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Risk of venous thromboembolism events in postmenopausal women using oral versus non-oral hormone therapy: A systematic review and meta-analysis

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ABSTRACT

Introduction: Hormone therapy (HT) is an effective treatment for climacteric symptoms. Nevertheless, combined estrogen-progestin therapy and the oral route seem to entail higher risk of venous thromboembolism (VTE) than estrogen-only therapy and transdermal administration. The present study aimed to investigate the risk of thromboembolic events in postmenopausal women using non-oral estrogen compared to women using oral estrogen and control groups (women receiving placebo or non-users of HT), as well as to assess the thrombotic impact of estrogens alone vs. combined estrogen-progestin therapy.

Materials and methods: Systematic review of MEDLINE, Cochrane CENTRAL, EMBASE, and ClinicalTrials.gov according to PRISMA guidelines.

Results: Twenty-two studies were included in the meta-analyses (9 case-control studies, 9 cohort studies, and 4 randomized controlled trials). As compared to control groups, VTE risk was not increased with non-oral HT, including users of estrogens and estrogens plus progestins (OR 0.97 [0.9–1.06]), non-oral estrogen therapy (ET)-only (OR 0.95 [0.81–1.10]), and non-oral combined estrogen-progestin therapy (OR 0.92 [0.77–1.09]). Conversely, increased risk of VTE was observed as compared with control groups in users of oral HT, including users of estrogens and estrogens plus progestins HT (OR 1.72 [1.47–2.01]), oral ET-only (OR 1.43 [1.34–1.53]), and combined oral estrogen-progestin HT (OR 2.35 [1.9–2.9]). The comparison of non-oral vs. oral HT showed increased VTE risk with oral HT (OR 1.66 [1.39–1.98]).

Conclusions: VTE risk was increased in postmenopausal women with no previous thromboembolic events using oral HT. Non-oral HT did not significantly affect this risk. The quality of the evidence produced in our meta-analyses is low to moderate, and further clinical trials are needed to sort out the impact of different types of progestin and different estrogen doses and administration routes on VTE risk.

1. Introduction

Hormone therapy (HT) is the most effective treatment for relieving climacteric symptoms, which affect up to 75% of menopausal women [1]. Vasomotor symptoms such as hot flushes and night sweats, which are the main complaints of menopausal women, can be disabling, leading to significant impairment of quality of life [2]. For some time, treatment of these symptoms relied mostly on oral estrogen-progestin therapy [3]. However, in 2002 the results of the Women's Health Initiative (WHI) raised concerns about the risk of cardiovascular disease and venous thromboembolism in association with this combined scheme [4]. Since then, further evidence has been produced suggesting that the risk of thromboembolic events might be higher in users of combined estrogen-progestin therapy than in users of estrogen-only therapy [5,6].

In addition, observational studies have shown that the risk of

Abbreviations: APC, Activated protein C; BMI, body mass index; CBG, cortisol-binding globulin; CRP, C-reactive protein; CEE, conjugated equine estrogens; CVD, Cardiovascular disease; ET, estrogen therapy; HDL-C, high-density lipoprotein cholesterol; HR, Hazard ratio; HT, Hormone therapy; IGF-1, Insulin-like growth factor 1; LDL-C, low-density lipoprotein cholesterol; NOS, Newcastle-Ottawa Scale; OR, odds ratio; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis; RCT, randomized controlled trials; SHBG, Sex hormone-binding globulin; TBG, thyroxine-binding globulin; TFPI, tissue factor pathway inhibitor; VTE, venous thromboembolism

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thromboembolic events is lower with transdermal estrogen therapy (ET) than oral therapy [7,8]. The prothrombotic impact of oral ET is related to first-pass metabolism, which induces undesirable effects such as increased triglyceride levels, decreased low-density lipoprotein particle size, and production of some coagulation factors and C-reactive protein [9,10]. The fact that these changes are not observed with transdermal therapy may be clinically relevant to patients at high risk of thromboembolic events [11,12].

In turn, the role of progestins in thromboembolic risk is still uncertain [13]. Progestins are used in HT exclusively for endometrial protection in non-hysterectomized women, and are associated with a decreased risk of endometrial hyperplasia and cancer. Different progestins have distinct pharmacological properties and clinical effects [14], with well-documented consequences of hormone contraceptives for the coagulation system and variable impacts on vessel blood flow and prothrombotic state [15–18].

Despite these observations, currently available information regarding the prevalence of thromboembolic events in users of HT is inconclusive [19–21]. In the present study, we reviewed the existing evidence about the risk of thromboembolic events in postmenopausal women using non-oral estrogen compared to placebo and to oral estrogen, and analyzed studies comparing the thrombotic impact of estrogens alone vs. combined estrogen-progestin therapy.

2. Materials and methods

This study was performed in accordance with Cochrane Collaboration guidelines and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [22]. The review protocol and all data used in the analyses are available in the text, tables, and figures.

2.1. Eligibility criteria, search strategy, and study selection

We gathered data from clinical trials and from case-control and cohort studies designed to assess venous thromboembolism (VTE) (pulmonary embolism and/or deep vein thrombosis) in postmenopausal women using oral or non-oral HT. Women receiving placebo or non-users of HT were considered as control groups. For clinical trials and cohort studies, only works including postmenopausal women with no previous VTE were selected. For multiple articles on the same sample, we selected the article containing the most complete information. Eligibility assessment was performed independently in an unblinded, standardized manner by two reviewers, and inconsistencies were settled by a third reviewer.

MEDLINE, Cochrane Central Register of Controlled Trials (Cochrane CENTRAL accessed through Wiley Science), and EMBASE were searched for studies published until February 2017. We also searched http://ClinicalTrials.gov to retrieve RCTs with unpublished results. The following medical subject headings (MeSH) were used in the search: postmenopause OR menopause AND “estrogen replacement therapy” OR “hormone replacement therapy” AND “pulmonary embolism” OR “venous thromboembolism” OR thromboembolism.

2.2. Data extraction and quality assessment

Titles and abstracts were independently evaluated by two investigators (D.R. and T.M.F.), who also selected the articles for inclusion in the analyses. When necessary, these investigators evaluated the full text of articles. Disagreements were resolved by consensus or by consultation with a third reviewer (P.M.S.). If the required data were not located in the published article, authors were contacted to provide the missing information.

The following data were collected: first author and study group, publication year, number of patients, mean age, time since menopause, pre-existing disease, medications, country of study, number of participants, detailed interventions, type of control (placebo or no treatment), duration of follow-up, and outcome. Non-adjusted VTE risk estimates were extracted from the studies.

Table 1
Newcastle-Ottawa Scale (NOS) and quality of the studies included in the meta-analysis[a].

