Recurrence after stopping anticoagulants in women with combined oral contraceptive-associated venous thromboembolism: A systematic review and meta-analysis

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RESEARCH PAPER

Recurrence after stopping anticoagulants in women with combined oral contraceptive-associated venous thromboembolism: A systematic review and meta-analysis

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Summary

The risk of recurrence after discontinuation of anticoagulation for a combined oral contraceptive (COC)-associated venous thromboembolism (VTE) is unclear. Therefore, we conducted a systematic review and meta-analysis to estimate the incidence of recurrent VTE among women with COC-associated VTE, unprovoked

VTE and to compare the incidence of recurrent VTE between the two groups. The Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Embase Classic +Embase and Medline ALL to July 2020 and citations from included studies were searched. Randomized controlled trials, prospective cohort studies and meta-analyses of these study types were selected. The analysis was conducted by random-effects model. Nineteen studies were identified including 1537 women [5828 person-years (PY)] with COC-associated VTE and 1974 women (7798 PY) with unprovoked VTE. Studies were at low risk of bias. The incidence rate of VTE recurrence was 1.22/100 PY [95% confidence interval (CI) 0.92–1.62, I^2 = 6%] in women with COC-associated VTE, 3.89/100 PY (95% CI 2.93–5.17, I^2 = 74%) in women with unprovoked VTE and the unadjusted incidence rate ratio was 0.34 (95% CI 0.26–0.46, I^2 = 3%). The recurrence risk in women after COC-associated VTE is low and lower than after an unprovoked VTE.

KEYWORDS
contraceptive agents, oestrogens, oral contraceptive, recurrence, venous thromboembolism, venous thrombosis, women

INTRODUCTION

Combined oral contraceptive (COC) use is associated with increased risk for venous thromboembolism (VTE), but the absolute risk of VTE recurrence after discontinuing anticoagulation for these events is unclear.[1] Estimating the long-term risk of VTE recurrence is crucial when determining an appropriate duration of anticoagulation. It is recommended that those with a low risk of VTE recurrence (e.g. index VTE provoked by a major surgery) should stop anticoagulation after the initial three-month treatment period, whereas those at high risk of recurrence (e.g. unprovoked index VTE), should be considered for extended anticoagulation beyond the initial treatment period as secondary prevention.[2]

Some studies have demonstrated a lower risk of VTE recurrence after stopping anticoagulation in women with COC-associated VTE compared to women with unprovoked events, suggesting that women who were COC users prior to VTE have a low recurrence risk.[3–6] Other studies have observed a similar risk of VTE recurrence between these groups, suggesting the observed low risk in COC users may have been due to confounding factors as such patients tend to be healthy young women.[7,8] Taken together, these studies have been limited by one or more being of small sample size, heterogeneity in patient characteristics, variability in follow-up periods and reporting of results.[9]

Providing precise and reliable estimates of the incidence of recurrence after a COC-associated VTE has importance for clinical decisions relating to the duration of anticoagulant therapy in such patients. Given this knowledge gap, we conducted a systematic review and meta-analysis to estimate the incidence of recurrent VTE after stopping anticoagulation among women with COC-associated VTE, among women with unprovoked VTE, and to compare the risk of recurrence between these two groups.

METHODS

The protocol for this systematic review was registered on PROSPERO on 28 April 2020 (CRD42020150304). The systematic review is reported in accordance with the MOOSE Guidelines.[10]

Data sources and searches

A comprehensive search strategy was conducted by a research librarian across the following databases: Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Embase Classic +Embase and Medline ALL (Medline and Epub Ahead of Print and In-Process, In-Data-Review & Other Non-Indexed Citations), all from the OvidSP platform, from the databases' inception to July 2020 (Supplementary Information). Each search strategy comprised a combination of controlled vocabulary terms and text words, adapting the database-specific search syntax with no language restrictions. We also identified additional studies by screening references of all eligible studies. No searches were conducted to locate grey literature or unpublished studies. EndNote software was used to identify and remove duplicate citations (Version 8.1, Clarivate, Philadelphia, PA, USA).

Eligibility criteria

We included prospective cohort studies, randomized controlled trials and meta-analyses of these study types that assessed adult women with: (1) objectively confirmed initial COC-associated VTE; who (2) received a minimum of three months of anticoagulation; (3) discontinued COC prior to or at time of discontinuation of anticoagulation; (4) whose time of follow-up began after anticoagulation was discontinued;

and (5) where recurrent VTE data were available. Index VTE types included pulmonary embolism (PE), deep-vein thrombosis (DVT), cerebral vein thrombosis (CVT) and splanchnic vein thrombosis. Studies were excluded if the women were systematically treated with an alternative pharmacologic agent intended to reduce the risk of recurrent VTE (e.g. aspirin) or if the diagnosis of recurrent VTE was not confirmed by objective testing. Studies only available as abstracts also were excluded.

If the data on a particular cohort were published in multiple articles, only the article with the most recent follow-up was included. Authors of the identified papers were contacted to resolve inquiries and to provide additional data on variables not reported in the respective publications.

Study selection

Two reviewers (Jameel Abdulrehman and Carolyne Elbaz) independently screened titles and abstracts of citations identified in the search using the Rayyan online tool for consideration of inclusion into the review.[11] The reviewers independently performed full text reviews on all citations considered eligible for inclusion. Any disagreements regarding inclusion were resolved through discussion and a third reviewer (Leslie Skeith) when needed.

Outcomes

The primary outcome was recurrent VTE in women objectively confirmed on diagnostic imaging.

