

# Risk of recurrence in women with venous thromboembolism related to estrogen-containing contraceptives: Systematic review and meta-analysis

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## Funding information

This study did not receive financial support.

## Abstract

**Background:** The risk of recurrence after a venous thromboembolism (VTE) related to estrogen-containing contraceptives is a key driver to guide anticoagulant treatment decisions.

**Objective:** To estimate the incidence rate of recurrent VTE after discontinuation of anticoagulant treatment in women with a first episode of VTE related to estrogen-containing contraceptives.

**Methods:** Embase, MEDLINE, and the CENTRAL were searched from 1 January 2008 to 27 May 2021 for prospective and retrospective studies reporting on recurrence after a first VTE related to estrogen-containing contraceptives. Risk of bias was assessed using QUIPS tool. Recurrence rates per 100 patient-years were pooled using Knapp-Hartung random-effects meta-analysis. Incidence rates were reported separately based on study follow-up duration ( $\leq 1$  year, 1–5 years, and  $> 5$  years) and for several subgroups.

**Results:** A total of 4,120 studies were identified, of which 14 were included. The pooled recurrence rate was 1.57 (95%-CI: 1.10–2.23;  $I^2 = 82\%$ ) per 100 patient-years. Recurrence rates per 100 patient-years were 2.73 (95%-CI: 0.00–3643;  $I^2 = 80\%$ ) for studies with  $\leq 1$  year follow-up, 1.35 (95%-CI: 0.68–2.68;  $I^2 = 44\%$ ) for studies with 1–5 years follow-up, and 1.42 (95%-CI: 0.84–2.42;  $I^2 = 78\%$ ) for studies with  $> 5$  years follow-up.

**Conclusion:** Among women with VTE associated with estrogen-containing contraceptives, the risk of recurrence after stopping anticoagulation is low, which favors short-term anticoagulation. Large prospective studies on VTE recurrence rates and risk factors after stopping short-term anticoagulants are needed.

## KEYWORDS

contraceptive agents, estrogens, systematic review, thrombosis, women

Hanke Wiegers, Jannet Knijp equally contributed to this work

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## 1 | INTRODUCTION

The use of estrogen-containing contraceptives is associated with a two- to six-fold increased risk of venous thromboembolism (VTE). However, whether an estrogen-containing contraceptive-related VTE can be classified as 'unprovoked' or 'provoked' remains controversial.<sup>1-3</sup> Although the American Society of Hematology guidelines define the use of estrogen-containing contraceptives as a minor transient risk factor, others consider estrogen-containing contraceptive related VTE to be unprovoked.<sup>2</sup> This classification is clinically relevant as it has implications for duration of treatment. Patients with VTE provoked by a major transient risk factor, such as surgery with general anesthesia for >30 min, can be treated with short-term anticoagulant therapy for 3–6 months as the estimated risk of recurrence is considered to be low. Indefinite treatment is suggested in those with an unprovoked VTE, i.e. without any risk factors, if the bleeding risk is low.<sup>4,5</sup> The duration of treatment in patients with a minor transient risk factor is, however, debatable. Whereas the ASH guidelines suggest short-term treatment of VTE associated with a minor transient risk factor, such as estrogen-containing contraceptives, the European Society of Cardiology (ESC) guideline states that indefinite treatment should be considered in women with VTE related to estrogen therapy based on an estimated long-term risk of recurrence of 3–8% per year.<sup>6</sup> However, if a pulmonary embolism (PE) occurs in the first 3 months after initiation of estrogen-containing contraceptives, discontinuation of anticoagulation after 3 months could be considered if hormonal contraceptives are also discontinued.<sup>7,8</sup>

Several studies evaluated the risk of recurrence after a first VTE related to estrogen-containing contraceptives, but often had a small sample size, included heterogeneous groups of women, or reported conflicting results. These limitations add to the uncertainty about the risk of recurrence after VTE related to estrogen-containing contraceptives, and whether these women can safely stop anticoagulant therapy after the initial treatment phase of 3 months. Summary data with precise estimates are needed to improve counselling and optimize treatment strategies. Therefore, the objective of this systematic review was to estimate the incidence rate of recurrent VTE after discontinuation of anticoagulant treatment in women with a first episode of VTE related to estrogen-containing contraceptives.

