

REVIEW ARTICLE

Sex Hormone Influences on Venous Thrombotic and Cardiovascular Risk

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SUMMARY

Thrombosis is a recognized complication of sex hormone therapy, which includes hormone replacement for deficiencies, contraceptive therapy, treatment of heavy menstrual bleeding, gender-affirming hormone therapy, suppression of ovulation, oncologic hormone therapy, and assisted reproduction. This review examines the effects of sex hormones on hemostasis and the vasculature and summarizes current evidence on thrombotic risk, including the effects of hormone formulation, thrombophilias, previous thrombosis, and common clinical factors. Practical guidance on the prevention and treatment of hormone-associated venous thromboembolism, as well as on perioperative care of patients receiving sex hormone therapy, is also provided.

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N Engl J Med 2026;394:1514-28.
DOI: 10.1056/NEJMr2202438
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SEX HORMONE THERAPY MAY INCREASE THE RISK OF VENOUS THROMBOEMBOLISM (VTE) and cardiovascular events. Sex hormone therapy includes sex hormone replacement for deficiencies (e.g., those associated with hypogonadism of menopause and andropause), contraceptive therapy, treatment of heavy menstrual bleeding, gender-affirming hormone therapy for transgender and gender-diverse persons (those with a gender identity that does not align with their recorded sex at birth),¹ suppression of ovulation, oncologic hormone therapy, and assisted reproduction. We review the effects of estrogen, progestogens (physiologic progesterone and synthetic progestins),² and testosterone, as used for treatment in these contexts, on hemostasis, the vasculature, and the risk of thrombosis. We also provide practical guidance on the prevention and management of hormone-associated VTE, as well as on perioperative care of patients receiving sex hormone therapy. Information related to assisted reproduction and oncologic hormone therapy is provided in the Supplementary Appendix, available with the full text of this article at NEJM.org. By better understanding sex hormone influences on thrombotic risk, clinicians can provide evidence-based information to help make informed, shared decisions with patients.

HORMONE FORMULATIONS

Combined oral contraceptives typically consist of ethinyl estradiol and a progestin (Table 1). Newer formulations have lower doses of ethinyl estradiol than previous formulations. Nonoral combined hormonal contraceptives include transdermal patches and vaginal rings. Progestin-only contraceptives include oral formulations, levonorgestrel-releasing intrauterine systems, implants, and injections. Hormone-replacement therapy formulations typically consist of 17 β -estradiol (hereafter termed estradiol) that is identical to that produced by the human ovary. For persons with a uterus, progestogen is added to prevent estrogen-induced endometrial

hyperplasia or cancer; for cisgender women without a uterus, estradiol alone is used. Cisgender men with hypogonadism are treated with testosterone (Table 1).

Gender-affirming hormone therapy for transfeminine persons (those who were assigned male sex at birth but whose sense of self is female or on the feminine spectrum³) consists of exogenous estrogen, often with an antiandrogen to reduce testosterone levels and allow for lower doses of estrogen (Table 1).¹ Progestogens can suppress testosterone, and anecdotal reports suggest improved breast development and mood when progestogens are added to gender-affirming hormone therapy. However, evidence for this improvement is limited, and data extrapolated from research on postmenopause in cisgender persons suggest that the combination of progestogens with estrogen may increase the risks of breast cancer, VTE, and stroke.^{1,4} Gender-affirming hormone therapy for transmasculine persons (those who were assigned female sex at birth but whose sense of self is male or on the masculine spectrum³) consists of exogenous testosterone. Transmasculine persons may also use combined or progestin-only hormones for menstrual suppression, contraception, or both. In addition, hormones are used as suppression therapy in breast and prostate cancers and in assisted reproduction.⁵ Details about mechanisms of action and thrombosis are provided in Table 2 for sex hormone therapy and in Table S1 in the Supplementary Appendix for assisted reproduction and cancer treatment.

INFLUENCES ON HEMOSTATIC VARIABLES AND THE VASCULATURE

The cause of VTE is related to Virchow's triad of venous stasis, hypercoagulability, and effects on the vasculature. The effects of hormone therapy on levels of individual hemostatic variables are modest; although changes are often statistically significant, values usually remain within normal ranges.⁹ The increased thrombotic risk with hormone therapy probably results from a combination of effects on multiple hemostatic variables and on the vasculature (Fig. 1). Most of the data on the effects on hemostatic variables are derived from studies involving cisgender persons.

Blood coagulation occurs as a series of complex steps, usually initiated by vessel injury, that involve activation of coagulation factors and end

in the generation of thrombin and the formation of a cross-linked fibrin clot. This process is modified by positive and negative feedback loops. Prevention of excess thrombus formation involves negative modulation by naturally occurring inhibitors, and dissolution of a fibrin clot results from activation of the fibrinolytic system.

The effects of estrogen on coagulation activation and fibrinolysis are shown in Figure 1 and listed in Table 2.^{6,9,10} These effects are influenced by the estrogen dose and structure. For example, in users of combined oral contraceptives with the same progestogens, higher ethinyl estradiol doses as compared with lower doses are associated with increased markers of hemostatic activation, decreased protein S levels, and increased acquired activated protein C resistance (APCR), which causes a diminished response to activated protein C, a natural anticoagulant agent involved in the inactivation of clotting factors Va and VIIIa. In transgender and gender-diverse persons who receive gender-affirming hormone therapy, oral ethinyl estradiol combined with cyproterone acetate is associated with increased effects on acquired APCR and protein S, as compared with cyproterone acetate combined with either transdermal or oral estradiol or cyproterone acetate alone.^{9,11} Although most of the hemostatic effects of combined hormonal contraceptives appear to be driven by the estrogen component, progestogens potentiate these effects (Fig. 1 and Table 2).⁶ For example, combined oral contraceptives containing cyproterone, drospirenone, gestodene, or desogestrel progestogens are associated with higher levels of acquired APCR, factor VII activity, and prothrombin fragment 1+2 (a marker of coagulation activation) and greater decreases in protein S levels than combined oral contraceptives containing levonorgestrel.⁹ Similar hemostatic effects have been seen with the transdermal vaginal ring^{6,12} and the ethinyl estradiol–norelgestromin patch.¹² The levonorgestrel-releasing intrauterine system is not associated with acquired APCR.^{6,13}

