Climacteric

ISSN: 1369-7137 (Print) 1473-0804 (Online) Journal homepage: https://www.tandfonline.com/loi/icmt20

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To cite this article: P.-Y. Scarabin (2018) Progestogens and venous thromboembolism in menopausal women: an updated oral versus transdermal estrogen meta-analysis, Climacteric, 21:4, 341-345, DOI: 10.1080/13697137.2018.1446931

To link to this article: https://doi.org/10.1080/13697137.2018.1446931

Published online: 23 Mar 2018.

CLIMACTERIC
2018, VOL. 21, NO. 4, 341–345
https://doi.org/10.1080/13697137.2018.1446931

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REVIEW

Progestogens and venous thromboembolism in menopausal women: an updated oral versus transdermal estrogen meta-analysis

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ABSTRACT

Postmenopausal hormone therapy (HT) is a modifiable risk factor for venous thromboembolism (VTE). While the route of estrogen administration is now well recognized as an important determinant of VTE risk, there is also increasing evidence that progestogens may modulate the estrogen-related VTE risk. This review updates previous meta-analyses of VTE risk in HT users, focusing on the route of estrogen administration, hormonal regimen and progestogen type. Among women using estrogen-only preparations, oral but not transdermal preparations increased VTE risk (relative risk (RR) 1.48, 95% confidence interval (CI) 1.39–1.58; RR 0.97, 95% CI 0.87–1.09, respectively). In women using opposed estrogen, results were highly heterogeneous due to important differences between the molecules of progestogen. In transdermal estrogen users, there was no change in VTE risk in women using micronized progesterone (RR 0.93, 95% CI 0.65–1.33), whereas norpregnane derivatives were associated with increased VTE risk (RR 2.42, 95% CI 1.84–3.18). Among women using opposed oral estrogen, there was higher VTE risk in women using medroxyprogesterone acetate (RR 2.77, 95% CI 2.33–3.30) than in those using other progestins. These clinical findings, together with consistent biological data, emphasize the safety advantage of transdermal estrogen combined with progesterone and support the current evidence-based recommendations on HT, especially in women at high VTE risk.

ARTICLE HISTORY
Received 12 January 2018
Revised 7 February 2018
Accepted 24 February 2018
Published online 26 March 2018

KEYWORDS
Postmenopausal hormone therapy; venous thromboembolism; estrogens; progesterone; progestin; progestogen

Introduction

Hormone therapy (HT) is the most effective treatment for menopause-related symptoms. Postmenopausal women with an intact uterus who use systemic estrogens are also prescribed progestogen to prevent the increased risk of endometrial cancer. Progestogens include progesterone, the only natural progestogen, and synthetic progestogens, often named progestins. All the progestogens used in HT may substantially differ with respect to their biological and clinical effects[1]. A large variety of progestogens are used in Europe, especially in France where micronized progesterone is the most commonly used, while medroxyprogesterone acetate (MPA) is almost exclusively used in the USA.

After being one of the best-selling drugs among women in the 1980s, HT use declined substantially after the results of randomized prevention trials, including the Women's Health Initiative (WHI) trials in the USA[2–4]. Over the past decade, the benefit–risk ratio of HT has become a highly debated topic and analysis of large-scale trials provided compelling evidence that venous thromboembolism (VTE) was the main serious adverse effect of HT[4]. In addition, characteristics of HT, including the route of estrogen administration as well as the presence and type of progestogen, emerged as major determinants of VTE risk in HT users[5]. In order to avoid the excess of VTE risk, optimizing HT represents an important challenge. This review summarizes the data on HT-related VTE risk, focusing on the route of estrogen administration, hormonal regimen and progestogen type.

Meta-analysis of venous thromboembolism risk

This is an updated meta-analysis based on previous reviews and the MedLine database[5–7].

Data selection

All comparative studies that included postmenopausal women using either oral or transdermal estrogens were considered. For studies to be included, they needed to report using both oral and transdermal estrogens. They also had to provide information on the presence and type of progestogens and had to include non-users of HT as a reference group.

The EStrogens THromboEmbolism Risk (ESTHER) study was the first one to show the safety advantage of transdermal versus oral estrogens with respect to VTE risk[8,9]. This finding was confirmed in several large-scale studies, including the E3N cohort study[10], the analysis of the General Practitioner Research Database from the UK[11], the Million Women and the Mega studies[12,13]. In addition, most of these studies have

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highlighted the important role of concomitant progestogens in determining VTE risk among HT users. These data have been summarized in systematic reviews and quantitative assessments of VTE risk in HT users[5–7]. More recently, the ThromboEmbolism Hormone Study (TEHS) using nationwide health databases in Sweden addressed these questions again and provided similar results[14].

