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Literature review

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Hormone replacement therapy in women with history of thrombosis or a thrombophilia

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Abstract

Findings from the Women's Health Initiative (WHI) randomised placebo-controlled trial (RCT) were published at the beginning of this century. They suggested that hormone replacement therapy (HRT) use increased the risk of cardiovascular disease and venous thromboembolism including pulmonary embolism and deep vein thrombosis The findings led to a decline in HRT prescriptions and negative publicity about the use of HRT for women with significant menopausal symptoms. Subsequent studies have shown that the risk of thrombosis with HRT relates to whether estrogen is combined with a progestogen and the route of administration of estrogen. In healthy women with no background medical problems, transdermal hormone replacement is not associated with an increased risk of thrombosis. However, much less is known about the safety of various HRT preparations in women with a high background risk of thrombosis. These cases can often be challenging for clinicians with uncertainties around testing for thrombophilia, use of anticoagulation and striking a balance between the risks and benefits of prescribing HRT. This article will review the mechanism of thrombosis with differing types of HRT and present the evidence from the relevant trials. The article will also present the evidence that specifically relates to women with a personal history of thrombosis or thrombophilia (heritable and acquired) to enable clinicians to better individualise the risk assessment for each woman requesting HRT and understand the role of thrombophilia screening or concomitant anticoagulation in such situations.

Keywords

hormone replacement therapy, menopause

Practice Points

VTE risk among HRT users depends on the route of estrogen administration and the type of progestogen.

Oral HRT preparations, rather than transdermal HRT, are associated with an increased VTE risk among postmenopausal women.

Data about risk of VTE with long-term HRT use in women with history of thrombosis or thrombophilia are limited and thus need to be interpreted with caution.

Every woman should have a personalised VTE risk assessment prior to the initiation of HRT.

Testing for thrombophilia prior to starting HRT is not routinely required and should be considered based on individualised risk assessment.

The presence of a heritable/acquired thrombophilia is not an absolute contraindication to HRT, the transdermal route should be used to reduce the risk of VTE.

A previous history of VTE does not mean an absolute contraindication to HRT but alternative treatments should be offered, and a clear discussion of the benefits versus risks documented if HRT use is considered.

Concomitant use of anticoagulation may be necessary in women with high risk of recurrence of thrombosis and this should be considered in conjunction with a Haematology team.

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Introduction

Vasomotor symptoms such as hot flushes and night sweats during menopausal transition can be debilitating. These symptoms are experienced by approximately 75% of women and can lead to a significant decrease in quality of life.[1] The most effective treatment for these symptoms is systemic hormone replacement therapy (HRT). HRT can be administered either as estrogen only (if the woman does not have a uterus) or as combined estrogen and progestogen therapy (if the woman retains her uterus as unopposed estrogen can lead to endometrial hyperplasia and/or cancer). Testosterone can be added to these two hormones for treatment of hypoactive sexual desire disorder. While the estrogen and progestogen components can be administered by oral or non-oral routes, testosterone is only administered by non-oral route.

At the beginning of the 21st century, findings from the Women's Health Initiative (WHI) randomised placebo-controlled trial (RCT) were published suggesting that HRT increased the risk of venous thromboembolism (VTE) including pulmonary embolism (PE) and deep vein thrombosis (DVT). These findings presented a challenge for prescribing HRT to those women who experienced debilitating menopausal symptoms and had significant risk factors for VTE or a personal history of VTE.

Subsequent studies have shown that the risk of thrombosis with HRT relates to whether estrogen is combined with a progestogen and the route of administration of estrogen. In healthy women with no background medical problems, transdermal hormone replacement is not associated with an increased risk of thrombosis. However, much less is known about the safety of various HRT preparations in women at high risk of thrombosis. This literature review will review the evidence for the use of HRT in women with a hereditary or acquired thrombophilia or a personal history of VTE.

