

## Venous thrombosis/thromboembolism risk and menopausal hormone therapy

### KEY POINTS

- The risk of DVT in most women is low.
- Prior to prescribing MHT an assessment of each woman's individual risk of DVT should be conducted. For low-risk women a thrombophilia screen is not necessary.
- Oral MHT increases the risk of VTE and is not recommended in women at increased risk of thromboembolic events.
- Transdermal MHT does not increase VTE risk and is recommended for management of menopausal symptoms in women who are at increased risk.
- There is no indication for anticoagulation therapy in women receiving MHT.
- Women who develop VTE while taking MHT can safely continue whilst receiving anticoagulation therapy. This gives an opportunity for considered review rather than abrupt cessation.

### Introduction

Venous thromboembolism (**VTE**) is a condition that occurs when a blood clot forms in a vein. Types of VTE includes deep vein thrombosis (**DVT**) and pulmonary embolism (PE) the latter occurring when a blood clot breaks loose from a vein and travels through the bloodstream to the lungs<sup>1</sup>. VTE risk increases with age with risk doubling every 10 years after age 40. Other risk factors for VTE include thrombophilia, family history, cancer, diabetes, high blood pressure, kidney disease, heart conditions, smoking, obesity and immobilization.

For women aged 50-59 the incidence of VTE is 1-2 per 1000 women per year<sup>2</sup>.

### **Menopausal hormone therapy (MHT) may increase VTE risk**

**Oral** menopausal hormone therapy (MHT) increases the risk of VTE<sup>3,4</sup>. For women aged 50-59 this risk principally relates to DVT whilst an increase in the risk of stroke and PE is seen in older women<sup>5</sup>. **Transdermal** MHT does not increase VTE risk<sup>13</sup>.

### **What causes the increased risk?**

Oral oestrogens have a prothrombotic effect via effects on the extrinsic pathway of the coagulation cascade with altered production of hepatic coagulation proteins

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thought to be secondary to the effect of the first pass through the hepatic circulation. Changes include increased activated protein C resistance, increased thrombin activation, decreased anti-thrombin III activity, decreased protein S levels, decreased Factor VII levels and decreased tissue factor pathway inhibitor<sup>6,7</sup>. Different effects are observed with oral combined MHT versus oestrogen alone<sup>8</sup>. The increased risk of a thrombotic event is greater within the first year of starting treatment, persists throughout the time of taking oral MHT and returns to baseline on cessation of MHT<sup>8</sup>.

Transdermal MHT has little or no effect on coagulation factors or risk of VTE<sup>13</sup>.

### How great is the risk?

In women aged 50-59 who do not take MHT the risk of thrombosis is small.

Taking oral combined MHT will increase the "baseline" risk of thrombosis approximately two-fold but a woman's overall or "absolute risk" will still be small at about 2 in 1000 per year for women aged 50-59 years<sup>7,8</sup>. (See AMS Information Sheet - Risks and benefits of MHT/HRT)).

The risk of VTE is higher in those who take combined oestrogen-progestin MHT than in those taking oestrogen-only MHT<sup>7,8</sup>. There is also some evidence that the type of progestogen may also influence VTE risk with oral micronized progesterone conferring a lesser risk than other oral progestogens<sup>9</sup>.

Tibolone was associated with an increased risk of stroke when initiated in women over age 60 but pooled data from four studies found no increased VTE risk for tibolone<sup>11,12</sup>.

Observational studies have not shown an increased risk of DVT in postmenopausal women using transdermal oestrogen<sup>13</sup>.

Age	VTE events – no of women per 1,000 per year			
	WHI oral E+MPA study		WHI oral E only study	
	Placebo	E+MPA	Placebo	E only
50-59 years	0.8	1.9	1.2	1.6
60-69 years	1.9	3.5	2.5	3.2
70-79 years	2.7	6.2	3.1	4.2
Body mass Index kg/m <sup>2</sup>				
<25	0.9	1.6	1.0	1.9
25-30	1.5	3.5	1.8	2.4
>30	2.5	5.1	3.0	3.9

### Managing Risk

Individuals seeking MHT should be assessed for any risk of VTE<sup>14</sup>.

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Routine thrombophilia screening is not considered necessary for low-risk women.

For women who are deemed to be at increased risk including those who are older, obese, smokers, immobile, have a personal or family history of VTE or a known or suspected genetic predisposition, thrombophilia screening may be appropriate.

Several recent Systematic Reviews examined the risk of VTE when MHT is used in these high risk populations<sup>15,16,17</sup> and consistently reported that in these populations, when MHT is indicated for the treatment of bothersome menopausal symptoms transdermal MHT should be preferred as it does not increase VTE risk above baseline.

The risk of recurrence of VTE in a woman with previous VTE depends on the setting in which that VTE has occurred<sup>18</sup>. VTEs occurring after surgery have a very low risk of recurrence. Those with non-surgical trigger factors, such as immobilisation, fracture, plaster cast, COCP, have an 8% risk of recurrence at 2 years, compared with 20% in patients with unprovoked VTE.

In these populations it is important to explain that whilst VTE risk is not increased with transdermal MHT the background risk of VTE associated with the applicable condition is still raised and minimisation of risk with lifestyle measures should be encouraged.

It is advisable for any woman who experiences chest pain, shortness of breath, calf pain or swelling in one limb to seek prompt medical advice.

### **Treating transgender patients.**

Feminising Gender Affirming Hormone Therapy (GAHT) is procoagulant because of its effect on thrombin production. Masculinising GAHT appear to be anticoagulant. Management of VMS in trans men presents poorly understood challenges and where necessary transdermal MHT should be considered to minimise VTE risk<sup>19,20</sup>.

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### **Authorship**

Professor Rod Baber AM

Obstetrician and Gynaecologist; Clinical Professor, Obstetrics and Gynaecology, The University of Sydney; Past President, International Menopause Society and Australasian Menopause Society

January 2026

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