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Sex-specific aspects of venous thromboembolism: What is new and what is next?

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Abstract

Men seem to have a higher intrinsic risk of venous thromboembolism (VTE) than women, regardless of age. To date, this difference has not been explained. By integrating state-of-the-art research presented at the International Society on Thrombosis and Haemostasis Congress of 2021 with the available literature, we address potential explanations for this intriguing risk difference between men and women. We discuss the role of exogenous and endogenous sex hormones as the most important known sex-specific determinants of VTE risk. In addition, we highlight clues on the role of sex hormones and VTE risk from clinical scenarios such as pregnancy and the polycystic ovary syndrome. Furthermore, we address new potential sex-specific risk factors and unanswered research questions, which could provide more insight in the intrinsic risk difference between men and women, such as body height and differences in body fat distribution, leading to dysregulation of metabolism and inflammation.

KEYWORDS
body fat distribution, hormones, metabolism, sex, venous thromboembolism

Essentials

- Men have an, unexplained, higher intrinsic venous thromboembolism (VTE) risk than women.
- Body height does not fully explain the sex-specific VTE risk difference.
- Exogenous estrogens increase VTE risk, for endogenous sex hormones this is largely unknown.
- Body fat distribution, metabolism and inflammation are of interest for future studies.

1 | SEX-SPECIFIC RISK OF VENOUS THROMBOEMBOLISM: IS THERE A DIFFERENCE?

Over the past several decades, several important sex-specific aspects of risk of venous thromboembolism (VTE) have been established. Nearly universally, studies on the sex-specific incidence of first VTE across age categories report the same pattern.[1-5] Most studies report a 2- to 3-fold higher incidence of first VTE in women during their fertile lifespan compared with men of similar age groups.[1-5] After age approximately 50 years, the observed incidence is slightly higher in men than in women. After the age of 70 years, the observed incidence increases steeply in both sexes and, in some studies, the incidence in women is again higher than in men[1,4,5] (see

Figure 1 for sex-specific incidence rates from large population based studies with corresponding incidence rate ratios per age groups). As a result, on average, the risk of VTE is considered more or less equal in both sexes. This observation is remarkedly in contrast to the risk of a recurrent event, which has consistently been shown to be twice as high in men than in women.[6-9]

Different explanations have been proposed for the observed variation in incidence of both first and recurrent VTEs across the lifespan of women and men. The observed higher incidence in women during the fertile lifespan is likely explained by the presence of transient risk factors related to reproductive factors such as use of hormonal contraceptives and pregnancy. When these women-specific risk factors during premenopausal ages are taken into account, it appears that the incidence of a first VTE is also two times higher in men in the younger age group, and accordingly fits with the increased recurrence risk as observed in men.[9] Hence, the intrinsic risk of VTE (i.e., the risk in the absence of extrinsic risk factors) appears to be higher in men than in women, at least up to the age of 70 years.[9]

For the very elderly (>age 70 years), fewer data are available. In a recent simulation study, in which the competing risk of death was taken into account, the estimated lifetime risk of first VTE (i.e., at