Hormone useage and risk of thrombosis

That estrogen containing oral contraceptives (COCs) have an altering effect on various pathways associated with clotting is well known. The physiological changes to these pathways are concisely described in reviews by Tchaikovski[2] and Gialeraki et al.[3] with the alterations including increasing levels of circulating procoagulant factors such as fibrinogen, prothrombin, factors VII, VIII and X as well as a decrease in antithrombin and protein S,[4] that results in greater tendency towards thrombosis.[3] Combined oral contraceptives have been shown to induce acquired resistance to Activated Protein C (APC)[4] and that increased risk of VTE seems to be more obvious, a nearly 2-fold comparative increase in risk, with third generation oral contraceptives compared to second generation COCs.[2,5] When assessing the risk of VTE relating to COCs, the route of administration does not seem to make a difference. A significant contribution to the procoagulant state seems to be the first pass metabolism of both estrogens and progestogens in the liver which leads to increased production of clotting factors.[4] However, COCs that are administered via alternate routes, transdermal or vaginal ring, appear to maintain the same prothrombotic effect.[2] This is likely related to the potent effect of ethinyl estradiol on thrombin generation.[6]

In contrast, the underlying mechanism relating hormone replacement therapy (HRT) to increased risk of thrombosis is less well understood. HRT induces changes in both the prothrombotic and anticoagulant pathways.[7] Contrary to the evidence for COCs, the route of HRT administration is an important determinant of VTE risk. A prospective cohort study investigated the effect of oral HRT and transdermal HRT, compared to non-users, on serum thrombin generation. Thrombin generation was felt to be useful as an overall marker for the coagulation pathway activation and as a surrogate for VTE risk. It showed that oral HRT generated thrombin was generated much more rapidly and to much higher levels when compared to transdermal HRT and non-users. Transdermal HRT resulted in thrombin levels similar to non-users. Oestrone levels, a potent inducer of liver protein synthesis, were significantly higher in oral HRT compared to transdermal HRT and correlated with peak thrombin production for oral HRT. This suggests that liver thrombin synthesis because of high oestrone levels following oral HRT, but not transdermal HRT, plays a significant role in the increased risk of VTE associated with HRT.[8] Other studies into the effect of transdermal HRT on the thrombotic pathway have shown little or no effect on haemostasis, the coagulation cascade or fibrinolysis,[7,9] whereas oral HRT consistently increases activated protein C resistance and increases prothrombin.[10,11]

Oral HRT and VTE

Women that use oral HRT (estrogen alone and estrogen with progestogen) are exposed to a 2–4 fold increased risk of VTE compared to non-users.[12] The risk of VTE is highest in the first 6–12 months of use and decreases thereafter.[3,13,14] The Women's Health Initiative trial showed that HRT users are at increased risk for VTE and cardiovascular events[15] resulting in the trial stopping early after a mean 5.2 years of follow-up. Several other randomised control trials were also closed prematurely as they showed an increased risk of VTE in HRT users.[14,16–18] A meta-analysis of over 250 000 women treated with oral HRT (both estrogen only HRT and combined HRT) showed an increased risk of VTE (OR 1.72 [1.47–2.01]).[9] When oral estrogen only HRT was independently assessed, the risk of VTE was found to be slightly less raised (OR 1.43, 95% CI 1.34–1.53) but

nevertheless significantly increased as compared to non-users.[9] In comparison to estrogen only HRT, the use of oral combined HRT increased the risk of VTE significantly more (OR 2.35 [1.9–2.9]).[9]

The meta-analysis by Rovinski et al. treated all estrogen only HRT as a single group and did not stratify according to pharmacological component. The VTE risk according to estrogen composition of HRT has been shown to differ between conjugated equine estrogens (CEE) and esterified estrogens (EE).[19] The risk of VTE with CEE is nearly twice as high as that of EE containing HRT (OR, 1.78; 95% CI, 1.11–2.84).[19]

When comparing estrogen only HRT and combined HRT, the risk of VTE is consistently higher in the combined HRT group.[3] The risk of VTE according to the progestogen content of the HRT has been assessed in several studies. The ESTHER study, a multicentre case-control study, showed that VTE risk differed between the different progestogen components of HRT irrespective of the route of estrogen administration.[13] It demonstrated that oral micronised progesterone and pregnane derivatives did not increase the thrombotic risk (OR 0.7, 95% CI 0.3–1.9, and OR 0.9, 95% CI 0.4–2.3, respectively), whereas norpregnane derivatives were associated with an increased VTE risk (OR 3.9, 95% CI 1.5–10.0).[20] In summary, the higher VTE risk associated with progestogen use should not be considered as a class effect but assessed based on the specific component prescrcibed.[13] Tibolone, a synthetic steroid used for the treatment of menopausal symptoms,[21] does not seem to be associated with an increased risk of VTE in comparison to other oral HRT (adjusted odds ratio 1.02, 95% confidence interval 0.90–1.15).[22]