## 2 | METHODS

The study protocol was developed using guidance from the preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) statement<sup>9</sup> and was registered in PROSPERO (ID: CRD42021243871). This report adheres to the PRISMA guidelines<sup>10</sup> (Table S1).

### 2.1 | Search strategy

Citations from three systematic reviews that also evaluated the recurrence risk after a first VTE were collected, as these systematic

### Essentials

- Data on recurrence risk after a venous thromboembolism related to estrogen use are conflicting
- Summary data with precise estimates are needed to guide anticoagulant treatment decisions
- The rate of recurrence after stopping anticoagulation is low (1.57 per 100 patient-years)
- These results support short-term anticoagulation

reviews used similar in- and exclusion criteria.<sup>11-13</sup> Thereafter, Embase, MEDLINE, and the Cochrane Central Register of Controlled Trials were searched from 1 January 2008 (date of the most recent previous systematic review) to 27 May 2021. The search included terms related to 'venous thromboembolism', 'recurrent', 'anticoagulant treatment' (see Table S2 for complete search string). The search was restricted to studies on adult humans. Reference lists of included articles were hand-searched for additional studies.

### 2.2 | Study selection

Two authors (JK, HW) independently screened titles, abstracts, and full text. Discrepancies were resolved with help of a third author (NvE). Randomized controlled trials, retrospective cohort studies, or prospective cohort studies were included if (1) studies enrolled patients with a mean age below 50 years with a first episode of objectively confirmed, symptomatic VTE (deep vein thrombosis or pulmonary embolism) related to estrogen use; (2) patients had completed at least 3 months of anticoagulant treatment; (3) patients were followed after discontinuation of anticoagulant treatment; (4) recurrent VTE events were reported during follow-up; (5) the rate of the recurrence was reported and (6) the article was written in English, Dutch, French, German or Spanish. If multiple studies reported on the same cohort, the most appropriate one for our study question was included. Studies were excluded if the study population was restricted to cancer.

### 2.3 | Data extraction

Two authors independently (JK, HW) extracted data from eligible studies using a standardized form. Data were extracted on study design, study population, age, follow-up period, site of index VTE, anticoagulant treatment, definition used for contraceptive-related index VTE, number of patients with contraceptive-related index VTE, number of patients with thrombophilia or other provoking factors during index VTE, number and/or rate of recurrent VTE and the number of patient-years of follow-up for our group of interest i.e. young women using estrogen-containing contraceptives.

## 2.4 | Assessment of risk of bias

Risk of bias was assessed for each selected study using the Quality In Prognosis Studies (QUIPS) tool using pre-specified criteria (Table S3). The domain 'confounding' was excluded from the assessment since we did not compare two groups in the main outcome, but rather an absolute rate rather, which is not subject to confounding. However, we did evaluate risk factors that could possibly affect this rate in several subgroup analyses. Risk of bias was judged as 'low', 'unclear/moderate', or 'high'. A sensitivity analysis was performed restricted to studies not judged to be at high risk of bias in any of the domains.

## 2.5 | Study population analysis

The primary analysis was restricted to our group of interest, i.e. young women using estrogen-containing contraceptives, which included combined oral estrogen-containing contraceptives and estrogen-containing vaginal patches or rings. This analysis comprised studies that either exclusively included women with a mean age of less than 50 years using estrogen-containing contraceptives or that provided outcomes for this specific subgroup in the manuscript. If the type of oral contraceptives was not specified in the study, we assumed that estrogens were included, as combined oral contraceptives are the most commonly used agents. When data were provided for various age subgroups, data from patients <50 years of age were used, since contraceptive users are usually younger. Studies reporting on combined groups including both HRT and OC were included only when the mean age was below 50 years. Studies reporting on combined groups including pregnant or postpartum patients were excluded since recurrence risk estimates may be different.

