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The risk of venous thromboembolism in women with superficial venous thrombosis who use combined hormonal contraceptives: a systematic review and meta-analysis

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ABSTRACT

Objective. The use of combined hormonal contraceptives (CHCs) has been linked to an elevated risk of thrombosis. Understanding the relationship between CHC use with the incidence of venous thromboembolism (VTE) in women with superficial venous thrombosis (SVT) becomes imperative to ensure patient safety. Limited evidence prompted this study to assess the associated risk.

Methods. Three databases (Cochrane Library, Scopus, PubMed) have been systematically searched for identifying relevant studies. A meta-analysis was conducted to assess the impact of CHCs on VTE incidence with women with SVT, employing a random-effects model with pooled ORs calculated using the Mantel-Haenszel method. Publication bias was evaluated through funnel plots.

Results. A total of 3,984 cases from five countries have been identified from nine studies (1 cross-sectional, 1 RCT, 7 longitudinal studies). The pooled OR was 0.85 (CI 0.58-1.23] $p = 0.38$, $I^2 = 0\%$), indicating no significant difference in the odds of VTE incidence between CHC users and controls. Subgroup analysis of RCT and longitudinal studies and leave-one-out sensitivity present no alteration in heterogeneity and significance. When adjusted for confounders (history of immobilization, cancer, and history of VTE), CHC use in SVT patients showed a non-significant increase in VTE odds (OR 1.43, CI 0.43-4.68] $p = 0.56$, $I^2 = 0\%$). No evidence of publication bias was observed.

Conclusions. This meta-analysis found no statistically significant link between CHCs use and the risk of developing VTE in women with SVT. Further research is recommended to clarify the risk.

INTRODUCTION

Superficial vein thrombosis (SVT) is a benign condition that requires less medical attention and most often affects the veins of the lower limbs [1, 2]. It is

characterized by the presence of a swollen, tender, red area and warm on palpation along the superficial vein of the lower part of the legs [2]. SVT is a self-limiting condition that is mainly found in primary healthcare facilities and is easily diagnosed

based on clinical presentation. The benign prognosis of SVT explains its underreporting, resulting in fewer studies and ongoing controversy about its epidemiology and whether it requires treatment at all [3, 4]. Although SVT has long been considered a benign condition with an uncomplicated course, the presence of concomitant deep vein thrombosis (DVT) and/or pulmonary embolism (venous thromboembolism [VTE]) has been reported repeatedly in patients with SVT, leading to severe complications that require more aggressive therapy [2, 5]. The percentage of patients with SVT who also develop DVT is estimated to range from 6% to 53%, while symptomatic VTE has been observed in 0% to 10% of SVT cases [6].

VTE, compared to SVT, is more complicated and considered to be life-threatening. Recent studies might show the correlation between SVT and VTE. This association has raised concerns about the potential need for more aggressive management of SVT, especially in high-risk populations. One such group is women using combined hormonal contraceptives (CHCs), as these medications are known to increase the risk of VTE independently [7]. The voluntary use of contraception by women is fundamental for protecting their reproductive rights. It is imperative that all women, from adolescence through adulthood, have access to evidence-based, comprehensive information, education, and counselling on contraceptive methods to facilitate informed decision-making. The process of selecting a contraceptive method typically necessitates weighing the advantages and disadvantages of various options, with the benefits and drawbacks differing according to individual circumstances, perceptions, and interpretations [8, 9].

The combination of SVT and combined hormonal contraceptives (CHCs) may further elevate the risk of developing serious thrombotic complications, warranting closer monitoring and potentially different treatment approaches. However, the evidence for the safety of CHCs use in SVT women is still scarce [8]. Therefore, this study was undertaken to examine the associated risk between the safety of CHCs uses in SVT patients.

MATERIALS AND METHODS

Search strategy

Systematically, a search was conducted across the main databases of Cochrane Library, Scopus, and

PubMed up to June 2024 limited only to English-language studies without applying date restrictions. The complete search strategy is further described in **Supplement 1**. This study adheres to the guidelines recommended by Enhancing the Quality and Transparency of Health Research (EQUATOR) network and is registered in PROSPERO under the ID CRD42024585529.

Study selection

We selected observational and randomized controlled trial (when available) studies that included women with SVT diagnosis who use CHCs that develop VTE. SVT is confirmed by the presence of a subcutaneous noncompressible hypoechoic area in the course of a superficial vein found by ultrasonography. Studies are excluded when they did not report the OR or if the OR could not be calculated. Additionally, case reports and case series studies are not included. Two investigators (S.S.S. and W.H.) independently performed an assessment of the studies that met the inclusion criteria, with disagreements addressed through discussion with another author (L.M.A.).

Risk of bias assessment

Each observational study included in this analysis underwent a risk of bias evaluation using the Revised Cochrane risk-of-bias tool for non-randomized studies of-exposure (ROBINS-E). The assessment for observational studies included the evaluation of study bias in the following domains: confounding variables, exposure measurement, participant selection, post-exposure interventions, missing data, outcome measurement, and selection of the reported result. These components were all factored into the overall risk of bias judgment. Two reviewers (A.D.S. and S.S.S.) independently conducted the assessments, and any disagreements were settled through consensus.

Data extraction

From a total of 9 studies, data were independently extracted and recorded by two reviewers (L.M.A. and S.A.R.S.). A third reviewer (S.S.S.) reviewed the collected data to identify any inconsistencies, and all other authors reached a consensus to address any discrepancies. From all of the selected studies, the data that were extracted include: authors, name of registry, study design, year of publication, location of study, race of population, sample size, population included, age, type and composition of

contraception, definition of SVT and VTE, and possible confounding factors including personal and family history of VTE, chronic venous insufficiency, thrombophilic abnormalities, local or systemic infections, congestive heart failure or respiratory insufficiency, active cancer, pregnancy or postpartum, BMI, history of immobilization, smoking, and use of elastic stockings (**Supplements 2-6**).

Predictor and outcome measures

The outcome measures analysed in this study include the incidence of VTE. VTE is described as a group of diagnoses of deep vein thrombosis (DVT) or pulmonary embolism (PE). DVT is defined as the formation of thrombi in the deep veins, while PE develops from the embolization of thrombi in DVT to pulmonary veins [10]. Predictors analysed in this study are CHCs including combined oral contraceptives, combined injectable contraceptives, combined contraceptive patches, and combined contraceptive vaginal rings [8].

Statistical analysis

All aspects of this meta-analysis have been performed in accordance with the PRISMA guideline provided by EQUATOR network. For statistical analysis, we used Review Manager (RevMan) version 5.4. Odds ratio described in each study is pooled using the generic invariance method with a ran-

dom effect model. Additionally, studies that report event rate will be converted to odds ratio using RevMan calculator. A 95% confidence interval was used, and statistical significance was considered when the p-value was below 0.05. Heterogeneity was assessed using I^2 with the following interpretations: $I^2 < 40\%$ indicating low heterogeneity, 30-60% as moderate, 50-90% as substantial, and 75-100% as considerable. Publication bias was evaluated using a funnel plot and subgroup analysis and sensitivity analysis were performed based on variables that could potentially confound results. We conduct leave one out analysis to determine the robustness of the result. We also conducted GRADE assessment to determine the level of certainty in the evidence generated.