For hormone-replacement therapy, prothrombotic changes are less pronounced with oral estradiol than with conjugated equine estrogen¹⁴ and are either absent or not as pronounced with transdermal estradiol replacement,¹⁵ perhaps because of avoidance of the hepatic first-pass effect. A lesser effect on APCR and prothrombin fragment 1+2 generation is reported with micronized progesterone than with other progestogens.¹⁵

Table 1. Types of Hormone Therapy and Formulations.*

Type of Hormone Therapy	Estrogen	Progestogen	Other Hormones
Combined hormone therapy†			
Combined oral contraceptives			
First generation	Ethinyl estradiol	Norethindrone, ethynodiol diacetate, lynestrenol, norethynodrel	—
Second generation	Ethinyl estradiol	Levonorgestrel, lynestrenol	—
Third generation	Ethinyl estradiol	Desogestrel, gestodene, norgestimate‡	—
Fourth generation or unclassified	Ethinyl estradiol, estrogen valerate, estradiol, estetrol	Cyproterone acetate, drospirenone, segesterone acetate, trimegestone, dienogest, nomegestrol acetate, drospirenone	—
Transdermal therapy	Ethinyl estradiol	Norelgestromin, levonorgestrel	—
Vaginal ring	Ethinyl estradiol	Etonogestrel, segesterone acetate	—
Progestin-only therapy			
Oral therapy	—	Norethindrone, desogestrel, drospirenone	—
Parenteral therapy	—	DMPA	—
Subdermal implant	—	Etonogestrel, levonorgestrel	—
Intrauterine system	—	Levonorgestrel	—
HRT for cisgender women			
Oral therapy	17β-Estradiol, estradiol valerate, conjugated equine estrogens	Micronized progesterone (Prometrium), pregnane derivatives (dydrogesterone, medrogestone, chlormadinone acetate, cyproterone acetate, MPA), norpregnane derivatives (nomegestrol acetate, promegestone, trimegestone, segesterone acetate), nortestosterone derivatives	—
Transdermal patch or gel	17β-Estradiol	Progestogen may or may not be included	—
Low-dose vaginal therapy	17β-Estradiol	—	—
Testosterone therapy for hypogonadal cisgender men and transmasculine persons§			
Oral therapy	—	—	Testosterone undecanoate
Transdermal therapy	—	—	Testosterone gel, testosterone enanthate or cypionate
GAHT for transfeminine persons			
Estrogen therapy¶			
Oral or sublingual therapy	17β-Estradiol	—	—
Transdermal gel or patch	17β-Estradiol	—	—
Parenteral therapy	Estradiol valerate, estradiol cypionate	—	—
Antiandrogen therapy	—	—	Spirolactone, cyproterone acetate, finasteride, GnRH agonist
Progestogen therapy	—	Micronized progesterone, MPA	—

* DMPA denotes depot medroxyprogesterone acetate, GAHT gender-affirming hormone therapy, GnRH gonadotropin-releasing hormone, HRT hormone-replacement therapy, and MPA medroxyprogesterone acetate.

† Combined hormone therapy may be used for noncontraceptive indications.

‡ Formulations with norgestimate are sometimes classified with second-generation combined oral contraceptives.

§ Additional therapy may be indicated for menstrual suppression, contraception, or both.

¶ Ethinyl estradiol and conjugated equine estrogens are no longer recommended for transfeminine persons. Progestins are not recommended in the guidelines but may be used on an individualized basis. Cyproterone acetate is currently not available in the United States.

Whereas administration of physiologic levels of testosterone does not affect levels of hemostatic variables,⁷ supraphysiologic therapy has been associated with a sustained decrease in the level of fibrinogen and an increase in the hematocrit level. Although an increased hematocrit level may increase blood viscosity, the association between testosterone-induced erythrocytosis and VTE is not clear.

As shown in Figure 1, estrogen also affects the vasculature through receptors in endothelial, vascular smooth-muscle, and myocardial cells that promote vasodilatation and antiinflammatory and antioxidant actions.^{16,17} Androgen receptors are found in vascular endothelial and smooth-muscle cells, and testosterone has both protective and injurious effects on the vasculature.¹⁸

THROMBOTIC RISK WITH HORMONE THERAPY

The interactive graphic shows guidelines for managing the thrombotic risk associated with hormone therapy, and guidance is provided in each section below. Generally, a patient-centered approach to prescribing hormone therapy should involve informed, shared decision making that involves consideration of the indication; the individual patient's risk of thrombosis, risk tolerance, and preferences; the cost of treatment; and goals relating to management options. With limited data, decision making is difficult. Discussing the risk of VTE with the patient is complicated, because many studies report the relative risk, but the patient's understanding of the risk may be improved when it is presented as an incidence.¹⁹ VTE is a multifactorial disease, and risk factors, including a personal or family history of VTE, further increase the risk of thrombosis with hormone therapy. In addition, the absolute risk of VTE that is associated with a specific hormonal agent increases with age. The baseline annual incidence of VTE is approximately 0.1 case per 1000 persons at the age of 20 years, 0.5 case per 1000 at the age of 40 years, and 8 cases per 1000 at the age of 80 years.^{20,21} Cardiovascular disease is similarly multifactorial, with the risks associated with hormone therapy depending on age and the nature and number of risk factors, as well as the type of hormone therapy.²² In addition, there is uncertainty about how

to handle different combinations of risk factors that have not been explicitly studied.