## 2.6 | Statistical analysis

For each included study, the rate of recurrence (with its 95% CI), expressed as the number of VTE events per 100 patient-years, was calculated from the number of recurrent VTE events and the number of patient-years of follow-up. If these data were not reported directly they were estimated from the provided data as follows: Patient-years could be calculated from the mean or median duration of follow-up and the number of patients. For example, if mean or median follow-up was 4 years and the number of patients was 100, we estimated the total number of patient-years to be 400 ( $n = 7$ ). The rate of recurrence could be estimated by annualizing the cumulative incidence reported by Kaplan–Meier estimates. For example, if the cumulative incidence at 5 years was 15%, we estimated the annualized rate of recurrence to be 3.0 per 100 patient-years ( $n = 1$ ).

Results were pooled using a random-effects model with inverse variance weighting and a logit transformation with 0.5 used as continuity correction. The Knapp Hartung method was applied and the Sidik-Jonkman estimator was used to estimate the between-study variance ( $\tau^2$ ). The degree of statistical heterogeneity between

studies was assessed using the  $I^2$  statistic (>75% considered substantial). Potential publication bias was explored by a funnel plot.

## 2.7 | Subgroup analyses

Subgroup analyses were performed for; (1) studies including patients with high-risk types of thrombophilia (defined as protein S or C deficiency, antithrombin deficiency, antiphospholipid syndrome, homozygous factor V Leiden or prothrombin gene mutation, heterozygosity for both factor V Leiden and the prothrombin gene mutation); (2) studies in which other provoking factors, as defined according to the ISTH,<sup>3</sup> were present at the time of the estrogen-containing contraceptive-related VTE; (3) studies including patients who used extended anticoagulation or started follow-up before discontinuation of treatment; (4) studies in which all patients definitely stopped hormonal use after the first VTE or were strongly discouraged to continue. In addition, studies were grouped according to their median or mean duration of follow-up:  $\leq 1$  year, 1–5 years, and >5 years.

Analyses were performed with R computing software, version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria; www.r-project.org), in particular using the *meta* package version 4.18–1.

## 3 | RESULTS

### 3.1 | Study selection

A total of 4120 records were identified by the database search and 41 citations were collected from previous systematic reviews. The flowchart is shown in Figure 1. 3777 records remained after removal of duplicates of which 3163 were excluded after screening of titles and abstracts. A further 600 articles were excluded after full text screening, mainly because no results were reported on our group of interest ( $n = 427$ ), the study population was not applicable to the primary analysis ( $n = 12$ ), the design was inappropriate ( $n = 105$ ), only data for recurrent VTE were reported during the initial treatment period ( $n = 27$ ), studies reported on the same cohort ( $n = 13$ ), or absolute numbers of events or rates were not reported ( $n = 5$ ).

### 3.2 | Characteristics of included studies

Characteristics of the remaining 14 studies, that investigated women with estrogen-containing contraceptives ( $n = 3112$ ) are shown in Table 1. Sample sizes ranged from 9 to 654 women. Eleven studies were prospective cohort studies and three were retrospective cohort studies. Mean/median follow-up durations ranged from 0.7 to 9.5 years. Two studies had a follow-up duration  $\leq 1$  years,<sup>14,15</sup> six studies 1–5 years,<sup>16–21</sup> and six studies >5 years.<sup>22–27</sup>