Data extraction

Two reviewers (Jameel Abdulrehman and David Aziz) independently extracted the following data from the included studies: (1) study characteristics (author, publication year, study design, number of women with COC-associated and unprovoked VTE, definition of COC-associated and unprovoked VTE groups, type of index and recurrent VTE, and if clinical risk scores were involved in the decision for anticoagulation discontinuation); (2) outcomes (number of recurrent VTE and follow-up time for women with COC-associated and unprovoked VTE, and age-adjusted comparisons for the risk of recurrent VTE between women with COC-associated and unprovoked VTE if available). Any disagreements regarding data extraction were resolved through discussion and a third reviewer (Leslie Skeith) when needed.

Risk of bias assessment

Two reviewers (Jameel Abdulrehman and Carolyne Elbaz) independently conducted risk-of-bias assessments in the included studies using the Newcastle–Ottawa Scale (NOS).[12] The NOS is designed to assess the quality of non-randomized studies in a meta-analysis and evaluates the risk of bias across the domains of selection of the study groups, comparability of the study groups and outcome ascertainment using a star system. A study with zero stars is considered at the highest risk, whereas a study with nine stars is considered at the lowest risk. The risk of bias was judged solely on the published text and not based on author clarifications. Any disagreements regarding risk of bias were resolved through discussion and a third reviewer (Leslie Skeith) when needed.

Data synthesis and analysis

The incidence rate of VTE recurrence in each study was estimated using the number of recurrent VTE events and the total follow-up time in person-years. To estimate the 95% confidence interval (CI) for studies that had zero events, a continuity correction of 0.5 was added to the number of events. Random-effects Poisson regression models with Hartung and Knapp adjustment was used to pool the incidence rates of VTE recurrence across the studies. No continuity correction was used for studies with zero events for the pooling of incidence rates. A similar approach was used to pool incidence rate ratios comparing women with COC-associated and unprovoked VTE and is presented as an incidence rate ratio. We also aimed to pool age-adjusted comparison between women with COC-associated and unprovoked VTE. The percentage of heterogeneity due to between-study heterogeneity was assessed using the I^2 measure. All analyses were performed in R 4.03 (www.r-project.org) using the *meta* package.

Subgroup analysis

To assess the sources of heterogeneity among the studies, subgroup analyses were performed for all outcomes pending data availability from the respective cohorts: (1) oestrogen-containing contraceptives only, i.e. no progesterone-only contraceptive, or hormone-replacement therapy (HRT); (2) cohorts deemed to be at lower risk for recurrence based on the individual study-specific criteria that predefined a low-risk subgroup based on a clinical prediction score and/or D-dimer values; and (3) cohorts that did not include distal DVT as a recurrent VTE. As most studies included in the review did not conduct an age-adjusted relative recurrence rate comparison between women with COC-associated and unprovoked VTE, an additional post-hoc subgroup analysis was conducted that included only women under 50 years of age at time of study enrolment in an attempt to assess the effect of age as a confounder.

RESULTS

Search for included studies

A total of 15 997 records were identified through the database search with an additional four records through other screening references by hand of eligible studies, of which

147 were selected for full-text screening and 19 were included in this review (Figure 1). The third reviewer was not needed to resolve any disagreements regarding study selection, data extraction, or risk of bias assessment. The study by Tait et al. was only available as an abstract, but was included in this review as it was described in detail in several full-text articles.[13] Authors of the respective studies contributed additional unpublished data in 16 of the 19 studies.

Characteristics of included studies

The 19 studies included a total of 1537 women (5828 person-years of follow-up) with an index COC-associated VTE and 1974 women (7798 person-years of follow-up) with an index unprovoked VTE. The total length of follow-up in the individual studies in the COC-associated and unprovoked VTE groups ranged from 31 to 1739 and 24 to 1532 person-years, respectively. Sixteen of the studies were prospective cohorts, two were extended follow-ups after randomized controlled trials and one was a secondary analysis of a randomized controlled trial (Table 1). Within the COC-associated VTE groups, seven studies grouped contraceptive and HRT-associated VTE together,[4,13–18] and one study grouped outcomes for COC-associated VTE and VTE that occurred while on progesterone-only contraceptive together.[19] A very conservative estimate would be approximately 10% of the patients in the COC arm were HRT-associated VTE. Three cohorts selectively discontinued anticoagulation after index VTE in individuals deemed to be at low risk for recurrence based on clinical decision rules and/or D-dimer status.[4,16,17] An additional six studies had patient data available for those with negative for D-dimers, but in these studies D-dimer did not play a role in the decision to discontinue anticoagulation.[13,14,20–23]

Overall, studies were at low risk of bias with a mean of 6.6 stars (Table 2). A risk of bias assessment was not performed on Tait 2007 as it was only available in abstract form.[13] Studies generally lost points for lack of description of ascertainment of COC exposure and for lack of adjusted comparison between women with COC-associated VTE and women with unprovoked VTE.

Incidence rate of VTE recurrence in women with COC-associated VTE

The pooled incidence rate of VTE recurrence in women with COC-associated VTE from 19 studies was 1.22 per 100 person-years (95% CI 0.92–1.62, I^2 = 6%) (Figure 2). The risk of recurrence was similar in the subgroup analyses (Supplementary Appendix).

