Royal College of Obstetricians and Gynaecologists

Setting standards to improve women's health

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# HORMONE REPLACEMENT THERAPY AND VENOUS THROMBOEMBOLISM

## 1. Introduction

Exogenous oestrogens 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 oestrogen but in the past was not considered to be associated with VTE.[3] The difference between these preparations was attributed to 'physiological' doses of natural oestrogens in HRT which contrasted with the 'pharmacological' doses of synthetic oestrogens of high potency in the pill. However, case–control studies and prospective randomised trials have shown a modest increase in the relative risk of VTE in women on oestrogen containing HRT (Tables 1, 2, 3).[4–13] In particular, the Women's Health Initiative study in the USA (www.nhlbi.nih.gov/whi/hrt.htm) assessed the major health benefit of oral HRT (0.625 mg conjugated equine oestrogen and 2.5 mg medroxyprogesterone acetate daily) in a randomised placebo-controlled clinical trial with more than 8000 women in each arm and confirmed an increase in risk of pulmonary embolism (hazard ratio 2.13, 95% CI 1.39–3.25).[12] Published data suggest that transdermal oestrogen containing HRT is safer than oral HRT with respect to thrombotic risk.[13]

## 2. Methodology

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 April week 1 2003), Embase (1980 to Week 15, 2003), Evidence-based Medicine Reviews, the Cochrane Database of Systematic Reviews and the Database of Abstracts of Reviews of Effectiveness to the first quarter 2003. This was complemented by hand searching from individual references identified from these original articles.

The definitions of the types of evidence used in this guideline originate from the US Agency for Health Care Research and Quality. 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. Possible mechanisms linking HRT and VTE

The mechanism whereby HRT provokes an increased risk of VTE is unclear. The haemostatic system is altered by the menopause, with increases in certain coagulation factors associated with vascular risk.[14–17] HRT produces a reduction in fibrinogen and factor VII activation,[18,19] such as von Willebrand's factor[20] and antithrombin,[18] and also enhances fibrinolysis.[21] In addition, it is associated with increased resistance to activated protein C.[22,23] Although many of these effects are opposing, the net effect appears to be an increase in thrombin generation. C-reactive protein also increases with oestrogen-containing HRT[24,25] and this

