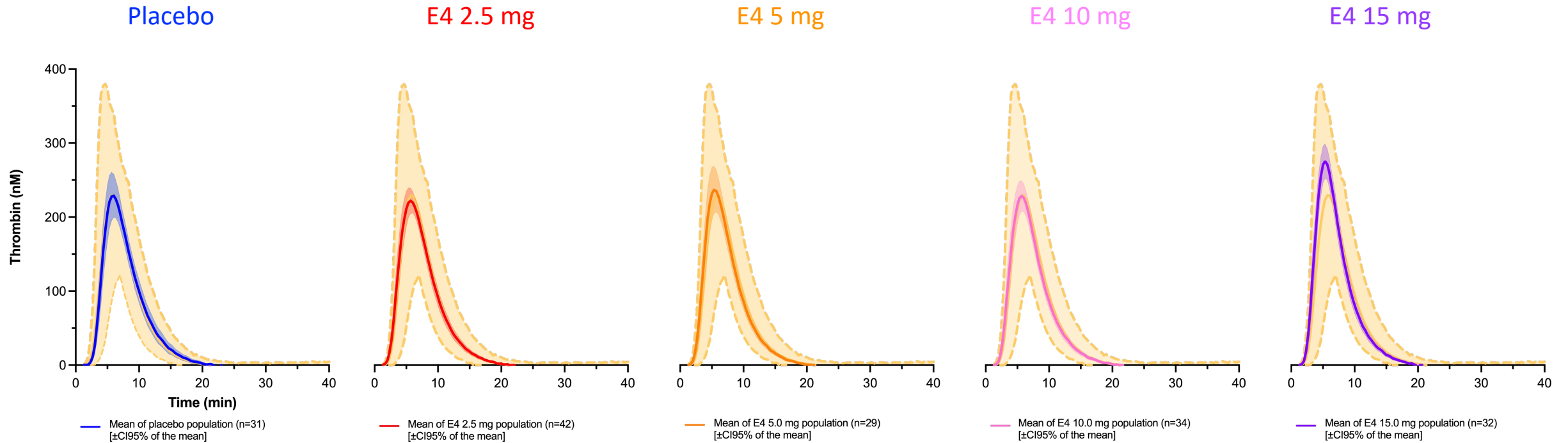
Reference interval of thrombin generation



