

Moderate cross-sex hormone-induced changes of hemostatic variables in transgender individuals. (Cardiovascular)

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Background

- Oral contraceptives (OC) expose women to changes in the coagulation system and a higher risk of venous thrombosis.¹
- Different effects of transdermal and oral estrogen are observed in OC users and transgender individuals.^{1,2}
- Cross-sex hormone treatment (CSHT) is associated with venous thrombosis.^{2,3}
- The effect of testosterone supplementation (TS) on coagulation still remains to be elucidated.^{2,4}

Objective

- Assess whether CSHT induces similar changes in hemostatic factors in transgender individuals as observed in biological men and women receiving hormone supplementation. In addition, it will be assessed whether dosage form influences the change in hemostatic factors.

Methods

- Analyzing plasma samples of 100 female-to-male (FtMs) and 98 male-to-female (MtFs) individuals at baseline and after 12 months of CSHT.
- Determining the levels of hormone-sensitive factors, e.g. factor II, IX, XI, fibrinogen, protein C, free protein S and normalized activated protein C sensitivity ratio (nAPCsr).
- Investigating whether the dosage form affects the alteration in coagulation.
- Comparing the observed changes with those reported in oral contraceptives and androgen supplementation.

Results

- FtMs:** Increase in factor IX, free protein S and nAPCsr, decrease in factor II, XI, protein C and fibrinogen.
- MtF:** Increase in factors II, IX, XI, fibrinogen, free protein S and nAPCsr, decrease in protein C.
- No differences in hemostatic factor alterations between dosage forms. There was no influence of age (data not shown).

Discussion

- FtMs:** The prothrombotic factor IX increases, while the rest seems to shift towards an antithrombotic state.
- MtFs:** The nAPCsr shifts to an antithrombotic state, in contrast to the remaining factors.
- No difference in change between dosage forms found.

Conclusion

- FtMs:** No anti- or prothrombotic state is induced in FtMs under CSHT, with similar changes compared to those found in TS.
- MtFs:** Moderate CSHT-induced prothrombotic state in MtFs, with similar changes compared to those observed in OC users, except for protein C and the nAPCsr.