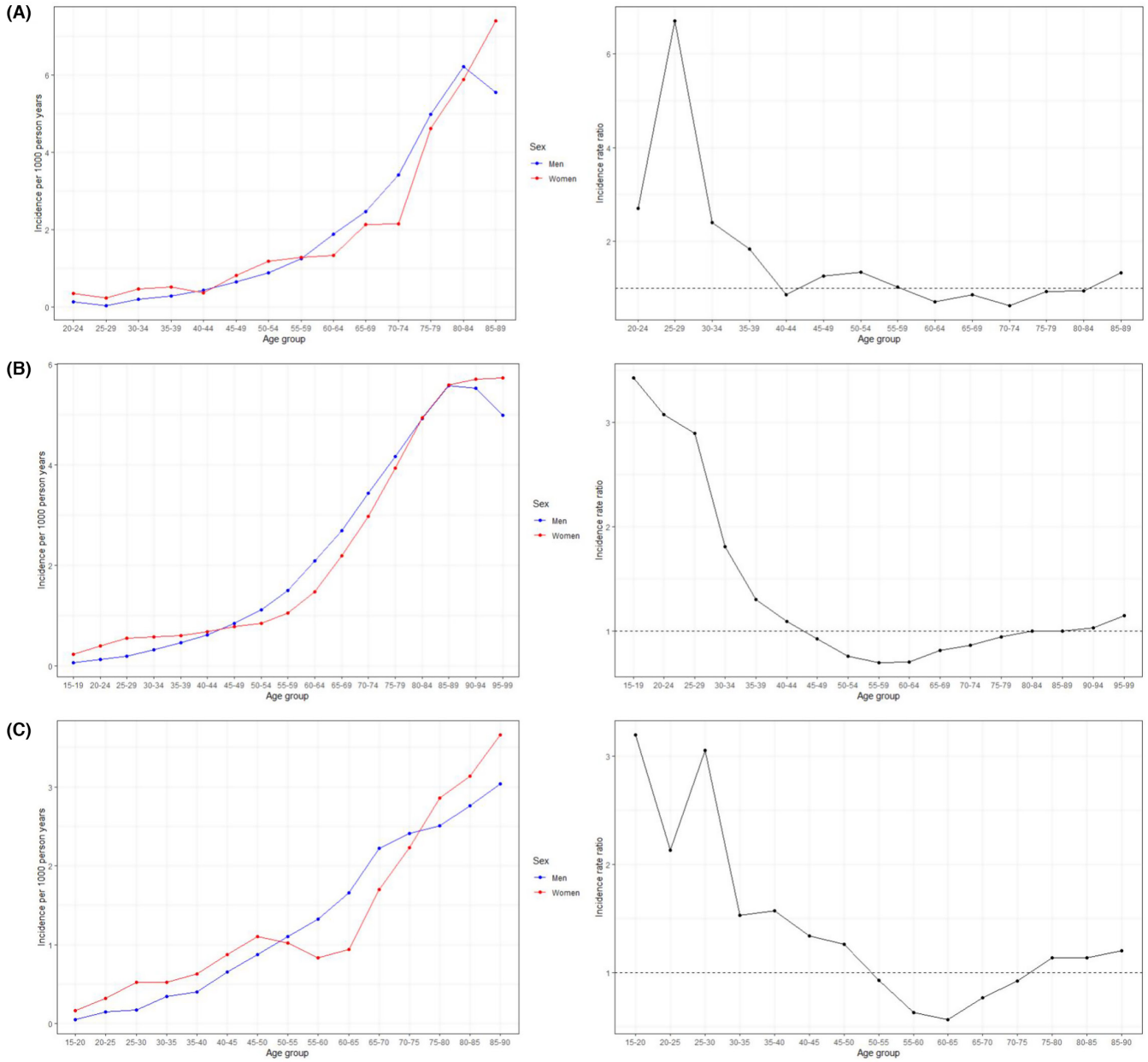

FIGURE 1 Left figures: observed incidence of first venous thromboembolism (VTE) by age group separately for women (red) and men (blue). Right figures: corresponding incidence rate ratio (IRR) of the risk of VTE comparing men with women by age groups. An IRR of 1 indicates no difference, an IRR > 1 indicates a higher incidence in women, an IRR of < 1 indicates a higher incidence in men. Based on available published data from large population-based studies that reported the incidence of first VTE separately for men and women with small (5-year) age categories available. (A) Naess et al.,[1] (B) Arnesen et al.,[5] (C) Kort et al[4]

100 years of age) was slightly higher in women than in men (9.3% vs. 8.1%); however, 50% of all first VTE events in women occur after the age of 70 years.[5] Hence, there seems to be a "catch-up" effect in women that is possibly explained by competing risks (e.g., death from other causes in men).[5]

Taken together, the observations from these studies demonstrate there is a substantial lifetime risk of VTE in both women and men and suggest that men have an intrinsic increased risk of VTE compared with women (see Figure 2 for a schematic illustration of this hypothesis). Intriguingly, to date, the mechanism for this higher intrinsic risk in men (or protective mechanism responsible for the lower intrinsic risk in women) has not been identified. In this International Society on Thrombosis and Haemostasis (ISTH) Congress of 2021 state-of-the-art review we will discuss the role of exogenous and endogenous sex hormones as the most important known sex-specific determinants of VTE risk. In addition, we will address new potential sex-specific risk factors and unanswered research questions, which may explain the intrinsic risk difference between men and women, such as body height and body fat distribution with subsequent changes in metabolism and inflammation. A summary of the hypothetical mechanisms that could contribute to the higher intrinsic VTE risk in men is provided in Table 1.

