

Menopausal Treatments and the Risk of Venous Thrombosis/Thromboembolism

Hormone Replacement Therapy (HRT) containing oestrogens in tablet form and also selective oestrogen receptor modulators (See AMS Information Sheet - [The Role of SERMS after Menopause](#)) increase the risk of deep vein thrombosis (DVT)⁽¹⁻⁶⁾ and pulmonary embolus (PE).

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 first pass effect. 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.^{(7) (8)} Different effects are observed with oral combined HRT versus oestrogen alone. By comparison, transdermal HRT has little or no effect on coagulation factors. The risk of a thrombotic event is greater within the first year of starting treatment⁽⁹⁾, however the increased risk persists throughout the time of taking HRT.

How big is the risk?

- In most women who do not take HRT, 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)⁽¹⁰⁾ and in association with illnesses including cancer and some autoimmune diseases⁽¹¹⁾ (See table below for the effect of age , body mass index and HRT on thrombosis risk).
- Taking HRT 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⁽⁴⁾.
(See AMS Information Sheet - [Treating the Menopause - The Concept of Risk and Benefit](#)).
This is shown in the table below (adapted from⁽¹¹⁾).

Incidence of venous thromboembolism (VTE)

Baseline age	Placebo (for oestrogen plus progestin) indicating a baseline risk	Oestrogen plus progestin HRT	Placebo (for oestrogen only)	Oestrogen only
	Number of women per 1000 per year		Number of women per 1000 per year	
50-59 years	0.8	1.9	1.2	1.6 (Not Significant)
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	1.9
25-30	1.5	3.5	1.8	2.4
>30	2.5	5.1	3	3.9



- The risk of VTE is increased in postmenopausal women taking oral oestrogens with or without progesterone⁽¹¹⁾. The risk of VTE appears to be higher in those who take combined oestrogen-progestin HRT than in those taking oestrogen - only HRT^{(12) (13) (14)}. There is some evidence that the type of progestogen may also influence VTE risk but more evidence is needed⁽²⁾.
- Observational studies have not shown an increased risk of DVT in postmenopausal women using transdermal oestrogen⁽¹¹⁾.

How to minimise the risk

- Women with a personal history or a family history of thrombosis can be screened for risk factors. However routine screening for low risk women before starting HRT is not considered necessary.
- Women who acquire temporary risk factors for clotting such as long distance travel, fracture of lower limbs, certain surgical procedures or any prolonged immobilisation may be advised to cease HRT in the short term (the use of compression stockings is recommended)⁽¹⁵⁾.
- Use transdermal oestrogen instead of oral oestrogen preparations as meta-analysis of observational studies indicates that transdermal oestrogen is not associated with an increased risk of VTE^{(16) (2) (14)}. The risk of tibolone is uncertain⁽¹⁷⁾. There has been some research showing tibolone did not seem to cause an increase in the number of clots⁽¹⁸⁾.
- In clinical practice, previous VTE and a high risk of clotting indicate a woman at high risk and a transdermal preparation and reduced oestrogen dose are 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.

Key points

- The risk of VTE in most women is low.
- Assess all women thoroughly for any risk factors predisposing them to the development of VTE prior to commencing HRT.
- Individualise all treatment based on the patient, her clinical features, her needs and her risk assessment.
- Use of oral HRT doubles the woman's baseline risk of VTE.
- If HRT is essential in a woman assessed to be at high risk of developing VTE, it is preferable to use a transdermal preparation.

Links

[The Role of SERMS after Menopause](http://www.menopause.org.au/for-women/information-sheets/27-the-role-of-serms-after-menopause)

www.menopause.org.au/for-women/information-sheets/27-the-role-of-serms-after-menopause

[Treating the Menopause - The Concept of Risk and Benefit](http://www.menopause.org.au/for-women/information-sheets/26-treating-the-menopause-the-concept-of-risk-and-benefit)

www.menopause.org.au/for-women/information-sheets/26-treating-the-menopause-the-concept-of-risk-and-benefit

Recommended reading

Archer DF, Oger E. Estrogen and progestogen effect on venous thromboembolism in menopausal women. *Climacteric*. 2012;15:235 – 40.

References

1. Anderson FAJ, Spencer FA. Risk Factors for Venous Thromboembolism. *Circulation*. 2003;107:19-16.
2. Canonico M, Plu-Bureau G, Lowe GDO, Scarabin P-Y. Hormone replacement therapy and risk of venous thromboembolism in postmenopausal women: systematic review and meta-analysis. *British Medical Journal*. 2008;336(7655):1227 - 31.
3. Cushman M, Kuller LH, Prentice R, Rodabough RJ, Psaty BM, Stafford RS, et al. Estrogen plus progestin and risk of venous thrombosis. *Jama*. 2004;292(13):1573-80.
4. Daly E, Vessey MP, Hawkins MM, Carson JL, Gough P, Marsh S. Risk of venous thromboembolism in users of hormone replacement therapy. *The Lancet*. 1996;348(9033):977 - 80.
5. Høibraaten E, Qvigstad E, Arnesen H, Larsen S, Wickstrøm E, Sandset PM. Increased Risk of Recurrent Venous Thromboembolism during Hormone Replacement Therapy Results of the Randomized, Double-blind, Placebo-controlled Estrogen in Venous Thromboembolism Trial (EVTET). *Thrombosis and Haemostasis*. 2000;84(6):961 - 7.
6. Wu O. Postmenopausal hormone replacement therapy and venous thromboembolism. *Gender medicine*. 2005;2 Suppl A:S18-27.
7. 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. *Cardiovascular Research*. 1999;41(1):21-4.
8. Meade TW. Oral contraceptives, clotting factors, and thrombosis. *American journal of obstetrics and gynecology*. 1982;142(6 Pt 2):758-61.
9. National Guideline Clearinghouse. Venous thromboembolism and hormone replacement therapy Rockville MD: Agency for Healthcare Research and Quality (AHRQ); 2004 [5/1/2014]. Available from: <http://www.guideline.gov/content.aspx?id=34965>.
10. Ornstein DL, Cushman M. Factor V Leiden. *Circulation*. 2003;107(107):e94 - e7.
11. Archer DF, Oger E. Estrogen and progestogen effect on venous thromboembolism in menopausal women. *Climacteric*. 2012;15:235 – 40.
12. Douketis JD, Julian JA, Kearon C, Anderson DR, Crowther MA, Bates SM, et al. Does the type of hormone replacement therapy influence the risk of deep vein thrombosis? A prospective case-control study. *Journal of thrombosis and haemostasis : JTH*. 2005;3(5):943-8.
13. Sare GM, Gray LJ, Bath PM. Association between hormone replacement therapy and subsequent arterial and venous vascular events: a meta-analysis. *European Heart Journal*. 2008;29(16):2031-41.
14. Canonico M, Plu-Bureau G, Scarabin PY. Progestogens and venous thromboembolism among postmenopausal women using hormone therapy. *Maturitas*. 2011;70(4):354-60.
15. 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-226S.
16. 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.
17. Zayas-Jaime FJ, Ornelas-Aguirre JM, Perez-Napoles DE. Reasons for abandonment of hormone replacement therapy with tibolone in menopausal women]. *Ginecologia y obstetricia de Mexico*. 2013;81(10):593-601.
18. Cummings SR, Ettinger B, Delmas PD, Kenemans P, Stathopoulos V, Verweij P, et al. The Effects of Tibolone in Older Postmenopausal Women. *New England Journal of Medicine*. 2008;359(7):697-708.