Statistical analysis

Statistical methods have been described[6,7]. Briefly, log-transformed risk ratios (RRs) were pooled using random-effect models[15]. Between-study heterogeneity was assessed with the Cochran's test, and the I^2 statistic was used as a measure of the degree of inconsistency in the study results[16]. A value of 0% indicates no observed heterogeneity, and larger values show increasing heterogeneity. Stratified analysis was conducted based on the route of estrogen administration, hormonal regimen (opposed and unopposed estrogen) and molecules of progestogens.

Results

Seven population-based observational studies (four case–control and three cohort studies) were included. No randomized trial was eligible. Studies included 26 471 VTE cases (735 users of transdermal estrogen, 3103 users of oral estrogen and 22 633 non-users). The main clinical outcome was a first episode of idiopathic VTE (deep vein thrombosis and/or pulmonary embolism), except for two studies either focusing on VTE recurrence[17] or including secondary VTE[14]. All these studies were well designed. Representativeness of cases and selection of controls were adequate. Cases and controls were most often matched on relevant factors. Data on HT were collected using standardized interview or reliable health databases. VTE was well defined and ascertainment of cases was based on an objective imaging procedure. Statistical analysis was well conducted and VTE risk was adjusted for relevant confounders. Overall, the risk of bias of included studies was low.

Figure 1(A) shows the pooled VTE risk in HT users by route of estrogen administration and hormonal regimen (opposed or unopposed estrogen). Among women using estrogen-only therapy, oral but not transdermal preparations were associated with increased VTE risk (RR 1.48, 95% CI 1.39–1.58; RR 0.97, 95% CI 0.87–1.09, respectively). In transdermal estrogen users, the pooled VTE risk was close to one with a narrow confidence interval and no between-study heterogeneity ($I^2 = 0\%$). In women using opposed estrogens, VTE risk significantly increased by 23% and 88%, respectively, among transdermal and oral estrogen users, and a large and significant heterogeneity across studies was detected ($I^2 > 50\%$, $p < 0.05$), especially in oral estrogen users.

Figure 1(B) shows VTE risk in users of transdermal estrogen by type of progestogen. Based on three studies[9,10,17], there was no change in estrogen-related VTE risk in women using progesterone (RR 0.93, 95% CI 0.65–1.33), whereas use of nomegestrol acetate or promegestone was associated with increased VTE risk (RR 2.42, 95% CI 1.84–3.18). These results were consistent across studies ($I^2 < 6\%$). VTE risk related to other progestins was intermediate with an important heterogeneity.

In users of oral estrogen, VTE risk substantially varied by progestogen type (Figure 1(C)). Based on three studies[12–14], MPA use was consistently associated with increased VTE risk (RR 2.77, 95% CI 2.33–3.30; $I^2 = 0\%$). When compared with preparations containing nortestosterone derivatives or other progestins, estrogen combined with MPA significantly increased VTE risk.

Interpretation

This updated meta-analysis confirms the lower VTE risk among transdermal versus oral estrogen users and highlights important differences between progestogen molecules. While no change in VTE risk could be detected in users of transdermal estrogen combined with progesterone, there was a clear rise in VTE risk related to nomegestrol acetate or promegestone among transdermal estrogen users as well as to MPA among oral estrogen users. An important implication of these findings is that the higher VTE risk associated with progestogen use should not be considered as a class effect. Compound-specific assessments of VTE risk are therefore needed. The misleading MPA classification into pregnane derivatives further justifies a molecular approach. However, sometimes because of the limited sample size, further stratification was not appropriate in this meta-analysis and some results remain inconclusive.

Other studies showed lower VTE risk in transdermal versus oral estrogen users. However, the absence of non-users as a reference group did not allow these studies to be included in the meta-analysis[18,19]. Randomized trials provided information on the specific role of MPA in the development of VTE. In the WHI trials, the risk of VTE was higher in women receiving estrogens combined with MPA than in women receiving estrogens alone[4]. The Women's International Study of Long Duration Oestrogen after Menopause (WISDOM) trial provided direct comparison between both regimens. The risk of VTE was more than two times higher in women using MPA than in women not using MPA, although this difference was of borderline significance[20].

In this meta-analysis, progestogens were identified as a main source of between-study variability. However, some degree of inconsistency remains in oral estrogen-only users. Study design (cross-sectional vs. cohort study), doses and types of estrogen may also contribute to the heterogeneity of results[5]. A meta-analysis showed a positive correlation between oral estrogen dose and VTE risk. By contrast, there was no relation between VTE risk and the dose of transdermal estrogen[21]. Changes in VTE risk according to the different types of estrogen have also been reported[22,23].