Limitations also affect interpretation of the literature. Many studies have evaluated the VTE risk associated with different generations of combined oral contraceptives. This approach has limitations because the thrombogenicity of combined oral contraceptives varies according to the estrogen dose and the progestins used, and this variability may not be a classwide effect. In addition, the populations studied differ over time, and the categorizations of some combined oral contraceptives are not consistent among studies. The literature evaluating the risk of VTE with gender-affirming hormone therapy in transgender and gender-diverse persons is challenging to interpret because most studies have not standardized the incidence of VTE to person-years of follow-up, and various combinations of exogenous estrogen and antiandrogen medications have been used, so the VTE rates cannot be directly compared between drug formulations. In reviewing the data on the thrombotic risk with hormonal cancer therapy, one should keep in mind that this risk has not typically been used as a primary end point in studies, which limits confidence in the accuracy and completeness of this information.

If a patient has a personal or family history of thrombosis or clinical risk factors and the health care provider is uncertain about how to proceed, consideration should be given to consulting a physician with expertise in thrombosis in order to determine the duration of anticoagulant therapy, safe hormonal options, and the potential role of thromboprophylaxis. Persons with cardiovascular risk factors for whom hormonal cancer therapy is indicated may benefit from referral to a cardio-oncologist.

ESTROGEN AND PROGESTOGEN THERAPY IN CISGENDER PERSONS

Users of combined oral contraceptives have a higher risk of VTE than nonusers (adjusted relative risk, 3.5; 95% confidence interval [CI], 2.9 to 4.3) (Table 3).³³ Because the baseline incidence of VTE in the age group most likely to use combined oral contraceptives is 1.9 to 3.7 cases per 10,000 person-years, this increased relative risk is acceptable for most patients.^{23,24} For example, in one study evaluating ethinyl estradiol at a dose of 30 to 40 μg with levonorgestrel, 6.2 VTE events per

 An interactive graphic is available at [NEJM.org](https://www.nejm.org)



Table 2. Sex Hormone Action and the Mechanism of Thrombosis.*

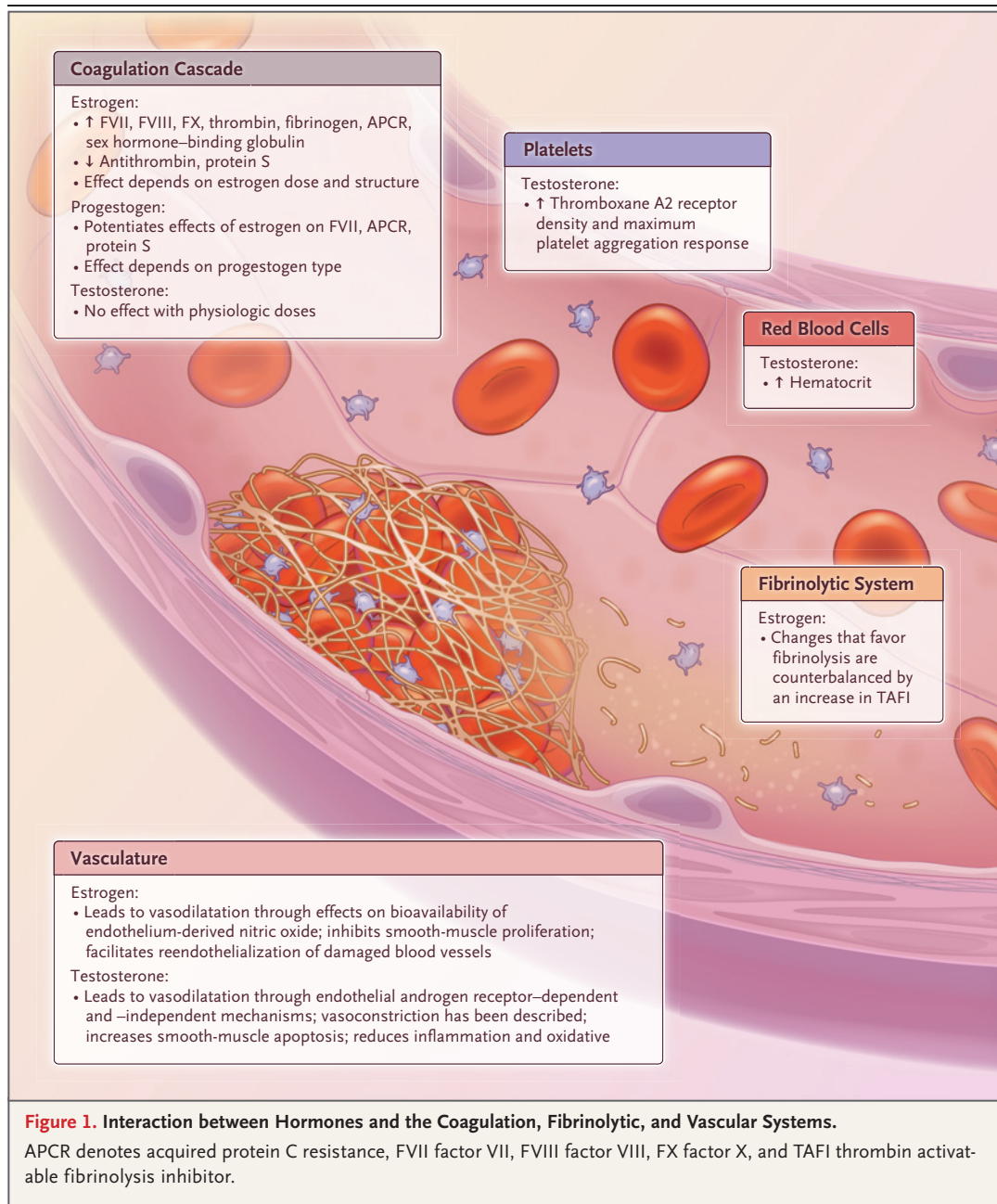
Hormone Type	Therapeutic Uses	Sex Hormone Action†	Mechanism of Thrombosis
Estrogen	Contraception, management of menstrual bleeding, GAHT, HRT	When used for contraception, estrogen exerts negative feedback on gonadotropin secretion, stabilizes the endometrium to prevent irregular shedding and breakthrough bleeding, and increases the potency of the progestogen component (see below). In women with abnormal menstrual bleeding, estrogen helps stabilize the endometrial lining; in postmenopausal women, it replaces estrogen the body no longer makes. Estrogen is used in GAHT for development of secondary sex characteristics.	The procoagulant effect of estrogen is mediated through decreased levels of inhibitors of coagulation (e.g., protein S, antithrombin, and tissue factor pathway inhibitor) and increased production of coagulation factors (e.g., fibrinogen, prothrombin, factor VII, factor VIII, and factor X), as well as through development of acquired APCR, which is a lack of response to APC, a protein that normally helps prevent blood from clotting excessively. Decreased levels of PAI-1 may lead to decreased fibrinolysis, but this effect may be counterbalanced by increased levels of TAFI. ⁶
Progestogen	Contraception, management of menstrual bleeding, GAHT, HRT	When used for contraception, progestogens inhibit ovulation through negative feedback on the hypothalamic–pituitary–ovarian axis and have local effects on cervical mucus and the endometrium. Continuous exposure to synthetic progestins leads to endometrial glandular atrophy and control of menstrual bleeding, whereas DMPA works through endometrial effects and inhibition of gonadotropin secretion from the pituitary.	Progestogens potentiate the effects of estrogen on factor VII, APCR, and protein S, with the effect dependent on the progestogen dose and type. ⁶
Testosterone	HRT, GAHT	Testosterone is given to replace hormones not produced in persons with hypogonadism or for secondary sex characteristics as part of GAHT.	Supraphysiologic therapy is associated with a sustained decrease in the fibrinogen level and increase in the hematocrit level; testosterone increases platelet thromboxane A2 receptor density and the maximum platelet aggregation response. ⁷

