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Centre for Research in Epidemiology and Population Health, U1018, hormones and Cardiovascular Disease and University Paris-Sud, UMR-S 1018, Villejuif, France

Adresse: Hôpital Paul Brousse
16 avenue Paul Vaillant-Couturier
94807 Villejuif Cedex, France
Tel: + 33 1 45 59 51 66
Fax: + 33 1 45 59 51 70
Email: marianne.canonico@inserm.fr

Corresponding author: Marianne Canonico (address above)

After a use in permanent increase until the end of the 90' [1], prescription rates of postmenopausal hormone therapy (HT) have dramatically reduced in the wake of the findings from Women's Health Initiative (WHI) clinical trials [2]. Yet, HT remains the most effective treatment to correct menopausal symptoms and therefore, many women are still prescribed this treatment worldwide. Nevertheless, medical guidelines have been modified and now recommend that only women suffering from moderate to severe symptoms be prescribe the lowest effective dose for the shortest possible duration [3]. In this context, middle-aged postmenopausal women represent the main candidate for this treatment and cardiovascular disease, including venous thromboembolism and stroke, becomes the major harmful effect of short-term oral HT. By contrast, short term use of HT little affects the risk of breast cancer and could be beneficial for coronary heart disease (CHD) among recently postmenopausal women [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 as a relevant strategy to improve the benefit/risk profile of HT. In 2003, the EStrogen and THromboEmbolism Risk (ESTHER) study, a French case/control study, showed for the first time a differential association of oral and transdermal estrogens with the risk of venous thromboembolism. Contrary to oral estrogens, transdermal estrogens were not associated with an increased risk of venous thromboembolism [5]. Few years later, final results of the ESTHER 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 as compared to oral estrogens [8].

In this issue of *Menopause*, results of a cohort study comparing the risk of venous thromboembolism between oral and transdermal estrogens 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 millions of subjects 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 (Vivelle-Dot®) or oral estrogen-only (Cenestin®, Estrace®, Premarin®) were selected at random from a subpopulation requiring to meet several inclusion criteria. However, these two cohorts consisted of both pre and postmenopausal women with

only one third of menopausal estrogen-only users who therefore represented the relevant population. Restricting the analysis to this postmenopausal population led to only 29 and 56 venous thromboembolism events among transdermal and oral estrogens users, respectively. Despites this few number of cases, results showed an incidence rate of venous thromboembolism significantly lower among transdermal estrogens users as compared to oral estrogens 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 which showed a significant difference in thrombotic risk between oral and transdermal estrogens users [4-8, 10]. However, since the incidence rate of venous thromboembolism in oral and transdermal estrogens users has never been compared to the one occurring in non users, this study did not allow highlighting the potential safety of transdermal estrogens with respect to thrombotic risk. With respect to the treatments assessed in this study, no attempt was made to separate the type of molecules as well as the estrogens doses. On one hand, the estrogens molecules differed by route of administration. While transdermal estrogens were exclusively 17β-estradiol (Vivelle-Dot®), oral estrogens included 17β-estradiol (Estrace®) but also synthetic conjugated estrogens (Cenestin®) and conjugated equine estrogens (Premarin®). Since no subgroup analysis was made to specifically compare the thrombotic risk among users of Vivelle-Dot® and Estrace®, 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 molecules. On the other hand, the estrogens doses were not necessarily comparable between oral and transdermal treatments. In this study, women treated by transdermal estrogens administered at 25 to 100 µg/day were compared to women using 1 mg/day (Estrace®) or 0.625 mg/day oral estrogens (Cenestin® and Premarin®). Taking into account this possible difference by specific subgroup analysis or global adjustment would have been of interest.

Among not hysterectomised women, progestogens are added to estrogens for preventing the risk of endometrial cancer associated to estrogens use [11]. Two French studies have recently showed that the type of progestogens could also be closely implicated in the thrombotic risk [6, 7]. While micronised progesterone was not associated with an increase thrombotic risk, some of synthetic progestins could be thrombogenic. Therefore, important is to take into account both the route of

estrogen administration and the type of progestogens for an overall evaluation of the HT thrombotic profile.

Stroke is another common adverse outcome of HT [2, 12] and reducing also the stroke risk now 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 of oral and transdermal estrogens with the risk of stroke [13]. Contrary to oral estrogens, standard doses transdermal estrogens were not associated with an increased risk of stroke among postmenopausal women, suggesting another important advantage of transdermal estrogens as compared to oral estrogens. This result is all the more important since it could be biologically plausible. Indeed, it has been recently shown that increased thrombin generation, which may be detected in plasma of women using oral but not transdermal estrogens [14], could have an important role in the etiology of stroke among postmenopausal women [15]. Thus, a hypercoagulabilty could at least in part explain the increased risk of stroke among women using oral estrogens and transdermal estrogens could be a safer option with respect this adverse outcome.

Uncertainty still remains regarding the role of HT on CHD among postmenopausal women. The re-analysis of WHI 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]. Admittedly, a potential beneficial effect of transdermal estrogens on CHD close to menopause has never been investigated so far but is this potential positive effect an expected benefit of HT for recently postmenopausal women? Currently, correction of menopausal symptoms is the only indication for estrogen use whatever the route of administration and other specific strategies can be used for preventing chronic diseases.

The findings by Laliberte et al together with 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 one year by transdermal estrogens use and this safer option would be especially noticeable for women at high risk for venous thromboembolism risk. Nevertheless, in spite increasing evidence for a neutral effect of transdermal estrogens on the risk of

venous thromboembolism, important is to notice that randomized controlled trials are needed to definitely demonstrate the safety of transdermal estrogens with respect to thrombotic risk. However, feasibility of such trials remains uncertain. .

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