RESULTS

Study selection and characteristics

The initial search across three databases (Cochrane Library, Scopus, PubMed) identified a total of 3996 identified studies. After removing 855 duplicates and screening titles, abstracts, and full-text articles, 9 studies were ultimately included in this analysis [1-6, 9-11] (**Figure 1**). A total of 2,937 women with SVT from 5 countries are included in which cases are identified from 1989-2017 and 283 of

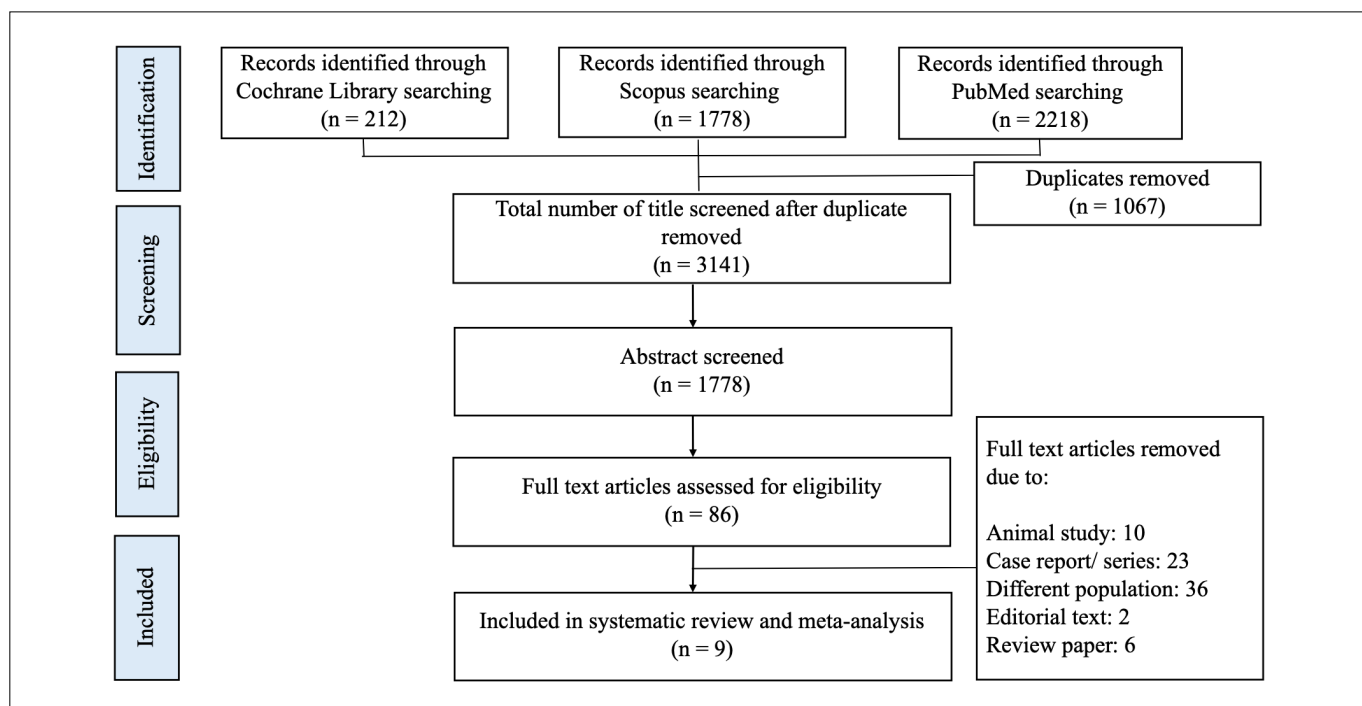


Figure 1. PRISMA flow chart.

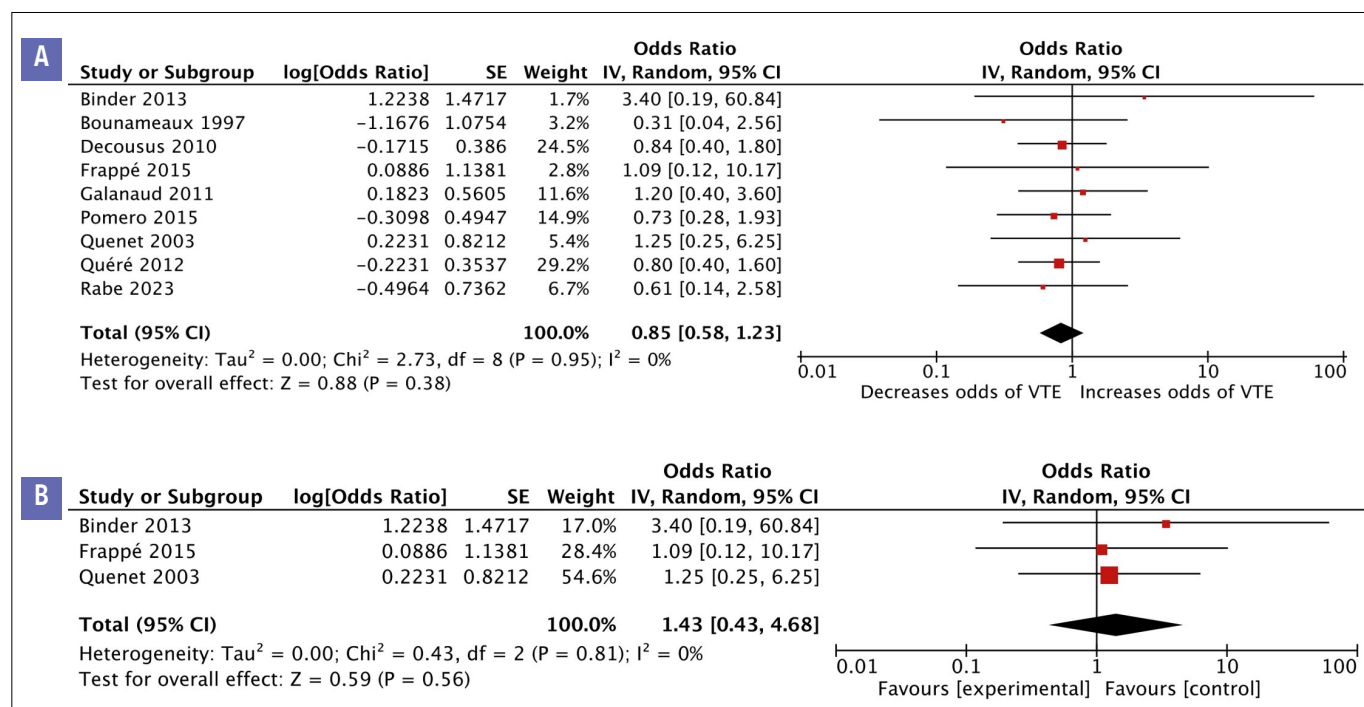


Figure 2. (A) The risk of VTE in women with SVT who use CHCs compared to non-CHC users shows a non-significant odd of VTE incidence. (B) After adjusting for potential confounders such as prior history of VTE, cancer, and history of immobilization, there remains a non-statistically significant increase in the odds of VTE incidence among SVT patients who use CHCs

these populations use CHCs. VTE was observed in 45 of these patients (15.9%). One study had a cross-sectional design [3], and the remainder had a longitudinal design. Three studies reported all VTE outcomes (DVT and/or PE) [4, 11, 12], two studies reported venous thrombotic complications (DVT, PE, recurrent SVT, and extending SVT) [1, 11], no study reported DVT and PE outcomes separately, six studies reported only DVT outcomes [2-6, 13] and no study reported only PE outcomes. There are two studies that reported two separate results, but we decided to use DVT and/or PE outcome [11] remembering the purpose of this study and DVT only [4] due to lack of data. All the included studies are univariate analysis studies.

