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EDITORIAL

Further evidence for promoting transdermal estrogens in the management of postmenopausal symptoms

After a continued increase in use until the end of the 1990s,[1] prescription rates of postmenopausal hormone therapy (HT) have dramatically declined in the wake of the findings of the Women's Health Initiative clinical trials.[2] However, HT remains the most effective treatment to alleviate menopausal symptoms; therefore, many women are still prescribed this treatment worldwide. Nevertheless, medical guidelines have been modified and now recommend that only women with moderate to severe symptoms be prescribed the lowest effective dose for the shortest possible duration.[3] In this context, early postmenopausal women represent the usual candidates for this treatment, and cardiovascular disease, including venous thromboembolism and stroke, becomes the major side effect of short-term oral HT. In contrast, short-term use of HT has little effect on the risk of breast cancer and might even be beneficial for coronary heart disease (CHD).[4] In addition, HT reduces the risk of colorectal cancer and osteoporotic fractures.[2] Based on these observations, reducing the excess risk of venous thromboembolism appears to be a relevant strategy toward improving the benefit/risk profile of HT. In 2003, the Estrogen and Thromboembolism Risk Study, a French case-control study, showed, for the first time, a differential association of oral and transdermal estrogens on the risk of venous thromboembolism. Contrary to oral estrogens, transdermal estrogens were not associated with an increased risk for venous thromboembolism.[5] A few years later, the final results of the Estrogen and Thromboembolism Risk study and the E3N French cohort study confirmed the potential safety of transdermal estrogens with respect to thrombotic risk.[6,7] Recently, a large cohort study set up in a United Kingdom health insurance database provided further evidence for a better thrombotic profile of transdermal estrogens compared with oral estrogens.[8]

In this issue of *Menopause*, the results of a cohort study comparing the risk of venous thromboembolism between oral and transdermal estrogen users in North America are presented.[9] This study was set up from the Thomson Reuters MarketScan database, a health insurance database covering about 30 million participants in Canada between January 2002 and October 2009. For the present analysis, two retrospective matched cohorts of 27,000 women using either transdermal estrogen–only or oral estrogen–only were selected at random from a subpopulation meeting several inclusion criteria. However, these two cohorts consisted of both premenopausal and postmenopausal women, with only one third of menopausal estrogen–only users representing the relevant population. Restricting the analysis to this postmenopausal population led to only 29 and 56 venous thromboembolism events among transdermal and oral estrogen users, respectively. Despite the low number of cases, results showed an incidence rate of venous thromboembolism that is significantly lower among transdermal estrogen users compared with oral estrogen users (incidence rate ratio, 0.44; 95% CI, 0.25-0.77; $P = 0.004$). These results are consistent with data from previous studies and meta-analyses that showed a significant difference in thrombotic risk between oral and transdermal estrogen users.[4-8,10] However, because the incidence rate of venous thromboembolism in oral and transdermal estrogen users has never been compared with the incidence rate occurring in nonusers, this study did not allow for the highlighting of the potential safety of transdermal estrogens with respect to thrombotic risk. No attempt was made to separate the type of estrogen or the dose. On one hand, the estrogens differed by route of administration. Although transdermal estrogens were exclusively 17β-estradiol, oral estrogens included not only 17β-estradiol but also synthetic conjugated estrogens and conjugated equine estrogens. Because no subgroup analysis was made to specifically compare the thrombotic risk among users of transdermal or oral estradiol, it was not possible to distinguish whether the difference in incidence rate of venous thromboembolism depended on the route of estrogen administration rather than on the types of estrogen. On the other hand, the estrogen doses were not necessarily comparable between oral and transdermal treatments. In this study, women treated with transdermal estrogens administered at 25 to 100 μg/day were compared with women using 1 mg/day (Estrace) or 0.625 mg/day of oral estrogens (Cenestin and Premarin). Taking into account this possible difference by specific subgroup analysis or global adjustment would have been of interest.

Among nonhysterectomized women, progestogens are added to estrogens to prevent the risk of endometrial cancer associated with estrogen use.[11] Two French studies have recently shown that the type of progestogens could also be closely implicated in the thrombotic risk.[6,7] Although micronized progesterone was not associated with an increased thrombotic risk, some synthetic progestins could be thrombogenic. Therefore,

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it is important to take into account both the route of estrogen administration and the type of progestogen for an overall evaluation of the HT thrombotic profile.