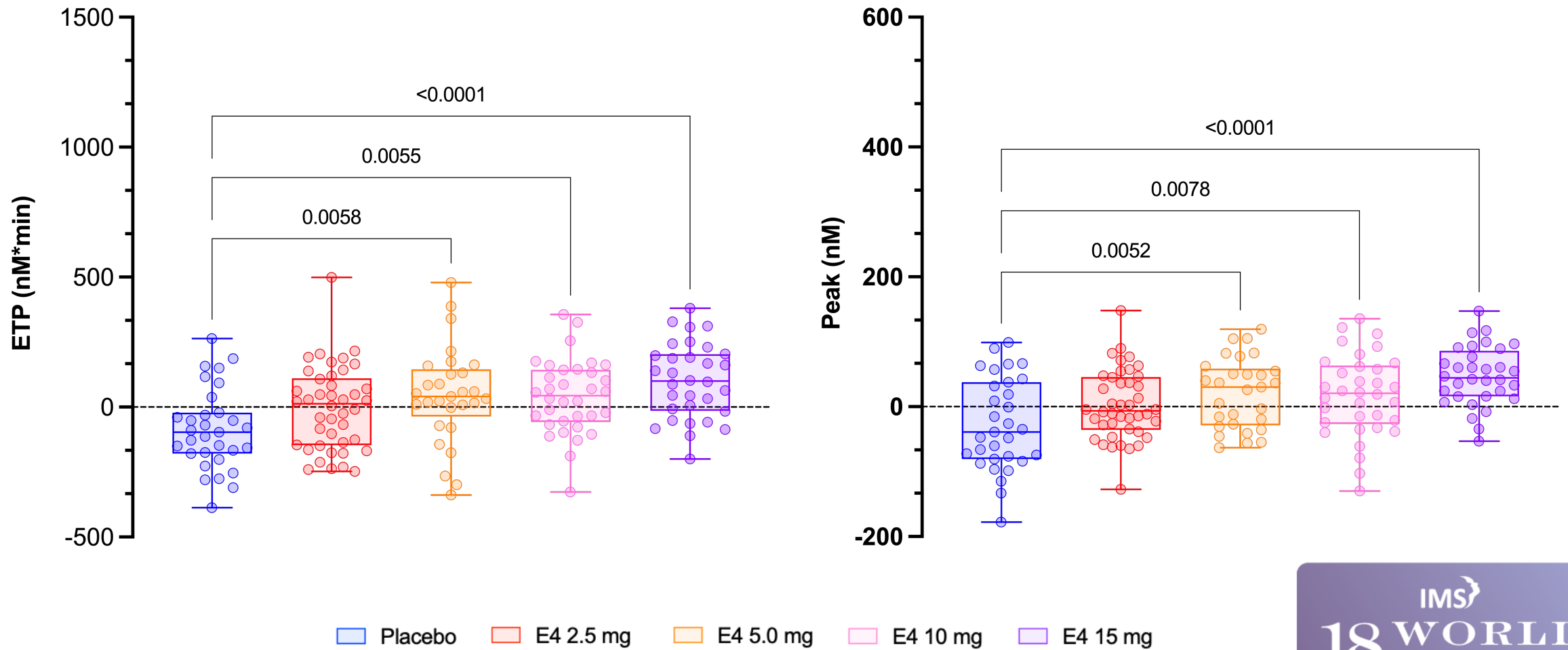
	Mean	2.5 th percentile	97.5 th percentile
Lag time (min)	3.0	2.1	4.3
Time to peak (min)	6.2	4.3	8.8
Peak (nM)	260	146	399
ETP (nM.min)	1447	1013	1893
mVRI (nM/min)	90.6	32.5	201.0

In accordance with the definition of reference values as reported in the Clinical & Laboratory Standard Institute (CLSI) EP-28-A3C

