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Venous Thromboembolism and Hormone Replacement Therapy

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Venous Thromboembolism and Hormone Replacement Therapy

This is the third edition of this guideline, originally published in 1999 and revised in 2004.

1. Introduction

Exogenous estrogens used in the combined oral contraceptive pill have long been recognised as causative factors in the pathogenesis of venous thromboembolism (VTE).[1,2] Hormone replacement therapy (HRT), either sequential or continuous combined, also exposes women to exogenous estrogen and a number of case–control studies and prospective randomised trials have shown an increase in the relative risk of VTE in women on estrogen-containing HRT.[3] In particular, the Women's Health Initiative (WHI) study in the USA assessed the major health benefits of oral HRT (0.625 mg conjugated equine estrogen and 2.5 mg medroxyprogesterone acetate [MPA] daily) in a randomised placebo-controlled clinical trial with more than 8000 women in each arm and confirmed an increase in the risk of pulmonary embolism (hazard ratio 2.13, 95% CI 1.39–3.25).[4] On the available evidence, however, a substantial risk of VTE may relate only to oral and not to transdermal preparations.[3] Thus, the risk of VTE and the type of preparation must be considered in women starting or continuing HRT.

2. Identification and assessment of evidence

This guideline was developed using the standard methodology for developing RCOG Green-top Guidelines.[5–7] Original articles for the evidence base for this guideline were obtained following a computer search for 'hormone replacement' as a keyword and also in combination with 'venous thrombosis' or 'deep venous thrombosis' (DVT) or 'pulmonary embolism' or 'thrombophilia' applied to Medline (1966 to week 1, 2010), Embase (1980 to week 1, 2010), Evidence-based Medicine Reviews, the Cochrane Database of Systematic Reviews and the Database of Abstracts of Reviews of Effectiveness to the last quarter of 2009. This was complemented by hand searching for individual references identified from these original articles. The levels of evidence and the grade of recommendations used in this guideline are detailed in RCOG Clinical Governance Advice No. 1a–c.[5–7] Where possible, recommendations are based on, and explicitly linked to, the evidence that supports them. Areas lacking evidence are highlighted and annotated as good practice points.

3. What are the changes in coagulation factors associated with HRT?

The mechanism whereby oral HRT provokes an increased risk of VTE is unclear. ✓

The haemostatic system is altered by the menopause, with increases in a number of coagulation factors which are known to be associated with vascular risk.[8–11] There have been a variety of assessments of the changes in coagulation factor levels associated with HRT. Not all of the changes that have been observed are prothrombotic. In particular, a reduction in fibrinogen[12] and a reasonably consistent decrease in plasminogen activator inhibitor-1 levels have been observed,[13–20] suggesting an overall enhancement of fibrinolytic potential in those taking HRT. In addition, combination,[21–23] though not unopposed,[21,24,25] HRT may reduce factor VII levels. By contrast, oral HRT also reduces plasma levels of the natural anticoagulant protein S,[12,26] although a consistent effect on reducing antithrombin levels has not been seen.[23,27,28] Thus, the net effect of these changes must be considered. When considering the formation of venous thrombosis, the most clinically relevant laboratory assessments may be those relating to thrombin and fibrin generation. In this regard, although HRT may be associated with an increase in soluble fibrin generation,[18] there is no consistent evidence of an increase in thrombin generation.[13–20,29] Resistance to the effect of activated protein C (APCR) is also associated with venous thrombosis. Classically associated with inheritance of the factor V Leiden (FVL) mutation, such resistance can also occur in the absence of the FVL mutation as an acquired phenomenon.[30] This form of

resistance also relates to the level of thrombin generation.[31] There are two main methods of assessment of acquired APCR and there is consistent evidence that oral HRT is associated with an increase in resistance when assessed by activation of the extrinsic pathway of coagulation.[26,32–34] By contrast, no consistent effect has been shown when the resistance is assessed by activated partial thromboplastin-based methods.[35–41] This is likely to relate to the differing sensitivities of the two methods to the plasma levels of coagulation factors. It is not clear, however, that higher APCR is associated with the occurrence of HRT-related VTE.[34] Higher C-reactive protein levels are associated with both VTE[42] and cardiovascular disease. Although estrogen-containing HRT does not increase all inflammatory markers,[44] it is associated with an increase in C-reactive protein;[41,44] however, this effect may be ameliorated by the addition of progestogen.[45] By comparison, transdermal HRT appears not to be associated with such an increase in C-reactive protein[46] and also has a lesser effect on coagulation than oral preparations.[26,41] This may reflect the fact that oral preparations undergo first-pass hepatic metabolism and therefore have a greater effect on factors produced by the liver than transdermal preparations, which avoid the first-pass effect.[23,41]