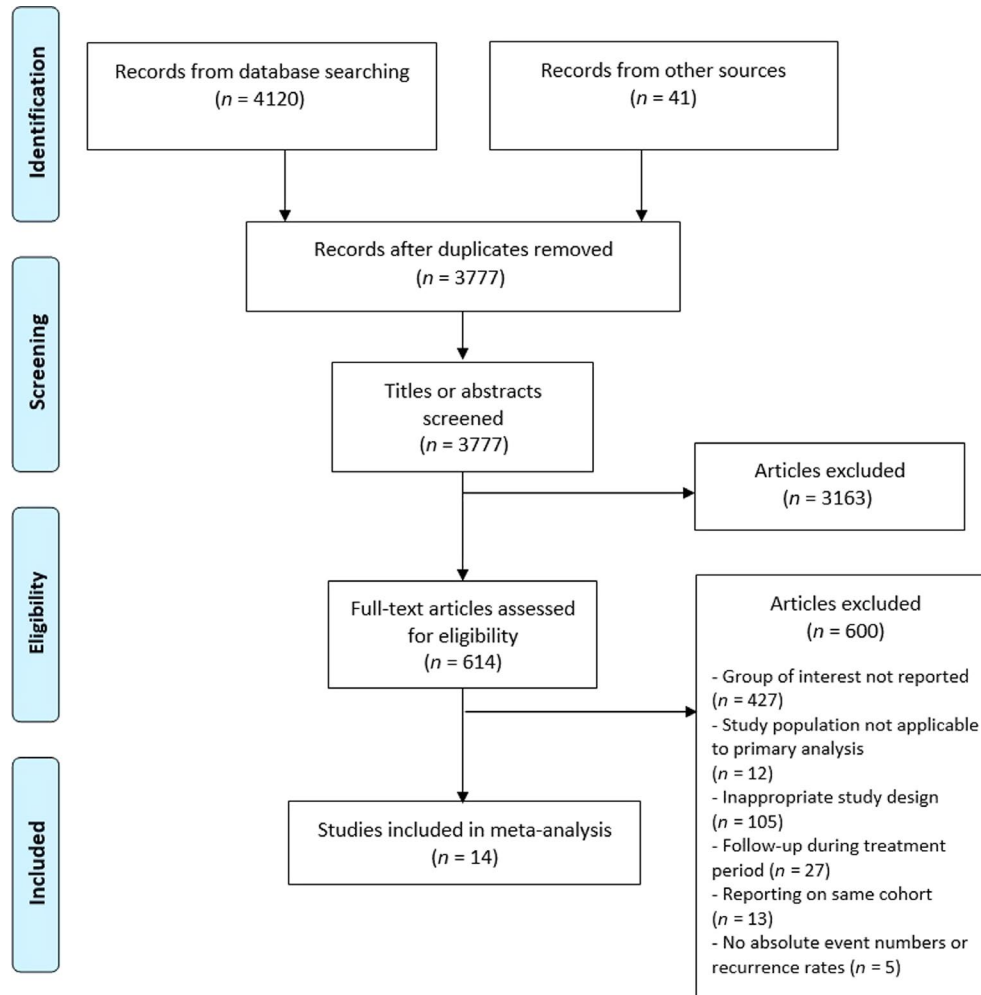


FIGURE 1 PRISMA Flowchart

### 3.3 | Risk of bias

Using the pre-specified QUIPS criteria, one out of 14 studies was judged to be at high risk of bias for one bias domain because of no clear description of recurrent event or follow-up period, Table S3 shows criteria used for risk of bias assessment and Table S4 summarizes the risk of bias assessment for all studies. Visual inspection of the funnel plot did not indicate selective reporting (Figure S1).

### 3.4 | Rate of recurrence

The pooled recurrence rate in women was 1.57 per 100 patient-years overall (95% CI: 1.10–2.23;  $I^2 = 82\%$ ) (Figure 2). The pooled recurrence rate per 100 patient-years was 2.73 (95%-CI: 0.00–3643;  $I^2 = 80\%$ ) in studies with  $\leq 1$  year follow-up, 1.35 (95%-CI: 0.68–2.68  $I^2 = 44\%$ ) for studies with 1–5 years follow-up, and 1.42(95%-CI: 0.84–2.42;  $I^2 = 78\%$ ) for studies with  $>5$  years follow-up (Table 2). Results were consistent in the sensitivity analysis in which one study, judged to be at high risk of bias in one bias domain, was excluded (pooled rate 1.41; 95% CI: 1.04–1.92;  $I^2 = 63\%$ ; Figure S2).