All of the studies reported the use of oral contraception. However, only one study provided detailed information on the composition of the contraception [5], identifying the contraception as CHCs. Given that combined oral contraception are the first-line contraceptive method, whereas progestin-only contraceptives are typically prescribed only for specific indications, it is reasonable to assume that the other reported oral contraceptives were also CHCs [8].

Risk of bias assessment

Risk of bias assessment with ROBINS-E tool found that one study [6] is regarded to have some concerns of bias while the remaining are assessed as low risk of bias. Bias due to confounding is found in 6 out of

9 studies. There was also found bias in participant selection in 3 out of 9 studies. Moreover, a different set of 3 out of 9 studies revealed bias due to missing data. One study is evaluated as some concern of bias due to post-exposure interventions. In all of the study, bias arising from confounding variables, measurement of the exposure, selection of participants, post-exposure interventions, missing data, measurement of the outcome, and selection of the reported result are considered low (Supplement 7).

Data synthesis

Nine studies reported the association of CHCs use in women with SVT where VTE is present in 45 of all 283 SVT cases. In our primary analysis, we found no significant association between CHCs exposure and the control group, with OR of 0.85 (CI 0.58-1.23; $p = 0.38$, $I^2 = 0\%$), indicating no increased risk of VTE associated with the use of CHC in women with SVT (Figure 2).

To further refine our findings, we conducted a meta-analysis limited to longitudinal and RCT and it also did not show a statistically significant odd nor alter the heterogeneity level (OR 0.84, CI [0.57-1.23] $p = 0.37$, $I^2 = 0\%$) (Supplement 8). Sensitivity analysis, performed by excluding one study at a time, did not alter the statistical significance and heterogeneity level (Supplement 9).

We carried out a separated analysis to control several potential confounders. Confounders were selected if there was a significant difference between cases and controls and if they were proven to be a significant risk factor for developing VTE with established evidence. Based on these considerations, we selected three variables as confounding factors: prior history of VTE, cancer, and history of immobilization.

For the first confounding factor, we excluded three studies that demonstrated a significant difference in prior history of VTE between users of CHCs and non-users. An analysis of six studies addressing the prior history of VTE was conducted, revealing that there are no statistically significant odds of VTE outcome. (CI 0.47-1.51] $p = 0.78$, $I^2 = 0\%$) (**Supplement 8**).

The second confounding factor (cancer) was evaluated using the same criteria. Four studies are excluded from the analysis. An analysis of five studies addressing cancer was conducted, revealing that women with SVT who use CHCs have no statistically significant odds of VTE outcome (CI 0.36-1.94] $p = 0.69$, $I^2 = 0\%$) (**Supplement 8**).

The last known confounding factor (history of immobilization) was also examined using the same means. Two studies are excluded from the analysis. An analysis of seven studies addressing the history of immobilization was conducted, exposing that women with SVT who use CHCs have no statistically significant odds of VTE outcome (CI 0.56-1.26] $p = 0.96$, $I^2 = 0\%$) (**Supplement 8**).

However, after addressing all potential confounders of prior history of VTE, cancer, and history of immobilization, at one separate analysis after excluding six studies [1, 2, 4, 6, 9, 11], we found an alteration of the course of the results. Three studies were analysed and it is shown that women with SVT who use CHCs have 1.43 times odds of developing VTE (95%CI 0.43-4.68] $p = 0.56$, $I^2 = 0\%$), although it is not statistically significant (**Figure 2**). Publication bias assessed by the funnel plot did not show any asymmetrical figure hence there is no significant publication bias in each of the predictors assessed (**Supplement 10**).

DISCUSSION

This study shows that there are no significant odds of developing VTE in women with SVT who use CHCs. Additionally, the result is still statistically not significant after excluding a cross-sectional study and adjusting for confounding factors (prior

history of VTE, cancer, and history of immobilization). The heterogeneity level of all the analyses was proven to be low ($I^2 = 0\%$), supporting the quality of this study.

CHCs are well-established risk factors for venous thrombosis. CHCs are known to enhance thrombin generation and elevate D-dimer levels, which are biomarkers of coagulation activation. The resulting increase in thrombin generation contributes to a hypercoagulable state, significantly raising the risk of clot formation in the venous system [14]. The World Health Organization (WHO) has published a medical eligibility criteria for contraceptive use, indicating that women with SVT can generally use CHCs, though the level of evidence supporting this recommendation is very low. On the other side, women with VTE who use CHCs are associated with an unacceptable health risk [8]. The insignificant odds of developing VTE depicted in our study indirectly mean that different pathogenesis underlying SVT and DVT exists.

Venous thrombosis can occur in superficial (SVT) or deep veins (DVT) and the pathophysiological basis of both diseases is explained by Virchow's triad: stasis, endothelial injury, and hypercoagulability [15]. Due to differences in anatomical site and thrombotic mechanism, the components of Virchow's have varying significance in venous thrombosis diseases. For example, SVT often results from recent venous punctures, such as those caused by blood draws, IV insertions, or catheter placement [16]. Moreover, because it is located close to the skin, superficial veins are more vulnerable to external trauma, which also contributes to endothelial injury. These differences in pathophysiological processes that lead to clot formation in different venous systems might explain why the influence of hormonal contraception does not extend an SVT into a DVT or its complication: PE.

Hypercoagulable states affect SVT and VTE independently. The presence of SVT, which typically occurs due to local inflammation, does not necessarily result in the thrombus extending into the deep veins when a hypercoagulable state is induced, such as with the use of combined hormonal contraceptives (CHCs). Instead, hypercoagulability increases the likelihood of thrombus formation in the deep veins, representing a separate event.

Previous meta-analysis has shown that several predictors are associated with the development of VTE from SVT, such as high age OR 2.41 (95%CI 1.84 to 3.15), male sex 2.40 (95%CI 1.44-3.99), hi-

story of VTE OR 2.01 (95%CI 1.11-3.64), and cancer OR 2.39 (95%CI 1.61-3.65) [17]. Our study also adds to the existing field of evidence where CHC is not associated with the development of VTE. Hence, CHCs can be safely used in women with SVT. Although this study used univariate analysis, the heterogeneity is promising, and the GRADE assessment shows high certainty (**Supplement 11**). The robustness of our data can also be inferred after conducting a subgroup analysis by excluding confounding factors of cancer, history of VTE, and history of immobilization. Given the limited number of studies in this area, these findings may provide some reassurance regarding the safety profile of CHCs in this population.

While the study's promising heterogeneity, high certainty in the GRADE assessment, and subgroup analysis support the robustness of the data, one important aspect remains overlooked: individual thromboembolic risk assessment. This includes consideration of genetic mutations in coagulation-related genes (e.g. Factor V Leiden) and highlights the need for personalized clinical decision-making based on each patient's unique profile. Furthermore, informed consent should accompany all CHC prescriptions to uphold reproductive autonomy, ensure safe and appropriate use, reduce thromboembolic risk, and provide legal protection to healthcare providers [18, 19].

LIMITATIONS AND RECOMMENDATION

The evidence presented in this review has the following limitations [20].

1. Sample Size:
 - The small sample size in this study limits the precision of the effect estimates, as reflected in the wide confidence intervals.
2. Outcome Measurement:
 - Some studies lacked outcome timing details, potentially leading to inconsistent measurements, reduced comparability, and misinterpretation of results.
3. Geographic Bias:
 - All the studies included were performed in high-income countries, restricting relevance to middle-to-lower-income countries where differences in healthcare accessibility and cultural practices could influence outcomes. The review processes used have the following limitations.