Transdermal HRT and VTE risk

Transdermal HRT has the benefit of avoiding first pass liver metabolism and as such the effect on the coagulation cascade is much less.[23] Following the concern raised about the increased risk of VTE identified with HRT in the WHI study at the start of the century, further work was done into whether that effect was consistent across all forms of HRT. A retrospective study of women in France showed that the increased risk was associated with oral HRT and not transdermal HRT (OR, 3.5, 95% CI 1.8–6.8, vs. OR 0.9, 95% CI 0.5–1.6).[24] Since that study, there have been several other large prospective studies, including the Million Woman Study, that have demonstrated an increased risk of VTE with oral HRT but not with transdermal HRT.[25,26] A systematic review and meta-analysis found that when compared to non-users of HRT there seems to be no increase in risk of VTE when using transdermal HRT (OR 0.97, 95% CI 0.9–1.06). This remained true whether the HRT was estrogen-only (OR 0.95, 95% CI 0.81–1.10) or combined HRT (OR 0.92, 95% CI 0.77–1.09).[9] This analysis did not stratify risk according to the progestogen component of the non-oral HRT nor the estradiol component or dose.

The type of progestogen used in HRT has been associated with differing risk of VTE for oral HRT users.[26] With regards to the risk associated with progestogen type – it was shown that medroxyprogesterone increased the risk of VTE while micronised progesterone and dydrogesterone appeared to be safe.[9] Compared with cHRT with medroxyprogesterone, the use of dydrogesterone or norethisterone was associated with 44% and 20% lower VTE risks, respectively, (0.56, 0.45 to 0.69, $p < .001$, and 0.80, 0.71 to 0.89, $p < .001$).[22]

Similarly, for transdermal HRT, the progestogen component also seems to influence the risk of VTE. A recent meta-analysis showed that estrogen only transdermal HRT did not increase VTE risk but that in combined HRT, the risk of VTE depended on progestogen use. The meta-analysis found that there was no change in VTE risk in women using transdermal estrogen with micronised progesterone (RR 0.93, 95% CI 0.65–1.33), whereas norpregnane derivatives were associated with an increased VTE risk (RR 2.42, 95% CI 1.84–3.18).[27] This finding was confirmed by a systematic review into the effect of micronized progesterone, as part of cHRT, on venous and arterial thrombosis which found that micronized progesterone has a neutral thrombotic effect and does not increase the risk of primary or recurrent VTE.[28] This difference in risk may be explained by the observation that women using transdermal estrogens combined with norpregnanes were less sensitive to APC than non-users or users of transdermal estrogens combined with micronised progesterone.[29] The mechanism by which norpregnane derivatives with transdermal estrogens effect APC resistance remains unclear.[29] It has been reported that changes in free protein S (PS) and Tissue Factor Pathway Inhibitor (TFPI) with oral HRT may affect APC sensitivity. However, these markers have not been shown to be the different in users of transdermal estrogens combined with norpregnane derivatives and transdermal estrogen with micronised progesterone.[29] Studies have also found that micronized progesterone is associated with either neutral or beneficial effects on body weight, fasting glucose and insulin levels.[30] A RCT comparing the effect of micronized progesterone and medroxyprogesterone acetate on coagulation pathway factors when combined with transdermal estradiol found both progestogens had a neutral effect.[31] These data provide a biological explanation for the epidemiological evidence that the progesterone component of HRT remains an important consideration even when prescribing non-oral HRT.[26]

Although there is no robust RCT evidence available for the risk of VTE comparing the route of HRT administration in specific populations (such as women with thrombophilia), there is high quality, large scale epidemiological evidence which demonstrates that transdermal HRT, with

micronised progesterone, does not seem to be associated with an increased risk of VTE in such women. The use of dydrogesterone with transdermal estrogen does not seem to increase the risk of VTE although this analysis was based on very low numbers of women.[22]

Although data are limited, among women with thrombophilia and/or previous VTE, cardiovascular risk markers have not been found to change significantly with use of Levonorgestrel intrauterine system without estrogen.[32]