* APC denotes activated protein C, APCR activated protein C resistance, PAI-1 plasminogen activator inhibitor 1, and TAFI thrombin activatable fibrinolysis inhibitor.

† The information on sex hormone action is from Okwuosa et al.⁵ and Hu et al.⁸

10,000 exposure-years were reported.²⁶ Different risks are reported with other formulations of combined oral contraceptives (Table 3). Lower doses of ethinyl estradiol (20 to 30 μg) with levonorgestrel are associated with a risk of VTE that is twice as high as that among persons who do not use hormone therapy; some other progestin types may further increase the risk (Table 3).^{23,25,34} One meta-analysis estimated an incidence of 7.6 VTE events, 11.1 VTE events, and 10.6 VTE events per 10,000 women per year for levonorgestrel, desogestrel, and drospirenone, respectively, when used with ethinyl estradiol at a dose of 30 to 40 μg .³⁴ Fewer data are reported for transdermal patches and vaginal rings, but they carry a thrombotic risk that is similar to or greater than the risk with combined oral contraceptives containing levonorgestrel or norgestimate (Table 3).^{25,26,35,36}

Progestogen-only contraceptives are also associated with thrombotic risk that varies according to the dose and formulation. A number of small studies suggest that the VTE risk with depot medroxyprogesterone acetate is two times as high as the VTE risk without contraceptive use,^{27,37} whereas a Danish registry study suggests an increase in the risk by a factor of 5.7 in persons who use depot medroxyprogesterone acetate.²⁵ The risk of VTE is not increased with the levonorgestrel-releasing intrauterine system and is either not increased or only minimally increased with low-dose progestin pills.²⁵⁻²⁸ Fewer data have been reported for progestin-only implants, but they are associated with a small increase in risk (adjusted incidence rate ratio, 2.4; 95% CI, 1.4 to 4.0), as compared with the risk for nonusers.²⁵ With the higher oral progestin doses typically



used in women with heavy menstrual bleeding, the VTE risk is five to six times as high as the risk for nonusers.²⁸

Hormone-replacement therapy regimens used in menopausal women carry a lower relative risk of VTE than contraceptive hormones.³⁰ However, the absolute VTE risk in this group may be similar to or higher than that among younger persons using contraceptive hormones because the baseline incidence of VTE increases with age (Table 3).

In a meta-analysis that compared the VTE risk among users of hormone-replacement therapy with the risk among nonusers, the risk appeared to be higher among women using combined oral estrogen-progestogens (odds ratio for use vs. nonuse, 2.4; 95% CI, 1.9 to 2.9) than among those using oral estrogens alone (odds ratio, 1.4; 95% CI, 1.3 to 1.5)³⁰ and was also higher in the first year of hormone-replacement therapy than in subsequent years.³⁸ No increase in thrombotic