4. How should VTE risk be approached when HRT is being considered?

All women commencing HRT should be counselled about the risk of VTE and the signs and symptoms of VTE. ✓

All women should be advised to access medical help rapidly if they suspect that they have developed a thrombosis. ✓

A recent systematic review of both observational studies and clinical trials examined the risk of VTE associated with the use of HRT in eight observational studies and nine clinical trials.[3] In the majority of studies, the endpoint was the first occurrence of idiopathic VTE. The clinical trial and the observational studies produced a similar odds ratio of VTE associated with oral estrogen, of 2.1 (95% CI 1.4–3.1) and 2.5 (95% CI 1.9–3.4), respectively. From a further UK observational study, a VTE incidence rate of 4.2/1000 patient-years was observed in a 50–79-year-old group never exposed to HRT.[47] This compares with an incidence rate of 5.8/1000 patient-years in women of a similar age exposed to combination HRT with conjugated estrogen. Reasonably comparable data from the US Women's Health Initiative (WHI) observational study[48] revealed a lower risk in those not exposed to HRT of 1.6/1000 patient-years (mean age 64.7 years), but again showed a higher rate of 2.4/1000 patient-years in those exposed to combination HRT with conjugated estrogen (mean age 60.7 years). Thus, there is consistent evidence to demonstrate an increased relative risk of VTE, although the absolute risk, particularly in the absence of other risk factors, is low. Overall, the risk of VTE increases with age,[49–52] with the absolute risk of VTE in women increasing particularly after the age of 45 years to around double that of younger women.[53–55] As noted below, the epidemiological data relate VTE to the 1st year of HRT exposure, thus age and estrogen alone cannot be responsible for all of the increased VTE risk with HRT. It is possible that the VTE risk also relates to other underlying conditions such as obesity[56] and thrombophilia.[57] Moreover, there is beginning to be some evidence that different HRT preparations (see section 5 below) may result in different VTE risks.

Evidence level 1+

Although information on transdermal preparations is limited, there are some data suggesting that transdermal therapy carries a lower risk of VTE than oral therapy, but the numbers studied have been small. The risk of VTE with transdermal compared with oral HRT is shown in Table 1. Of the six studies which provide some information,[49,58–62] all show non-significant risks associated with transdermal preparations, with studies reporting an odds ratio greater than one being confined to those with fewer than 10 exposed cases.[45,60,61] Consistent with this, Smith et al. did not find any significant risk associated with transdermal preparations irrespective of the dosage used (using 0.625 mg of estradiol as an index).[63] A systematic review of HRT, which pooled the results of four of the above studies, revealed a non-significant odds ratio of VTE in association with transdermal

Evidence level 2+

Table 1. Risk of venous thromboembolism with transdermal compared with oral hormone replacement therapy

Study	Year	Preparation	Transdermal exposed cases	VTE OR transdermal (95% CI)	Oral exposed cases	VTE OR oral (95% CI)
Scarabin et al.[56]	2004	Predominantly EE + P	25	0.9 (0.5–1.6)	31	3.6 (1.9–7.0)
Canonico[62]	2007	Predominantly EE + P	67	0.9 (0.4–2.1)	45	4.2 (1.5–11.6)
Guthann et al.[60]	1997	Oral CEE TD EE	7	2.1 (0.9–4.6)	20	2.1 (1.3–3.6)
Daly et al.[45]	1996	Oral EE/CEE TD EE	5	2.0 (0.5–7.6)	37	4.6 (2.1–10.1)
Douketis et al.[59]	2005	Not specified	3	0.8 (0.3–2.8)	24	2.7 (1.4–5.1)
Varas-Lorenzo et al.[61]	1998	TD not specified	6	2.3 (1.0–5.3)	–	–

FCEE = conjugated estrogen; CI = confidence interval; EE = esterified estrogen; OR = odds ratio; P = progestogen; TD = transdermal; VTE = venous thromboembolism.

estrogen of 1.2 (95% CI 0.9–1.7), with very little evidence of statistical heterogeneity.[3] However, this absence of thrombotic effect may not relate to all transdermal hormone therapy as an increased risk of VTE has been reported in association with a combined transdermal contraceptive containing 0.75 mg of estradiol.[64]

Evidence level 2+

Women starting or continuing HRT should be counselled with regard to the perceived benefits and possible risks for their individual situations, including consideration of alternative therapies.