Women with a personal history of venous thrombosis

The only RCT in women with a personal history of VTE was stopped prematurely due to an increased incidence of VTE in women on HRT compared to placebo.[14] The EVTET study was stopped early based on an observation that showed a 10.7% incidence of new thrombotic events in HRT users with previous VTE vs. 2.3% in the placebo group.[9,14] It is important to note that the HRT used in the EVTET study was oral combined HRT. This is in contrast to the Menopause, Estrogen and Veins (MEVE) cohort study that found no increased risk of VTE recurrence in women with transdermal HRT (RR 1.0, 95% CI 0.4–2.4) when compared to oral HRT (RR 6.4, 95% CI 1.5–27.3).[33] The recent systematic review of vascular events when using micronized progesterone as part of cHRT found recurrent VTE risk was not affected by transdermal estradiol with micronized progesterone.[28] The Endocrine Clinical Practice Guideline states that 'A prior history of VTE confers the highest risk. If the patient has a known inherited coagulation defect, such as Factor V Leiden, oral HRT should be avoided because research has shown a high risk of VTE recurrence. A history of VTE due to pregnancy, oral contraceptives, unknown aetiology or blood clotting disorders poses a contraindication to any estrogen therapy, whereas VTE due to past immobility, surgery, or bone fracture would be a contraindication to oral but not necessarily transdermal MHT'.[34] The British Menopause Society in conjunction with Women's Health Concern recommend that 'In the presence of known risk factors for VTE, including personal history of VTE or family history of VTE, the combination of transdermal estrogen and micronised progesterone offers a safer option that is unlikely to significantly increase VTE risk above the individual's intrinsic risk. Discussion with a haematologist should be considered in postmenopausal women at particularly high risk for VTE who are being assessed for HRT'.[35]

Any consideration about using HRT in women with previous DVT should be take into account the severity of menopausal symptoms, risk factors for VTE, circumstances at the time of past VTE, use of anticoagulants, medical comorbidities and where necessary a decision about treatment should be reached in liaison with the haematology team.

Women with a hereditary thrombophilia

Thrombophilias are conditions which can increase the risk of venous or arterial thrombosis. Thrombosis is a multifactorial condition with many well-established risk factors such as smoking, hypertension, obesity, surgery and malignancy.[36] Therefore, the role of thrombophilia screening prior to starting HRT is controversial.[37] The most common inherited thrombophilias are Factor V Leiden and Prothrombin 20210 gene mutation with Protein S deficiency, Protein C deficiency and Antithrombin deficiency being the rarer inherited conditions.[38,39]

Factor V Leiden. Activated factor V is an essential cofactor for the conversion of prothrombin (factor II) to thrombin in the common procoagulant pathway and activated factor V is inactivated by APC.[40] A variation in the factor V gene (G1691 A, known as factor V Leiden) leads to an increased APC resistance.[41] This inability to inactivate factor V results in a predisposition to thrombosis. Approximately 5% of the population carries at least one copy of the FVL gene[42] and one copy of the mutated gene appears to be present in approximately 18% of patients with venous thromboembolic events.[43] FVL and the combined oral contraceptive increases the risk of VTE by a factor of nearly 16 (OR 15.62; 95% CI 8.66–28.15)[44] and by a factor of 13 (OR 13.16; 95% CI 4.28–40.47) in women taking oral HRT.[44] A case-control analysis of patients enrolled in the Heart and Estrogen/Progestin Replacement Study (HERS) and the Estrogen Replacement and Atherosclerosis (ERA) trial found that both oral HRT usage and FVL heterozygosity each significantly increased the risk of VTE.[45] Women with FVL using HRT had an excess VTE risk of 14.1 (95% CI, 2.7–72.4) when compared to unaffected women using placebo.[45] A case-control study based on data gathered during a prospective cohort study found that the odds of having a VTE was 17 times higher (95% CI, 3.7–78) in women with FVL on combined HRT compared to unaffected women not on HRT.[46] The same study found that there was no increased risk of DVT with estrogen only HRT (OR, 1.7; 0.3–9.0).[46] Most of these studies mainly assessed the risks of women taking combined oral HRT and therefore extrapolation to non-oral and non-progestogen containing HRT should be avoided. Table 1