4. Search strategy:

- The search strategy is limited only to English-language studies, creating potential language bias.

5. Data synthesis:

- Due to a limited number of studies, this study used univariate studies and only assessed a single predictor at a time. This approach does not fully capture the complexity of daily clinical practice, where multiple predictors must be accounted to evaluate the risk of developing potentially fatal VTE in women with SVT who use CHCs.

The results have the following implications for practice, policy, and future research.

1. For Practice:

- Healthcare providers should incorporate individual thromboembolic risk assessment into the prescription of CHCs.
- Informed consent should be conducted in all prescriptions of CHCs.

2. For Policy:

- Policies regarding the implementation of standardized informed consent protocols for prescribing contraception should be supported and reinforced.

3. For Future Research:

- Future studies should be conducted using multivariate methods, a broader range of predictors, and larger samples to provide a more comprehensive understanding of the risks associated with CHCs use.

CONCLUSIONS

This study did not find a statistically significant association between the use of CHCs and the development of VTE in women with SVT, suggesting that CHCs may be safe for use in this population.

COMPLIANCE WITH ETHICAL STANDARDS

Authors' contribution

S.S.S., W.H.: Conceptualization. S.S., L.M.A., S.A.R.S.: Data curation. S.S., W.H.: Formal analysis, investigation, methodology. S.S.S., L.M.A., S.A.R.S., A.D.S.: Writing – review & editing, writing – original draft. S.S.S., W.H., L.M.A., S.A.R.S., A.D.S.: Validation.

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Study registration

PROSPERO registration: CRD42024585529.

Disclosure of interests

The authors declare that they have no conflict of interests.

Ethical approval

N/A.

Informed consent

N/A.

Data sharing

Data are available along with the review.

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SUPPLEMENTS

Supplement 1. Search Strategy.

PubMed, Scopus, CochraneLibrary:

((("superficial venous thrombosis" OR "superficial vein thrombosis" OR "superficial thrombophlebitis" OR "thrombophlebitis" OR "phlebitis")) AND (("venous thromboembolism" OR "VTE" OR "venous thrombotic complications" OR "deep vein thrombosis" OR "deep-vein thrombosis" OR "deep venous thrombosis" OR "DVT" OR "venous thrombosis" OR "pulmonary embolism" OR "PE"))) AND (("association" OR "associations" OR "correlation" OR "correlations" OR "associated factor" OR "associated factors" OR "predictive factor" OR "predictive factors" OR "factors predictive" OR "risk" OR "risks" OR "risk factor" OR "risk factors" OR "prognostic factor" OR "prognostic factors" OR "contributing factor" OR "contributing factors" OR "contributing factor" OR "contributing factors" OR "predictor" OR "predictors" OR "determinant" OR "determinants")) AND NOT (("case report" OR "case series" OR "case study" OR "clinical report" OR "clinical case" OR "systematic review" OR "systematic literature review" OR "systematic analysis" OR "review" OR "narrative review" OR "critical review" OR "comprehensive review" OR "meta-analysis" OR "meta-analyses"))

Supplement 2. Characteristics of the included studies

Author	Name of Study	Year	Study Time Period	Design	Country	Race	Sample Size (total)	Sample Size (case)	Sample Size (control)	Cases		Control	
										VTE	No VTE	VTE	No VTE
Binder (2013)	Association Between Superficial Vein Thrombosis and Deep Vein Thrombosis of the Lower Extremities	2013	November 2006 - June 2007	Prospective study	Austria	-	32	2	30	1	1	8	22
Bounameaux (1997)	-	1997	1989-1994	Case-control study	Switzerland	-	79	10	69	1	9	15	54
Decousus (2010)	POST (Prospective Observational Superficial Thrombophlebitis)	2010	March 2005 - October 2006	Cross-sectional and prospective cohort study	France	-	548	41	507	9	32	127	380
Frappé (2015)	The Incidence of Superficial Vein Thrombosis (STEPH) Study Group	2015	November 2011 - November 2012	Cross-sectional study	France	-	99	5	94	1	4	19	75
Galanaud (2011)	OPTIMEV (Optimisation de l'Interrogatoire dans l'évaluation du risque thrombo-embolique Veineux) study	2011	November 2004 - January 2006	Cross-sectional and prospective study	France	-	502	31	471	8	23	126	345
Pomero (2015)	-	2015	-	Retrospective cohort study	Italy	-	314	40	274	5	35	52	222
Quenet (2003)	STENOX (Superficial Thrombophlebitis treated by Enoxaparin) study"	2003	March 1996 - December 1998	Prospective RCT	France	-	263	49	214	10	39	29	185
Quéré (2012)	POST (Prospective Observational Superficial Thrombophlebitis)	2012	March 2005 - October 2006	Observational prospective study	France	-	538	40	498	8	32	118	380
Rabe (2023)	The Investigating Significant Health Trends in the management of Superficial Vein Thrombosis (INSIGHTS-SVT) study	2023	2016 - 2017	Observational prospective study	German	Caucasian (99.7%)	562	65	497	2	63	26	471

Supplement 3. Characteristics of the included studies.

Author	Population		SVT definition	VTE definition
	Inclusions	Exclusions		
Binder (2013)	Outpatients with clinical signs of SVT and underwent color-coded duplex sonography and compression USG of all venous segments to confirm the diagnosis of SVT and to detect and/or DVT	-	SVT confirmed by ultrasonography	-
Bounameaux (1997)	All patients with lower limb SVT	-	-	DVT is confirmed by combination of continuous wave Doppler and venous occlusion plethysmography
Decousus (2010)	Symptomatic SVT of the lower limbs that was at least 5 cm on compression ultrasonography	Patients who had undergone surgery in the past 10 days, those who experienced SVT after sclerotherapy within the past 30 days, and those for whom follow-up was deemed infeasible"	-	DVT is confirmed by compression USG or venography. PE is confirmed by ventilation-perfusion scan or helical CT scan or at autopsy.
Frappé (2015)	Patients with SVT confirmed at compression USG	Unproven SVT at compression USG; concomitant PE; inpatients	SVT and DVT were diagnosed with the use of complete bilateral compression USG	
Galanaud (2011)	Objectively confirmed SVT (with or without DVT/PE)	Other VTE event (isolated proximal, distal PE; PE with DVT without SVT, upper limb DVT, undetermined); False negative; Controls; Non lower limb; Age < 18 years old; No suspicion of VTE; Enrolled in overseas territories; Living outside of France; Homeless; Delayed in case report form completion; Decline participation; Loss to follow up	SVT/DVT confirmed if there was incompressibility of the vein PE confirmed according to PIOPED criteria and after validation by independent expert committee"	
Pomero (2015)	All patients with objectively diagnosed SVT	All patients with concomitant signs or symptoms of PE and/or with an established diagnosis of PE	SVT is confirmed by compressive B-mode ultrasound or echo-colour Doppler	-
Quenet (2003)	Patients with acute SVT of the lower limbs at least 5 cm long at duplex ultrasound; Age > 18 years old	Patients with ≥ 2 SVTs; Concomitant DVT; Symptomatic PE; Known thrombophilia; Required ligation of sphenofemoral junction or thrombectomy	-	DVT is detected with systemic ultrasound between day 8 and 12 and whenever thrombosis were suspected PE is confirmed by high-probability lung scanning, pulmonaryangiography, helical CT or autopsy"
Quére (2012)	Patients with isolated SVT at least 5 cm long; Age ≥ 18 years old	Patient exhibiting an SVT with concomitant PE without DVT; Undergone surgery ≤ 10 days; SVT occurred < 30 days after sclerotherapy; Could not participate	The presence of a subcutaneous noncompressible hypoechoic area in the course of an identified superficial vein ≥ 5 cm"	DVT confirmed by incompressibility of a deep vein or a lack of spontaneous or reverse-flow intraluminal colour filling after augmentation manoeuvres PE suspicion confirmed by ventilation-perfusion scan or a helical CT scan"
Rabe (2023)	Patients with objectively confirmed acute isolated SVT of the lower extremities	Patients with a proximal extension of SVT located 3 cm from the saphenofemoral junction (SFJ); Concomitant DVT by compression ultrasound or duplex sonography; no symptoms of PE	-	-

Supplement 4. Characteristics of the included studies.