Table 3. Risk of VTE with Hormone Therapy in Cisgender Persons.*

Type of Hormone Therapy	Baseline Incidence of VTE (95% CI)†	Adjusted Risk with Hormone Use vs. Nonuse (95% CI)‡	Incidence of VTE with Hormone Use (95% CI)
Combined hormone therapy			
Combined oral contraceptives§			
Overall	Unexposed population: 1.9–3.7 ^{23,24} , 2.0 (1.9–2.1) ²⁵ <i>no. of events/10,000 person-yr</i>	3.5 (2.9–4.3) ³³	6.2 events/10,000 exposure-yr ⁶
Ethinyl estradiol, 20 µg, plus levonorgestrel	—	2.5 (1.3–4.6) ²⁵	5.0 events (1.4–12.5)/10,000 person-yr ²⁵
Ethinyl estradiol, 20 µg, plus desogestrel	—	6.3 (5.2–7.6) ²⁵	12.8 events (9.6–16.9)/10,000 person-yr ²⁵
Ethinyl estradiol, 20 µg, plus gestodene	—	5.8 (4.8–7.0) ²⁵	15.4 events (11.2–20.6)/10,000 person-yr ²⁵
Ethinyl estradiol, 20 µg, plus drospirenone	—	4.9 (3.2–7.3) ²⁵	6.7 events (3.5–11.7)/10,000 person-yr ²⁵
Ethinyl estradiol, 30–40 µg, plus norethisterone	—	2.24 (1.12–4.51) ²³	2.9 events/10,000 exposure-yr ³
Ethinyl estradiol, 30–40 µg, plus levonorgestrel	—	3.6 (3.2–4.0) ²⁵	7.6 events (6.6–8.6)/10,000 person-yr ²⁵
Ethinyl estradiol, 30–40 µg, plus norgestimate	—	5.4 (4.3–6.9) ²⁵	13.2 events (8.4–19.7)/10,000 person-yr ²⁵
Ethinyl estradiol, 30–40 µg, plus desogestrel	—	7.9 (6.0–10.3) ²⁵	16.2 events (11.6–22.2)/10,000 person-yr ²⁵
Ethinyl estradiol, 30–40 µg, plus gestodene	—	6.7 (5.6–7.9) ²⁵	14.7 events (11.6–18.3)/10,000 person-yr ²⁵
Ethinyl estradiol, 30–40 µg, plus drospirenone	—	5.8 (4.3–7.8) ²⁵	13.6 events (9.0–19.7)/10,000 person-yr ²⁵
Ethinyl estradiol, 30–40 µg, plus cyproterone	—	5.9 (4.3–7.8) ²⁵	11.6 events (7.0–17.9)/10,000 person-yr ²⁵
Ethinyl estradiol, 50 µg, plus NEA	—	6.24 (2.95–13.2) ²³	10.2 events/10,000 exposure-yr ²³
Ethinyl estradiol, 50 µg, plus levonorgestrel	—	4.49 (2.94–6.85) ²³	9.3 events/10,000 exposure-yr ²³
Estradiol plus noregestrol or dienogest	—	3.6 (1.9–6.7) ²⁵	5.0 events (2.3–9.7)/10,000 person-yr ²⁵
Transdermal contraceptives	Unexposed population: 2.0 ²⁵	5.0 (2.1–12.0) ²⁵	8.1 events (1.5–25.1)/10,000 person-yr ²⁵
Vaginal ring	Unexposed population: 2.0 ²⁵	4.5 (3.1–6.5) ²⁵	8.0 events (4.6–12.8)/10,000 person-yr ²⁵
Progestin-only therapy			
Oral (low dose for contraception)			
Overall	General population, 25–29 yr of age: 2.4 ²¹	0.9 (0.6–1.5) ²⁷	2.2 events/10,000 person-yr¶
Desogestrel	Unexposed population: 2.0 ²⁵	1.8 (1.4–2.3) ²⁵	3.6 events (2.8–4.7)/10,000 person-yr ²⁵
Oral (higher dose for management of bleeding in women <50 yr of age ²⁶)	General population, 25–29 yr of age: 2.4 ²¹ ; 45–49 yr of age: 5.4 ²¹	5.3 (1.5–18.7) ²⁸ 5.9 (1.2–30.1) ^{28,34*}	General population, 25–29 yr of age: 12.7 events/10,000 person-yr¶; 45–49 yr of age: 28.6 events/10,000 person-yr¶
Injectable DMPA	Unexposed population: 2.0 ²⁵ ; general population, 25–29 yr of age: 2.4 ²¹	5.7 (3.5–9.3) ²⁵ 2.7 (1.3–5.5) ²⁷	11.9 events (4.4–25.6)/10,000 person-yr ²⁵ 6.5 events/10,000 person-yr¶

Intrauterine system	Unexposed population: 2.0 ²⁵ ; general population, 25–29 yr of age: 2.4 ²¹	1.0 (0.8–1.1) ²⁵ 0.6 (0.2–1.5) ²⁷	2.1 events (1.7–2.6)/10,000 person-yr ²⁵ 1.4 events/10,000 person-yr [¶]
Subdermal implant	Unexposed population: 2.0 ²⁵	2.4 (1.4–4.0) ²⁵	3.4 events (1.7–6.3)/10,000 person-yr ²⁵
HRT in cisgender women			
Oral estrogen alone	Unexposed population: 16.0 ²⁹	1.4 (1.3–1.5) ^{28,30}	—
Overall	—	1.5 (1.4–1.6) ²⁹	8 additional events/10,000 women in 1 yr ²⁹
Conjugated equine estrogen	—	1.3 (1.2–1.4) ²⁹	4 additional events/10,000 women in 1 yr ²⁹
Estradiol	Unexposed population: 16.0 ²⁹	2.4 (1.9–2.9) ³⁰ 1.7 (1.7–1.8) ²⁹	—
Oral estrogen plus progestogen	Unexposed population: 17 ³¹ ††	2.1 (1.9–2.3) ²⁹	35 events/10,000 person-yr ³¹ ‡‡ 18 additional events/10,000 women in 1 yr ²⁹
Overall	—	1.7 (1.6–1.9) ²⁹	12 additional events/10,000 women in 1 yr ²⁹
Conjugated equine estrogen plus MPA	—	1.4 (1.1–1.9) ²⁹	7 additional events/10,000 women in 1 yr ²⁹
Conjugated equine estrogen plus NG	—	1.2 (0.98–1.4) ²⁹	—
Estradiol plus MPA	—	1.7 (1.6–1.8) ²⁹	11 additional events/10,000 women in 1 yr ²⁹
Estradiol plus dydrogesterone	—	1.4 (1.0–2.0) ²⁹	—
Estradiol plus NEA	General population, 50–54 yr of age: 11.8 ²¹	0.96 (0.88–1.04) ²⁹	11.3 events/10,000 person-yr [¶]
Estradiol plus NG or estradiol plus drospirenone	—	—	—
Transdermal estrogen alone	General population, 50–54 yr of age: 11.8 ²¹	0.86 (0.73–1.01) ²⁹	—
Overall	—	0.93 (0.65–1.33) ³²	11 events/10,000 person-yr [¶]
Micronized progesterone	—	2.42 (1.84–3.18) ³²	28.3 events/10,000 person-yr [¶]
Norpregnane derivatives (norgestrel acetate or promegestone)	—	1.37 (0.97–1.93) ³²	16.5 events/10,000 person-yr [¶]
Pregnane and nortestosterone derivatives	—	—	—

* NEA denotes norethisterone acetate, NG norgestrel, and VTE venous thromboembolism.