**Table 1. Epidemiological studies of VTE and HRT**

| Authors | Study design | Relative risk | Absolute risk |
|---|---|---|---|
| Jick *et al.*[4] | Population-based nested case–control study of idiopathic VTE in the USA 1980–94 | 2.1–6.9, dependent upon dose for current users for idiopathic VTE | 9/100 000 versus 32/100 000 women/year for non-users/users of HRT |
| Daly *et al.*[5] | UK hospital-based case–control study in women aged 45–64 years with idiopathic VTE in 1993–94 | 3.5 (95%CI 1.8–7.0) for idiopathic VTE in current users (note: risk appeared higher in short-term current users) | 11/100 000 versus 27/100 000 women/year for non-users/users of HRT |
| Grodstein *et al.*[6] | Questionnaire study on primary PTE in Nurses Health Cohort in USA 1976–92 | 2.1 (95% CI 1.2–3.8) for idiopathic primary PTE in current users | 8/100 000 versus 14/100 000 women/year for non-users/users of HRT |
| Gutthann *et al.*[7] | Population-based nested case–control in UK using the general practice research database | 2.1 (95% CI 1.4–3.2) for current users for idiopathic VTE<br>4.6 (95% CI 2.5–8.4) during the first six months of use | 11/100 000 versus 23/100 000 women/year for non-users/users of HRT |
| Varas-Lorenzo *et al.*[8] | Case–control study in Italy | 2.3 (95% CI 1.0–5.3) for current users for idiopathic VTE | < 20/100 000 versus < 60/100 000 women/year for non-users/users of HRT |
| Hulley *et al.*[9]<br>Grady *et al.*[10] | Randomised, double-blind placebo-controlled trial of HRT (equine conjugated oestrogens and medroxyprogesterone acetate) for secondary prevention of coronary heart disease in USA | VTE: 2.7 (95% CI 1.4–5.0)<br>DVT: 2.8 (95% CI 1.3–6.0)<br>PTE: 2.8 (95% CI 0.9–8.7)<br>for current users<br>(note: an increase was reported in risk of coronary events in women in the first four months of use followed by a reduction in risk over the last two years of this trial, which was conducted over 4.1 years) | 230 versus 620/100 000 women years for non-users versus users (note: reflects older higher-risk population compared with the above studies) |
| Hoibraaten *et al.*[11] | Population-based case–control study in 1990–96 for VTE in Scandinavia using oestradiol-based HRT in women aged 44–70 years | 1.22 (95% CI 0.76–1.94) overall, 3.54 (95% CI 1.54–8.2) in first 12 months of use and 0.66 (95%CI 0.39–1.10) after the first year of use for primary and secondary VTE | Not available |
| Writing Group for the Women's Health Initiative Investigators[12] | Randomised controlled primary prevention trial in 1993–98 with HRT (oral conjugated equine oestrogens, 0.625 mg/day, plus medroxy-progesterone acetate, 2.5 mg/day) or placebo in 16 608 postmenopausal women aged 50–79 years with an intact uterus at baseline | VTE: 2.11 (95% CI 1.58–2.50)<br>DVT: 2.07 (95% CI 1.49–2.87)<br>PE: 2.13 (95% CI 1.39–3.25) | VTE: 340 versus 160 per 100 000 woman-years |
| Scarabin *et al.*[13] | multicentre hospital-based case–control study during 1999–2002 in women aged 45–70 years comparing oral HRT (mainly 17-beta oestradiol 0.5–2 mg/day) and transdermal HRT (50–100 micrograms/day) | Oral HRT:<br>VTE: 3.5 (95% CI 1.8–6.8)<br>Transdermal VTE:<br>VTE:0.9 (95% CI 0.5–1.6) | Not available |

PTE: pulmonary thromboembolism; VTE: venous thromboembolism; the evidence is consistent in demonstrating an increased relative risk of VTE although the absolute risk, particularly in the absence of other risk factors, is low. There is some evidence that the effect is dose related, as Grodstein *et al.*[6] found that the relative risk of VTE increased from 3.3 (95% CI 1.4–7.8) to 6.9 (95% CI 1.5–33.0) with 0.625 mg and 1.25 mg of oestrogen respectively. This is in agreement with the data of Daly *et al.*[5] who found an increase in relative risk from 3.7 (95% CI 1.3–10.2) with 0.625 mg oestrogen to 6.6 (95% CI 2.2–19.6) with 1.25 mg oestrogen, but not all studies have shown a dose effect.[7] There is also a clear association with duration of use (Table 2). The highest risk occurred in the first 6–12 months of use. The study by Varas-Lorenzo *et al.*[8] reported no cases after the first 12 months of use. Although information is limited, there are some data that suggest that transdermal therapy carries a lower risk than oral therapy (Table 3), but the numbers studied were small.

inflammatory marker is a risk factor for cardiovascular events including VTE. Transdermal therapy has less effect on coagulation than oral administration. This reflects 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.[18,25]

The incidence of VTE in postmenopausal women is around double that of premenopausal women and the risk of VTE increases with age.[4,5,26,27] However, as the epidemiological data relate VTE to the first year of HRT exposure, age and oestrogen alone cannot be responsible for all of the increased risk of VTE with HRT. It is possible that the risk of VTE on HRT relates to underlying thrombophilia, which is known to pose a risk in hyperoestrogenic situations (Table 4).[2,28–37]