Author	DVT/PE	Type of Contraception	Contraception		Outcomes	Age
			Composition	Combined/ Non-combined		
Binder (2013)	DVT	Oral	Marvelon (150ug destoden and 30ug ethinyl estradiol); Harmonette (75ug gestogen and 20ug ethinylestradiol)	Combined	-	Mean ± SD 67±14.5
Bounameaux (1997)	DVT	Oral	-	-	Late thromboembolic events three months after first observation	Median (Range) 64 (19-84)
Decousus (2010)	DVT	Oral	-	-	Symptomatic VTE (DVT of the lower limb, PE, or extension or recurrence of SVT) events at 3 months	Median (IQR) 65 (50–74)
Frappé (2015)	DVT	Oral	-	-	ICARO score for predicting concomitant DVT	Median (IQR) 66.0 (54.8–78.0)
Galanaud (2011)	DVT	Oral	-	Oral	Recurrent VTE; Major bleeding; Overall mortality at 3 months	-
Pomero (2015)	DVT	Oral	-	-	ICARO score for predicting concomitant DVT	Mean ± SD 56.3 ± 17.9
Quenet (2003)	DVT and/or PE	Hormone therapy (oral contraception/ hormone replacement therapy)	-	-	Venous thrombotic complications at 3 months; DVT, PE, both, recurrence SVT or extension of SVT toward the sphenofemoral junction	Mean ± SD 62.5 ± 14.2
Quééré (2012)	DVT and/or PE	Oral	-	-	-	Median (Range) 70 (61-78)
Rabe (2023)	DVT, PE, or recurrent or extending SVT	-	Hormone replacement or estrogen-containing contraception with/without tamoxifen	-	Incidence of symptomatic VTE, defined as a composite of DVT, PE, and recurrent or extending SVT at three months of follow up	Mean ± SD 60.6 ± 14.5

Supplement 5. Characteristics of the included studies.

Author	History of VTE	Family history of VTE	Active cancer	History of Immobilization	Chronic venous insufficiency	Thrombophilic abnormalities
Binder (2013)	Isolated SVT = 4/11 SVT + VTE = 11/35	-	-	-	-	All patients with DVT had an elevated D-dimer level
Bounameaux (1997)	Isolated SVT = 21 (23) SVT + VTE = 9 (29)	-	Isolated SVT = 5 (5) SVT + VTE = 2 (6)	Isolated SVT = 13 (14) SVT + VTE = 11 (36)	-	-
Decousus (2010)	Isolated SVT = 120 (19.4) SVT + VTE = 60 (29.4)	Isolated SVT = 206 (32.7) SVT + VTE = 51 (25.4)	Isolated SVT = 24 (3.8) SVT + VTE = 26 (12.7)	Permanent Isolated SVT = 34 (5.4) SVT + VTE = 30 (14.5) Recent, past 20d, Bedridden (>3 d) Isolated SVT = 32 (5.1) SVT + VTE = 29 (13.8) Recent, past 20d, Hospitalization Isolated SVT = 30 (4.7) SVT + VTE = 49 (23.3) Recent, past 20d, Travel Isolated SVT = 59 (9.3) SVT + VTE = 8 (3.8) Recent, past 20d, Trauma Isolated SVT = 41 (6.5) SVT + VTE = 5 (2.4) Recent, past 60d, Surgery Isolated SVT = 25 (3.9) SVT + VTE = 11 (5.2)	Isolated SVT = 547 (86.3) SVT + VTE = 143 (68.4)	Isolated SVT = 34 (5.4) SVT + VTE = 14 (6.8)
Frappé (2015)	Isolated SVT = 33 (28.0) SVT + VTE = 8 (29.6)	Isolated SVT = 25 (25.3) SVT + VTE = 6 (22.2)	Isolated SVT = 5 (4.3) SVT + VTE = 0 (0)	Isolated SVT = 0 (0) SVT + VTE = 0 (0)	Isolated SVT = 96 (86.5) SVT + VTE = 21 (77.8)	-
Galanaud (2011)	Isolated SVT = 212/556 (38) SVT + VTE = 101/227 (44)	Isolated SVT = 100/556 (18) SVT + VTE = 46/227 (20)	Isolated SVT = 28/556 (5) SVT + VTE = 37/227 (16)	-	-	-
Pomero (2015)	Isolated SVT = 68/415 (16.4) SVT + VTE = 17/79 (21.5)	Isolated SVT = 129/399 (32.3) SVT + VTE = 17/72 (23.6)	Isolated SVT = 24/403 (6.0) SVT + VTE = 21/77 (27.3)	Isolated SVT = 45/404 (11.1) SVT + VTE = 12/76 (15.8)	-	Isolated SVT = 116/269 (43.1) SVT + VTE = 15/38 (39.4)
Quenet (2003)	62/427 (14.5)	-	-	3/427 (0.7)	Asymptomatic = 10/427 (2.3) Mild = 111/427 (26) Moderate = 278/427 (65.1) Severe = 28/427 (6.6)	-
Quéré (2012)	Isolated SVT = 120/617 (19.4) SVT + VTE = 56/192 (29.2)	Isolated SVT = 206/629 (32.7) SVT + VTE = 48/189 (25.4)	Isolated SVT = 24/630 (3.8) SVT + VTE = 26/192 (13.5)"	Isolated SVT = 49/632 (7.7) SVT + VTE = 55/198 (27.8)	Isolated SVT = 514/597 (86.1) SVT + VTE = 113/171 (66.1)	Isolated SVT = 34/630 (3.8) SVT + VTE = 14/194 (7.2)
Rabe (2023)	Isolated SVT = 136 (16.4) SVT + VTE = 12 (28.6)	Isolated SVT = 138 (16.6) SVT + VTE = 7 (16.7)	Isolated SVT = 60 (7.2) SVT + VTE = 3 (7.1)	-	Isolated SVT = 661 (79.6) SVT + VTE = 37 (88.1)	Isolated SVT = 47 (5.7) SVT + VTE = 3 (7.1)

Supplement 6. Characteristics of the included studies.