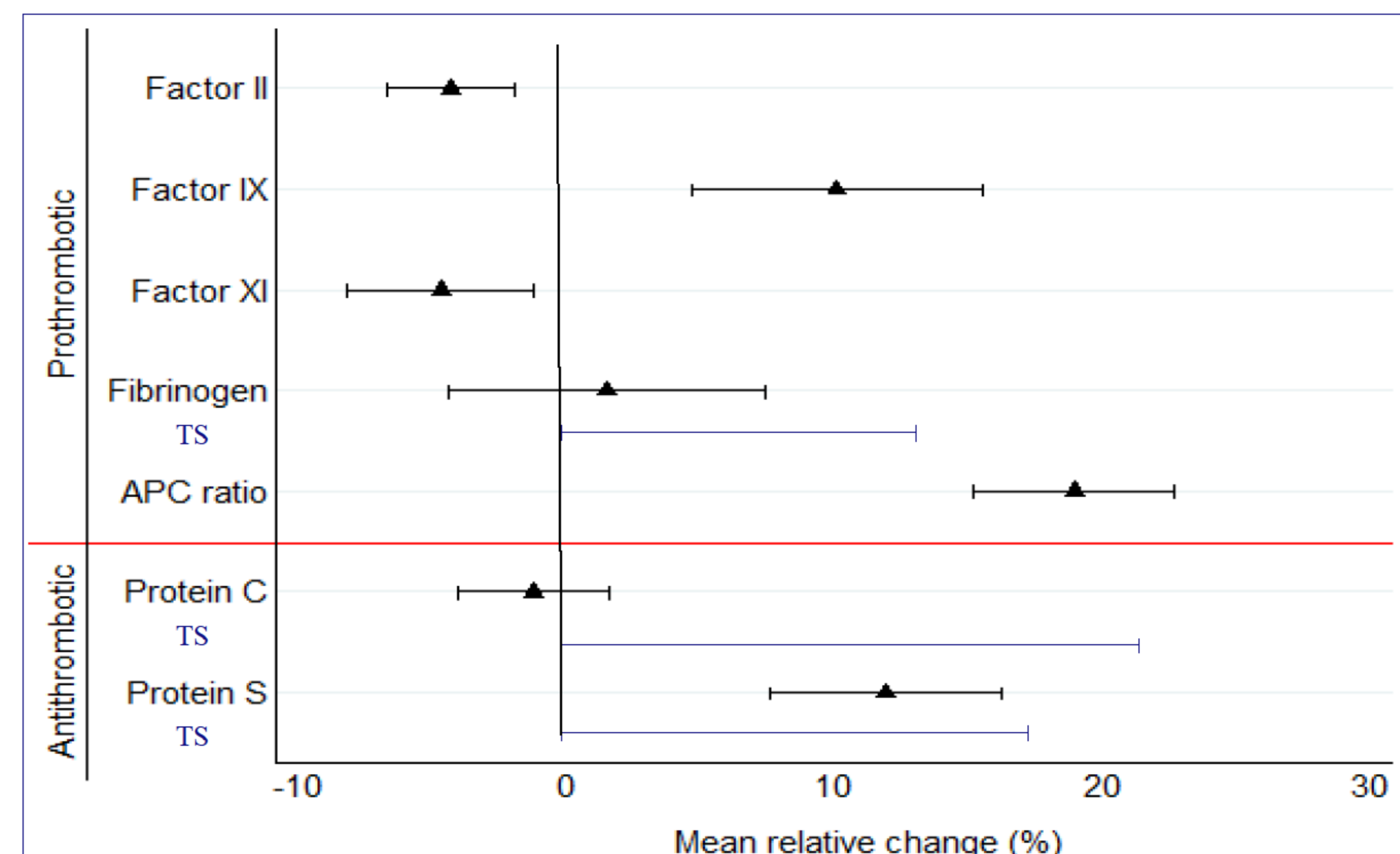


Figure 1. Mean relative change in hemostasis after 12 months CSHT in female-to-male individuals. The lines noted with TS reflect the effects of testosterone supplementation on hemostatic factors in biological men as reported in the literature.⁵