A

A number of randomised controlled clinical trials have investigated the risks and benefits of HRT in postmenopausal women. Of these, the WHI study[4] was designed to assess the prevention of coronary heart disease in women taking combined conjugated equine estrogen and MPA. After 5.2 years of follow-up, the trial was stopped as there was an increased risk of coronary heart disease (hazard ratio 1.29, 95% CI 1.02–1.63), stroke (hazard ratio 1.41, 95% CI 1.07–1.85) and breast cancer (hazard ratio 1.26, 95% CI 1.0–1.59), as well as pulmonary embolism. The WISDOM trial was also designed with an emphasis on cardiovascular disease and dementia.[65] Although terminated early on account of the WHI trial, analysis at a median of 11.9 months of follow-up (with the mean age of those randomised 62.8 years) also revealed a significant increase in the number of major cardiovascular events and VTE associated with the combined therapy of conjugated equine estrogen and MPA. However, neither trial specifically examined those younger subjects taking combined oral HRT for perimenopausal symptom relief. In younger individuals, the WHI group has also reported a reduction in coronary artery calcification in women who were 50–59 years of age and receiving estrogen only.[66] From further analysis of WHI data,[48,67] it seems likely that, at worst, HRT in younger women may be neutral with regard to the risk of cardiovascular disease and may be associated with an overall reduction in all-cause mortality. However, an increased risk of VTE[48,67] and stroke[68] at all ages still seems a likely consequence of HRT. It is clear, however, that the final interpretation of the WHI data is still a matter of considerable debate and controversy.[69]

Evidence level 1+

5. Do HRT type and duration influence VTE risk?

The risks of VTE in association with HRT may be influenced by the type of preparation and the duration of its use.

✓

From the available evidence, the most convincing evidence relates to a greater risk in the 1st year of use than in subsequent years and a lack of continuing risk in those who have stopped HRT. Although requiring confirmation in larger studies, it also seems likely that there is a substantially lesser risk with transdermal compared with oral preparations and that the overall VTE risk with combination preparations may be influenced by the type of progestogen used.

5.1 *The influence of estrogen type*

The risk of VTE may be less with esterified estrogens compared with conjugated equine estrogen. **D**

There is very limited information on whether the thrombosis risk varies with the type of estrogen.[63] Although the risk of VTE may be less with esterified estrogens compared with conjugated equine estrogen,[63] there is still evidence of a significant VTE risk with both types of estrogen.[58]

Evidence level 2+

5.2 *The effect of combination HRT*

There may be a greater risk of VTE with combination therapy and definitive information on individual estrogen types is still lacking. However, the results to date suggest that therapy with estrogen alone is associated with a significant VTE risk. **C**

A number of studies allow some assessment of the potential influence of the addition of progestogen to estrogen therapy. For oral conjugated equine estrogen therapy, one study observed a significant VTE risk (OR 2.94, 95% CI 1.60–5.40) with the addition of progestogen to estrogen, while observing a non-significant risk with estrogen alone.[63] However, this study used unopposed esterified estrogen as the reference group for both comparisons and an assessment of the risk associated purely with the addition of a progestogen to conjugated estrogen (i.e. using conjugated estrogen alone as the reference group) was not calculated. Data derived from two WHI studies[4,70] show a non-significant increased VTE risk with conjugated equine estrogen alone, with a significant increase in risk observed in a separate study of combination therapy. A comparable observation was made in studies of the UK General Practice Research Database[71] when those receiving conjugated estrogen alone were compared with those receiving conjugated estrogen in combination with either MPA or norgestrel.[63] This comparison revealed a significantly higher hazard ratio in those exposed to combined therapy. Similarly, with oral estradiol, a non-significant risk has been observed with estradiol alone and either a non-significant (OR 1.50, 95% CI 0.91–2.47)[63] or significantly increased risk (OR 3.6, 95% CI 1.9–7.0)[58] with combination therapy. Other studies[49,50,59–61] (with the notable exception of that by Jick et al.[50]) employing a variety of preparations also report an increased VTE risk associated with combination therapy. Two of these five studies also reported an increased risk associated with estrogen alone.[49,50] A recent systematic review and meta-analysis[3] which included four of the above studies[49,50,60,61] as well as unpublished combined data on (predominantly) estradiol revealed a significant risk (with only moderate statistical heterogeneity) associated with estrogen alone (pooled OR 2.2, 95% CI 1.6–3.0) and no significant additional risk associated with the addition of progestogen to oral estrogen (pooled OR 2.6, 95% CI 2.0–3.2).