1.1 | Role of genes and environment

The role of genes and environmental factors as a potential explanation for the higher VTE risk in men has been discussed in detail previously.[10] The most important (based on their prevalence and risk size) genetic VTE risk factors that have been identified include the Factor V Leiden and prothrombin G20201A gene mutation, non-O blood group and an inherited deficiency of protein C, protein S, and antithrombin.[11,12] However, these mutations are not located on the sex chromosomes and are thus likely not distributed differently between men and women. This was confirmed in the MEGA case control study, in which there was no difference in VTE risk size of these mutations between men and women.[10] The genes that code for coagulation factor (F) VIII and IX, of which higher levels are both associated with VTE risk,[13,14] are located on the X chromosome and thus could result in sex-specific differences of VTE risk.[15] However, in a large population-based study (2533 men and 2440 women), FVIII levels were slightly higher in women than in men.[16] In a smaller study among healthy controls (272 women, 201 men) there was also no difference in factor IX levels.[14] Hence, sex-specific differences in factors VIII and IX levels do not seem to contribute the intrinsic sex-specific VTE risk differences. Also, Y chromosomal haplogroup variation in men was not associated with differences in first or recurrent VTE risk, and it was also considered unlikely that chromosome Y variation can explain the difference in VTE risk between women and men.[17]

Regarding the role of the environment, the incidence of VTE is continuously subject to changes in prevalence of risk factors in a population.[18] Environmental factors could also play a role in the observed sex-specific incidence of VTE; for example, if men would more frequently suffer from trauma and subsequent immobilization than women, this would influence the incidence of VTE. However, in previous studies, no differences were found for the prevalence of acquired strong VTE risk factors between men and women such as surgery, immobilization, malignancy, and chronic disease.[10,19] However, more subtle cultural and/or lifestyle differences between men and women could still contribute. For example, on average, women may tend to choose professions associated with more physical activity such as in education or health care, whereas men on average may have more seated professions, such as driver or office worker.[20] Even within similar job occupations, men were found to have more seated hours.[21] On a population level, more seated hours on a daily basis may result in a higher VTE risk, which might play a role in the underlying mechanism for the observed VTE risk difference between men and women.

2 | INFLUENCE OF SEX HORMONES

2.1 | Exogenous use of sex hormones

The role of hormonal contraceptives and hormone therapy as VTE risk factors in women has been firmly established.[22] The associated VTE risk is dependent on both dose and type of estrogen and progestogen and also on mode of delivery.[23,24] In men, however, studies on exogenous testosterone use and VTE risk have reported conflicting results, and testosterone use may be associated with a modestly increased VTE risk.[25-28] Testosterone (as opposed to hormonal contraceptives in women) is typically only used in case of concomitant disease that can be associated with an increased VTE risk in and of itself. Examples of such clinical scenarios include hypogonadism or testosterone replacement therapy after cancer treatment.[25,29] In addition, use of estrogen-like therapies for management of prostate cancer are also associated with an increased risk of VTE.[30]

Important clues on the contribution of exogenous sex hormones to risk of VTE, independent of other morbidity and assigned sex at birth, can be derived from hormone use in the transgender population. Transwomen (persons born with male sex and female gender identity) who use gender-affirming hormone therapy (typically estrogen with antiandrogens) seem to have an increased risk of both venous and arterial thrombotic events compared with control cismen (persons born with male sex assigned at birth and a male gender identity).[31-35] When comparing coagulation profiles before and after start of hormone therapy in these persons, the coagulation profiles were overall more procoagulant after the start of hormone therapy.[36]

On the risk of venous and arterial thrombotic events in transmen (persons born with female sex assigned and male gender identity) who use testosterone as gender-affirming hormone therapy, only few data are available.[31,33-35] In the available studies, there does not seem to be an increased risk of thrombotic events compared with control ciswomen (persons born with female sex assigned at birth