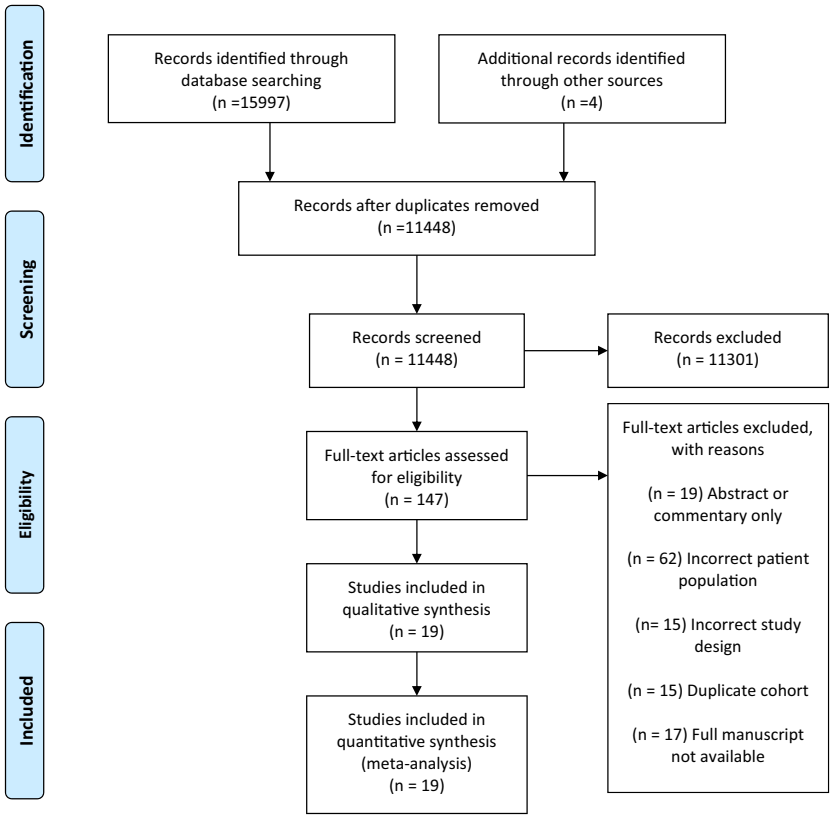

FIGURE 1 Study identification and selection flow diagram

TABLE 1 Characteristics of included studies

Study	Source	Study design	Number of women with COC-VTE	Definition of COC-VTE group	Number of women with unprovoked VTE	Definition of unprovoked-VTE group	Index VTE type	Clinical decision rule involving D-dimer status for stopping anticoagulation	Recurrent VTE type	Total length of follow-up of COC-VTE (years)	Total length of follow-up of unprovoked-VTE (years)
1	Palareti 2002[22]	Prospective cohort study	19	Oestrogen-containing contraceptives	75	Excluded major risk factors, minor risk factors and APS	DVT in legs or PE	None	DVT in legs or PE	31	120
2	Schulman 2006[18]	Extended follow-up after randomized controlled trial (DURAC) — only arm that discontinued anticoagulation after 6 months	11	Oestrogen-containing contraceptives or hormone replacement therapy	107	Excluded major risk factors, minor risk factors and inherited thrombophilia	DVT in legs or PE	None	DVT in legs or PE	110	1017.5
3	Shrivastava 2006[23]	Secondary analysis of randomized controlled trial (PREVENT) – only arm that discontinued anticoagulation	17	Age 30 years or greater and combined oral contraceptives	27	Age 30 years or greater and excluded major risk factors, minor risk factors and APS	DVT in legs or PE	None	DVT in legs or PE	36.2	50.5
4	Tait 2007[13]	Prospective cohort study	33	Oestrogen-containing contraceptives or hormone replacement therapy	37	N/A	DVT or PE	None	DVT or PE	57.5	66.1
5	Baglin 2008[14]	Prospective cohort study	19	Combined oral contraceptives or hormone replacement therapy	65	Excluded major risk factors, minor risk factors and APS	Proximal DVT in legs or PE	None	Proximal DVT in legs or PE	77.2	211.5
6	Poli 2008[20]	Prospective cohort study	31	Combined oral contraceptives	55	Excluded major risk factor, minor risk factor and APS	DVT in legs or PE	None	DVT in legs or PE	87.3	126.5
7	Christiansen 2005[19]	Prospective cohort study (LETS cohort)	77	Age 55 or younger and combined oral contraceptives or progesterone-only contraceptives	96	Age 55 or younger and excluded major risk factors and minor risk factors	Proximal DVT in legs or arms	None	Proximal DVT in legs or arms or PE	621	706

(Continues)

TABLE 1 (Continued)