Evidence level 2++

5.3 *The influence of progestogen type*

There is preliminary information available from Canonico et al.[62] on the influence of particular progestogens on VTE risk. The group examined a combination of combined preparations including micronised progesterone, pregnane derivatives (dydrogesterone, medrogestone, chlormadinone acetate, cyproterone acetate and MPA) and norpregnane derivatives (nomegestrol acetate and promegestone), showing that micronised progesterone and pregnane derivatives may carry a lower thrombotic risk compared with norpregnane derivatives. These data on a differential risk varying by the type of progestogen need to be confirmed in further studies, with specific data also required on the VTE risk associated with newer progestogens such as drospirenone.

5.4 *VTE relationship to estrogen dose*

There is some evidence that the effect of estrogen therapy may be dose related. **D**

There is some evidence that the effect of estrogen therapy may be dose related, with no significant VTE risk associated with doses of oral estrogen of around 0.3 mg.[49,63,72] A number of studies,[49,50,58,60,72]

Evidence level 2+

while often examining a mixture of estrogen types, show a higher VTE risk with estrogen doses of ~1.25 mg or more (reporting ORs between 2.4 and 6.9) compared with 0.625 mg (with ORs between 1.7 and 4.3), although in many cases the confidence limits of these risks overlap. Interestingly, Smith et al.[63] described a significant dose–response relationship with conjugated estrogen but not with estradiol. Consistent with the results of Smith et al.,[63] Canonico et al.[62] describe no difference in risk in those receiving ≤1.5 mg oral or ≤50 micrograms transdermal (predominantly) estradiol preparations compared with the remainder of their study group. Overall, the results for conjugated equine estrogens are consistent with the demonstration that combined lower-dose HRT with conjugated equine estrogen produces no significant increase in prothrombin fragment 1+2 and a lesser reduction in antithrombin than higher-dose HRT.[27]

Evidence level 2+

5.5 Transdermal preparations

Transdermal preparations are associated with a substantially lower risk of VTE than oral preparations. ✓

As discussed above, the available evidence suggests that transdermal preparations are associated with a substantially lower risk of VTE than oral preparations.

5.6 Duration of therapy

The risk of VTE is highest in the 1st year of HRT use, with no evidence of continuing risk on stopping HRT. B

There is a clear association between VTE and duration of HRT use (Table 2), particularly with a recent systematic review showing a significantly higher risk in those who had been taking oral estrogen for less than 1 year compared with those who had been taking it for more than 1 year.[3] In this study, a combined odds ratio of 4.0 (95% CI 2.9–5.7) compared with 2.1 (95% CI 1.3–3.8) was observed.

Evidence level 2++

Table 2. Risk of venous thromboembolism with duration of use of hormone replacement therapy

Study	Year	Study type	Diagnosis	Exposed cases	Preparations	RR VTE <1 year (95% CI)	RR VTE >1 year (95% CI)	Comments
Jick et al.[50]	1996	CC	Objective first idiopathic VTE	7	CEE and EE ± P	6.7 (1.5–30.8)	2.8 (0.6–11.7)	≤1 year versus >1.1–4.9 years
Grodstein et al.[72]	1996	CC	Objective first idiopathic PTE	22	Not specified	2.6 (1.2–5.2)	1.9 (0.9–4.0)	<5 years versus ≥5 years
Daly et al.[49]	1996	CC	Non-objective first idiopathic VTE	44	EE and CEE ± P ± TD	6.7 (2.1–21.3)	4.4 (1.6–11.9)	6 months versus <1–2 years
Guthann et al.[60]	1997	CC	Non-objective first idiopathic VTE	35	EE and CEE ± P ± TD	4.6ff (2.5–8.4ff)	1.1 (0.6–2.1)	≤6 months versus >1 year
Varas-Lorenzo et al.[61]	1998	CC	Objective first idiopathic VTE	6	Not specified ± P ± TD	2.9 (1.2–6.9)	0 (0.0–4.1)	
Høibraaten et al.[87]	1999	CC	Objective VTE	45	EE ± P ± TD	3.5 (1.5–8.2)	0.7 (0.4–1.1)	
Douketis et al.[59]	2005	CC	Objective first idiopathic DVT	36	EE and CEE	1.9 (0.9–4.1)	1.2 (0.7–2.0)	
Smith et al.[63]	2004	CC	Objective first VTE	121	EE ± P	1.3 (0.6–2.8)	1.1 (0.5–2.2)	
Smith et al.[63]	2004	CC	Objective first VTE	86	CEE ± P	0.9 (0.4–2.0)	1.5 (0.7–3.3)	
Scarabin et al.[58]	2003	CC	Objective first idiopathic VTE	32	EE (majority) ±P	8.1 (0.9–74.4)	5.0 (1.2–20.4)	<1 year versus 13–30 months

Comparisons other than <1 year versus >1 year are as indicated in the comments section.
CC = case–control study; CEE = conjugated estrogen; CI = confidence interval; EE = esterified estrogen; P = progestogen; RR = relative risk; TD = transdermal; ± = may have included.