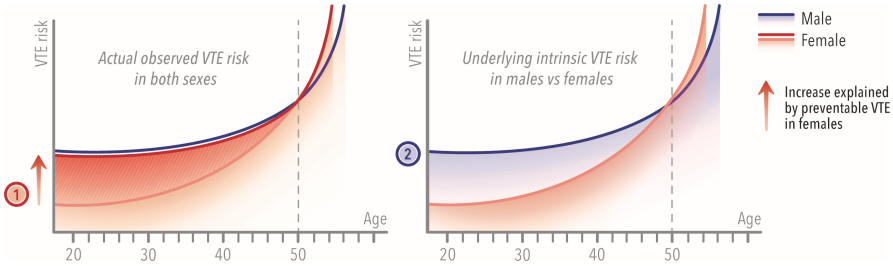

FIGURE 2 Schematic overview of the sex-specific incidence of first venous thromboembolism (VTE) with and without events related to reproductive risk factors in women. (1) Observed risk of first VTE in women (red) and men (blue), (2) incidence in women (red) and men (blue when taking reproductive risk factors of VTE into account). Based on available literature: Ref. [1,6,10], adapted from Krishnaswamy[73]

TABLE 1 Hypothetical mechanisms for the higher intrinsic VTE risk in men

Risk factor	Hypothetical mechanisms	Related literature
Likely contributes		
Average higher body height and leg length in men	Potentially resulting in higher risk of stasis	[19,52]
Of interest for further exploration		
Cultural and/or lifestyle differences resulting in VTE risk factor differences	If men would on average have more seated hours during the day because of differences in job occupation, leading to more stasis	[20,21]
Androgenicity	Mechanistic clues from the polycystic ovary syndrome population. Here, androgenicity and visceral and liver fat deposition seems associated with metabolic and inflammatory changes, which could result in higher VTE risk	[44-47,66]
Body fat distribution (i.e., more visceral fat deposition)	Differences in body fat distribution (as between the sexes) are associated with metabolic and inflammatory changes, which could result in higher VTE risk	[63,65]

Abbreviation: VTE; venous thromboembolism

and a female gender identity).[31,33,34] In line with this, the overall coagulation profiles of transmen after start of testosterone therapy did not appear more procoagulant than before start of therapy.[36]

Taken together, these observations suggest that use of exogenous estrogens (frequently combined with progestogens) results in procoagulant changes and increased VTE risk in both women and persons with male sex assigned at birth. Procoagulant changes in response to estrogen exposure seem of evolutionary benefit because these could result in decreased blood loss during labor.[37] Interestingly, the responsible biological mechanism seems in place also in persons with male sex assigned at birth. In contrast, the use of testosterone does not appear to have a clear prothrombotic effect.

2.2 | Influence of endogenous sex hormones

Few data are available on endogenous sex-hormone levels and risk of VTE in either women or men. In a large Danish cohort study, there was no apparent association between endogenous estrogen and testosterone levels and VTE risk in either women or men.[38] There were few events in few premenopausal women, and the time from blood sampling to the observed events was substantial with several years in between; hence, fluctuations in estrogen level could not be taken into account.[38] Similar results in middle-aged to older men and postmenopausal women not using hormone replacement therapy were observed in the large Atherosclerosis Risk in Communities study.[39] Here, levels of endogenous testosterone, dehydroepiandrosterone sulfate, or sex-hormone binding globulin (SHBG) were not associated with a substantial risk of VTE. In this cohort study, the time between blood draw and observed events was also several years (median follow-up 17.6 years).[39] In contrast, in the MEGA case-control study (with limited time between blood draw and VTE events) in young women, levels of endogenous estradiol and SHBG were found to be associated with the risk of first VTE.[40] Moreover, the relation between endogenous sex hormones in women and VTE risk is apparent from pregnancy. Because pregnancy progresses in parallel with estrogen and progestogen levels, levels of coagulation factors and the risk of VTE increase correspondingly.[41]