The combination of thrombogenic mutations and oral estrogen, with or without progestogen use, further increases the risk of VTE (OR 8.0, 95% CI 5.4–11.9) compared with women without mutations who did not use any treatment.[47] However, the review by Canonico et al.[47] reported that one study found no increased risk of VTE in women with FVL or Prothrombin gene G20210 A mutation

Table 1. Relative risk of venous thromboembolism in users and non-users of hormone replacement therapy for the most common heritable thrombophilias[37] (Adapted from Stevens et al., 2016).[37]

Inherited thrombophilia	Prevalence in population	Relative risk of VTE in non-users HRT (absolute yearly risk)	Relative risk of VTE in HRT users (absolute yearly risk)
Factor V Leiden heterozygous	2–7 %	3.48–5.51 (0.05–0.2%)	1.4–13.16 (1.6–5.97%)
Factor V Leiden homozygous	0.06–0.25%	6.79–19.29 (0.8%)	Uncertain
Prothrombin Gene G20210 A heterozygous	1–2%	2.25–3.48 (0.13%)	(2.85%)
Protein S deficiency	0.1–0.7%	9.6 (0.7–3.2%)	(2.3%)
Protein C deficiency	0.2–0.5%	10 (0.4–2.3%)	(2.96%)
Antithrombin deficiency	0.02%	10–30 (1.2–4.4%)	(5.73%)

when using transdermal estrogen.[47,48] A multicentre case-control study into the risk of VTE in women using oral HRT with thrombophilia found that the presence of Factor V Leiden increased the risk 3.4 times (2.0–5.8, 95% CI). In their analysis, the presence of a prothrombotic gene mutation and oral HRT resulted in a significantly increased risk of thrombosis compared to untreated women (OR 25.0, 95% CI 6.9–95.0).[38] Their analysis also demonstrated that the use of transdermal HRT did not increase the risk of VTE above non-users with the same thrombophilic mutation (OR, 4.4; 95% CI, 2.0 to 9.9; and OR, 4.1; 95% CI, 2.3 to 7.4, respectively).

Prothrombin G20210 A is the second most common inherited thrombophilia[49] with approximately 2% of the population as heterozygous carriers. A study assessing the risk of HRT and FVL or prothrombin gene mutation found that the presence of the prothrombin mutation was associated with a 4.8-fold increased VTE risk (95% CI 2.5–9.4) when using oral HRT. In contrast, transdermal HRT was associated with the same risk of VTE for women with the prothrombin gene mutation as non-users.[38]

Data about HRT use in women with other heritable thrombophilias are much more limited. In a prospective cohort study of asymptomatic carriers of deficiency of antithrombin, protein C or protein S, the annual incidence of venous thrombosis was 1.5% (95% CI 0.7–2.8) with approximately half being provoked.[50] There are no RCT trial data on the thrombotic risk of oral or transdermal HRT in women with these inherited thrombophilias.

Testing for thrombophilia may be justified in women with a strong family history of VTE, such as multiple first-degree relatives affected by VTE under the age of 50 years. Criteria for thrombophilia testing as described in the British Journal of Haematology suggest that testing for a heritable thrombophilia is only indicated if a first-degree relative with venous thrombosis has been tested and the result is positive but only as it may aid counselling if a high-risk variant was identified. At that point, the prescriber should offer the woman transdermal HRT before offering testing as a negative thrombophilia screen result does not exclude an increased risk of venous thrombosis.[51] The British Menopause Society advises that testing for thrombophilia may be justified in limited circumstances such as women with a strong family history of VTE (multiple first-degree relatives affected by VTE under the age of 50 years), recurrent VTE or a positive family history of a specific thrombophilia. Women with a personal history of VTE within the last 12 months, who are over 50 years old, should be screened for an underlying medical cause, such a as malignancy, as well as thrombophilia.[1] While many women with inherited thrombophilias will safely be able to use transdermal HRT this should be at the lowest effective dose. In women with multiple pre-existing risk factors for VTE and significant menopausal symptoms, transdermal HRT could be considered alongside the thromboprophylaxis/anti-coagulation treatment that has been advised or initiated by the haematology team.