Indeed, two studies[49,60] provide data indicating that the highest risk may occur in the first 6 months of use (Table 2). Data from a WHI study[73] show a continuing (although decreasing) trend of risk with increasing duration of use, with a hazard ratio of 1.74 in year 3 and 1.70 in year 4. Scarabin et al.[58] also show a continuing significant risk (OR 2.5, 95% CI 1.0–6.3) at a duration of more than 4 years. The increase in risk in later years did not reach statistical significance in the studies by Daly et al.[49] at 3 years, Douketis et al.[59] after 4 years and Grodstein et al.[72] at 5 years.

Evidence level 2++

5.7 Past use of HRT

A pooled analysis of four studies in a recent systematic review revealed no significant pooled VTE risk with those who had used oral estrogen HRT in the past (OR 1.2, 95% CI 0.9–1.7).[3]

Evidence level 2++

6. What is the role of screening for heritable thrombophilia when assessing the VTE risk associated with HRT?

Universal screening of women for thrombophilic defects before prescribing or before continuing the prescription of HRT is inappropriate.

C

There is limited information on the natural history of thrombophilias, the mechanism of estrogen-associated thrombosis and how these two factors interact. The absolute risk of VTE with HRT is, however, low. The cost-effectiveness of screening women for thrombophilia has been examined in a number of at-risk clinical circumstances[74] and screening selected women before prescribing oral HRT may be the most cost-effective method. However, on the available evidence, universal screening of women for thrombophilic defects before prescribing or before continuing the prescription of HRT is inappropriate and should be discouraged.[75]

A number of case–control studies have examined the interaction between heritable thrombophilias and the risk of VTE with HRT. The ESTHER study examined the occurrence of a first idiopathic VTE in postmenopausal women and hospital controls (mean age ~61 years).[76] The vast majority of those on oral therapy at the time of the VTE event were using estradiol. For subjects carrying either the prothrombin 20210A (PT) or FVL mutation, the use of oral estradiol was associated with a 25.5-fold increased risk of VTE (95% CI 6.9–95.0, adjusted for age and body mass) compared with non-carriers not on HRT. The combination of any prothrombotic mutation and transdermal estrogen gave an odds ratio of 4.4 (95% CI 2.0–9.9), results similar to those observed for women with mutations not receiving HRT. Similar results were observed for individuals carrying only the FVL mutation, with an odds ratio associated with oral estrogen use of 16.4 (95% CI 4.3–62.2) and with transdermal estrogen of 4.6 (95% CI 1.6–13.8). Smith et al. studied the impact of first post-/perimenopausal VTE associated with the PT or FVL mutations and the use of either conjugated or esterified estrogen.[57] Joint exposure to conjugated estrogen and a thrombophilia mutation led to an odds ratio for VTE of 9.1 (95% CI 4.5–18.2) compared with controls with no mutation not using HRT. Perhaps owing to small numbers, a non-significant result was observed for the PT mutation alone (OR 2.4, 95% CI 0.6–9.3), although not for the FVL mutation alone (OR 14.8, 95% CI 6.7–32.8). In this study, exposure to esterified estrogen did not result in a significant increased risk of VTE. Joint exposure to esterified estrogen and a thrombophilia also resulted in a non-significant increased VTE risk with an odds ratio of 2.1 (95% CI 0.6–6.8) and a five-fold lesser risk than the combination of thrombophilia and conjugated estrogen. In a study by Lowe et al.,[77] women between 45 and 64 years of age using HRT had a significantly higher risk of VTE associated with increased APCR, low antithrombin or high factor IX levels. Extending this study, Rosendaal et al.[78] observed an odds ratio of 15.5 (95% CI 3.1–76.7) in those with the FVL mutation and receiving HRT compared with those with neither exposure. A systematic review of these studies concluded that the combination of HRT and one prothrombotic mutation gives a combined odds ratio of 8.0 (95% CI 5.4–11.9) compared with women without exposure to either risk factor.[3]