Another common women-specific clinical scenario in which levels of endogenous sex hormones play a crucial role is that of the polycystic ovary syndrome (PCOS). PCOS entails a heterogenous group of patients with key characteristics including hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology.[42,43] In at least two cohort studies, women with PCOS had an approximately 2-fold increased risk of VTE compared with control women.[44,45] In a case-control study in young women, a high free androgen index (>4.5) was associated with an increased risk of VTE.[40] The free androgen index is a ratio between the total serum testosterone and SHBG and high values

indicate hyperandrogenism (being one of the hallmarks of PCOS). In several studies, androgen excess in women has been associated with both increased levels of procoagulant and inflammatory markers.[46-49]

On the whole, outside pregnancy and PCOS, little is known on the relevance of endogenous sex hormone levels in the context of VTE risk. The available data suggest a modestly increased VTE risk with higher levels of estrogens and especially with hyperandrogenism in young women. The latter finding is of interest in light of the intrinsic higher VTE risk in men and does not seem to be explained only by testosterone levels as discussed in previous sections. Hyperandrogenism in young women (with PCOS) is associated with dysregulation of metabolism and inflammation.[50] The question arises whether the responsible mechanism is also present in men and whether this could explain the higher intrinsic VTE risk that is observed in men.

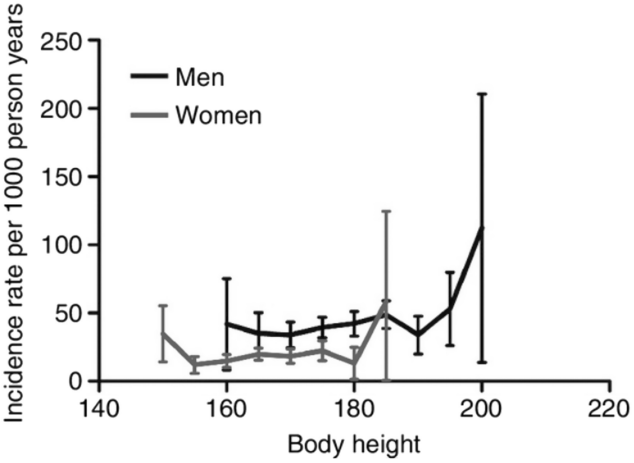

FIGURE 3 Incidence rate of recurrent venous thromboembolism per body height category separately for women ($n = 2315$) and men ($n = 1949$) in the study by Flinterman et al.[52] Bars indicate 95% confidence intervals. This is from the figure in the original study, printed with permission from John Wiley and Sons

3 | BODY HEIGHT AND SEX-SPECIFIC VTE RISK

One of the most evident physical differences between men and women is body height. Men are on average taller than women, with a global average height for men of 171 cm and 159 cm for women (aged 18 years in 2014).[51] Body height has been identified as a risk factor for VTE both in men and women, where especially the tallest persons are at higher risk.[19,52] In addition, a sedentary lifestyle and long-haul flights are risk factors that increase the risk even further in tall persons.[52,53] However, taller height does not seem to completely explain the risk difference. In men and women with a first VTE and similar body height, the recurrence risk was still 2-fold higher in men for every height (Figure 3 depicts the results as observed in the original study).[52] Accordingly, adjustment for body height only slightly attenuated the difference in recurrence risk between men and women.[52] In line with these observations, in a recent abstract reporting on a population-based study from Tromsø on the same matter, body height was found to be a risk factor for first VTE in both women and men.[54] However, in this study, adjustment for body height did attenuate the risk difference for a first VTE between men and women up to the age of 70 years, whereas this risk difference in persons older than age 70 years did not change.[54]

In short, body height is a well-established VTE risk factor that could partially explain the observed higher VTE risk in men; however, this does not seem to be the full explanation.