### 3.5 | Subgroup analyses

The pooled rate of recurrence among studies including patients with high-risk thrombophilia ( $n = 4$ ) was 1.95 per 100 patient-years (95% CI: 0.83–4.59;  $I^2 = 67\%$ ) compared to 1.40 per 100 patient-years (95% CI: 0.88–2.23;  $I^2 = 85\%$ ) among studies that had excluded women with high-risk thrombophilia (Figure S3). The pooled rate of recurrence among studies including women with other provoking factors ( $n = 5$ ) was 1.56 per 100 patient-years (95% CI: 0.64–3.82;  $I^2 = 67\%$ ), compared to 1.55 per 100 patient-years (95% CI: 0.98–2.46;  $I^2 = 86\%$ ) among studies including women without other provoking factors (Figure S4). The pooled rate of recurrence among studies with anticoagulant treatment during follow-up ( $n = 1$ ) was 0.97 per 100 patient-years (95% CI: 0.43–2.15;  $I^2 =$  not applicable) compared to 1.62 per 100 patient-years (95% CI: 1.11–2.35;  $I^2 = 82\%$ ) among studies without anticoagulant treatment during follow-up (Figure S5). The pooled rate of recurrence among studies in which all patients definitely stopped hormonal use after the first VTE or were strongly discouraged to continue ( $n = 8$ ) was 1.31 per 100 patient-years (95% CI: 0.71–2.4;  $I^2 = 87\%$ ) compared to 1.87 per 100 patient-years (95% CI: 1.18–2.96;  $I^2 = 68\%$ ) among studies

TABLE 1 Characteristics of studies included in meta-analysis on women using estrogen-containing contraceptives

Author, year	Study design	Overall Women in study, n	Mean or median age, year*	Mean or median follow-up duration, year*	Women in the group of interest, n	Definition of hormonal contraceptive use
Aziz <sup>23</sup>	Prospective cohort	322	32, COC users <50 years	5.7	49	Using COC at the time of index VTE
Blanco-Molina <sup>16</sup>	Retrospective cohort	1513	32, COC users	1.4	654	COC containing users
Christiansen <sup>24</sup>	Prospective cohort	272	43, all women	7.3	77	OC use <30 days before VTE
De Moreuil <sup>25</sup>	Prospective cohort	560	33, all women	9.5	318 (4 HRT, 314 estrogen containing contraceptives)	VTE related to estrogen-containing treatment: HRT or estrogen-containing contraceptives
Eischer <sup>26</sup>	Prospective cohort	630	38, estrogen users	6.3	275 (third generation oral contraceptives, 209; first or second generation oral contraceptives, 26; vaginal ring, 2; transdermal patch, 5; unspecified, 33)	Estrogen containing contraceptives at the time of index VTE
Galanaud <sup>17</sup>	Prospective cohort	220	36, COC-users distal DVT; 32 proximal DVT; 31 PE	3.0	79	COC use <3 months preceding index VTE
Kearon <sup>19</sup>	Prospective cohort	179	38 estrogen users	5.0	58	VTE while on estrogen therapy (contraceptives or HRT)
Kiconco <sup>14</sup>	Prospective cohort	4170	32, hormone users aged 15–44	0.7	602 (OC n = 562 (of which 465 COC); HRT n = 40)	Hormone users: OC or HRT in the 6 months prior to index VTE
Kyrle <sup>18</sup>	Prospective study	453	45 all women	5.0	175	VTE occurring during OC use
Ljungqvist <sup>22</sup>	Prospective cohort	974	36, women aged <50 years	5.2	240	Use of CHC (oral tablets, dermal patches and intravaginal devices) or menopausal HT at the time of VTE
Rodger <sup>15</sup>	Prospective cohort	1213	54, all patients, subgroup <50 years	1.0	291	Exogenous estrogen (patch, ring, OC or HRT)
Vaillant-Roussel <sup>27</sup>	Retrospective cohort	172	26, all women	6.2	160	VTE during COC use or less than 1 month after discontinuation of COC
Vlijmen <sup>21</sup>	Prospective cohort study	125	29, CHC users	3.1	125	Women with CHC-associated first VTE
Zabczyk <sup>20</sup>	Prospective cohort	74	44, all patients	4.2	9	Oral contraceptive use <3 months before index VTE

Note: \*Data reported in studies most applicable.

Abbreviations: AC, Anticoagulation; CHC, Combined hormonal contraceptives; CI, Confidence interval; COC, Combined oral contraceptives; DVT, Deep vein thrombosis; HRT, Hormone replacement therapy; IQR, Inter quartile range; PE, Pulmonary embolism; SD, Standard deviation; VTE, Venous thromboembolism.