† The baseline incidence of VTE in the study population (i.e., before exposure to hormone therapy) was reported if the data were available in the individual studies. In the case of missing data on the baseline incidence of VTE, the incidence in the general population was reported. Age groups are listed when information from the general population is used. One limitation of reporting the relative risk and absolute risk of VTE with hormone use from the same study is that only the relative risk may be adjusted for other baseline characteristics.

‡ Values indicate the relative risk, unless otherwise specified; for HRT in cisgender women, values are adjusted odds ratios.

§ Reported estimates of risk in the study by Lidegaard et al.²³ (see Table 3) include only those in which VTE events were confirmed by evidence of anticoagulation therapy in a national registry of medicinal products.

¶ Since data were not available, the VTE incidence with hormones was calculated as the baseline VTE incidence in the population multiplied by the relative risk of hormone exposure.

One limitation of the calculation strategy is that it does not take into account the fact that some persons in the baseline population were using hormone therapy.

|| Values indicate the relative risk.

** Values indicate the adjusted odds ratio.

†† The incidence is for the placebo group in the Women's Health Initiative randomized, controlled trial.³¹

‡‡ The incidence is for the treatment group in the Women's Health Initiative randomized, controlled trial.³¹

risk is apparent with nonoral estradiol, such as the transdermal patch, when used alone.³⁰ When combined with a transdermal estrogen, micronized progesterones and most pregnane progestogens do not appear to carry a thrombotic risk, but other progestogen formulations may do so (Table 3).³² Hormone-replacement therapy for premature ovarian insufficiency involves higher doses of either a transdermal patch or an oral formulation. Data on the VTE risk in this context are lacking.³⁹

The use of combined hormonal contraceptives is associated with small increases in the risk of myocardial infarction and the risk of stroke as compared with nonuse, with higher doses of estrogen and the presence of cardiovascular risk factors associated with greater risk. However, these outcomes are very uncommon in the population of women who use contraceptives.

Whether there is an association between hormone-replacement therapy and cardiovascular disease has been controversial. The risk depends on individual cardiovascular risk factors, and these are common among women of menopausal age. In general, as long as these risks are appropriately managed, they are not considered contraindications to hormone-replacement therapy, and the cardiovascular risk is not increased when therapy is started shortly after menopause or in women younger than 60 years of age, for whom the baseline risk is low.^{4,22,40} Some guidelines suggest that the potential risks outweigh the benefits for women with previous myocardial infarction or stroke (see the interactive graphic).^{4,41}

HORMONE THERAPY IN TRANSGENDER AND GENDER-DIVERSE PERSONS

Various estrogen and antiandrogen formulations and doses are used in transfeminine persons, depending on cost, access, medical conditions, and preference. Common exogenous estrogens are oral or transdermal estradiol and injectable estradiol valerate. Ethinyl estradiol and conjugated equine estrogens are no longer recommended because of the higher thrombotic risk and greater variability of hormone levels in the blood with these estrogens than with other formulations (see the interactive graphic).⁴² Transdermal estradiol has a better risk profile than oral estrogens, with studies showing either no VTE events or only a small number of events.^{43,44} Cyproterone acetate

is a strong synthetic antiandrogen with progestogen-like activity, and spironolactone is a mineralocorticoid receptor antagonist and potassium-sparing diuretic that is a weak antiandrogen without progestogen activity (Table 1).

In database studies, the incidence of VTE among transfeminine persons was higher than that among cisgender women or cisgender men⁴⁵ and was similar to the incidence among cisgender women who were using hormone-replacement therapy (42.8 cases per 10,000 person-years).⁴⁶ A possible signal indicating an increased risk of arterial events in transfeminine persons receiving gender-affirming hormone therapy has been noted, but high-quality data are lacking.⁴⁷ Study limitations include variations in information on cardiovascular risk factors, differences in formulations, and confounding factors of socioeconomic status and stress associated with being part of a marginalized group.

In a retrospective cohort of 816 transfeminine persons with 10,152 person-years of follow-up, the average annual VTE incidence was 0.4%, with the highest incidence (2.6%) in the first year after the initiation of gender-affirming hormone therapy.⁴⁸ However, events occurred primarily in persons receiving oral ethinyl estradiol (100 μ g per day) before the standard practice changed to the use of transdermal estradiol in persons older than 40 years of age.^{42,45,49} VTE events have been reported with other regimens that include oral estradiol or estradiol valerate with cyproterone acetate or spironolactone, but in absolute terms, the risk is low and acceptable for most persons.⁵⁰ For example, in a retrospective cohort study involving 676 transfeminine persons who received oral estradiol and spironolactone, an incidence of 7.8 VTE events per 10,000 person-years was reported.⁵¹

In some transmasculine persons who use exogenous testosterone, additional hormone therapy is indicated for suppression of the menstrual cycle, contraception, or both. Since direct data for guidance of management are sparse, however, we rely on estimates of VTE risk extrapolated from the cisgender population.