4 | OBESITY, VISCERAL AND LIVER FAT, AND THEIR EFFECTS ON METABOLISM AND SUBSEQUENT INFLAMMATION IN RELATION TO COAGULATION AND VTE RISK

Over the past several decades, important insights have been obtained in the pathogenesis of arterial or also called atherosclerotic thrombotic events. Inflammation and dysregulation of metabolism seem intertwined, playing a key role in the pathogenesis, and have received much attention.[55] Although classically VTE and arterial thrombotic events have been considered separate diseases, it has been established that they share several risk factors such as inflammation.[56-58] Although mechanisms are not yet understood, inflammation has been well recognized as a risk factor for VTE. Especially overwhelming inflammatory states are strongly associated with an increased VTE risk. Well-known examples include sepsis-induced disseminated intravascular coagulation, the antiphospholipid syndrome, inflammatory bowel disease, and the recently described COVID-19-associated coagulopathy is a timely issue.[59,60]

Whether low-grade inflammation as is observed in obesity and metabolic syndrome is of relevance in VTE pathogenesis, as in the case of arterial thrombotic disease, is largely unknown and has not been widely studied. High body mass index and obesity are well-established VTE risk factors.[61] Its important components, total body fat and amount of visceral fat, have been associated with increasing procoagulant levels.[62,63] In addition, higher liver triglyceride content (a marker of fatty liver disease) has been found to be associated with increases of coagulation factor IX, beyond body fat and visceral adipose tissue.[63] In another study, the prevalence of nonalcoholic fatty liver disease was approximately three times higher among VTE cases than in controls.[64] Moreover, important differences in body fat distribution between men and women have been described, where women have more body fat overall, yet in men the proportion of visceral and liver fat is higher,[65] which also seems the case in women with PCOS.[66-68] However, it is not known whether these differences contribute to the difference in VTE risk.

Further studies are needed investigating obesity, visceral and liver fat, and their effects on metabolism and subsequent inflammation in relation to coagulation and VTE risk. Investigations assessing these mechanisms and the significance of sex differences, in light

of the higher risk in men are of interest. In addition, given the high prevalence of PCOS and increasing prevalence of obesity and disorders of fatty liver, these mechanisms are definitely of interest, and a better understanding could result in improved prevention or management strategies of VTE.

5 | ISTH CONGRESS REPORT

During the ISTH Congress of 2021, several interesting abstracts were presented that relate to the focus of this state-of-the-art review. In line with previous studies, Oakes et al. analyzed data from a large study population of transgender persons using testosterone ($n = 923$) and showed that although erythrocytosis as a consequence was common (up to one in five persons), the risk of thromboembolic events seemed low.[69]

Chulkov and colleagues highlighted the important relationship between obesity and coagulation in young adults. Higher levels of leptin were associated with higher levels of fibrinogen and plasminogen activator inhibitor-1 in persons with an unhealthy metabolic profile.[70] In a similar scope, the close relation between coagulation and inflammation was further evaluated by Pallares Robles et al., who showed an interesting interaction between FXI activity and thrombo-inflammation and lipid metabolism.[71]

The study by Houghton and collaborators provides further insight in the mechanism that may explain increased risk of VTE in taller persons. They showed that reduced calf pump function as a measure of stasis was associated with the risk of ipsilateral deep vein thrombosis.[72]

6 | SUMMARY AND FUTURE DIRECTIONS

In summary, men have a higher intrinsic VTE risk than women, regardless of age. To date, this difference has not been explained. Body height is a well-established risk factor for VTE but only seems to contribute partially to the observed higher VTE risk in men. Exogenous use of estrogens (combined with progestogens) increases the risk of VTE both in women and transwomen. Exogenous use of testosterone is associated with a slightly increased VTE risk in men and more robust data on use in transwomen are needed.

Overall, little is known on the relevance of levels of endogenous sex hormones and (sex-specific) VTE risk. Inflammation and dysregulation of metabolism are important determinants of arterial thrombotic risk and seem also of interest with respect to underlying mechanisms in VTE. Populations at higher risk of arterial thrombotic disease in which dysregulation of endogenous hormones and metabolism are key features, such as women with PCOS and subjects with differences in body fat distribution including liver fat disposition, form interesting target groups for future research. Overall better understanding of these mechanisms could result in improved (sex-specific) prevention and management strategies of VTE.

AUTHOR CONTRIBUTIONS

Luuk J. J. Scheres, Astrid van Hylckama Vlieg, and Suzanne C. Cannegieter wrote the manuscript and approved the final version.

RELATIONSHIP DISCLOSURE

The authors report no conflict of interest.

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