Evidence level 2+

In a nested case–control study derived from two randomised clinical trials of conjugated estrogen (with or without MPA) compared with placebo in subjects with coronary heart disease,[79] Herrington et al. observed that the odds ratio for VTE in those with FVL and HRT was 14.1 (95% CI 2.7–72.4) compared with those with neither FVL nor HRT. Their estimated absolute incidence of VTE was 15.4/1000 per year in those with FVL and HRT compared with 2/1000 per year in those without FVL and taking placebo. Results from the nested case–control WHI study of conjugated estrogen and MPA versus placebo[73] observed that the combination of FVL and HRT resulted in an odds ratio of 6.7 (95% CI 3.1–14.5) for VTE compared with those with neither exposure. No effect was observed for the PT mutation. From this, an estimated absolute risk of VTE with the combination of conjugated estrogen, progestogen and FVL (either as a heterozygote or a homozygote) of 8/1000 per year was calculated – half the risk seen in those with pre-existing coronary artery disease reported by Herrington.[79] In a prospective study, 236 female asymptomatic carriers of the FVL mutation (with a mean age of 43 years) were identified by screening the first-degree relatives of symptomatic probands.[80] Of these, 21 women used HRT for a total of 34 years, with one woman developing a deep venous thrombosis, giving an incidence of VTE related to HRT of 2.9% (95% CI 0.8%–15.3%) per year of use.

Evidence level 2+

In the study by Høibraaten et al. on recurrent VTE,[81] 71 subjects with previous VTE were randomised to receive combination HRT with estradiol. Of the eight subjects who experienced a further VTE, three were noted to carry FVL and two had detectable anticardiolipin antibodies. Although this gave a significant relative risk of recurrence of 2.6 (95% CI 1.3–5.4) associated with thrombophilia compared with no thrombophilia, the relative risk associated with FVL was non-significant at 1.4 (95% CI 0.4–5.3).

In women without a personal history of VTE but with a high-risk thrombophilic trait (such as deficiency of antithrombin, protein C or protein S) that has been identified through screening because of a symptomatic family member, oral HRT should be avoided and specialist advice sought.

D

Where there is no personal history of VTE but an underlying thrombophilic trait is identified through screening carried out because a first-degree relative has a history of previous VTE (e.g. apparently spontaneous VTE, or VTE at a young age, or VTE events in two or more family members), HRT should be avoided in high-risk situations such as type 1 antithrombin deficiency or combinations of defects. Specialist advice should be sought. With other thrombophilic defects, there is insufficient evidence at present to indicate that HRT should be completely avoided, although, as noted above, evidence indicates around an overall eight-fold increase in risk of VTE.[3] An assessment of other risk factors for VTE should be made. In the presence of multiple risk factors for VTE, HRT should be avoided. If HRT is to be used, a clear discussion of the potential excess risk should occur with the woman and transdermal therapy may be best. As this remains a controversial and rapidly developing area, advice should be sought from clinicians with special expertise in thrombophilia.

Evidence level 4

7. How should HRT be managed in those with a previous VTE?

A personal history of thrombosis is a contraindication to oral HRT.

C

If it is considered that quality of life is so severely affected that the benefits of HRT outweigh the risks, a transdermal preparation should be used.

D

There is very little direct evidence on VTE risk in those with a history of prior VTE. One randomised controlled trial of 140 subjects with previous VTE,[81] who were randomised to receive oral combined HRT (with 2 mg estradiol and 1 mg norethisterone or placebo), observed a 1.3-year incidence of 10.7% in those with a previous VTE (aged 42–69 years) compared with 2.3% in non-users. This equates to around a five-fold higher risk of recurrent VTE. In another randomised

Evidence level 2+

controlled trial of oral conjugated equine estrogen and MPA compared with placebo, 141 subjects were identified as having a prior history of VTE. Of the eight cases of recurrent VTE observed, seven occurred in the treatment arm of the trial, giving a hazard ratio of 3.87 (95% CI 0.45–33.34).[73] Although neither study is of sufficient size to draw definitive conclusions, both are strongly suggestive of an increased risk of VTE recurrence with oral HRT therapy in those with a previous history of VTE. Where the woman has had a previous VTE, oral HRT should usually be avoided in view of the relatively high risk of recurrence. However, women must be considered as individuals. In each case, the woman's requirement for estrogen replacement must be defined and the potential benefits for her weighed against the risks.[81]

Evidence level 2+

If it is considered that HRT is desirable for a particular woman, the risk of recurrence should be discussed carefully with her and she must be advised to report promptly if any symptoms compatible with VTE arise. Where HRT is to be used in those with prior VTE, prophylactic anticoagulant therapy may be considered while the woman is taking HRT. However, if anticoagulant thromboprophylaxis has to be used, the risk of haemorrhage must be considered in the risk–benefit analysis. On standard anticoagulant thromboprophylaxis, major haemorrhage occurs at a rate of around 1% per year of treatment and 25% of these bleeds are fatal.[82]

As discussed in section 4, transdermal therapy may be best in such a situation. Specialist advice from a clinician with expertise in thrombosis and thrombophilia should be sought.

