AUSTRALASIAN MENOPAUSE SOCIETY
EMPOWERING MENOPAUSAL WOMEN

Information Sheet

Venous thrombosis/thromboembolism risk and menopausal treatments

KEY POINTS

- The risk of DVT in most women is low.
- Take note of risk factors predisposing women to VTE prior to commencing MHT.
- Individualise all treatment based on the patient, her clinical features, her needs and her risk assessment.
- If MHT is to be used in a woman assessed to be at high risk of developing a DVT, a transdermal preparation should be used.

Menopausal hormone therapy (MHT) containing oestrogens in tablet form increase the risk of deep vein thrombosis (DVT) and pulmonary embolus (PE) (1, 2). The thrombotic effects of MHT containing oral oestrogen are associated with a slightly increased risk of stroke and venous thrombo-embolism (VTE) but not of coronary heart disease (3).

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 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 (4, 5). Different effects are observed with oral combined MHT versus oestrogen alone (6, 7). 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 (8).

By comparison, transdermal MHT has little or no effect on coagulation factors or risk of VTE.

How great is the risk?

- In most women who do not take MHT, the risk of thrombosis is small. The "baseline" risk of thrombosis increases with increasing age, increased body weight, smoking, inherited predisposition to clotting (e.g. Factor V Leiden affecting about 5% of the

Caucasian population) and in association with illnesses including cancer and some autoimmune diseases (See table below for the effect of age, body mass index and oral MHT on thrombosis risk).

- Taking oral combined MHT will increase the "baseline" risk of thrombosis approximately two-fold (a "relative risk" increase) but a woman's overall or "absolute risk" will still be small at about two in 1000 per year for women aged 50-59 years (6, 7) . (See AMS Information Sheet - Risks and benefits of MHT/HRT)).
- The risk of VTE appears to be higher in those who take combined oestrogen-progestin MHT than in those taking oestrogen-only MHT (6, 7). 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 (9).
- Tibolone has been associated with an increased risk of stroke but the pooled data from four studies did not find that tibolone was associated with the risk of VTE (10, 11).

	VTE events – no of women per 1,000 per year			
	WHI oral E+MPA study		**WHI oral E only study**	
Age	**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/m²				
<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

- Observational studies have not shown an increased risk of DVT in postmenopausal women using transdermal oestrogen (12).

How to minimise the risk

- Women with a personal history or a family history of venous thrombosis can be screened for risk factors to assist decision on the route of delivery for MHT. However routine thrombophilia screening for low risk women before starting MHT is not considered necessary.
- Women who acquire temporary risk factors for clotting including fracture of lower limbs, certain surgical procedures or any prolonged immobilisation may be advised to cease oral MHT in the short term. The use of compression stockings +/- short term anticoagulation may be recommended (13).

- Meta-analyses of observational studies indicate that transdermal oestrogen is not associated with an increased risk of VTE (14). In clinical practice, previous VTE and thrombophilias indicate a woman at higher risk and a transdermal oestrogen preparation is preferred.
- 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.

Risk of recurrence of VTE

The risk of recurrence of VTE in a woman with previous VTE depends on the setting in which that VTE has occurred. 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.

There is no additional significant association between recurrent VTE and use of transdermal oestrogens (hazard ratio, 1.0; 95% CI, 0.4-2.4) (15).

Likewise, thrombophilias increase the risk of a first VTE but, unlike oral MHT, transdermal MHT is not associated with an additional increase in risk (16).

Recommended reading

1. Archer DF, Oger E. Estrogen and progestogen effect on venous thromboembolism in menopausal women. Climacteric. 2012;15:235– 40.
2. Scarabin PY. Progestogens and venous thromboembolism in menopausal women: an updated oral versus transdermal estrogen meta-analysis. Climacteric. 2018:23

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4. Levi M, Middeldorp S, Buller HR. Oral contraceptives and hormonal replacement therapy cause an imbalance in coagulation and fibrinolysis which may explain the increased risk of venous thromboembolism. Cardiovasc Res. 1999;41(1):21-4.

5. Scarabin P-Y, Hemker HC, Clement C, Soisson V, Alhenc-Gelas M. Increased thrombin generation among postmenopausal women using hormone therapy: importance of the route of estrogen administration and progestogens. Menopause. 2011;18(8):873-9.

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11. Canonico M, Plu-Bureau G, Scarabin P-Y. Progestogens and venous thromboembolism among postmenopausal women using hormone therapy. Maturitas. 2011;70(4):354-60.

12. Scarabin PY. Hormones and venous thromboembolism among postmenopausal women. Climacteric. 2014;17 Suppl 2:34-7.

13. Kahn SR, Lim W, Dunn AS, Cushman M, Dentali F, Akl EA, et al. Prevention of VTE in nonsurgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):e195S-e226S.

14. Canonico M, Oger E, Plu-Bureau G, Conard J, Meyer G, Levesque H, et al. Hormone therapy and venous thromboembolism among postmenopausal women: impact of the route of estrogen administration and progestogens: the ESTHER study. Circulation. 2007;115(7):840-5.

15. Olie V, Plu-Bureau G, Conard J, Horellou M-H, Canonico M, Scarabin P-Y. Hormone therapy and recurrence of venous thromboembolism among postmenopausal women. Menopause. 2011;18(5):488-93.

16. Straczek C, Oger E, Yon de Jonage-Canonico MB, Plu-Bureau G, Conard J, Meyer G, et al. Prothrombotic mutations, hormone therapy, and venous thromboembolism among postmenopausal women: impact of the route of estrogen administration. Circulation. 2005;112(22):3495-500.