Another meta-analysis recently confirmed the safety advantage of transdermal vs. oral estrogens with respect to VTE risk[24]. However, the authors pooled all the studies, regardless of concomitant progestogens, and the heterogeneity reported in this meta-analysis was mainly due to the

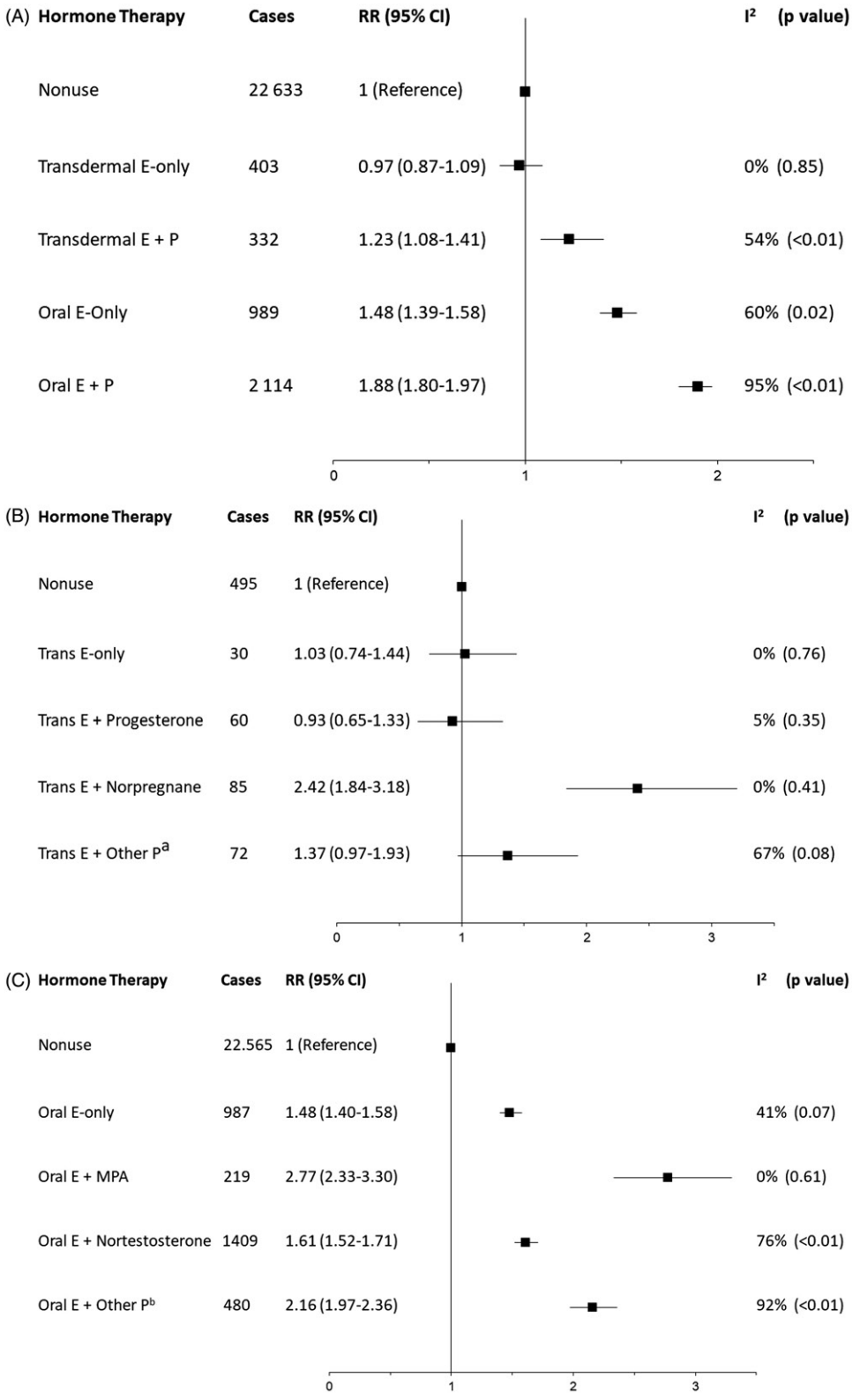

Figure 1. Pooled risk of venous thromboembolism among women using hormone therapy according to (A) the route of estrogen administration and hormonal regimen, (B) the type of progestogen (P) in transdermal estrogen users, and (C) the type of progestogen in oral estrogen users. Norpregnane derivatives include nomegestrol acetate and promegestone. Other progestogens include (a) pregnane and nortestosterone derivatives and unspecified (b) progesterone, pregnane and norpregnane derivatives and unspecified P. RR, risk ratio; CI, confidence interval; E, estrogen.

progestogens but not to the route of estrogen administration[25]. Thus, any valid quantitative assessment of VTE risk related to the route of estrogen administration should be based on women using estrogens alone or opposed estrogens with progestogens having a similar effect.