Study	Selection	Comparability	Exposure
Daly 1996 [27]	**	*	***
Jick 1996 [28]	**	*	***
Grodstein 1996 [33]	*	*	***
Pérez Gutthann 1997 [29]	****	*	***
WHI I 2002 [4]	****	*	***
Scarabin 2003 [7]	***	*	***
WHI II 2004 [34]	****	*	***
Douketis 2005 [6]	**	*	***
ESTHER 2007 [8]	**	*	***
WISDOM 2007 [35]	****	*	***
Schneider 2009 [36]	****	*	***
Ohira, 2010 [38]	****	*	***
E3N 2010 [37]	****	*	***
Renoux 2010 [30]	****	*	***
Laliberte 2012 [39]	***	*	***
MILLION 2012 [40]	****	*	***
Schierbeck, 2012 [41]	****	*	***
Roach 2013 [31]	****	*	***
Lee 2015 [42]	****	*	***
Bergendal 2016 [32]	****	*	***
Dinger 2016 [43]	**	*	***
Simon 2016 [44]	**	*	***

[a] Quality of selection (minimum 1–maximum 4 stars); comparability (minimum 0–maximum 1 star); exposure (minimum 1–maximum 3 stars).

Two investigators (D.R and R.B.R) used the Newcastle-Ottawa Scale (NOS) to assess the quality of the case control and cohort studies included in the meta-analyses (Table 1). This scale uses a “star system” according to which included studies are judged on three broad perspectives: selection of the study groups; comparability of the groups; and ascertainment of outcome of interest.

2.3. Statistical analysis

Statistical analysis was performed using R version 3.3.0 (R Foundation for Statistical Computing, Vienna, Austria). Meta-analyses were run in R using the meta for package [23]. The odds ratio (OR) with 95% confidence intervals (CIs) was used as the effect size estimator. Because of the differences in study design and sample characteristics, considerable heterogeneity was expected between the studies. Therefore, the pooled OR was calculated using random-effects models with the DerSimonian-Laird estimator [24], which is based on a normal distribution.

Heterogeneity in effect sizes across studies was assessed using the I^2 statistic and Cochran's Q test (with $p < 0.10$ indicating significant heterogeneity) [25]. Risk of publication bias was assessed using funnel plot graphics, analyzed both visually and with the Egger test. The significance of the intercept was evaluated by *t*-test, with $p < 0.10$ indicating significant publication bias [26].

3. Results

3.1. Study selection

Fig. 1 provides details of the study selection. The initial search identified 836 articles. After title and abstract screening and exclusion of duplicates, 43 potentially eligible studies were retrieved for full text review. Of these 43 articles, 21 were excluded: 13 did not report on the outcome of interest (VTE) and eight included women with cardiovascular disease or previous VTE. Therefore, 22 studies were included in the meta-analyses [4,6–8, 27–44]. Of these, nine were case-control

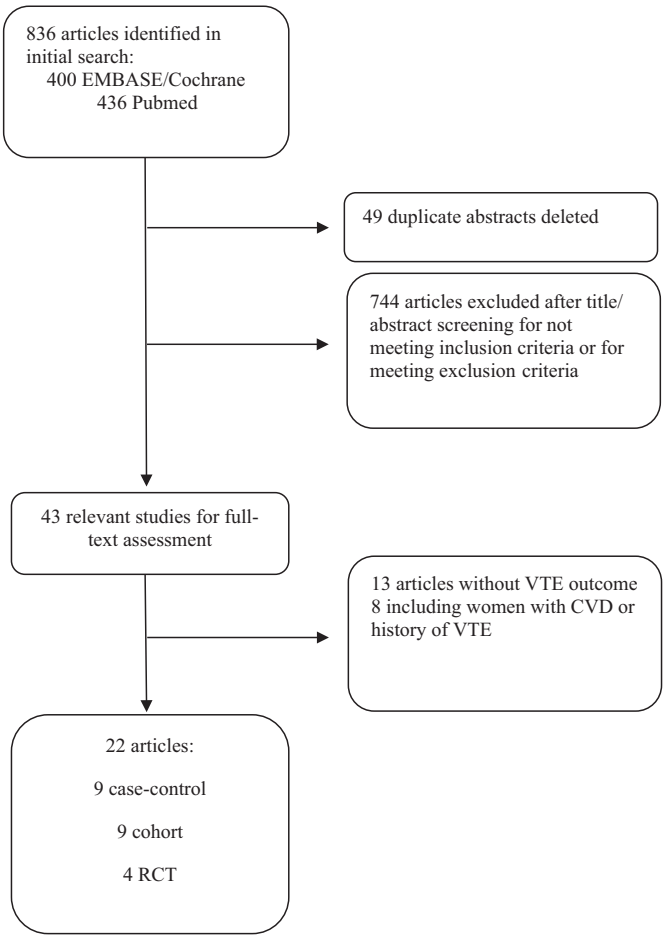

Fig. 1. Flow diagram of the study selection process.

studies investigating the occurrence of VTE in postmenopausal using oral or non-oral HT as compared to controls [6–8, 27–32]. Nine cohort studies were also included. In these studies, postmenopausal women who were not using HT were compared to postmenopausal women using oral or non-oral HT [33,36–40, 42–44]. Finally, four randomized controlled trials (RCTs) were included. These RCTs assessed the risk of VTE with oral HT, but not with non-oral HT [4,34,35,41].

3.2. Description of the studies

Table 2 summarizes the characteristics of the nine case-control studies. Table 3 describes the nine cohort studies and the four RCTs included in the meta-analyses.

VTE was defined as any thromboembolic outcome (pulmonary embolism and/or deep vein thrombosis) in women without previous events. One study did not inform the age range among the inclusion criteria [6], but the age of participants was similar to that of the women included in the other 21 studies (mean age ranging from 48 to 65.9 years). Most studies were performed in European countries, Canada, and the United States. NOS scores for the included studies ranged from 5 to 8 (Table 1).

All 22 studies included postmenopausal women with no history of VTE, with at least one group using oral or non-oral HT. Except for three studies directly comparing oral vs. non-oral HT [39,43,44], all others included a control or placebo group. Seven studies [7,27,30,33,37,38,40] compared never-HT users with past HT users; in one of these studies [30], past users were stratified according to time since HT discontinuation. In nine studies [4,28,33–36, 38,41,42], oral HT was not compared to non-oral HT. Therefore, these studies were excluded from non-oral HT analyses.

In two RCTs, only women without previous VTE events were included [35,41]. The other two RCTs were large trials, WHI I and WHI II [4,34]. Despite having been designed to evaluate healthy women, approximately 1% of the participants in these trials had prior VTE, and a low proportion also had established cardiovascular disease.

In the studies we analyzed, CEE, micronized estradiol, or estradiol valerate were not stratified for VTE risk. This was also the case for non-oral HT (17β estradiol in all cases): separate analyses were not performed for patches or gel, and risk was not analyzed according to dose. Thus, for the present purposes, all oral formulation types were included in a broad oral HT group. The same was true for non-oral HT, i.e., all doses and presentations were analyzed as a single non-oral HT group.