PERSONS WITH RISK FACTORS FOR THROMBOSIS

Although some guidelines state that combined hormonal contraceptives are contraindicated in persons with known thrombophilia (see the interactive graphic),⁵² we believe that the data indicate

an opportunity for a more nuanced perspective. Among cisgender women with thrombophilias who are considering combined hormonal contraceptives, the absolute VTE risk remains modest if the thrombophilia is mild, such as in the case of heterozygosity for the factor V Leiden mutation or a prothrombin gene mutation. In women who use combined hormonal contraceptives, family cohort studies show a higher VTE risk among those with severe thrombophilia, such as an antithrombin, protein C, or protein S deficiency, than among those with mild thrombophilia (4.3 to 4.6 events vs. 0.5 to 2.0 events per 100 pill-years).⁵³ These data suggest that combined oral contraceptive therapy could be considered in women with low-risk thrombophilias and no other risk factors for VTE who have unacceptable side effects from other reliable forms of contraception.

Regardless of thrombophilia status, a family history of VTE increases the thrombotic risk by a factor of 2 to 4, so patients faced with making a decision about hormone therapy do not necessarily need to undergo thrombophilia testing if their risk tolerance for thrombosis is low.⁵⁴ Among persons receiving hormone-replacement therapy, the risk of VTE in those who have factor V Leiden is 6.7 times as high (95% CI, 3.1 to 14.5) as the risk in those who do not.³¹ Fewer data are available to inform decision making about hormone-replacement therapy for persons with more severe thrombophilias. Avoidance, at least of oral estrogens, is usually suggested (see the interactive graphic).⁴¹ Overall, the limited data on hormone therapy in transgender and gender-diverse persons with inherited thrombophilias are reassuring, and in most cases, thrombophilia screening before initiation of therapy is not recommended.⁴³

In cisgender women receiving hormone therapy, other risk factors associated with an increased incidence of VTE, such as older age, obesity, and smoking, and transient risk factors, such as surgery, hospitalization, and immobilization or fracture, should be considered in assessing the risk of VTE.⁵⁵ Among persons 45 to 49 years of age, the adjusted relative risk of VTE associated with combined oral contraceptive use is 6 times as high as the risk among those 15 to 19 years of age.²³ One study that examined the effect of body-mass index (BMI; the weight in kilograms divided by the square of the height in

meters) on the risk of VTE showed that relative to the risk among women with a normal BMI (<25) who did not use oral contraceptives, the risk of VTE was 11.6 times as high among those with overweight (BMI, 25 to <30) who used oral contraceptives and 23.8 times as high among those with obesity (BMI, ≥30) who used oral contraceptives.⁵⁶ Although laboratory tests of hypercoagulability, such as D-dimer tests, have been proposed as a surrogate for baseline risk, more research is needed.⁵⁷ The effects of various hormonal formulations may differ according to risk factors. Fewer data are available for transfeminine persons who have additional risk factors, but the data that are available suggest that the risk for such persons is similar to that for cisgender women.⁵⁸

PERSONS WITH PREVIOUS HORMONE-ASSOCIATED THROMBOSIS

After an initial 3 to 6 months of anticoagulant therapy, the decision to stop or continue therapy for secondary VTE prevention is guided by estimates of the risk of recurrence with the cessation of anticoagulant therapy (as well as the risk of bleeding with continued therapy). The risk of recurrence is based largely on whether the VTE event was unprovoked or associated with transient or persistent risk factors. Hormone therapy is traditionally considered an intermediate or minor risk factor for VTE.⁵⁹ For VTE with transient nonsurgical risk factors (including hormone therapy), the rate of recurrence of VTE at 24 months after cessation of anticoagulant therapy is 4.2% (95% CI, 2.8 to 4.6) per person-year, as compared with 0.7% (95% CI, 0 to 1.5) per person-year for surgically associated VTE and 7.4% (95% CI, 6.5 to 8.2) per person-year for unprovoked VTE.⁵⁹ However, this risk of recurrence is probably affected by patient characteristics, the type of hormone therapy at the time of the initial VTE, and the presence or absence of other VTE risk factors.

In two meta-analyses, the rate of VTE after cessation of anticoagulant therapy among persons with an initial contraceptive-associated event was low, at 1.22 to 1.57 events per 100 person-years.^{60,61} This low risk of recurrence probably reflects, in part, the younger age and overall better health of women using these hormones. Thus, for many women with contraceptive-related VTE, long-term anticoagulant therapy is not re-

quired. Among women who are older or have other VTE risk factors, the risk of recurrence is less certain and may be higher.⁶² Similar data for VTE associated with hormone-replacement therapy are lacking.

Few studies have evaluated the risk of recurrent VTE among women with previous VTE who are receiving hormone-replacement therapy. A randomized trial comparing oral estradiol and norethisterone with placebo in postmenopausal women with previous VTE was stopped early because of an increased risk with hormone therapy (the incidence of VTE was 10.7% vs. 2.3%; risk ratio, 7.8; 95% CI, 1.0 to 60.5).⁶³ A cohort study that followed 1023 postmenopausal women with previous VTE, of whom 130 received hormone therapy, confirmed an increased risk of recurrence with oral estrogen (adjusted hazard ratio, 7.2; 95% CI, 1.6 to 31.2) but not with transdermal estrogen (adjusted hazard ratio, 0.9; 95% CI, 0.9 to 3.0).⁶⁴

Data support the safety of continuing hormone therapy after VTE in cisgender women while they are receiving anticoagulant therapy.^{65,66} These results can probably be extrapolated to transfeminine persons, for whom discontinuation of gender-affirming hormone therapy is often not possible from the patient's perspective, given the effects on psychological well-being and quality of life.