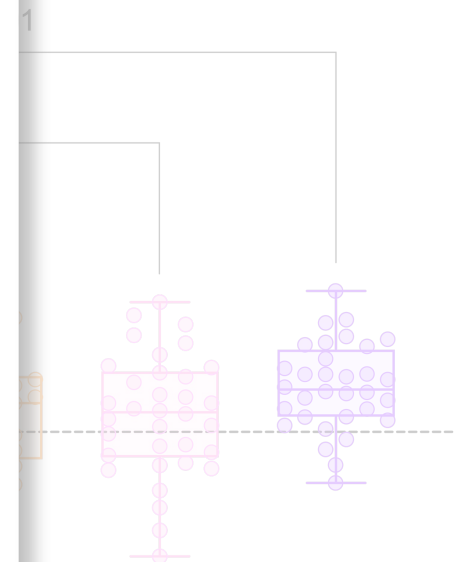
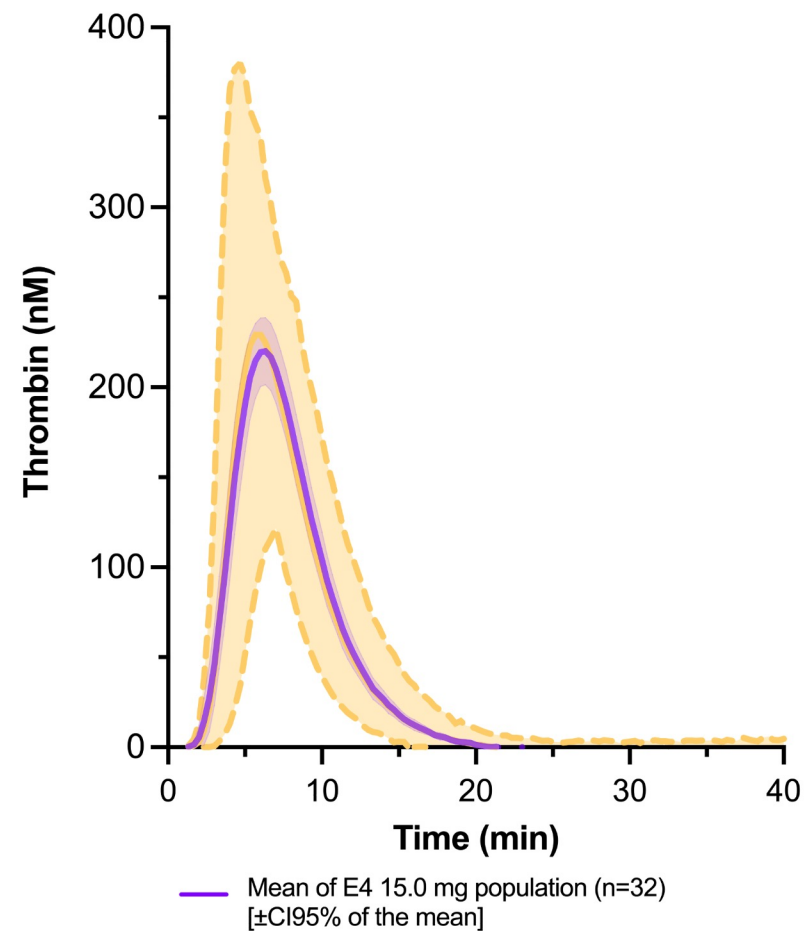
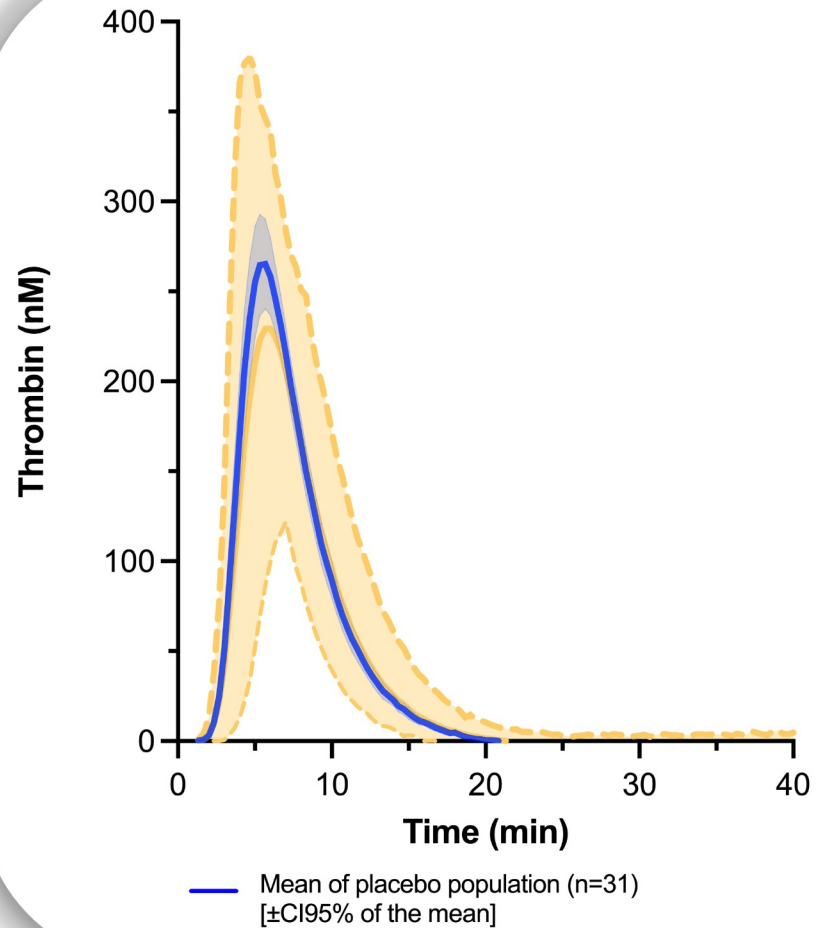
Thrombograms : impact after 12 weeks of treatment