Stroke is another common adverse outcome of HT,[2,12] and thus reducing stroke risk becomes a new challenge to further improve the benefit/risk profile of short-term HT. A large cohort study has recently found a differential association between oral and transdermal estrogens on the risk of stroke.[13] Contrary to oral estrogens, standard-dose transdermal estrogens were not associated with an increased risk of stroke among postmenopausal women, suggesting another important advantage of transdermal estrogens compared with oral estrogens. This result is all the more important because it could be biologically plausible. Indeed, it has been recently shown that increased thrombin generation, which may be detected in the plasma of women using oral but not transdermal estrogens,[14] could have an important role in the etiology of stroke among postmenopausal women.[15] Therefore, hypercoagulabilty could at least partly explain the increased risk of stroke among women using oral estrogens, and transdermal estrogens could be a safer option with respect to this adverse outcome.

Uncertainty still remains regarding the role of HT on CHD among postmenopausal women. The reanalysis of Women's Health Initiative clinical trials by age or time since menopause has shown that hormone timing may play a crucial role in determining the coronary risk among HT users (the "timing hypothesis"). Women who initiated HT closer to menopause tended to have a reduced CHD risk than do women more distant from menopause.[16] Currently, the alleviation of menopausal symptoms is the only indication for estrogen use, whatever route of administration, and other specific strategies are used for preventing chronic diseases.

The findings by Laliberte et al,[9] together with the findings of previous studies, may be of great clinical relevance in minimizing the risk of venous thromboembolism among women who require HT. For example, among 10,000,000 postmenopausal women including 20% HT users, around 1,000 cases of pulmonary embolism could be avoided for 1 year through transdermal estrogen use, and this safer option would be especially noticeable for women at high risk for venous thromboembolism. Nevertheless, despite increasing evidence for a neutral effect of transdermal estrogens on the risk for venous thromboembolism, it is important to notice that randomized, controlled trials are needed to definitely demonstrate the safety of transdermal estrogens with respect to thrombotic risk. However, the feasibility of such trials remains uncertain.

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REFERENCES

1. Haas JS, Kaplan CP, Gerstenberger EP, Kerlikowske K. Changes in the use of postmenopausal hormone therapy after the publication of clinical trial results. *Ann Intern Med* 2004;140:184-188.
2. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002;288:321-333.
3. The North American Menopause Society. Estrogen and progestogen use in postmenopausal women: July 2008 position statement of The North American Menopause Society. *Menopause* 2008;15:584-602.
4. Olie V, Canonico M, Scarabin PY. Risk of venous thrombosis with oral versus transdermal estrogen therapy among postmenopausal women. *Curr Opin Hematol* 2010;17:457-463.
5. Scarabin PY, Oger E, Plu-Bureau G. Differential association of oral and transdermal oestrogen-replacement therapy with venous thromboembolism risk. *Lancet* 2003;362:428-432.
6. Canonico M, Oger E, Plu-Bureau G, et al. Hormone therapy and venous thromboembolism among postmenopausal women: impact of the route of estrogen administration and progestogens: the ESTHER study. *Circulation* 2007;115:840-845.
7. Canonico M, Fournier A, Carcaillon L, et al. Postmenopausal hormone therapy and risk of idiopathic venous thromboembolism: results from the E3N cohort study. *Arterioscler Thromb Vasc Biol* 2010;30:340-345.
8. Renoux C, Dell'Aniello S, Suissa S. Hormone replacement therapy and the risk of venous thromboembolism: a population-based study. *J Thromb Haemost* 2010;8:979-986.
9. Laliberte F, Dea K, Sheng Duh M, Kahler KH, Rolli M, Lefebvre P. Does the route of administration for estrogen hormone therapy impact risk of venous thromboembolism? Estradiol transdermal system versus oral estrogen-only hormone therapy. *Menopause* 2011;18:1052-1059.
10. Canonico M, Plu-Bureau G, Lowe GD, Scarabin PY. Hormone replacement therapy and risk of venous thromboembolism in postmenopausal women: systematic review and meta-analysis. *BMJ* 2008;336:1227-1231.
11. The North American Menopause Society. Role of progestogen in hormone therapy for postmenopausal women: position statement of The North American Menopause Society. *Menopause* 2003;10:113-132.
12. Anderson GL, Limacher M, Assaf AR, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA* 2004;291:1701-1712.
13. Renoux C, Dell'aniello S, Garbe E, Suissa S. Transdermal and oral hormone replacement therapy and the risk of stroke: a nested case-control study. *BMJ* 2010;340:c2519.
14. Scarabin PY, 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;18:873-879.
15. Carcaillon L, Alhenc-Gelas M, Béjot Y, et al. Increased thrombin generation is associated with acute ischemic stroke but not with coronary heart disease in the elderly. The Three-City Cohort Study. *Arterioscler Thromb Vasc Biol* 2011;31:1445-1457.
16. Rossouw JE, Prentice RL, Manson JE, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. *JAMA* 2007;297:1465-1477.

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