Study	Source	Study design	Number of women with COC-VTE	Definition of COC-VTE group	Number of women with unprovoked VTE	Definition of unprovoked-VTE group	Index VTE type	Clinical decision rule involving D-dimer status for stopping anticoagulation	Recurrent VTE type	Total length of follow-up of COC-VTE (years)	Total length of follow-up of unprovoked-VTE (years)
8	Cosmi 2010[15]	Extended follow-up after randomized controlled trial (PROLONG) — only those who did not resume anticoagulation	58	Age 85 or younger and oestrogen-containing contraceptives or hormone replacement therapy	186	Age 85 or younger and excluded major risk factor, minor risk factors, inherited thrombophilia and APS	Proximal DVT in legs or PE	Patients with a negative D-dimer 1 month after anticoagulation cessation continued off anticoagulation. Patients with an elevated D-dimer were randomized to either resume or stay off anticoagulation	Proximal DVT in legs or PE	165	461
9	Miranda 2010[38]	Prospective cohort study (ISCVT cohort)	63	Combined oral contraceptives	17	Excluded major risk factors, minor risk factors, inherited thrombophilia and APS	Cerebral vein thrombosis	None	Cerebral vein thrombosis, DVT in legs or arms, PE, abdominal or pelvic vein thrombosis	79	24.3
10	Olié 2012[28]	Prospective cohort study (FARIVE cohort)	144	Oestrogen-containing contraceptives	179	Excluded major risk factors and minor risk factors	Proximal DVT in the legs or PE	None	Proximal DVT in the legs or PE	341.3	431.7
11	Le Moigne 2013[7]	Prospective cohort study	132	Age 50 or younger and combined oral contraceptives	44	Age 50 or younger and excluded major risk factors and minor risk factors	DVT in legs or PE	None	DVT in legs or PE	726	279
12	Eischer 2014[3]	Prospective cohort study (AUREC cohort)	275	Oestrogen-containing contraceptives	297	Excluded major risk factors, minor risk factors, inherited thrombophilia and APS	DVT in legs or PE	None	DVT in legs or PE	1739	1532
13	Palareti 2014[16]	Prospective cohort study (DULCIS cohort) – only those who did not resume anticoagulation	100	Oestrogen-containing contraceptives or hormonal replacement therapy	155	Excluded major risk factors, inherited thrombophilia and APS	Proximal DVT in the legs or PE	Patients with a negative D-dimer on anticoagulation discontinued anticoagulation. Patients had serial D-dimer testing and were recommended to resume anticoagulation at the first positive D-dimer	Proximal DVT in the legs or PE	173	233

TABLE 1 (Continued)

Study	Source	Study design	Number of women with COC-VTE	Definition of COC-VTE group	Number of women with unprovoked VTE	Definition of unprovoked-VTE group	Index VTE type	Clinical decision rule involving D-dimer status for stopping anticoagulation	Recurrent VTE type	Total length of follow-up of COC-VTE (years)	Total length of follow-up of unprovoked-VTE (years)
14	Rodger 2016[21]	Prospective cohort study (REVERSE I cohort)	50	Combined oral contraceptives	272	Excluded major risk factors, minor risk factors, inherited thrombophilia and APS	Proximal DVT in the legs or PE	None	Proximal DVT in the legs or PE	352.4	1485.0
15	Nagler 2018[30]	Prospective cohort study	44	Combined oral contraceptives	73	Excluded major risk factors, minor risk factors, inherited thrombophilia and APS	Proximal DVT in the legs	None	DVT, PE, or other venous thrombosis	221.1	324.5
16	Rodger 2017[17]	Prospective cohort study (REVERSE II cohort)	291	Age younger than 50 and oestrogen-containing contraceptives or hormonal replacement therapy	138	Age younger than 50 and excluded major risk factors, minor risk factors and APS	Proximal DVT in the legs or PE	Patients with HERDOO2 score 0 or 1 discontinued anticoagulation	Proximal DVT in the legs or PE	277.55	129.8
17	Zabczyk 2017[39]	Prospective cohort study	9	Age 65 or younger and combined oral contraceptives	40	Age 65 or younger and excluded major risk factors, minor risk factors and inherited thrombophilia	DVT in legs or PE	None	DVT in legs or PE	37.7	156.2
18	Kearon 2019[4]	Prospective cohort study (DODS cohort)	58	Age 75 or younger Oestrogen-containing contraceptives or hormone replacement therapy	81	Age 75 or younger and excluded major risk factors and minor risk factors	Proximal DVT in the legs or PE	Patients with a negative D-dimer on anticoagulation and remaining negative 1 month after discontinuation of anticoagulation remained off anticoagulation	Proximal DVT in the legs or PE	235	316
19	Pires 2019[40]	Prospective cohort study	106	Combined oral contraceptives	30	Excluded major risk factors and minor risk factors	Cerebral vein thrombosis	None	Any venous site	460.3	127.4

Abbreviations: APS, antiphospholipid syndrome; COC, combined oral contraceptive; DVT, deep-vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

TABLE 2 Risk of bias assessments

Study number	Source	Selection (/4)	Comparability (/2)	Outcome (/3)	Total
1	Palareti 2002	★★★	0	★★★	6
2	Schulman 2006	★★★	0	★★★	6
3	Shrivastava 2006	★★★	0	★★	5
4	Tait 2007	N/A	N/A	N/A	N/A
5	Baglin 2008	★★★	0	★★★	6
6	Poli 2008	★★★	0	★★★	6
7	Christiansen 2005	★★★★	0	★★★	7
8	Cosmi 2010	★★★	0	★★★	6
9	Miranda 2010	★★★	0	★★★	6
10	Olié 2012	★★★★	0	★★★	7
11	Le Moigne 2013	★★★★	★★	★★★	9
12	Eischer 2014	★★★★	★★	★★★	9
13	Palareti 2014	★★★	0	★★★	6
14	Rodger 2016	★★★★	★★	★★★	9
15	Nagler 2018	★★★★	0	★★★	7
16	Rodger 2017	★★★★	0	★★	6
17	Zabczyk 2017	★★★	0	★★★	6
18	Kearon 2019	★★	0	★★★	5
19	Pires 2019	★★★★	0	★★★	7

Incidence rate of VTE recurrence in women with unprovoked VTE

In women with unprovoked VTE, the pooled incidence rate from 19 studies was 3.89 per 100 person-years (95% CI 2.93–5.17, I^2 = 74%) (Figure 3). The incidence rate was similar in the subgroup that excluded distal DVT (3.7 per 100 person-years, 95% CI 2.54–5.41), but was lower in the low-risk subgroup (2.79 per 100 person-years, 95% CI 1.61–4.83) and the subgroup aged younger than 50 years old (2.87 per 100 person-years, 95% CI 1.90–4.35) (Supplementary Appendix).