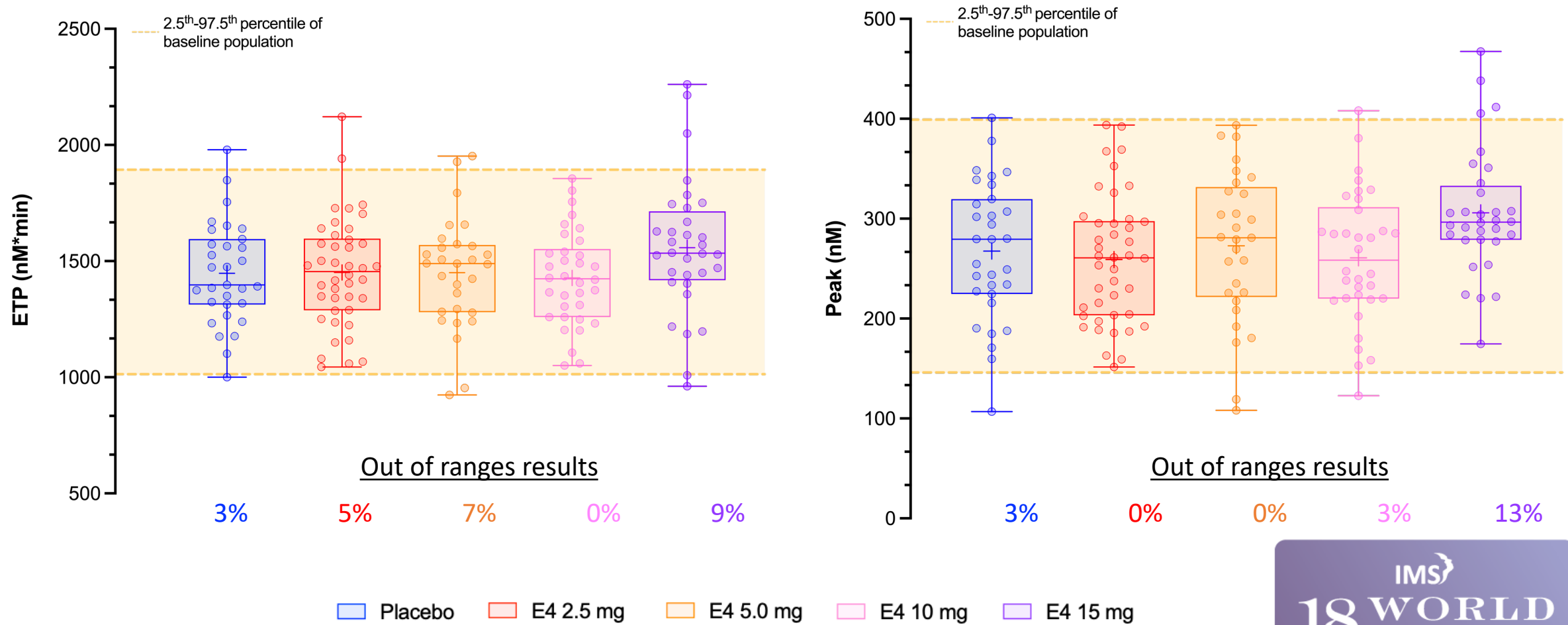
TGA parameters: absolute change from baseline