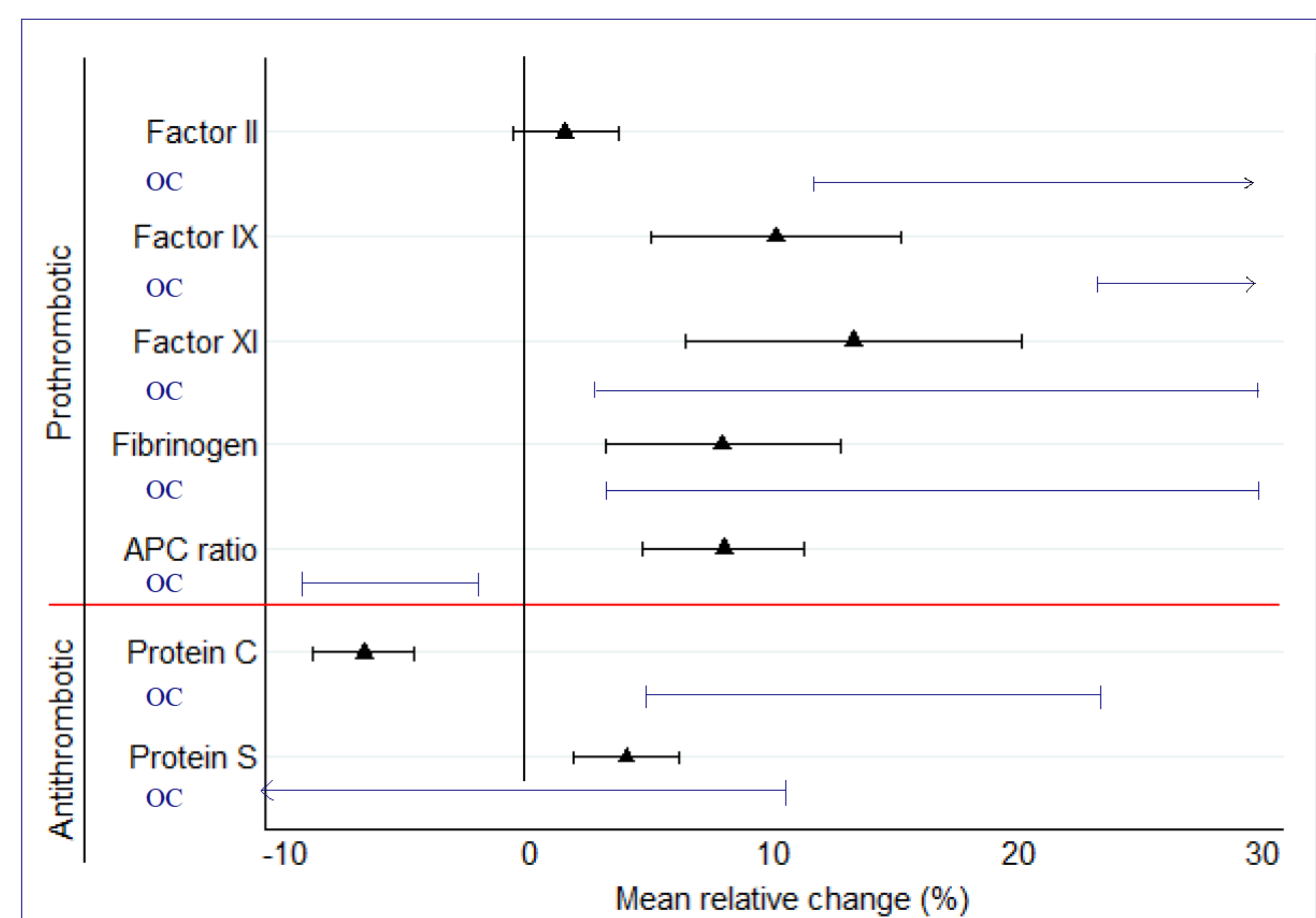


Figure 2. Mean relative change in hemostasis after 12 months of CSHT in male-to-female individuals. The lines noted with OC reflect the effects of oral contraceptives on hemostatic factors in biological women as reported in the literature.⁶

Table 1. Linear regression coefficients and 95%CI for the differences in the ratios of the measured hemostatic factors between the dosage forms in MtF and FtM individuals. nAPCsr: normalized APC sensitivity ratio, FtMs: female-to-males individuals, intramuscular injection vs. transdermal use, MtF: male-to-females individuals, oral vs. transdermal use.

	MtF subjects (n=98)	FtM subjects (n=100)
Factor II	0.014 (-0.028, 0.057)	-0.028 (-0.076, 0.019)
Factor IX	-0.068 (-0.168, 0.033)	-0.065 (-0.171, 0.041)
Factor XI	-0.048 (-0.183, 0.087)	-0.005 (-0.074, 0.064)
Protein C	0.004 (-0.038, 0.047)	-0.051 (-0.107, 0.004)
Protein S	0.046 (0.003, 0.089)	0.024 (-0.063, 0.112)
Fibrinogen	0.070 (-0.023, 0.164)	-0.061 (-0.178, 0.056)
nAPCsr	-0.004 (-0.069, 0.062)	-0.003 (-0.080, 0.073)

¹Reitsma *et al.* Mechanistic view of risk factors for venous thromboembolism. *Arter Thromb Vasc Biol.* 2012;32(3):563-8

²Asscheman *et al.* Venous thromboembolism as a complication of cross-sex hormone treatment of male-to-female transsexual subjects: a review. *Andrologia.* 2014;46(7):791-5

³Toorians *et al.* Venous thrombosis and changes of hemostatic variables during cross-sex hormone treatment in transsexual people. *J Clin Endocrinol.* 2003;88(12):5723-9

⁴Layton *et al.* Comparative safety of testosterone dosage forms. *JAMA Int Med.* 2015; 75(7):1187-96

⁵Ferenchick *et al.* Anabolic-androgenic steroid abuse in weight lifters: evidence for activation of the hemostatic system. *Am J Hematol.* 1995;49(4):282-8

⁶Kemmeren *et al.* Effects of second and third generation oral contraceptives and their respective progestagens on the coagulation system in the absence or presence of the factor V Leiden mutation. *Thromb Haemost.* 2002;87(2):199-205