Unadjusted incidence rate ratio of VTE recurrence comparing women with COC-associated VTE to women with unprovoked VTE

Comparing women with COC-associated VTE to women with unprovoked VTE, the unadjusted incidence rate ratio was 0.34 (95% CI 0.26–0.46, I^2 = 3%) (Figure 4). The results were similar across the oestrogen-containing-contraceptives-only subgroup (0.37, 95% CI 0.26–0.54), the low-risk subgroup (0.33, 95% CI 0.15–0.70) and the subgroup that excluded distal DVT (0.34,95% CI 0.22–0.53), but the age under 50 years subgroup had a higher unadjusted incidence rate ratio of 0.51 (95% CI 0.24–1.06) (Supplementary Appendix).

Age-adjusted incidence rate ratio of recurrent VTE comparing women with COC-associated VTE to women with unprovoked VTE

Meta-analysis of the age-adjusted incidence ratio of recurrent VTE could not be conducted as only three studies presented age-adjusted analyses, each with a different effect measure. The Eischer 2014 cohort adjusting for age, site of VTE and congenital thrombophilia and the relative risk ratio was 0.4 (95% CI 0.2–0.8).[3] The Kearon 2019 cohort adjusting for age alone calculated a hazard ratio of 0.11 (95% CI 0.01–0.85).[4] Lastly, the Le Moigne 2013 cohort adjusting for age alone reported an incidence rate ratio of 1 (95% CI 0.3–3.2).[7]

DISCUSSION

This systematic review, including 19 studies with a total of 1537 women with COC-associated VTE (5828 person-years of follow-up) and 1974 women with unprovoked VTE (7798 person-years of follow-up) found a low risk of recurrence after a COC-associated VTE at 1.22 per 100 person-years, which was lower than in women with unprovoked VTE at 3.89 per 100 person-years. The pooled unadjusted incidence rate ratio was 0.34, but we were unable to calculate a pooled comparison adjusted for age.

The finding of a low risk of recurrence after a COC-associated VTE is clinically relevant. The decision to