Nine of the 22 studies [6,7,28,30–32, 35,40,42] provided data regarding subgroups of users or non-users of progestins. Therefore, in addition to evaluating the impact of estrogen route on VTE risk, the impact on VTE risk of adding progestins to estrogen therapy was also analyzed. Seven studies [4,8,31,35–37, 40] described the type of progestin added to estrogen therapy, but did not provide information on the number of women receiving estrogen combined with these progestins or estrogen only. Therefore, a meta-analysis of progestin subgroups was not possible.

Seven studies [7,27,30,33,37,38,40] compared never-HT users with past HT users (oral route only). Six of them did not report changes in VTE risk when never users and past users were compared (Supplemental Table). One study reported a slight, but significant increase in risk of VTE in past HT users (relative risk [RR] 1.11 95%CI 1.04–1.19) [30]. That study [30] also stratified the past user group according to time since therapy discontinuation, and showed increased VTE risk

Table 2
Characteristics of case-control studies including patients with venous thromboembolism using or not HT.

Study	Country	Inclusion criteria	Exclusion criteria	Study duration (years)	Oral HT	Non-oral HT
Daly 1996 [27]	UK	45–64 years Case: PE, DVT, or both (mean age 53.9 ± 5.9 years) Control: no VTE (mean age 53.9 ± 5.6 years)	History of PE, DVT, or MI and history of surgery in the previous 6 weeks or illness necessitating bed rest for longer than 1 week, history of cancer of the breast, ovary, endometrium or other recent or active cancer, serious heart disease or use of anticoagulants	1.8	Low dose: CEE 0.625 mg, 1 mg 17B Estradiol or 1.5 mg piperazine estrone sulphate High dose: CEE 2.5 mg or 2 mg 17B E2	Low dose: Transdermal preparations delivering 50 μg 17B E2 High dose: 100 μg 17B E2
Jick 1996 [28]	USA	50–74 years Case: VTE (n = 42) Control: no VTE (n = 168) (mean age not informed; 50% of the population between 60 and 69 years)	Trauma or surgery in the previous 6 months, epilepsy, stroke, cancer, renal failure or coronary artery disease	14	CEE 0.325 mg, 0.625 mg or > 1.25 mg/day	–
Pérez Gutthann 1997 [29]	UK	50–79 years Case: VTE Control: no VTE (mean age not informed; 80% of the population between 50 and 70 years)	History of VTE or risk factors for VTE	3.7	Low dose: CEE 0.625 mg High dose: CEE 1.25 mg	Low dose: Transdermal E2 25–50 μg High dose: transdermal E2 100 μg
Scarabin 2003 [7]	France	45–70 years Case: VTE (mean age 62.1 ± 6.8 years) Control: no VTE (mean age 62 ± 6.8 years)	Previous episode of VTE or predisposing factor for VTE	3	Low dose: CEE 0.625 mg, 1 mg E2 or 1 mg estradiol valerate High dose: CEE 1.25 mg, 1.5-2 mg E2, or 2 mg estradiol valerate	Low dose: < 50 μg E2 High dose: 50-100 μg E2
Douketis 2005 [6]	Canada, Italy, and the Netherlands	Postmenopausal women, any age Case: DVT Control: no DVT (mean age not informed; 80% of the population between 50 and 79 years)	PE, ovarian failure, language barrier or cognitive impairment	3	Oral estrogen only or estrogen plus progestin	Transdermal estrogen
ESTHER 2007 [8]	France	Postmenopausal women, any age Case: VTE (mean age 61.6 ± 6.7 years) Control: no VTE (mean age 61.5 ± 6.6 years)	History of VTE, contraindication for HT or predisposing factor for VTE	6	Oral estrogen only or associated with progestin (most frequently 17B E2 0.5–2 mg/day)	Transdermal estrogen alone or associated with progestin (mostly < 50 μg/day)
Renoux 2010 [30]	UK	Postmenopausal women, 50–79 years Cases: VTE (mean age 65.9 ± 8.5 years) Control: no VTE (mean age 65.8 ± 8.5 years)	History of VTE	20.2	Oral estrogen alone or with progestogen Low dose: CEE < 0.625 mg or E2 < 2 mg High dose: CEE 0.625 mg or E2 2 mg	Transdermal estrogen alone or with progestogen Low dose: ≤ 50 μg High dose: > 50 μg
Roach 2013 [31]	Nether-lands	Postmenopausal women, 50–70 years (mean 59 years) Case: VTE Control: no VTE	Severe psychiatric problems and not speaking Dutch	5.5	Micronized E2 alone, CEE 0.625 mg + MPA and Micronized E2 (1 mg or 2 mg) + NETA	Transdermal patches containing micronized E2
Bergendal 2016 [32]	Sweden	40–64 years not using combined hormonal contraception Case: 1st DVT episode (mean age 54.6 ± 6.5 years) Control: no DVT (mean age 54.5 ± 6.5 years)	Not speaking Swedish, previous thrombosis or current malignancy	6	17B E2 alone or with NETA or MDX	Transdermal estrogen alone or with progestogen

PE: pulmonary embolism; DVT: deep vein thromboembolism; VTE: venous thromboembolism; MI: myocardial infarction; CEE: conjugated equine estrogen; MPA: medroxyprogesterone acetate; HT: hormone therapy; NETA: norethisterone acetate; DRSP: drospirenone; E2: estradiol; CVD: cardiovascular disease.

Table 3
Characteristics of cohort studies and randomized controlled trials.

Study	Country	Inclusion criteria and age of participants	Exclusion criteria	Follow-up (years)	Oral HT	Non-oral HT	Outcome
Grodstein 1996 [33] Cohort	USA	40–55 years, postmenopausal women (mean age not informed)	History of previous PE, cancer (except non-melanoma skin cancer), angina, MI, stroke or other cardiovascular disease	12	Most HT consisted of estrogen alone, without added progesterone (CEE 0.3.0 mg, 0.625 mg or > 1.25 mg/daily)	–	Pulmonary embolism
WHI I 2002 [4] RCT	USA	50–79 years, postmenopausal women(only women with an intact uterus were analyzed)	Any medical condition likely to be associated with a predicted survival of < 3 years, prior breast cancer or other cancer within the last 10 years (except non-melanoma skin cancer), low hematocrit or low platelet counts or adherence concerns	5.2	CEE 0.625 mg + MPA 2,5 mg	–	Cardiac heart disease (primary outcome) VTE (secondary outcome)
WHI II 2004 [34] RCT	USA	50–79 years, postmenopausal women, with prior hysterectomy	Any medical condition likely to be associated with a predicted survival of < 3 years, prior breast cancer or other cancer within the last 10 years (except non-melanoma skin cancer), low hematocrit or low platelet counts or adherence concerns	6.8	CEE 0.625 mg	–	Cardiac heart disease (primary outcome) VTE (secondary outcome)
WISDOM 2007 [35] RCT	UK, Australia and New Zealand	50–69 years Oral Combined HT: mean age 61.7 ± 5.1 years and 63.3 ± 4.7 years ET: mean age 61.9 ± 5.1 years) Control: mean age 63.3 ± 4.6 years)	Breast cancer, any other cancer in the past 10 years (except basal or squamous cell skin), endometriosis or endometrial hyperplasia, VTE, gall bladder disease, MI, unstable angina, cerebrovascular accident, subarachnoid hemorrhage, transient ischemic attack, or use of HT in previous 6 months	1	CEE 0.625 mg isolated or combined with MPA 2.5/5.0 mg orally daily	–	VTE (secondary outcome)
Schneider 2009 [36] Cohort	UK	UK-based General Practice Research Database, postmenopausal women aged < 70 years (mean age not informed; 54% of the population between 50 and 59 years)	Cancer, stroke, MI, VTE	6.0	Group 1: at least one prescription for any dosage form of estradiol/dydrogesterone Group 2: at least one prescription for oral CEE plus norgestrel, oral estradiol (valerate) plus norethisterone (acetate) or oral CEE plus MPA Group 3: had never received any prescription for HT	–	VTE (secondary outcome)
E3N 2010 [37] Cohort	France	Postmenopausal women from E3N prospective cohort study (mean age 54 years)	History of VTE and cancer other than basal cell carcinoma	10.1	Mostly 17B E2, associated or not with micronized progesterone, pregnane derivatives, norpregnane derivatives or nortestosterone derivatives	Mostly 17B E2, associated or not with micronized progesterone, pregnane derivatives, norpregnane derivatives or nortestosterone derivatives	VTE
Ohira 2010 [38] Cohort	USA	Post-menopausal women Cases: VTE (mean age 64 years) Control: no VTE (mean age 61 years)	Women who were not white or black or were scarcely represented in some field centers, prior VTE or cancer, warfarin users	11.8	Oral estrogen alone or with progestin	–	VTE