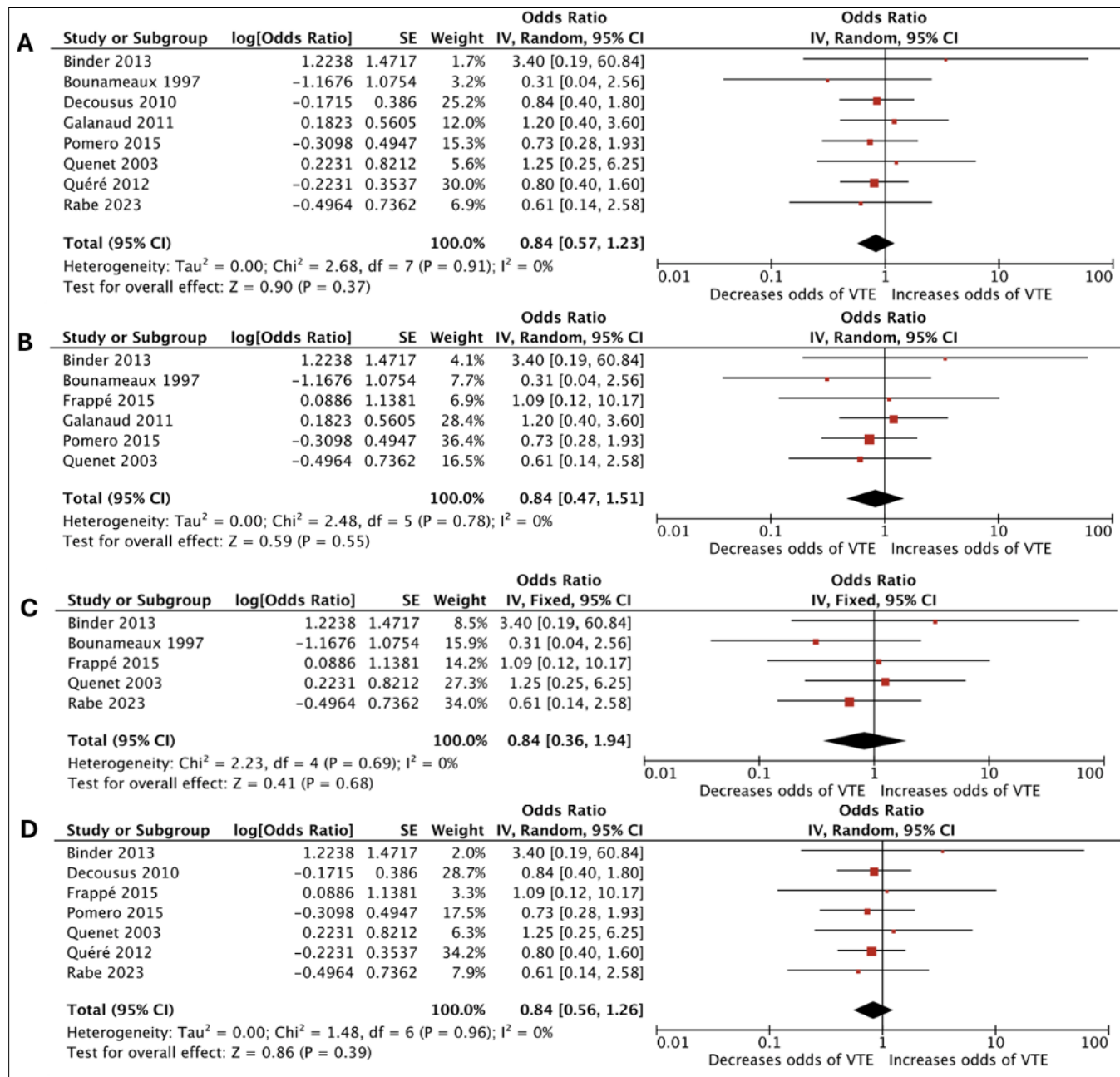
Author	Local or systemic infections	Congestive heart failure or respiratory insufficiency	Pregnancy or postpartum	BMI	Smoking	Use of elastic stockings
Binder (2013)	-	-	-	Mean (SD) Isolated SVT = 27.1 (3.9)	-	Isolated SVT = 27/35 SVT + VTE = 5/11
Bounameaux (1997)	-	-	-	-	-	-
Decousus (2010)	Isolated SVT = 18 (2.8) SVT + VTE = 12 (5.7)	Isolated SVT = 33 (5.3) SVT + VTE = 18 (8.6)	Isolated SVT = 36 (5.7) SVT + VTE = 2 (1.0)	BMI > 30 Isolated SVT = 183 (29.0) SVT + VTE = 59 (28.2)	-	-
Frappé (2015)	Isolated SVT = 8 (7.0) SVT + VTE = 0 (0)	-	-	BMI ≥ 30 Isolated SVT = 25 (25.0) SVT + VTE = 8 (30.8)	-	-
Galanaud (2011)	Isolated SVT = 6/556 (1) SVT + VTE = 3/227 (1)	Isolated SVT = 21/556 (4) SVT + VTE = 9/227 (4)	Isolated SVT = 23/556 (4) SVT + VTE = 2/227 (1)	BMI >30 Isolated SVT = 91/556 (16) SVT + VTE = 36/227 (16)	Isolated SVT = 29/556 (5) SVT + VTE = 23/227 (10)	-
Pomero (2015)	Isolated SVT = 21/403 (5.2) SVT + VTE = 6/77 (7.8)	Cardiac failure Isolated SVT = 17/402 (4.2) SVT + VTE = 6/77 (7.8) Respiratory failure Isolated SVT = 10/403 (2.5) SVT + VTE = 5/77 (6.5)	-	BMI ≥ 30 Isolated SVT = 78/401 (19.5) SVT + VTE = 13/77 (16.9)	-	-
Quenet (2003)	15/427 (3.5)	-	-	BMI ≥ 30 93/427 (21.8)	-	396/427 (95.9)
Quéré (2012)	Isolated SVT = 18/633 (2.8) SVT + VTE = 12/198 (6.1)	Isolated SVT = 33/625 (5.3) SVT + VTE = 17/196 (8.7)	-	Isolated SVT = 183/632 (29) SVT + VTE = 57/197 (28.9)	-	-
Rabe (2023)	Isolated SVT = 39 (4.7) SVT + VTE = 3 (7.1)	Cardiac insufficiency Isolated SVT = 22 (2.7) SVT + VTE = 0 (0) Respiratory insufficiency Isolated SVT = 31 (3.7) SVT + VTE = 2 (4.8)	-	BMI < 30 Isolated SVT = 521 (62.8) SVT + VTE = 16 (38.1) BMI ≥ 30 Isolated SVT = 309 (37.2) SVT + VTE = 26 (61.9)	Isolated SVT = 130 (15.7) SVT + VTE = 6 (14.3)	-

Supplement 7. Risk of Bias Assessment with ROBINS-E Tool.