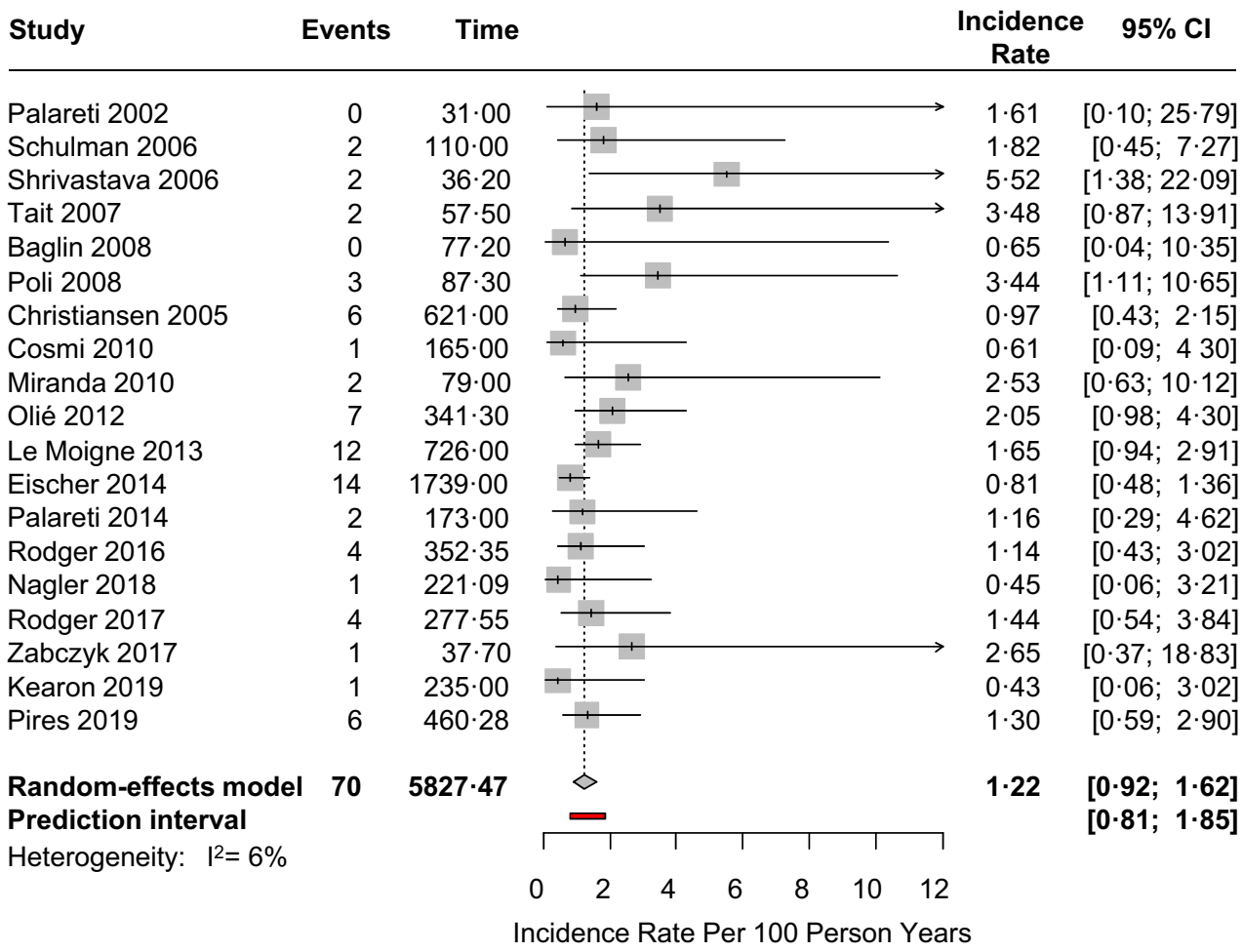

FIGURE 2 Incidence rate of VTE recurrence in women with COC-associated VTE

continue anticoagulation after the initial three-month treatment period with the associated risk of major bleeding must be weighed against the risk of recurrent VTE off anticoagulation. The estimated incidence of major bleeding on extended anticoagulation on vitamin K antagonists and direct oral anticoagulants is 1.74 and 1.12 events per 100 person-years, respectively.[24] The risk of major bleeding is lower in young people, with a risk approximately 1/3 of those older than 65 years of age.[24] While the case fatality rate of major bleeding is estimated at 10 per 100, this is likely lower in young women.[24] One must also consider complications of heavy menstrual bleeding on anticoagulation in the demographic of young women. In our analysis, the estimated risk of recurrence after a COC-associated VTE was low at 1.22 per 100 person-years; likely low enough to warrant anticoagulation discontinuation after the initial treatment period.

Despite methodological differences, findings in this study were in keeping with meta-analysed data assessing the risk of recurrent VTE in women after COC-associated VTE.[25] In that study, Wiegers et al. estimated the pooled recurrence rate in women with COC-associated VTE as 1.57 (95% CI 1.10–2.23, $I^2 = 80\%$) per 100 person-years compared to 1.22 (95% CI 0.92–1.62, $I^2 = 6\%$) per 100 person-years in this analysis. Wiegers et al. included 14 studies of both retrospective and prospective designs, whereas this study included 19 studies of only prospective designs. Compared to prospective cohorts, retrospective cohort studies are at higher risk of bias due to missing or poor-quality data pertaining to exposure or outcomes. The larger number of studies with prospective data in this analysis is a testament to the extensive contributions by study authors that provided additional unpublished data. In addition, Wiegers et al. focused solely on the risk of recurrence in women after COC-associated VTE, whereas this study also calculated the risk of recurrence in women after unprovoked VTE and a risk comparison between women with COC-associated VTE and unprovoked VTE.

The finding of a decreased risk of recurrent VTE in women after COC-associated VTE compared to unprovoked VTE, is in keeping with the findings of the DASH study, which used meta-analysed data from several prospective cohorts.[26] In addition to abnormal D-dimer after anticoagulation discontinuation, age less than 50 years old and male sex, VTE not associated with hormonal (COC or HRT) therapy was found to be a major predictor for increased recurrence risk in the DASH predictive model.[26,27] Similar to the pooled unadjusted incidence rate ratio of 0.34 in this study, the DASH study estimated an optimism-corrected hazard ratio