(*continued on next page*)

Table 3 (*continued*)

Study	Country	Inclusion criteria and age of participants	Exclusion criteria	Follow-up (years)	Oral HT	Non-oral HT	Outcome
Laliberte 2011 [39] Cohort	Canada	Postmenopausal women aged ≥35 years, recent users of HT, with 2 or more prescription refills (mean age: 48.9 ± 7.1 years)	History of VTE	10.1 (± 4.6)	Oral estrogen only, conjugated equine estrogens and micronized estradiol 17-beta (Cenestin, Estrace, Premarin)	Transdermal estrogen only (E2 transdermal system, Vivelle-Dot)	VTE, DVT and PE
MILLION 2012 [40] Cohort	UK	Postmenopausal women, 50–64 years (mean age: 56.7 ± 4.5 years)	Pre or perimenopausal, history of cancer or clotting problem, surgery in the 12 weeks prior to recruitment or unknown use of HT	3.1	CEE or E2 isolated or associated with MPA, NETA or norgestrel	Patch or gel formulation of 17beta estradiol with or without a progestin (not specified)	VTE
Schierbeck 2012 [41] RCT	Denmark	Recently postmenopausal white women, 45–58 years, last menstrual bleeding 3–24 months before study entry or perimenopausal symptoms in combination with recorded postmenopausal FSH levels HT: mean age 49.5 ± 2.7 years Control: mean age 50 ± 2.8 years	History of bone disease, uncontrolled chronic disease, previous or current cancer or thromboembolic disease, current or past treatment with glucocorticoids for more than six months, current or past use of HT in the past 3 months, and alcohol or drug dependence	10.1 during HT + 5.7 post-treatment	Triphasic estradiol and norethisterone acetate (intact uterus) or estradiol 2 mg/day (who undergone hysterectomy)	–	VTE (secondary outcome)
Lee 2015 [42] Cohort	Taiwan	50–79 years (randomly selected from National Health Insurance database: women who had a prescription for HT or medical service for a post-menopausal condition; or had neither prescription for HT nor medical service for a postmenopausal condition) HT: mean age 60.7 ± 8.1 years Control: mean age 59.5 ± 7.6 years	Prior VTE, who were ever prescribed HT in the past 3 years, hysterectomy	2	A list of all medications containing estrogens and/or progestogens recommended for HT and available in Taiwan during the study period was extracted from the database. In Taiwan, there were no pharmaceutical products for transdermal HT, tibolone or estradiol implant during the study years.	–	VTE
Dinger 2016 [43] Cohort	7 European countries	HRT starters (first-ever users), HRT switchers or HRT restarters (mean age: 54 ± 7.3 years)		8.5	DRSP 2 mg + E2 1 mg, other oral continuous combined HRT preparations containing a progestin other than DRSP or other oral HRT preparations	Non-oral estrogen preparations (not specified)	VTE, DVT or PE
Simon 2016 [44] Cohort	USA	Postmenopausal women, 50 years or more, at least 2 HT prescription refills (mean age: 55 years)	Other type of HT, CVD, cancer, thrombophilia or liver disease	10.6	Oral estrogen alone	E2 transdermal system, Vivelle-Dot	VTE, DVT or PE

RCT: randomized clinical trial; PE: pulmonary embolism; DVT: deep vein thromboembolism; VTE: venous thromboembolism; MI: myocardial infarction; CEE: conjugated equine estrogen; MPA: medroxyprogesterone acetate, HT: hormone therapy; NETA: norethisterone acetate; DRSP: drospirenone; E2: estradiol; CVD: cardiovascular disease.

compared to never users in past HT users who had discontinued oral HT for ≤4 months (RR past users: 1.43 [95%CI 1.23–1.66]; RR never users: 1.27 [95%CI 1.11–1.45]). However, the study reported that > 4 months of oral HT discontinuation rendered past user VTE risk similar to that of never users (RR 0.98 [95%CI 0.87–1.11]).

3.3. Data synthesis and meta-analyses

Meta-analyses were performed to evaluate two aspects: risk of any VTE event in postmenopausal women using HT considering administration route (oral vs. non-oral HT); and risk of any VTE event considering use of estrogen only vs. combined use of estrogen-progestin.

3.3.1. Non-oral HT vs. control groups

We performed three analyses with non-oral HT users to assess the risk of VTE. First we analyzed non-oral HT, including women receiving placebo or users of estrogens and estrogens plus progestins, to control groups (Fig. 2A). Data from nine studies [6,8,27,29–32, 37,40] were available for this analysis, totaling 740,722 control women and 80,433 non-oral HT users. The risk of VTE did not increase with non-oral HT (OR 0.97 [0.9–1.06]). Heterogeneity between the studies was 0%.

The second analysis compared users of non-oral ET-only with a control group (Fig. 2B). Six studies were included [6,7,30–32, 40], totaling 702,813 non-users and 42,884 users of non-oral ET. No increase in risk of VTE was detected in users of non-oral ET-only (OR 0.95 [0.81–1.10]). Heterogeneity between the studies was low (I^2 14%).

The third analysis focused on data from five studies [7,30–32, 40] describing VTE risk in users of non-oral combined HT (estrogen plus progestin) (Fig. 2C), totaling 10,573 users vs. 702,327 non-users of HT. Again, no increase in risk of VTE events was observed (OR 0.92 [0.77–1.09]). Between-study heterogeneity was 0%.