Study	Bias due to confounding	Bias arising from measurement of exposure	Bias in selection of participants	Bias due to post-exposure interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall risk of bias judgement
Binder, 2013	Some concerns	Low	Some concerns	Low	Low	Low	Low	Low
	Some concerns	Low	Low	Low	Low	Low	Low	Low
Decousus, 2010	Some concerns	Low	Low	Some concerns	Some concerns	Low	Low	Some concerns
Frappé, 2015	Some concerns	Low	Low	Low	Low	Low	Low	Low
Galanaud, 2011	Some concerns	Low	Low	Low	Some concerns	Low	Low	Low
Pomero, 2015	Low	Low	Some concerns	Low	Low	Low	Low	Low
Quenet, 2003	Low	Low	Some concerns	Low	Low	Low	Low	Low
Queré, 2012	Some concerns	Low	Low	Low	Low	Low	Low	Low
Rabe, 2023	Low	Low	Low	Low	Some concerns	Low	Low	Low

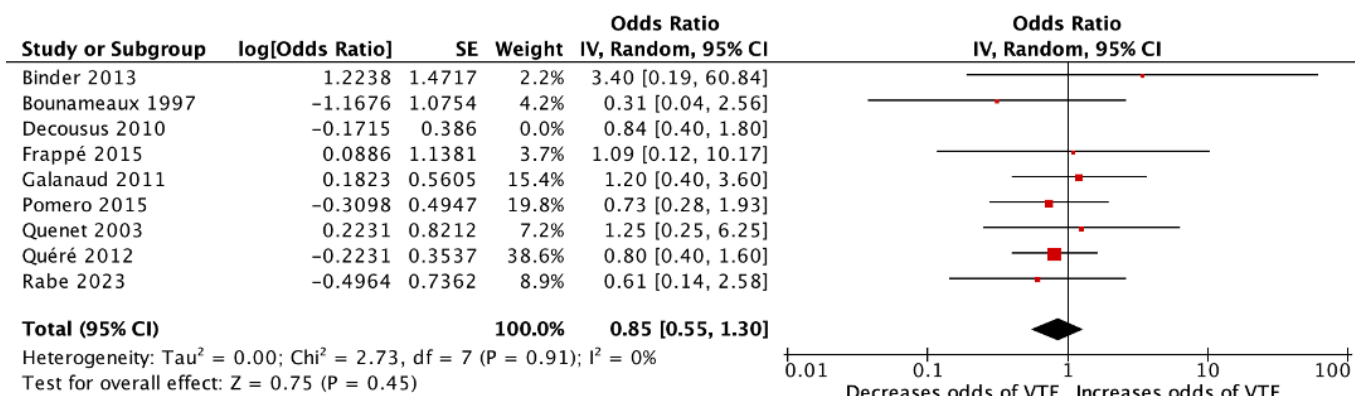
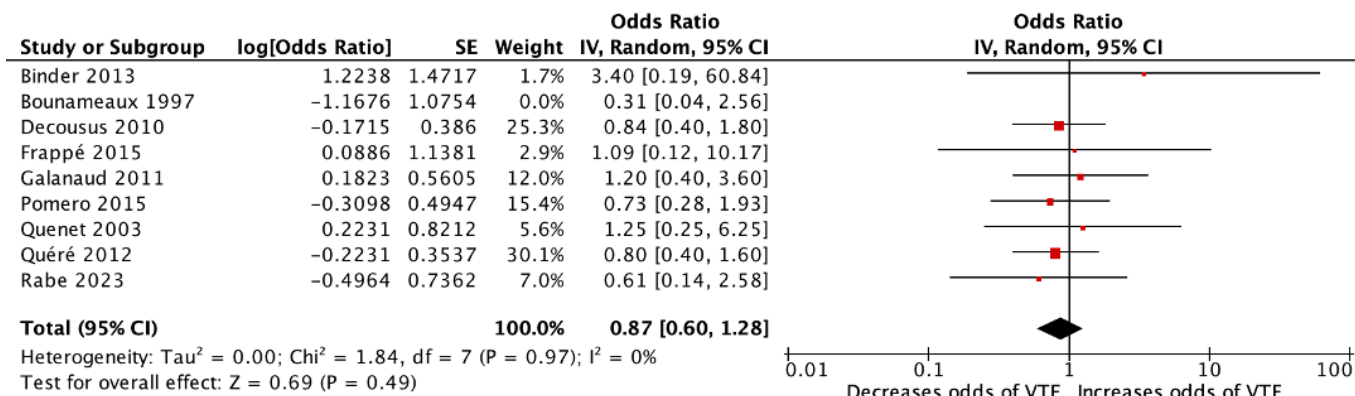
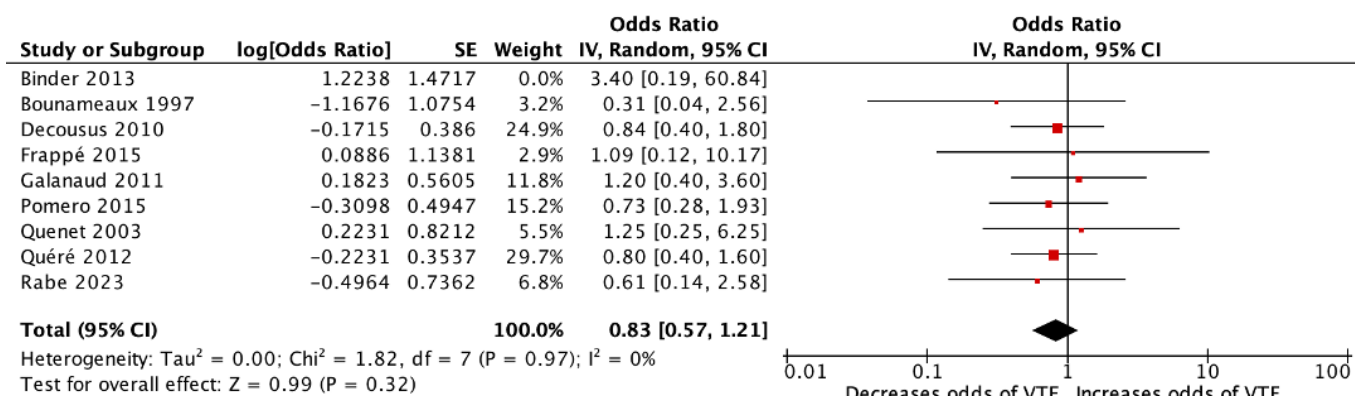
Supplement 8. The risk of VTE in women with SVT who use CHCs compared to non-CHC users shows a non-significant odd of VTE incidence.