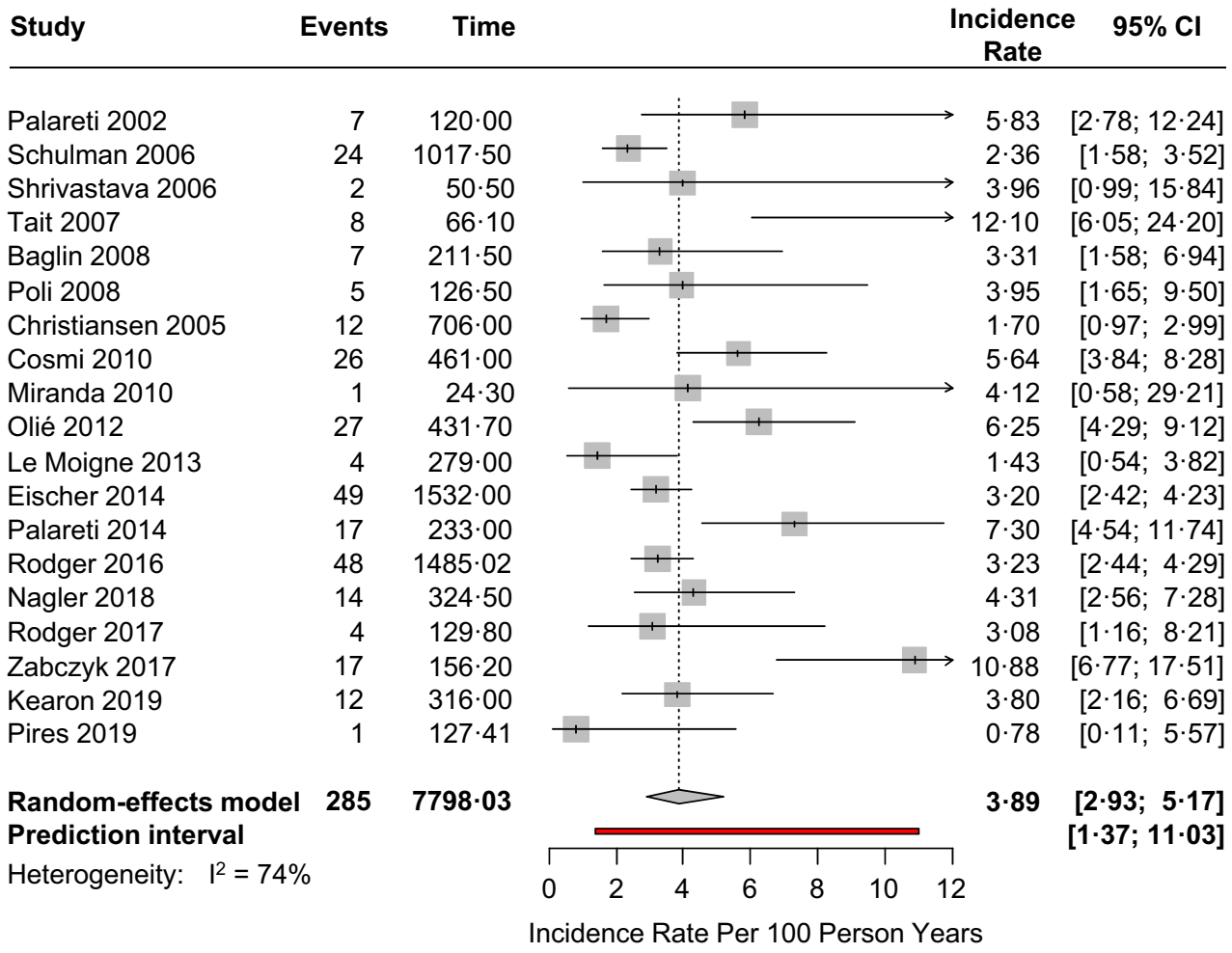

FIGURE 3 Incidence rate of VTE recurrence in women with unprovoked VTE

recurrence of 0.35 in women with hormonal -associated VTE compared to women not taking hormonal therapy.[26]

It remains unclear if the difference in recurrence risk between women with COC-associated VTE and women with unprovoked VTE can be attributed to the confounder of COC users being generally healthy young women. The use of COC is predominantly in younger women and decreases with age, while the risk of recurrent VTE increases with age, with a hazard ratio for recurrence in women of 1.3 (95% CI 1.1–1.5) for every 10-year increase in age.[28,29] In our review, both age-adjusted analysis from Eischer et al. and Kearon et al. cohorts demonstrated a lower risk of recurrence after COC-associated VTE, but the age-adjusted analysis in the cohort by Le Moigne et al. was inconclusive given the wide confidence intervals.[3,4,7] It must be noted that in the Kearon 2019 cohort, anticoagulation was selectively discontinued in those deemed at low risk for recurrent VTE based on D-dimer being negative on anticoagulation and after one month off anticoagulation.[4] In the unadjusted analyses, seven of the 19 studies, including the Eischer 2014 and Kearon 2019 cohorts, had a lower risk of recurrence after COC-associated VTE.[3,4,15,16,21,28,30] However, the subgroup analysis for those under 50 years failed to find a difference in recurrence risk. Although the relative risk remains unclear, the low absolute risk of recurrence after a COC-associated VTE is reassuring and is more clinically relevant when counselling these patients regarding discontinuation of anticoagulation.

The potential limitations of this review must also be considered. First, there was substantial clinical heterogeneity in the study populations, including differing age groups and VTE types. Several of the included studies did not differentiate between women who had VTE while on COC, HRT, or progestin-only preparations, which is a limitation to combining studies in our meta-analysis. Compared to non-users, COC use increases the risk of VTE two- to fourfold and HRT use by 1.5- to twofold, whereas progestin-only pills, progesterone intrauterine devices and transdermal oestrogen-only HRT preparations do not seem to increase the risk of VTE.[9] Separating these groups may also be important as the VTE risk of a specific preparation is correlated with its 'total estrogenicity', increasing with higher oestrogen doses, but decreasing based on the anti-oestrogenic activity of specific progestins.[31–35] Accurately describing the type of hormonal risk factor for VTE has prognostic importance, as the risk of recurrence is inversely correlated with the thrombogenicity