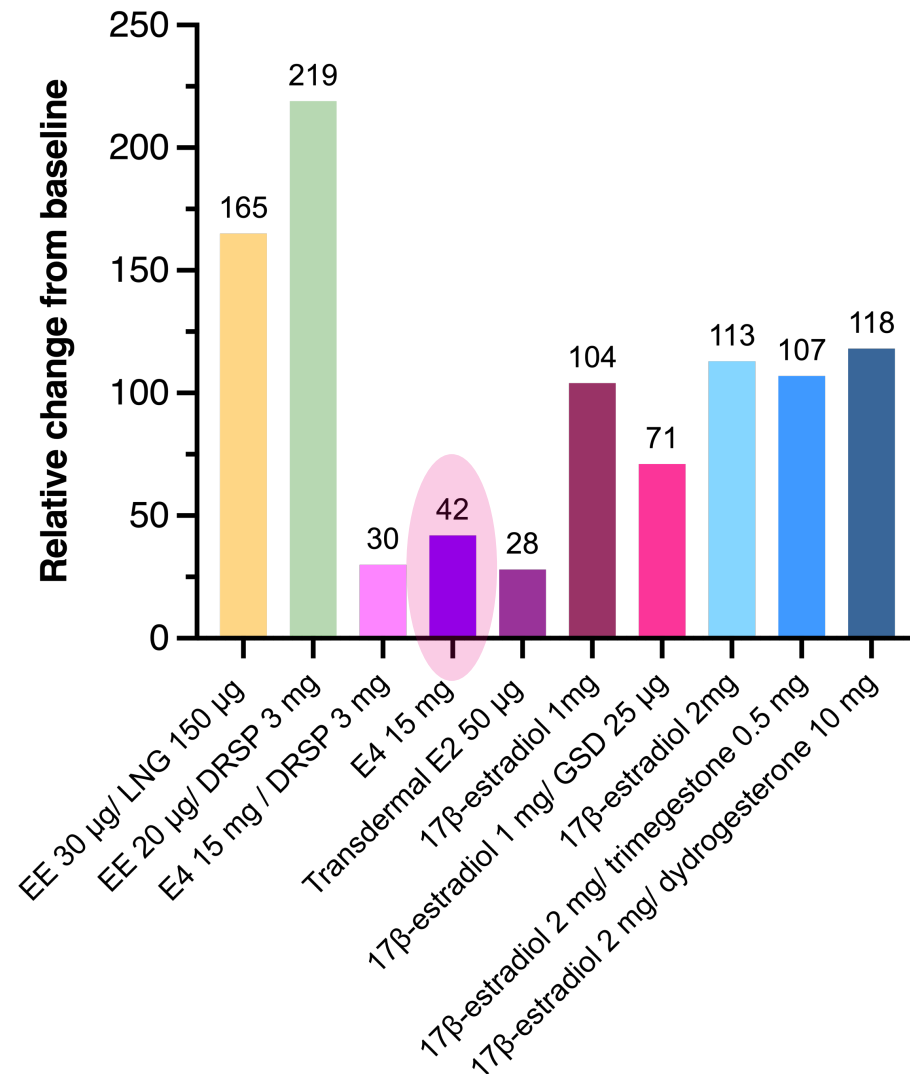
Impact of thrombin generation at baseline



TGA parameters : absolute value after 12 weeks of treatment



Low impact of E4 on APC resistance



Compared to **oral EE (contraception) or oral E2 (menopause)** 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**

Take home messages

- ✓ The mean thrombogram, even with the higher dose of E4, remained within the **reference interval** established according to CLSI standards
- ✓ At the individual level, the impact of E4 on thrombin generation was very limited since **only very few subjects** had abnormal TGA parameters after 12 weeks of treatment compared to placebo
- ✓ These data are in lines with the **low impact of E4 on APC resistance**, considered as an independent risk factor of VTE

Take home messages

✓ The mean thrombogram, even with the higher dose of E4, remain within the **reference interval** established according to CLSI standards

✓ These surrogate biomarkers, that are thrombin generation and the nAPCsr, may highlight prothrombotic changes induced by hormonal therapies and could therefore become a sensitive way to discriminate the risk of VTE among these different hormonal therapies