The main limitation of the present meta-analysis is the observational nature of the included studies, which affects the quality of evidence. Misinterpretation of the observational data led recently to discrepancies in rating the quality of evidence[24,25]. However, a fair analysis of current data, as

well as consideration of all components of the GRADE system or a similar approach, suggests that the overall quality of evidence supporting the safety benefit of transdermal estrogens is moderate[26].

The difference in VTE risk between oral and transdermal estrogen is supported by biological data. There is high-quality evidence for differential effects of HT on hemostatic variables by route of estrogen administration[5]. Randomized trials consistently showed that oral but not transdermal estrogen use induced reversible prothrombotic changes in hemostatic variables, including resistance to activated protein C (APC)[27,28]. While impaired biosynthesis of coagulation proteins is probably due to a hepatic first-pass effect of estrogens when administered orally, the mechanism(s) underlying the APC resistance are not fully understood. However, APC resistance may be partly mediated through lower protein S and tissue factor pathway inhibitor levels[5]. Increased thrombin generation in the absence of APC has also been reported among postmenopausal women using oral estrogens but not among transdermal estrogen users[29].

In postmenopausal women using HT, the impact of concomitant progestogen on hemostasis has been scarcely investigated. Consistent with the clinical findings, two randomized controlled trials showed no change in clotting factors or APC resistance among transdermal users of HT combined with micronized progesterone[27,28]. One study suggested that transdermal estrogen combined with norpregnane derivatives might activate blood coagulation and induce APC resistance[30]. Interestingly, increased VTE risk has been found in women using injectable depot-MPA contraceptives[31], but no major change in hemostatic variables has been reported in users of MPA alone or combined with estrogen.

Clinical implications

VTE is a global health concern because of its significant morbidity and mortality[32]. The incidence of VTE markedly increases with age, reaching close to 1/1000 women-years around 50 years. Risk factors for VTE include history of VTE, obesity and inherited thrombophilia. VTE is the more prevalent adverse effect of HT, and therefore a strategy to decrease VTE risk is relevant to improving the benefit–risk ratio of HT[6]. Clinical and genetic risk factors may interact with HT to increase the incidence of VTE[33,34]. Acknowledgement of these interactions is of major importance to identify high-risk women and to prevent VTE among women who consider using HT. Since transdermal estrogens may not confer additional risk in women at high VTE risk, a substantial reduction in the number of VTE clinical events is expected by switching from oral to transdermal estrogens combined with progesterone[35].

During the past years, most debates about the risk–benefit profile of HT have focused on breast cancer and the role of age in modifying the effects of HT on the development of coronary heart disease. Meanwhile, promoting transdermal estrogens for VTE prevention has not been a major challenge. However, a consensus for managing menopause is emerging and the most recent clinical guides recommend transdermal estrogens combined with progesterone for women at high VTE risk requiring HT[36–38]. The European Menopause and Andropause Society was the first to recommend this HT regimen among women with a history of VTE[36]. The Endocrine Society also made a strong recommendation for using the non-oral route of HT among women at increased VTE risk[37]. The International Menopause Society has recently published updated HT recommendations in a well-documented guide including levels of evidence, grades of recommendations, and key messages for clinical practice[38]. Finally, the North American Menopause Society acknowledges that non-oral routes of administration may offer potential advantage, but additional research is urgently needed on the thrombotic risk of oral vs. transdermal estrogen[39]. However, the VTE statement is under-referenced and the feasibility of a trial is questionable. In addition, despite the high prevalence of obesity and its major role in HT-related VTE risk[40], no recommendation is made for women at high risk for VTE. Overall, based on the current clinical guidelines, changes in medical practice are expected. Significant shifts from oral to transdermal estrogen and from progestins to micronized progesterone have been reported[41].

Conclusion

Based on the best available evidence, transdermal estrogen combined with micronized progesterone appears to be the safest option with respect to VTE risk among postmenopausal women requiring HT. The most recent clinical guides recommend this HT regimen for women at high VTE risk. More research and action are needed to increase awareness of hormone-related VTE. Improving individual risk stratification and a personalized approach to HT are a major challenge for future work.

Conflict of interest The author reports no conflicts of interest.

Source of funding Nil.

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