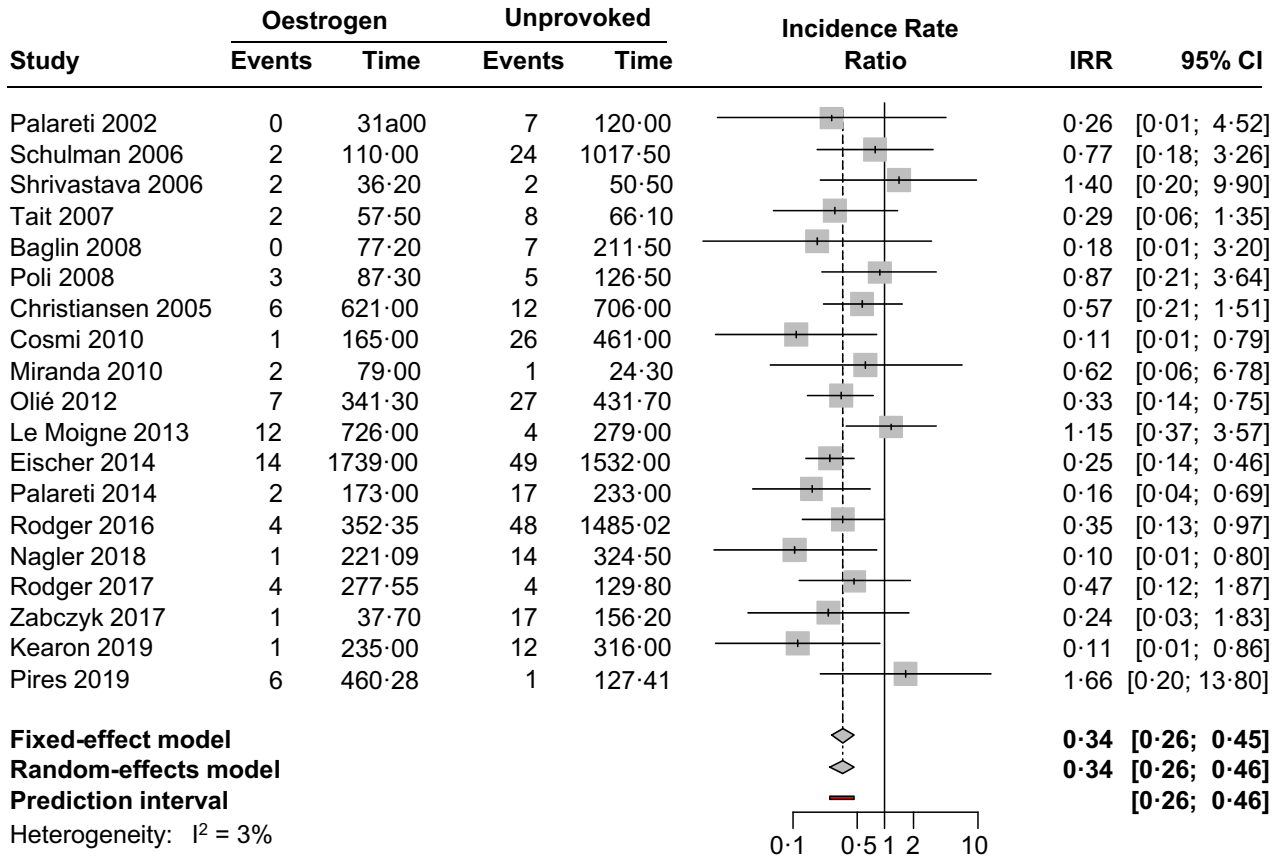

FIGURE 4 Unadjusted incidence rate ratio of VTE recurrence comparing women with COC-associated VTE to women with unprovoked VTE

of the risk factor.[1] We conducted subgroup analyses to attempt to account for variations in study populations. Second, we were unable to estimate a pooled age-adjusted comparison of the risk of recurrence between women with COC-associated VTE and women with unprovoked VTE. Therefore, it is not possible to rule out that the lower risk of recurrence observed after a COC-associated VTE is confounded by the younger age of COC users, compared to women with unprovoked events. Third, the risk of COC-associated VTE may vary, as the clinical phenotype may be closer to provoked VTE if the event occurs soon after COC initiation (i.e., within one year) or with a higher oestrogen dose of COC and closer to unprovoked VTE if the event occurs several years after COC initiation or with lower-dose oestrogen of COC.[32]

A potential bias in the calculation of the recurrence risk must also be examined. We calculated the risk of recurrence in the individual studies based on the number of recurrent events divided by the total follow-up time in person-years. As the risk of recurrent VTE decreases with time after anticoagulation discontinuation, studies that had longer follow-up may artificially have a mean lower risk of recurrence per year compared to studies with shorter follow-up.[36] As almost all included studies had greater than one year follow-up, our calculated recurrence risk after a COC-associated VTE of 1.22 per 100 person-years may underestimate the recurrence risk at one year. Nonetheless, it is unlikely that the risk would be greater than the 5% recurrence risk at one year threshold deemed to be appropriate for continuing anticoagulation as secondary prevention.[37]

To conclude, the estimated risk of recurrence is low in women with COC-associated VTE and is lower than in women with unprovoked VTE; however, age differences between these groups may be a major confounder. These findings may help clinicians and patient shared decision-making regarding the risk of recurrent VTE after anticoagulation discontinuation. The low number of women with COC-associated VTE included in this study highlights the need for more research in this demographic.

AUTHOR CONTRIBUTIONS

Gregoire Le Gal, Clive Kearon and Leslie Skeith conceived the study. Jameel Abdulrehman, Carolyne Elbaz, Sameer Parpia, Gregoire Le Gal, Clive Kearon and Leslie Skeith designed the study. Rouhi Fazelzad designed the search strategy. Jameel Abdulrehman and Carolyne Elbaz conducted the primary and secondary screens and risk of bias assessments. Sameer Parpia, Lisbeth Eischer, Marc A. Rodger, Suzanne C. Cannegieter, Arina ten Cate-Hoek, Michael Nagler, Sam Schulman, Suely M. Rezende, Valérie

Olié, Gualtiero Palareti, Maura Marcucci, James Douketis, Daniela Poli, Michal Zabczyk, Diana Aguiar de Sousa, Bruno Miranda, Mary Cushman and Alberto Tosetto contributed unpublished data. Jameel Abdulrehman and David Aziz extracted data from the included studies. Sameer Parpia conducted the meta-analysis. Jameel Abdulrehman, Sameer Parpia, Gregoire Le Gal and Leslie Skeith drafted the manuscript. All authors critically revised and approved the manuscript.

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CONFLICTS OF INTEREST

Sam Schulman has received research funding from Octapharma and Boehringer-Ingleheim and honoraria from Boehringer-Ingelheim, Alnylam, Bayer, Bristol-Myers Squibb, Daiichi-Sankyo and Sanofi. Leslie Skeith has received research funding from CSL Behring and honoraria from Leo Pharma and Sanofi.

DATA AVAILABILITY STATEMENT

Research data are not shared.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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