**Table 2.** Risk of VTE with duration of use of HRT

| Study | Duration of use (months) | Relative risk | 95% CI |
|---|---|---|---|
| Jick *et al.*[4] | < 12 | 6.7 | 1.5–30.8 |
| | 12–60 | 2.8 | 0.6–11.7 |
| Grodstein *et al.*[6] | < 60 | 2.6 | 1.2–5.2 |
| | > 60 | 1.9 | 0.9–4.0 |
| Daly *et al.*[5] | < 12 | 6.7 | 2.1–21.3 |
| | 13–24 | 4.4 | 1.6–11.9 |
| | 25–60 | 1.9 | 0.5–7.8 |
| | > 60 | 2.1 | 0.8–6.1 |
| Gutthann *et al.*[7] | < 6 | 4.6 | 2.5–8.4 |
| | 7–12 | 3.0 | 1.4–6.5 |
| | > 12 | 1.1 | 0.6–2.1 |
| Hoibraaten *et al.*[11] | < 12 | 3.5 | 1.5–8.2 |
| | > 12 | 0.7 | 0.4–1.1 |

**Table 3.** Risk of VTE with oral and transdermal HRT

| Study | HRT route | RR | 95% CI |
|---|---|---|---|
| Daly *et al.*[5] | Oral | 4.6 | 2.1–10.1 |
| | Transdermal | 2.0 | 0.5–7.6 |
| Gutthann *et al.*[7] | Oral | 2.1 | 1.3–3.6 |
| | Transdermal | 2.0 | 0.9–4.6 |
| Scarabin *et al.*[13] | Oral | 3.5 | 1.8–6.8 |
| | Transdermal | 0.9 | 0.5–1.6 |

**Table 4.** Prevalence of major thrombophilic gene defects in white populations

| Thrombophilic defect | General population (%) | Women presenting with their first VTE (*n*) | |
|---|---|---|---|
| | | Unselected[a] | Selected[b] |
| Antithrombin defect | 0.02 | 1 | 4–5 |
| Protein C defect | 0.30 | 3 | 6–8 |
| Protein S defect[47] | 0.03–0.13 | 1 | 3–6 |
| Factor V Leiden | 3.00–15.00 | 20 | 50–60 |
| Factor II 20210A | 2.00–3.00 | 6 | 18–20 |

[a] consecutive women with first VTE; [b] women with first VTE plus family history of VTE

There are few published data currently available on congenital thrombophilias and HRT. One case–control study has investigated the association between HRT and thrombophilic factors.[38] In women using HRT, the risk of VTE was significantly associated with increased resistance to activated protein C, low antithrombin and high factor IX (Table 5). Where multiple risk factors such as HRT and one or more prothrombotic states are present, this leads to substantial increase in risk. Overall, this study found that, regardless of the underlying prothrombotic tendency, HRT resulted in around a three-fold increase in risk. In an extension to this study, Rosendaal *et al*.[39] reported an eight-fold increased risk of VTE in women with a prothrombotic mutation (factor V Leiden or prothrombin 20210A) using HRT.

Thus, multiple defects or combinations of acquired and/or inherited risk factors are likely to be important in the clinical expression of thrombophilias.[40] Risk factors include patient factors such as age, obesity, varicose veins, previous VTE, deep venous insufficiency, immobility and disease or surgical factors such as trauma or surgery to the pelvis or leg, malignancy and myeloproliferative disorders, cardiac failure, paralysis of lower limbs, infection, inflammatory bowel disease and nephrotic syndrome. HRT must now be added to the list of established risk factors for VTE. This increase in relative risk associated with HRT has to be viewed in the context of that associated with other risk factors.[8] These relative risks are substantially higher than that associated with HRT use (Table 6). The potential for interaction between risk factors must not be underestimated. A randomised double-blind placebo-controlled trial of oral HRT (2 mg oestradiol plus 1 mg

| Table 5. Odds ratio for haemostatic factors adjusted to include HRT status; from Lowe *et al.*[38] | |
|---|---|
| **Prothrombotic factor** | **Adjusted odds ratio (95% CI)** |
| High factor IX | 2.34 (1.26–4.35) |
| increased resistance to activated protein C | 4.06 (1.62–10.21) |
| Low antithrombin | 3.33 (1.15–9.65) |

| Table 6. Association of VTE and risk factors including HRT; from Varas-Lorenzo *et al.*[8] | | |
|---|---|---|
| **Risk factor** | **Adjusted odds ratio** | **95% CI** |
| Varicose veins | 6.9 | 4.3–11.0 |
| Obesity | 4.6 | 2.2–9.7 |
| Osteoarthritis | 2.4 | 1.7–3.3 |
| Age (65–80 years versus 45–64 years) | 2.3 | 1.6–3.2 |
| HRT (current use) | 2.3 | 1.0–5.3 |
| Diabetes | 1.9 | 1.2–2.3 |
| Hypertension | 1.6 | 1.2–2.3 |