3.3.2. Oral HT vs. control groups

Similar analyses were performed to assess VTE risk with oral HT. Eighteen studies [4,6,8,27–38, 40–42] were included, totaling 252,538 women receiving oral HT (ET-only or estrogen plus progestin) and 868,514 women without HT (Fig. 3A). Increased risk of VTE was detected (OR 1.72 [1.47–2.01]). Between-study heterogeneity was high (I^2 86%).

Considering women using oral ET-only, 10 studies were included in the analysis [6,7,28,30–32, 34,35,40,42], with 80,313 ET-only users and 783,888 non-users (Fig. 3B). Again, an increased risk of VTE was detected in ET-only users (OR 1.43 [1.34–1.53]). Between-study heterogeneity was 0%.

The analysis of combined oral HT users vs. controls (Fig. 3C) included data from 10 studies [4,6,7,28,30–32, 35,40,42], with 786,561 control women and 153,426 combined oral HT users. An increase greater than twofold in the risk of VTE was found in the group of combined oral HT users (OR 2.35 [1.9–2.9]). Between-study heterogeneity was high (I^2 88%).

3.3.3. Non-oral HT vs. oral HT

Twelve studies were analyzed [6,8,27,29–32, 37,39,40,43,44], including case-control studies, cohort studies, and RCTs (Fig. 4A), for a total of 113,059 women using non-oral HT and 281,018 using oral HT. VTE risk was increased with oral HT (OR 1.66 [1.39–1.98], I^2 58%).

The next step was a sensitivity analysis. This sensitivity analysis was restricted to studies including participants without risk factors for VTE, cancer, previous HT use, or use of other (oral) HT-containing co-medication or other medication (aspirin) that could possibly influence VTE risk. A total of 33.024 users of non-oral HT and 57.793 users of oral HT from seven studies were considered [6,8,31,32,39,43,44] (Fig. 4B). In this analysis, higher risk of VTE was maintained for oral HT users (OR 1.80 [1.35–2.39] I^2 46%).

Publication bias may have occurred in the comparisons of controls vs. combined oral HT users (Fig. 5-F) ($p < 0.10$). Conversely, no publication bias was detected in any other comparisons ($p \geq 0.10$; Fig. 5A–H).

4. Discussion

The present systematic review with meta-analysis, including 22 studies, detected increased risk of VTE associated with oral ET, especially when combined with progestins. In contrast, patients using transdermal HT had similar risk of VTE events as compared to non-users of HT. To the best of our knowledge, this is the first systematic review with meta-analysis about VTE risk in postmenopausal women using HT that strictly included studies with participants who did not have previous VTE events.

Indeed, while oral HT was associated with a 1.7-fold increase in the risk of VTE compared to not using HT, non-oral HT did not significantly influence thrombotic events. These findings are supported by our meta-analyses comparing non-oral vs. oral HT, which also showed an increased risk of VTE with oral HT. A sensitivity analysis including only studies whose participants did not have risk factors for VTE, cancer, or previous HT use further confirmed the higher risk of VTE with oral HT as compared to non-oral HT. This is important because these factors would be likely to influence VTE risk.

A previous meta-analysis comparing users of oral or non-oral HT vs. non-users of HT (8 observational studies and nine RCTs) concluded that the risk of VTE was substantially increased in relation to oral estrogen use, whereas no additional risk was detected with transdermal estrogen use [19]. However, in that meta-analysis, only four studies assessed the risk of VTE in relation to non-oral estrogen therapy [6,8,27,29]. More recently, a review of observational studies [45] confirmed the positive link between oral estrogen and VTE risk, even in low doses, mainly in women at increased risk for VTE. No association between VTE risk and transdermal estrogen use was detected. Additionally, the analysis of progestin type showed increased risk of VTE with medroxyprogesterone, whereas micronized progesterone appeared to be safe [45]. Similarly, higher risk of VTE in oral HT users was detected in a meta-analysis including 16 RCTs [20]. Nevertheless, it should be noted that some of the 16 RCTs, such as the HERS study, included participants with previous cardiovascular events [46].

A meta-analysis performed by Mohammed et al. including 15 observational studies and clinical trials reported a 1.63-fold increase in risk of VTE with oral HT when compared to non-oral HT [21]. However, that meta-analysis pooled all the studies regardless of concomitant progestogen use, and high between-study heterogeneity was reported. As a consequence of this inconsistency, the quality of the evidence (e.g., for the comparison of oral vs. non-oral estrogens) was very low. Since the publication of the study by Mohammed et al., five new studies directly comparing the impact of oral vs. non-oral HT on VTE events have become available and were added to our meta-analyses [7,29,31,43,44].

Because current evidence suggests that HT is not safe for women with prior thrombotic events or any other established cardiovascular disease, we only included studies with postmenopausal women who did not have diseases that could increase the risk of VTE events. This exclusion criterion is supported by the early termination of the EVTET study based on circumstantial evidence emerging during the trial which showed a 10.7% incidence of new thrombotic events in HT users with previous VTE vs. 2.3% in the placebo group [47].

In contrast, after 6.5 years of follow-up, Olié et al. [48] concluded that non-oral HT did not increase VTE risk in women who had already experienced a thromboembolic event. Although recent guidelines also suggest that the metabolic effects of non-oral HT are less deleterious effects than those of oral HT, the safety of these preparations in patients at high cardiovascular risk has not been evaluated in RCTs, and reliable evidence is still lacking [49,50].

The Endocrine Society Clinical Practice Guideline considers history of VTE due to pregnancy, oral contraceptives, unknown etiology, or