Testing for thrombophilia in selected women (e.g. those with previous severe unprovoked or recurrent VTE) may be helpful in assessing the overall thrombotic risk in women with a personal history of VTE, but the result will not alter the advice that oral HRT should be avoided. In general, testing for thrombophilia in unselected women who have experienced a first episode of VTE is not routinely recommended, as there is insufficient evidence that testing reduces the risk of recurrence or that the results should influence the duration of anticoagulant therapy.[75] Testing when a severe defect (such as deficiency of antithrombin, protein C or protein S) is suspected may be helpful in assessing the overall thrombotic risk. If thrombophilia testing is suggested, the limitations of testing should be discussed.

8. How should HRT be managed in those who develop VTE while receiving HRT?

It is recommended that, when a woman who is on HRT develops a VTE, HRT should be discontinued. C

If it is considered desirable that a woman should continue HRT after a VTE has occurred on therapy, she should be referred to a clinician with special expertise in managing women at increased thrombotic risk requiring HRT. ✓

As further VTE may be prevented by anticoagulation, consideration can be given to postponing the withdrawal of HRT until the woman is due to stop anticoagulant therapy for her VTE. ✓

As noted above, a randomised double-blind placebo-controlled trial of oral HRT (2 mg estradiol plus 1 mg norethisterone) in women with a previous confirmed VTE found that the incidence of VTE was 10.7% in the HRT group and 2.3% in the placebo group within 262 days of starting therapy.[79]

Evidence level 2+

9. What other risk factors should be considered when assessing the risk of VTE associated with HRT?

Before commencing HRT, any personal or family history of VTE should be assessed. C

A history of VTE in a first-degree relative (i.e. parent, sibling or offspring) is a relative contraindication to HRT. C

Where there is a family history in a first-degree relative, alternatives to oral HRT should be suggested. If HRT is considered desirable, transdermal preparations are associated with a significantly lower risk of venous thrombosis.

D

As VTE is usually dependent on multiple risk factors coming together, it is important to be aware of the presence of pre-existing thrombotic risk factors. The prescriber should specifically ask whether there is a previous personal history of VTE or a history of VTE in a first-degree relative.[83] The presence of multiple pre-existing risk factors for VTE may suggest that HRT, itself a risk factor, might be best avoided. In particular, women with a previous VTE are at high risk of recurrence. However, it is important to review the overall situation for each individual. Given the polygenic nature of VTE, even where a familial thrombophilia has been identified, the risk of VTE may also be increased in those members of the family who do not carry that thrombophilia.[83] Consequently, a negative thrombophilia result does not necessarily exclude an increased risk. Therefore, thrombophilia testing may not be informative in predicting risk without consideration of individual risk factors and the nature of the family history. Where a heritable thrombophilia has been detected in an affected family member, testing for heritable thrombophilia will not provide a definitive estimate of risk in most cases and is not routinely recommended. However, where a high-risk heritable thrombophilia has been identified in a symptomatic family member (e.g. deficiency of antithrombin, protein C or protein S), testing for thrombophilia may assist in the counselling of overall thrombotic risk.

Evidence level 2+

HRT should be avoided in women with multiple pre-existing risk factors for VTE.

D

Data from the ESTHER study[56] showed an increased risk of VTE associated with increasing weight. This resulted in an odds ratio of 2.7 (95% CI 1.7–4.5) associated with being overweight (body mass index [BMI] 25 to ≤30 kg/m^2) and an odds ratio of 4.0 (95% CI 2.1–7.8) associated with being obese (BMI >30 kg/m^2). With exposure to (predominantly) estradiol, the risk associated with being overweight was 10.2 (95% CI 3.5–30.2) and with obesity was 20.6 (95% CI 4.8–88.1). The use of transdermal HRT did not increase the risk associated with weight. Similarly, data from the WHI study observed an increased VTE risk of 1.63 (95% CI 0.83–3.20) associated with being overweight (BMI 25–30 kg/m^2) and with obesity (BMI >30 kg/m^2) of 2.87 (95% CI 1.52–5.40). On additional exposure to esterified estrogen and MPA, the VTE risk associated with being overweight was 3.80 (95% CI 2.06 –6.94) and with obesity was 5.61 (95% CI 3.12–10.11).[73]

Evidence level 2++

Thus, multiple defects or combinations of acquired and/or inherited risk factors are likely to be important in VTE risk. Such additional risk factors include patient factors, as detailed below. Consequently, the increase in relative risk associated with HRT has to be viewed in the context of that associated with other risk factors and the potential for interaction between risk factors should not be underestimated.