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.[41]

## 4. Women starting or continuing HRT

**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.** C

In the Women's Health Initiative study, the primary outcome measure was coronary heart disease. 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.[12] The overall health risks from HRT in this study exceeded the gains from reduced hip fracture and reduced risk of colorectal cancer, indicating that such combined oral HRT should not be prescribed for the primary prevention of arterial disease. Evidence level Ib

**All women commencing HRT should be counselled about the risk of VTE, should be aware of the signs and symptoms of VTE and should be able to access medical help rapidly if they suspect that they have developed a thrombus.** ✓

The small risk of VTE with HRT should be discussed with the woman prior to commencing HRT but it should be placed firmly in the context of the overall benefits for her particular situation.

**Universal screening of women for thrombophilic defects prior to or continuing the prescription of HRT is inappropriate.** C

There is limited information on the natural history of thrombophilias, the mechanism of oestrogen-associated thrombosis and how these two factors interact. The absolute risk of VTE with HRT is low. On the available evidence, universal screening of women for thrombophilic defects prior to or continuing the prescription of HRT is inappropriate and should be discouraged. Evidence level IV

**Prior to commencing HRT, a personal history and a family history assessing the presence of VTE in a first- or second-degree relative should be obtained.** C

| Table 7. Investigations for potential thrombophilia [48] | |
|---|---|
| | **Investigation** |
| Thrombophilia screen | Activated partial thromboplastin time and prothrombin time<br>Antithrombin activity<br>Protein C activity<br>Total and free protein S antigen<br>Modified activated protein C resistance (after predilution in factor V deficient plasma)<br>Factor V Leiden (optional if modified APC resistance abnormal)<br>prothrombin 20210A variant<br>lupus anticoagulant and anticardiolipin antibodies (immunoglobulins G and M) |
| Routine haematology and biochemistry | Full blood count including platelet count<br>Urea and electrolytes, liver function tests and urinalysis for protein |

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

As VTE may be dependent upon multiple risk factors coming together, it is important to be aware of the presence of pre-existing thrombotic risk factors.[42] In particular, the prescriber should specifically ask whether there is a previous personal history of VTE or a history of VTE in a first- or second-degree relative. If positive, thrombophilia testing (Table 7) may be considered. 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.[43]

Evidence level IV

## 5. Women with a personal or family history of VTE

**Testing for thrombophilia should be discussed with and available for women with a personal or family history of VTE.** **C**

Testing for thrombophilia (as set out in Table 7) may be helpful in women with a personal or family history of VTE. An attempt should be made to assess the severity of any previous event and whether or not it was objectively confirmed. The clinical diagnoses of DVT and pulmonary thromboembolism are unreliable and objective testing is required. However, in the past, objective testing was less available. A history of prolonged anticoagulant therapy would be compatible with a significant previous event.

Evidence level IV

**It is recommended that, in women with a previous VTE, with or without an underlying heritable thrombophilia, oral HRT should usually be avoided in view of the relatively high risk of recurrent VTE.** **A**

Where the woman has had a previous VTE, with or without an underlying thrombophilia, 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 oestrogen replacement must be defined and the potential benefits for her weighed against the risks.[41]

Evidence level Ib

If it is considered that HRT is necessary 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. In this situation, prophylactic anticoagulant therapy can be used 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 one-quarter of these bleeds are fatal.[43] Transdermal therapy may be best in such a situation. Specialist advice from a clinician with expertise in thrombosis and thrombophilia should be sought.