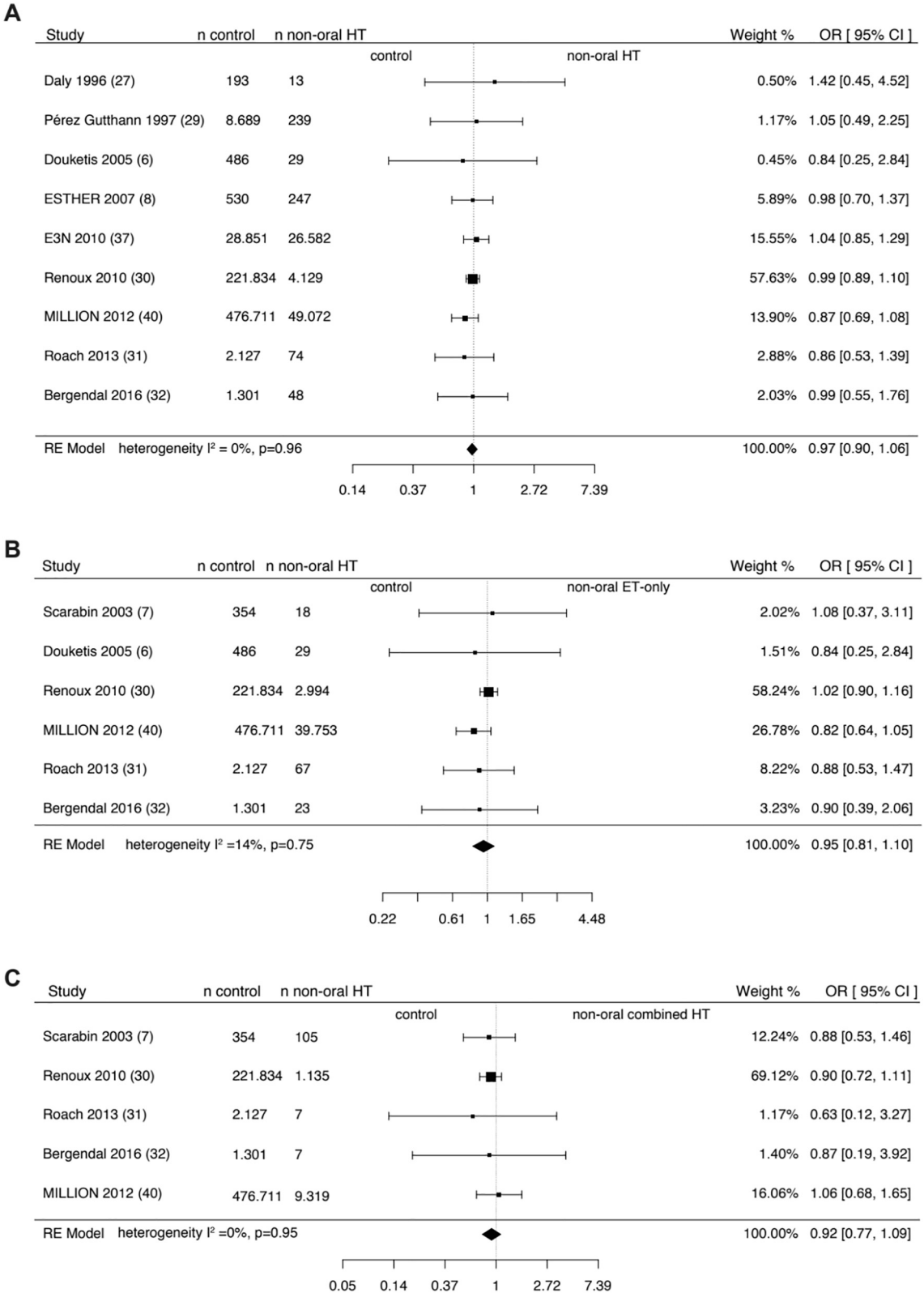

Fig. 2. Forest plot showing venous thromboembolism events in postmenopausal women using non-oral HT vs. controls. (A) Estrogen-only and combined estrogen and progestin therapies; (B) non-oral estrogen therapy only; and (C) combined non-oral estrogen plus progestin therapy.

blood clotting disorders a contraindication for any ET, whereas VTE due to past immobility, surgery, or bone fracture would be a contraindication for oral but not necessarily transdermal therapy [49]. NICE guidelines recommend special care with women who experienced previous VTE events [50]. The decision to offer (or not) HT to these women is complex and therefore the involvement of a hematologist is recommended for assessment of thrombophilia risk, unless anticoagulant therapy is already in use. Other risk factors should be considered, such as age, genetic abnormalities, obesity, smoking, and inherited thrombophilia, and transdermal rather than oral HT should be the preferred

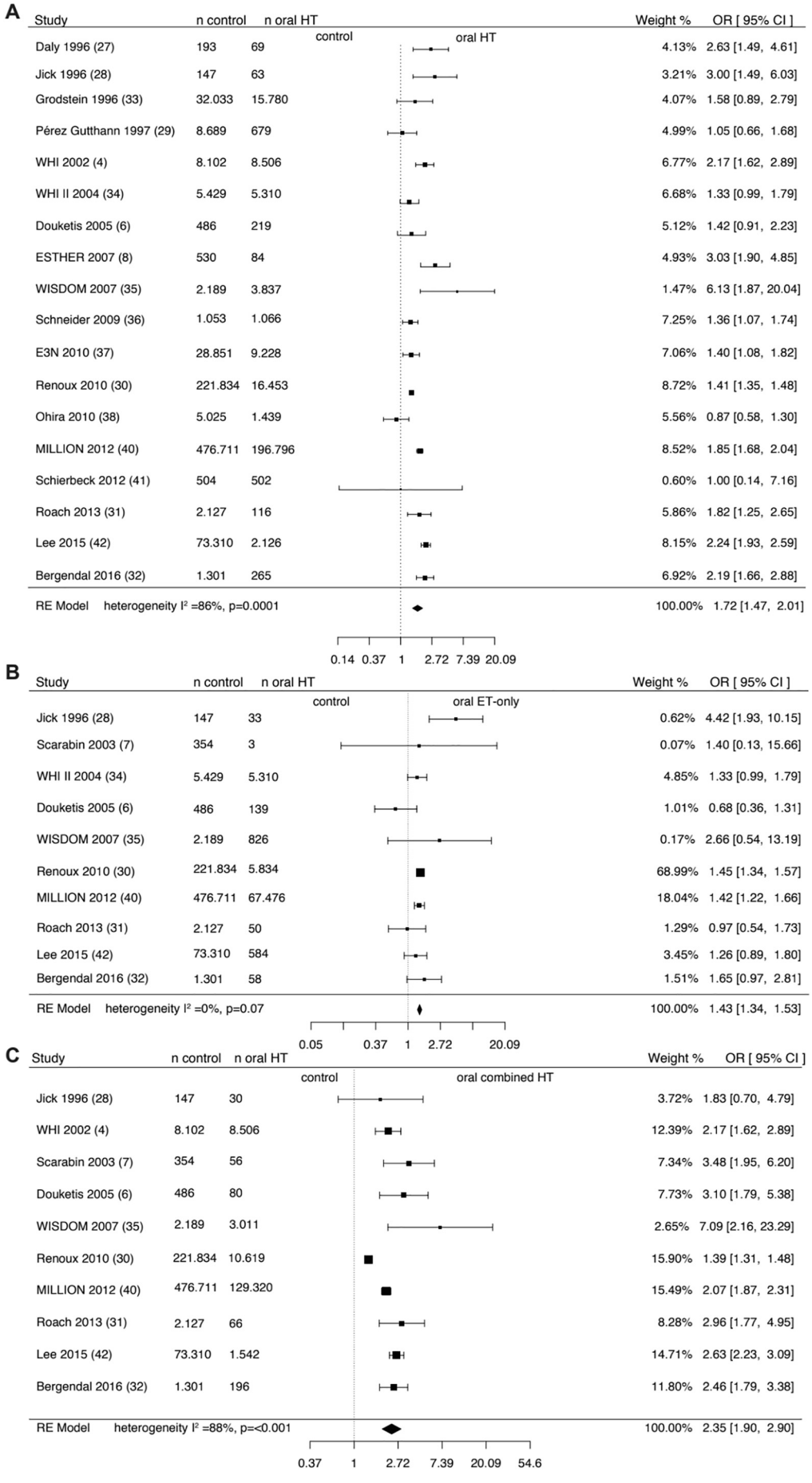

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Fig. 3. Forest plot showing venous thromboembolism events in postmenopausal women using non-oral HT vs. controls. (A) Oral estrogen-only and combined estrogen and progestin therapies; (B) oral estrogen-only; and (C) combined oral estrogen plus progestin therapy.

choice for women at high risk of VTE [51].