In patients with strong risk factors for VTE or those with previous VTE in whom anticoagulant therapy has been discontinued, hormone therapy should be stopped or switched to a nonthrombotic formulation. Continued use of combined hormonal contraceptives after cessation of anticoagulant therapy was associated with a risk of recurrence that was 2.4 times as high (95% CI, 1.2 to 5.0) as that among nonusers in one study⁶⁵ and, in another study, with a recurrence rate that was 4.6 times as high (95% CI, 1.9 to 11.5) as that among women in the same age group who stopped using oral contraceptives.⁶⁷ For the treatment of heavy menstrual bleeding, a levonorgestrel-releasing intrauterine system may be used if indicated, but caution is needed with higher-dose oral progestin therapy.

TESTOSTERONE THERAPY

Testosterone is used for the treatment of cisgender male hypogonadism and as gender-affirming

hormone therapy for transmasculine persons (Table 1). The effect of testosterone replacement on the risk of VTE remains poorly understood. Large observational studies have had inconsistent results, from no increase in risk to a risk that is increased by a factor of 4,⁶⁸ with some of the studies suggesting an increased risk in the first 3 to 6 months after initiation of treatment.^{69,70} In a meta-analysis involving 5050 cisgender men from 13 randomized trials in which testosterone therapy was compared with placebo or an active agent (e.g., growth hormone or gonadotropin-releasing hormone antagonists), no increase in the risk of VTE (relative risk, 1.03; 95% CI, 0.49 to 2.14) was noted.⁷¹ However, the quality of evidence was judged to be low, and insufficient data were available to examine important variables, such as age, route of administration, duration of therapy, and prescription indication.

Most meta-analyses have shown that the risk of cardiovascular events with testosterone therapy is no higher than that with placebo,⁷² although certainty is limited by low study quality and lack of long-term follow-up data. However, in a multicenter, randomized, double-blind, placebo-controlled trial involving 5246 men with hypogonadism who had preexisting cardiovascular disease or were at high risk for cardiovascular disease, testosterone gel replacement was noninferior to placebo with respect to major adverse cardiac events (hazard ratio, 0.96; 95% CI, 0.78 to 1.17) over a mean (\pm SD) follow-up period of 33.0 \pm 12.1 months.⁷³

Fewer data address the risk of VTE or cardiovascular disease among transmasculine persons. In one meta-analysis, the pooled relative risk was 1.3 (95% CI, 1.0 to 1.6) for stroke, 1.7 (95% CI, 0.8 to 3.6) for myocardial infarction, and 1.4 (95% CI, 1.0 to 2.0) for VTE.⁴⁷

PERIOPERATIVE MANAGEMENT OF HORMONE THERAPY

The hemostatic effect of combined hormonal contraceptives mostly resolves within 2 to 4 weeks after cessation of hormone therapy.⁷⁴ On the basis of surrogate biomarker data with expert opinion and consensus, the American College of Obstetricians and Gynecologists (ACOG) has recommended stopping combined hormonal contraceptives 4 to 6 weeks before major surgery

KEY POINTS

SEX HORMONE INFLUENCES ON VENOUS THROMBOTIC AND CARDIOVASCULAR RISKS

- Oral contraceptives with a combination of hormones increase the risk of venous thromboembolism (VTE) by a factor of 3.5, and hormone-replacement therapy increases the risk by a factor of 2; in most cases, the absolute risk is low.
- For persons at increased risk for VTE who are considering contraception, a levonorgestrel-releasing intrauterine system or low-dose progestin may be preferred. Information about risks associated with progestin implants is limited. For hormone-replacement therapy or gender-affirming hormone therapy, transdermal estradiol is preferred. Micronized progesterone is associated with a low thrombotic risk.
- Most persons with hormone-associated VTE can stop anticoagulant therapy after 3 to 6 months, as long as hormone therapy has been stopped.
- Ongoing, well-managed anticoagulant therapy can allow for continued use of hormone therapy (contraceptive therapy, hormone-replacement therapy, or gender-affirming hormone therapy).
- Testosterone replacement does not increase the risk of VTE; less is known about the risk in the transmasculine population than in the general population, and information about the cardiovascular risk is limited.

when prolonged immobilization is anticipated, with resumption of therapy when physical activity has returned to a nearly normal level.⁷⁵ For decisions about perioperative use of menopausal hormone therapy, ACOG recommends an individualized risk assessment based on clinical risk factors and shared patient–physician decision making.⁷⁵ However, we advocate for continuing hormone therapy around the time of surgery (instead of stopping therapy) and using thromboprophylaxis, depending on the clinical scenario. Stopping hormones weeks ahead of a surgery so that the thrombotic risk can return to baseline is often impractical, with the added downside of increased risks of pregnancy, menstrual bleeding, and resumption of menopausal symptoms during the preoperative period and postoperative recovery. The Caprini risk score for VTE prophylaxis includes hormone therapy, along with other risk factors for VTE.⁷⁶ We recommend the same strategy for transfeminine persons. Two guidelines note the absence of good-quality data suggesting that transgender and gender-diverse persons should stop gender-affirming hormone therapy before and after surgery. However, the decision to continue such therapy should be based on an informed discussion of the benefits and drawbacks of doing so, as well as appropriate use of thromboprophylaxis (see the interactive graphic).^{42,77}

FUTURE DIRECTIONS

Evidence-supported strategies are needed for discussing the risks of hormone therapy with patients, including transgender and gender-diverse persons. Awareness among health care providers of the risk of thrombosis with gender-affirming hormone therapy is important.⁷⁸ Further research is needed to better understand the VTE risk with hormone therapy in persons with multiple risk factors, younger women with premature ovarian insufficiency, and those with previous VTE who are considering transdermal hormone-replacement therapy. Additional data are needed to provide more definitive statements on the safety of the progestogen subdermal implant. Finally, data are still needed to characterize the risks of VTE and cardiovascular disease among transgender and gender-diverse persons, especially those who are older or who have additional risk factors for thrombosis.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank Drs. Nathalie Saad and Lorraine Lau at the University of Calgary for providing content expertise in the area of transgender persons, gender-affirming hormone therapy, and hormone-replacement therapy.

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