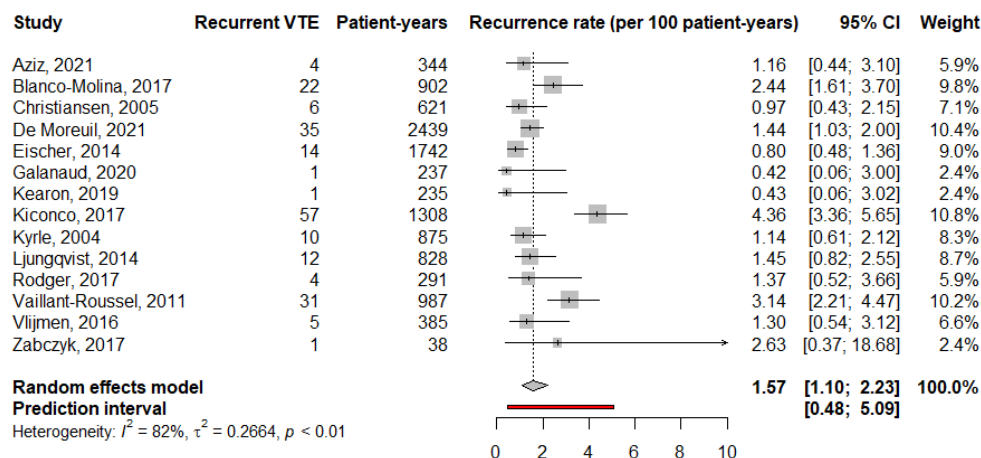


FIGURE 2 Pooled rate of recurrent VTE in women with estrogen-containing contraceptives

TABLE 2 Pooled rates of recurrent venous thromboembolism classified by duration of follow-up in women with estrogen-containing contraceptives

Duration of follow-up	Studies, n	Pooled rate per 100 patient-years (95% CI)
≤1 year	2	2.73 (0.00–3643.43; $I^2 = 80\%$ )
1–5 years	6	1.35 (0.68–2.68; $I^2 = 44\%$ )
>5 years	6	1.42 (0.84–2.42; $I^2 = 78\%$ )

including patients who did not stop during follow-up or was not reported. (Figure S6).

## 4 | DISCUSSION

In this systematic review, the rate of recurrence after stopping anticoagulant treatment for a VTE in younger women using estrogen-containing contraceptives was low, with a pooled rate of 1.57 per 100 patient-years. These findings suggest that only short-term anticoagulation for 3–6 months after an estrogen-containing related VTE could be appropriate.

Our systematic review indicates that the risk of recurrent VTE among women with a VTE related to estrogen-containing contraceptives is equivocal, likely due to differences in study design, follow-up durations, and studied populations. This is reflected by the wide confidence intervals and substantial heterogeneity ( $I^2 = 82\%$ ) across studies in the meta-analysis.

Currently, it is still debated whether anticoagulation can safely be stopped in women after an estrogen-containing contraceptive related VTE. Three prospective studies concluded that the risk after recurrence was similar for women with hormone related versus unprovoked VTE.<sup>2,15,23</sup> Yet, the point estimate of the hazard ratio indicated a 40%–50% lower incidence although not statistically significant. However, in the counselling for long-term secondary

prevention, this is less relevant than the absolute recurrence rate in women with a hormone related VTE.

Consistent guidance on decisions regarding treatment duration for a VTE related to estrogen-containing contraceptives is lacking. The 2020 American Society of Hematology (ASH) guideline recommends short-term treatment of 3–6 months for patients with VTE provoked by a transient risk factor, which includes estrogen use.<sup>4</sup> In contrast, the 2019 ESC guideline categorizes estrogen use within the group of ‘intermediate’ recurrence risk (3%–8% per year), which includes both unprovoked VTE and VTE provoked by minor transient risk factor, suggesting extended (also termed long-term, or indefinite) oral anticoagulation.<sup>6</sup> Only in women with a diagnosis of PE within 3 months after the initial start of estrogen-containing contraceptives, discontinuation of anticoagulation could be considered.<sup>7,8</sup>

The overall pooled recurrence rate of 1.57% per year in this systematic review is well below the ESC threshold to classify patients as ‘intermediate’ recurrence risk. Even in the analysis restricted to studies with a follow-up duration of ≤1 year and, in various high-risk subgroup analysis, the risk point estimate of the did not exceed this threshold of 3% per year, which has been considered by some as the threshold above which the benefit of long-term anticoagulation in preventing recurrent VTE outweighs the major bleeding risk.