Considering that not all of the 22 studies included in the present systematic review provided details about the main risk factors for VTE events, we were not able to stratify the risk of VTE according to smoking, age, or obesity, which may explain the high between-study heterogeneity detected in some of our analyses. In this sense, Canonico et al. observed increased risk of VTE with oral HT in the presence of overweight or obesity, while transdermal estrogen did not confer additional risk in this subgroup of women. Therefore, transdermal estrogen might be safe regarding thrombotic risk, particularly among obese women; however, the safety of transdermal estrogen has yet to be confirmed in randomized trials [51].

VTE is a common disease, with an annual incidence rate of > 1 per 1000 individuals in the general population. Mortality is also high, particularly when associated with pulmonary embolism [52]. Established risk factors for VTE include age, a prior thrombotic event, surgery, trauma, immobilization, prothrombotic mutations, obesity, and HT [51,53]. Observational studies as well as RCTs consistently demonstrate increased risk of VTE with oral HT [4,46]. In the WHI trials, when the entire cohort was analyzed, estrogen-progestin therapy entailed 18 additional VTE events per 10,000 women per year of therapy, while estrogen-only therapy entailed 7 additional VTE events per 10,000 women per year of therapy [51]. It should be noted that these randomized studies have been criticized in relation to patient age

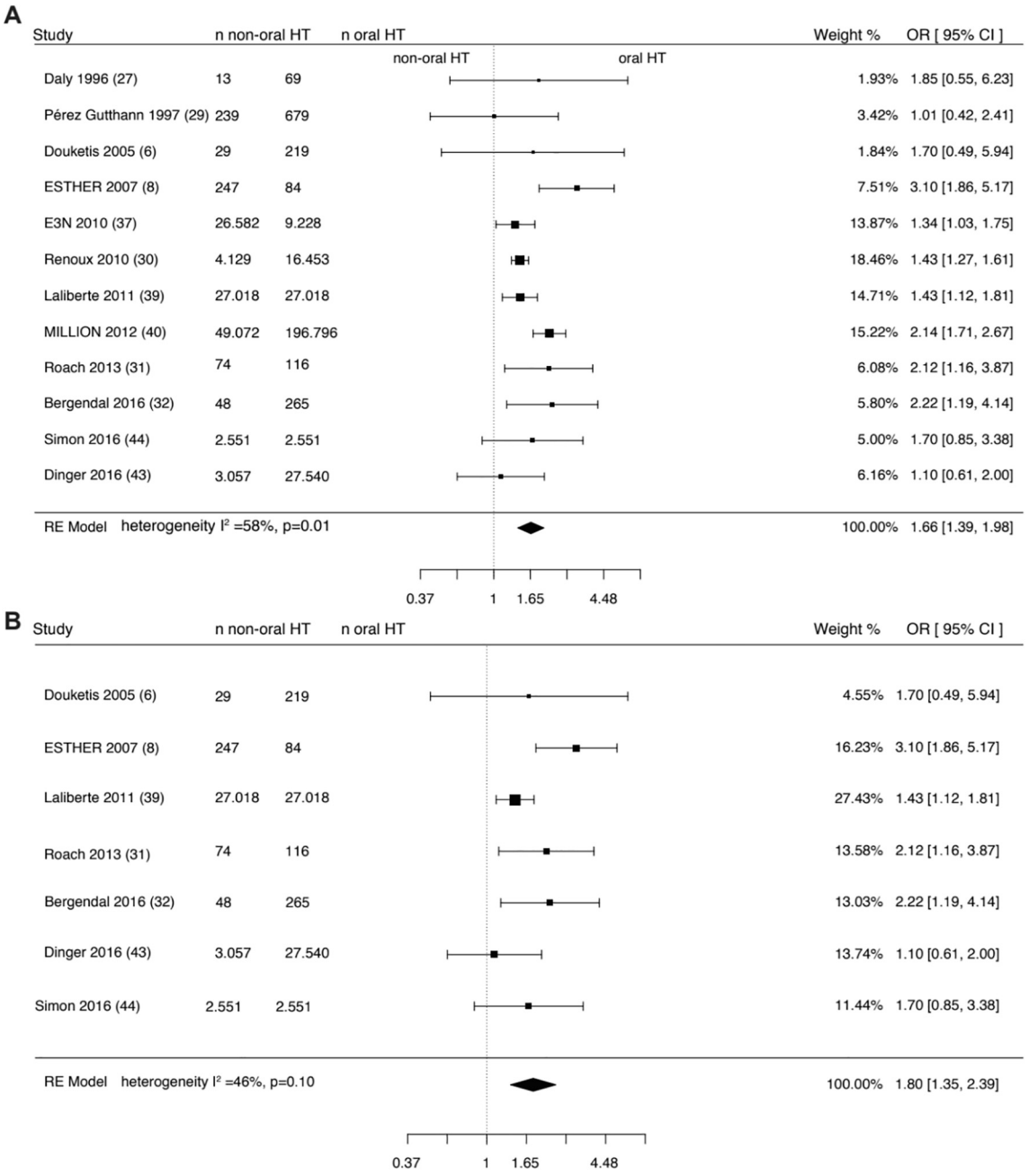

Fig. 4. Forest plot showing venous thromboembolism events in postmenopausal women using oral HT vs, non-oral HT. (A) Analysis with case-control and cohort studies and (B) sensitivity analysis including only studies whose participants did not have risk factors for VTE, cancer, or previous HT use.