Evidence level IV

**In women without a personal history of VTE but with an underlying thrombophilic trait that is identified through screening, HRT is not recommended in high risk situations such as Type 1 antithrombin deficiency or with combinations of defects or additional risk factors for VTE and specialist advice should be sought.** **B**

Where there is no personal history of VTE but an underlying thrombophilic trait is identified through screening, because a first- or second-degree relative has a history of previous VTE (e.g. apparently spontaneous VTE, VTE at young age, 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 and specialist advice should be sought. With other thrombophilic defects, there is insufficient evidence at present to indicate that HRT should be completely avoided, although evidence indicates around an eight-fold increase in risk of VTE. An assessment of other risk factors for VTE should be made. In the presence of multiple risk factors for VTE, HRT should be avoided.

Evidence level III

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. Consideration should be given to 'covering' oestrogen replacement with anticoagulant thromboprophylaxis taking into account the risk of haemorrhage. The risk of anticoagulant-related haemorrhage probably outweighs the risk of HRT-related venous thrombosis in women with a family history of VTE but no personal history of VTE, who have no identifiable thrombophilic defect or who have one of the defects usually associated with a lesser risk of VTE (heterozygosity for factor V Leiden or the prothrombin 20210A polymorphism). As this is a controversial and rapidly developing area, advice should be sought from clinicians with special expertise in thrombophilia.

**In women over 50 years with a history of VTE within the previous year, a full clinical history and examination with appropriate investigations is warranted for underlying disease.** **C**

VTE may be precipitated by an underlying malignancy or connective tissue disease, so it is important to consider such a diagnosis in assessing women over 50 years of age with a recent pVTE.[44]

Evidence level IV

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

**It is recommended that, if a woman requires to continue on HRT after a VTE, long-term anticoagulation should be considered.** **C**

A randomised double-blind placebo-controlled trial of oral HRT (2 mg oestradiol 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.[41]

Evidence level Ib

## 6. Risk of VTE in users of selective oestrogen receptor modulators (SERMs)

**SERMs should be considered to carry the same risk of thrombosis as oestrogen-containing HRT.** **B**

There is limited information about the risk of VTE in users of SERMs but in a randomised placebo-controlled trial the relative risk of VTE in users of raloxifene was 3.1 (95% CI 1.5–6.2), suggesting that the risk is similar to that with oestrogen-containing HRT.[45]

Evidence level Ib

## 7. Women on HRT undergoing surgery

**HRT should be considered a risk factor for VTE when assessing women preoperatively. However, HRT does not require to be routinely stopped prior to surgery provided that appropriate thrombo-** **C**

**prophylaxis, such as low-dose or low-molecular-weight heparin, with or without thromboembolic deterrent stockings, is used.**[41,45]

HRT is often seen as a risk factor for postoperative thromboembolism, although there are no data to support such a view. Nonetheless, the combination of HRT and the changes in coagulation and venous function following surgery might combine to provide a significant increase in risk. This risk is likely to be small and virtually all women who receive HRT will meet the criteria for thromboprophylaxis set out in guidelines such as the THRIFT consensus and previous editions of this guideline.[40,46]

Evidence level IV

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## APPENDIX

Clinical guidelines are: 'systematically developed statements which assist clinicians and patients 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: *Guidance for the Development of RCOG Green-top Guidelines* (available on the RCOG website at www.rcog.org.uk/clingov1). 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 may 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

| | |
|---|---|
| Ia | Evidence obtained from meta-analysis of randomised controlled trials. |
| Ib | Evidence obtained from at least one randomised controlled trial. |
| IIa | Evidence obtained from at least one well-designed controlled study without randomisation. |
| IIb | Evidence obtained from at least one other type of well-designed quasi-experimental study. |
| III | vidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies. |
| IV | Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities. |

### Grades of recommendations

| | |
|---|---|
| A | Requires at least one randomised controlled trial as part of a body of literature of overall good quality and consistency addressing the specific recommendation. (Evidence levels Ia, Ib) |
| B | Requires the availability of well controlled clinical studies but no randomised clinical trials on the topic of recommendations. (Evidence levels IIa, IIb, III) |
| C | Requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates an absence of directly applicable clinical studies of good quality. (Evidence level IV) |

### Good practice point

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

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The final version is the responsibility of the Guidelines and Audit Committee of the RCOG.

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