Women with an acquired thrombophilia

Antiphospholipid syndrome (APS) has been described as the 'sine qua non' example of an acquired thrombophilia.[37] APS is defined by the development of venous and/or arterial thromboses, often multiple, and pregnancy morbidity (mainly, recurrent miscarriage but also preterm delivery), in the presence of antiphospholipid antibodies. Estimates predict that about 5% of the populations have circulating antibodies, but the incidence of APS is only five cases per 100,000 people. This is because the diagnosis requires clinical and laboratory findings to be simultaneously present.[52,53] Unfortunately, no robust data for VTE risk from HRT use exist for women with APS.[54,55]

Testosterone

The major androgens found in women are dehydroepiandrosterone sulphate (DHEAS), dehydroepiandrosterone (DHEA), androstenedione, testosterone and dihydrotestosterone

(DHT). DHEAS, DHEA and androstenedione act as prohormones, requiring conversion to testosterone or DHT to express their androgenic effects.[56] The ovaries and the adrenal glands are the major sources of androgen synthesis in women.[57] Several randomised, placebo-controlled clinical trials suggest that testosterone therapy significantly improves sexual function in postmenopausal women with decreased libido.[58]

Data in both male and female patients have suggested that transdermal testosterone therapy may be associated with a transient increased risk of thromboembolism within the first 6 months of use.[59,60] The data are of low quality, however, a recent meta-analysis of testosterone use in men found no increased risk of VTE with transdermal testosterone.[61] A study into transdermal testosterone prescribed as gender affirming hormone therapy with masculinising intent, thus at much higher doses than in HRT, found no cases of thrombosis in 428 transgender men with a median duration of 577 days.[62] Case reports have suggested a link with testosterone treatment for libido and an increased risk of VTE in women with a heritable thrombophilia.[63] A study into thrombophilia and testosterone treatment including 79 men and 9 women (indication of improving libido) found a significant increased risk of VTE in women with thrombophilia: FVL heterozygosity (OR 17.7, 95% CI 2.02–155.3), for prothrombin gene heterozygosity (OR 11.72, 95% CI 1.51–90.9) and for high anticardiolipin antibody IgM (OR 16.7, 95% CI 1.9–146.2).[64] These VTE events occurred at a median duration of 3 months from beginning transdermal testosterone. The conclusion of the authors was that the risk to benefit ratio for transdermal testosterone use for low libido in women with a thrombophilia was high.[64] This conclusion was based on a very low number of women and therefore the data should be interpreted with caution. The Global Consensus Position Statement on the Use of Testosterone Therapy for Women advises that 'A nonsignificant trend for an increased risk of deep venous thrombosis has been seen with testosterone therapy; however, the role of concurrent estrogen therapy in possible venous thrombosis risk cannot be excluded (Level I, Grade A)'.[65]

Conclusion

VTE risk among HRT users depends on the route of estrogen administration. Indeed, consistent trial data shows that oral, rather than transdermal HRT, are associated with an increased VTE risk among postmenopausal women. In addition, the type of concomitant progestogen has emerged as a contributing factor to the VTE risk in women using HRT.[13]

Although there is plenty of evidence that transdermal HRT does not increase VTE risk in healthy women with no background problems, data in women with history of thrombosis or thrombophilia are limited. Extrapolation of results from one group to another should be done with caution.

VTE risk from HRT needs to be individualised to each woman's personal history. A previous history of VTE does not mean an absolute contraindication to HRT, however, careful counselling of the risks and consideration of alternative treatment should be included in any treatment decision-making process. If the decision is to proceed with HRT, then low dose transdermal estrogen, with oral micronised progesterone or levonorgestrel intrauterine system where required, should be the preferred formulations. Although the dose of estradiol does not seem to be directly linked to VTE risk,[22] rather the route is most important, using the lowest dose required seems prudent from first principles. It is important to note that data regarding use of levonorgestrel intrauterine system in women at risk of thrombosis are limited and larger studies are desirable.

Concomitant use of anticoagulation may be necessary in some cases with high risk, but this decision should be made in liaison with a haematologist. Testing for thrombophilia prior to starting HRT is not routinely required but if a woman has a strong personal history or family history of VTE, then this should be considered.[66] The presence of a heritable/acquired thrombophilia is not an absolute contraindication to HRT, but transdermal treatment should be used after individualised assessment of benefits and risks.

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GM and VT devised, wrote and reviewed the manuscript.

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