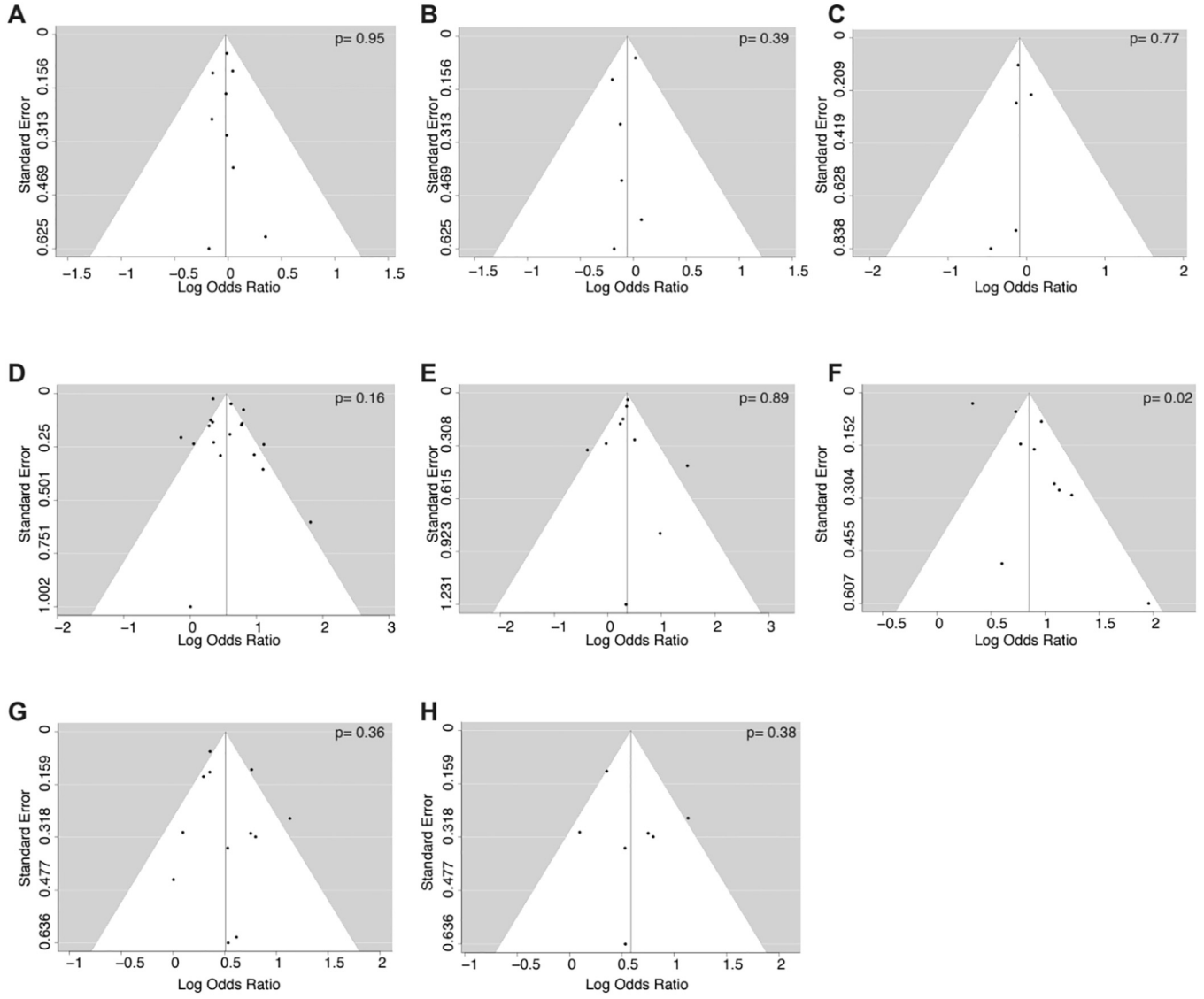

Fig. 5. Funnel plots for risk of publication bias for: (A) controls vs. non-oral HT, (B) controls vs. non-oral ET-only, (C) controls vs. non-oral combined HT, (D) controls vs. oral HT, (E) controls vs. oral ET-only, (F) controls vs. oral combined HT, (G) non-oral HT vs. oral HT, and (H) non-oral HT vs. oral HT in studies whose participants did not have risk factors for VTE, cancer, or previous HT use.

(patients were on average 10 years older than the age at which HT is usually recommended) and hormone regimen (a fixed regimen was employed, without variation in terms of drugs, dose, and administration route) [54].

Indeed, the route of HT administration may induce different impacts on hemostatic parameters and may explain the differences in the intensity of activated protein C (APC) resistance and the risk of VTE [55,56]; by inactivating factors Va and VIIIa, APC plays a role in anticoagulation. As discussed by Olié et al. [57], APC resistance in hormone users has not yet been fully explained, with protein S and tissue factor pathway inhibitor (TFPI) being likely candidates to explain this association. In that sense, evidence is available regarding decreased protein S levels in postmenopausal women using oral estrogens [57].

In the present meta-analyses, VTE risk was not increased in non-oral HT groups, regardless of the addition of progestins. However, the combination of progestins and oral ET was associated with additional increases in the risk of VTE. Little is known about the mechanisms that determine a deleterious effect of combining progestins and oral ET on the risk of VTE. The different progestin molecules and the various HT combinations for treating menopausal women contribute to this uncertainty. Sare et al. compared the risk of VTE linked to ET-only or combined estrogen-progestin HT in postmenopausal women and concluded that the association of a progestin increased VTE risk. However, additional sub-analyses for transdermal therapy and progestogen types were not available [20]. In fact, some evidence suggests that progestin-related VTE risk depends on the type of molecule and should not be viewed as a class effect. Recent data have shown that nor-pregnane derivatives, but not micronized progesterone, increase the risk of VTE among transdermal estrogen users [58]. In the E3N study, Canonico et al. also showed different thrombotic risk according to the type of progestin. While micronized progesterone, pregnane derivatives, or nortestosterone derivatives were not significantly associated with VTE risk, norpregnane derivatives increased thrombotic risk (HR 1.8; 95% CI 1.2–2.7) [37]. Moreover, micronized progesterone added to transdermal ET seemed not to interfere with APC action while norpregnane derivatives affected APC resistance, possibly activating blood coagulation [59].

Our data suggest that oral estrogen administration is linked to increased risk of VTE independently of progestin use. In turn, substantial heterogeneity in the analyses of the oral HT vs. control groups and moderate heterogeneity in the analyses of oral vs. non-oral HT groups was found, possibly due to differences in progestin type and dose in the

oral HT group analyses. However, we were unable to determine whether specific progestins could alter the risk of VTE, since few of the studies we reviewed addressed this information. Therefore, the quality of the evidence produced in our meta-analyses is low to moderate, and further RCTs comparing specific progestins added to oral estrogens are needed in order to shed light on this aspect.

It should be noted that none of the four included RCTs contributed information on the risk of VTE associated with non-oral HT. In fact, this assessment was based on data from observational studies that may present selection biases, since physicians prescribing HT are influenced by knowledge of VTE risk factors. Therefore, additional clinical trials, especially those designed to directly compare oral vs. non-oral HT, are warranted and could produce invaluable results in the context of VTE risk in the postmenopause.

Other limitations of our work include the small number of studies available in literature, not allowing us to analyze the effects of different estradiol doses on VTE risk. However, different doses of HT were evaluated in a previous meta-analysis performed by our group regarding cardiovascular risk factors. In that study, the effect of low-dose HT did not differ from that of placebo or conventional-dose HT regarding weight, BMI, blood pressure, CRP, or HDL-C. In contrast, low-dose HT was associated with better lipid profile vs. placebo, and induced higher total and LDL-C and lower triglycerides vs. conventional-dose HT [60].

5. Conclusion

Considering only women without previous VTE events, VTE risk was increased in oral HT users when compared to non-users, while non-oral HT did not significantly affect this risk. This finding may suggest less impact of transdermal HT on VTE risk. However, the quality and design of the included studies is insufficient to allow any firm conclusion on the VTE risk of oral vs. non-oral hormone therapy; further clinical trials with larger populations and longer follow-up periods are needed to sort out the impact of different types of progestins, in particular micronized progesterone, and different estrogen doses and administration routes on VTE risk.

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Declarations of interest

None.

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