Evidence level 4

Additional risk factors for venous thromboembolism

- Increasing age
- Obesity (body mass index > 30)
- Previous VTE
- Post-thrombotic syndrome
- Varicose veins with phlebitis
- First-degree family history of VTE
- Immobility for more than 3 days
- Surgical procedures (anaesthesia and surgical time > 60 minutes)
- Other disorders, e.g. malignancy, myeloproliferative disorders, cardiac disease, paralysis of lower limbs, systemic infection, inflammatory bowel disease, nephritic syndrome, sickle cell disease

10. What other assessments should be considered in those presenting with VTE?

In women over 50 years of age with a history of VTE within the previous year, a full clinical history and examination are warranted to detect underlying disease. The need for any additional investigations should be determined by the clinical assessment.

✓

VTE may be precipitated by an underlying malignancy or connective tissue disease, so it is important to consider such diagnoses when assessing women with recent (particularly unprovoked) VTE. With regard to undiagnosed malignancy, the nature and benefits of additional screening (beyond a standard clinical assessment) in those without clinical signs or symptoms remains controversial. In those presenting with VTE, there is some evidence that an extensive screening strategy may detect more underlying malignancy than limited screening.[84] However, at present there is insufficient evidence to determine whether extensive screening strategies are either cost-effective or will have a substantial impact on the morbidity or mortality associated with the diagnosed malignancy.[84]

Evidence level 4

11. How should HRT be managed in those requiring surgery?

Each woman requires an individual assessment of the risks and benefits of stopping HRT before elective surgery. HRT may not need to be stopped before surgery provided that appropriate thromboprophylaxis is used.

✓

HRT is often seen as a risk factor for postoperative thromboembolism, although there are no direct data to support such a view. Nonetheless, the combination of HRT and the changes in coagulation and the occurrence of venous stasis following surgery might combine to provide a significant increase in risk. However, this risk is likely to be small and virtually all women who receive HRT will meet the criteria for thromboprophylaxis. Both the British National Formulary[85] and the National Institute for Health and Clinical Excellence[86] advise women to consider stopping HRT 4 weeks before elective surgery. However, they also acknowledge that this may not be necessary if appropriate thromboprophylaxis is used. This interpretation of the available evidence appears to be made on the basis that the effects of stopping HRT are not life threatening and that the risks may, in some women, outweigh the benefits of continuing therapy. Consequently, an individual assessment is required in each woman to balance the risks of postoperative VTE against any changes in the quality of life which may result from cessation of therapy.

Evidence level 4

12. Suggested audit topics

- Evidence of counselling on the risks and benefits of HRT before prescribing HRT or when continuing HRT.
- Evidence of a formal assessment of VTE risk before prescribing HRT or when continuing HRT.
- Inclusion of HRT use in preoperative VTE risk assessments
- Consideration of current/future hormone therapy use when planning the management of an acute VTE

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APPENDIX

Clinical guidelines are 'systematically developed statements which assist clinicians and women in making decisions about appropriate treatment for specific conditions'. Each guideline is systematically developed using a standardised methodology. Exact details of this process can be found in Clinical Governance Advice No.1: *Development of RCOG Green-top Guidelines* (available on the RCOG website at **http://www.rcog.org.uk/guidelines**). These recommendations are not intended to dictate an exclusive course of management or treatment. They must be evaluated with reference to individual patient needs, resources and limitations unique to the institution and variations in local populations. It is hoped that this process of local ownership will help to incorporate these guidelines into routine practice. Attention is drawn to areas of clinical uncertainty where further research might be indicated.

The evidence used in this guideline was graded using the scheme below and the recommendations formulated in a similar fashion with a standardised grading scheme.

Classification of evidence levels

1++	High-quality meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias
1–	Meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a high risk of bias
2++	High-quality systematic reviews of case–control or cohort studies or high-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
2+	Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2-	Case–control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal
3	Non-analytical studies, e.g. case reports, case series
4	Expert opinion

Grades of recommendations

A	At least one meta-analysis, systematic review or randomised controlled trial rated as 1++ and directly applicable to the target population; or A systematic review of randomised controlled trials or a body of evidence consisting principally of studies rated as 1+ directly applicable to the target population and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++ directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+ directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+

Good practice point

✓	Recommended best practice based on the clinical experience of the guideline development group

This guideline was produced on behalf of the Guidelines Committee of the Royal College of Obstetricians and Gynaecologists by:
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The final version is the responsibility of the Guidelines Committee of the RCOG.

The guideline review process will commence in 2014 unless evidence requires earlier review.