The present study has limitations. First, we found evidence of substantial heterogeneity in most of the meta-analyses. The most likely explanation for this heterogeneity is a difference in study populations between studies, as differences were observed in age, types of hormones and additional risk factors. We performed several pre-specified subgroup analyses, which could not fully explain the heterogeneity. This issue could potentially be explored better in future studies using a meta-analysis of individual patient data or in large prospective natural history studies of VTE recurrence rate and risk factors for recurrence in patients who stop anticoagulation after 3–6 months. Second, although the vast majority of women used estrogen contraceptive pills, some patients used different types of estrogen-containing hormones (i.e. patches or rings) which may be associated with different recurrence rates. In addition, different formulations of estrogen contraceptive pills were used, which may also



be associated with varying recurrence rates. Insufficient data were available in the original studies to perform subgroup analyses on type of estrogen-containing contraceptives. Besides limited data on this specific patient population, knowledge on what risk factors for recurrence are contributing - such as age, BMI, length of estrogen-contraceptive use prior to VTE, post thrombotic syndrome, D-dimer results, were also lacking. Third, the duration of anticoagulation prior to discontinuation differed across studies. However, many studies have shown that the duration of the initial anticoagulation period is unlikely to significantly impact the recurrence rate, as long as at least 3 months of anticoagulation have been given.<sup>12</sup> Fourth, in this systematic review we did not estimate incidence rates for standardized time intervals. We restricted our systematic review to data provided by studies instead of individual patient data and studies did not provide VTE events per time interval. Lastly, we did not assess long-term sequelae of recurrent VTE, such as impact on quality of life or post-thrombotic syndrome, that should also be taken into account in guidance of optimal anticoagulant treatment.

The risk of VTE recurrence in women with estrogen-containing contraceptives appears to be low, which supports short-term anticoagulation for 3–6 months after VTE related to estrogen-containing contraceptives. However, data and contributing risk factors for this specific patient population are limited and strong recommendations about duration of anticoagulants cannot be made. Large prospective studies on VTE recurrence rates and risk factors for recurrence are needed in patients with VTE associated with estrogen-containing contraceptives who stop anticoagulation after 3–6 months.

#### CONFLICT OF INTEREST

HW and JK have nothing to disclose. NvE reports advisory board fees from Bayer, Daiichi Sankyo, and LEO Pharma, which were transferred to his institution, all outside the submitted work. MC reports personal fees from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, CSL Behring, Daiichi Sankyo, Pfizer, Portola, and Sanquin Blood Supply, all outside the submitted work. STM reports consulting fees from Bristol-Myers-Squibb, outside the submitted work. FAK reports research grants from Bayer, Bristol-Myers-Squibb, Boehringer-Ingelheim, Daiichi-Sankyo, MSD and Actelion, the Dutch Heart foundation (2017T064) and the Dutch Thrombosis association, all outside the submitted work. SAM reports grants and personal fees from Bayer, BMS Pfizer, Boehringer Ingelheim, Daiichi Sankyo, Portola, all during the conduct of the study; personal fees from Abbvie, personal fees from Sanofi, all outside the submitted work.

#### AUTHOR CONTRIBUTIONS

Saskia Middeldorp and Stephan Moll conceived the study. Hanke Wiegiers and Jannet Knijp designed the study protocol, performed the search, screened for eligible studies and performed data extraction. Hanke Wiegiers and Jannet Knijp performed all statistical analyses, supervised by Nick van Es. Hanke Wiegiers and Jannet Knijp drafted the manuscript. All authors interpreted the results, reviewed drafts and approved the final draft of the manuscript.

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#### SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

**How to cite this article:** Wiegers HMG, Knijp J, van Es N, et al. Risk of recurrence in women with venous thromboembolism related to estrogen-containing contraceptives: Systematic review and meta-analysis. *J Thromb Haemost*. 2022;20:1158-1165. doi:[10.1111/jth.15661](https://doi.org/10.1111/jth.15661)