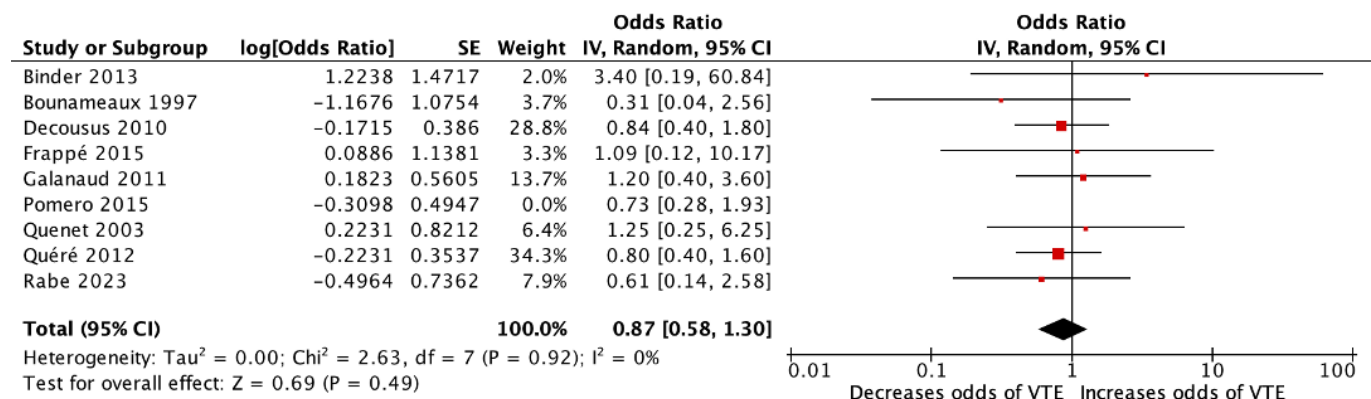
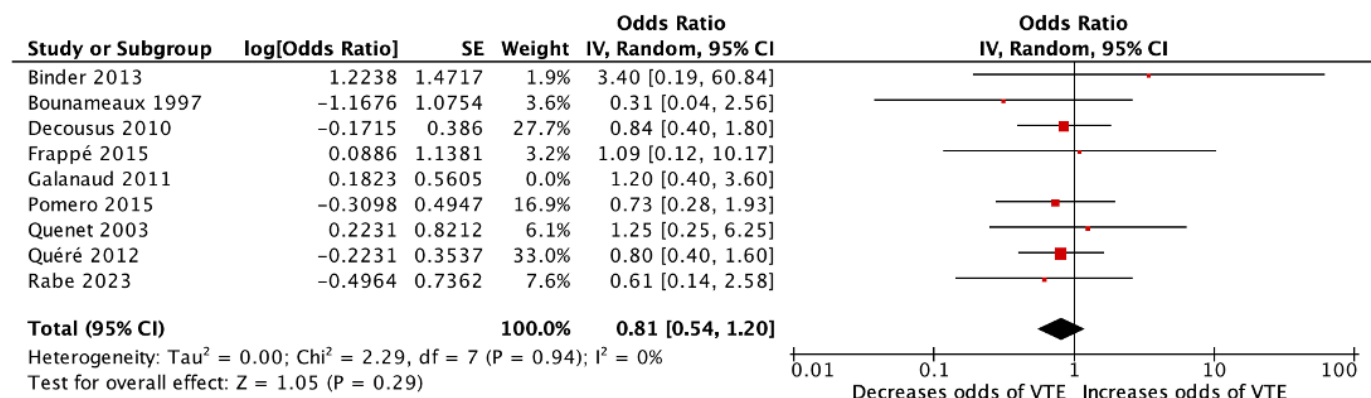
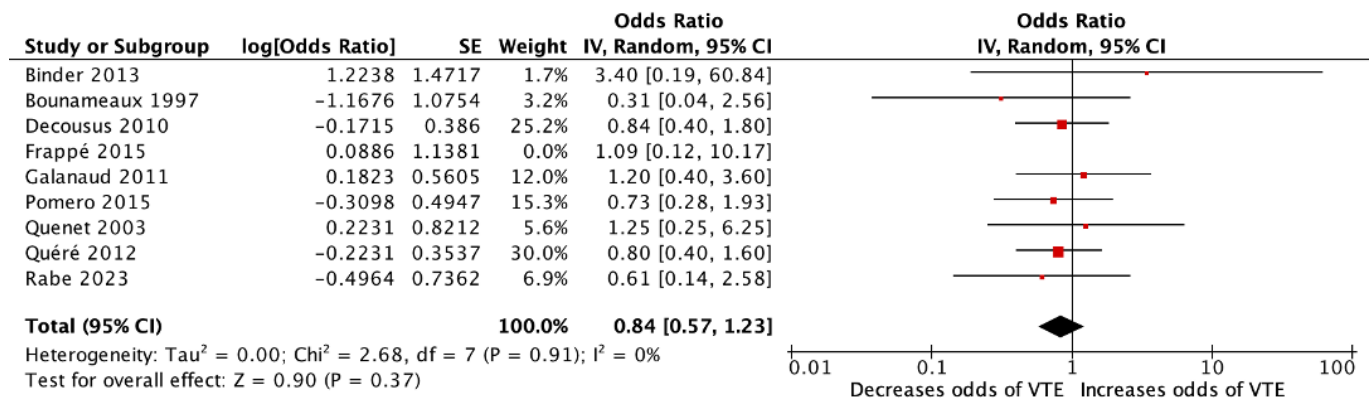
(A) Analysis limited to longitudinal studies and RCTs. (B) Subgroup analysis considering prior history of VTE as a confounding factor. (C) Subgroup analysis considering prior cancer as a confounding factor. (D) Subgroup analysis considering prior history of immobilization as a confounding factor.

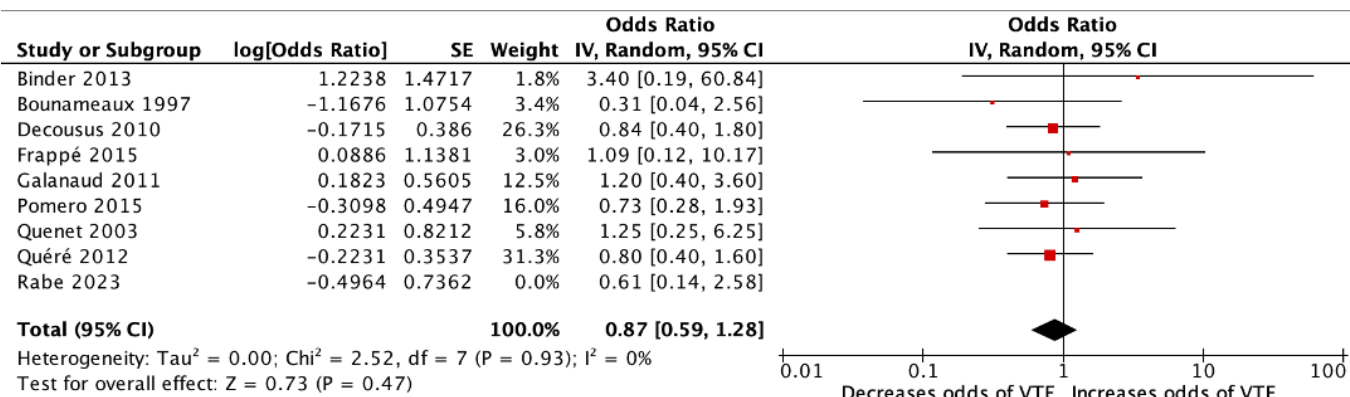
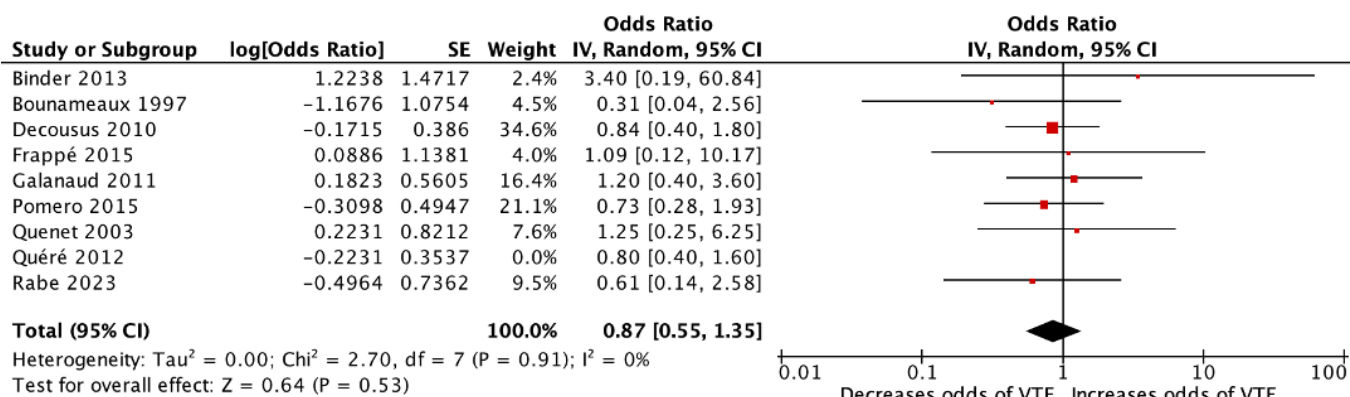
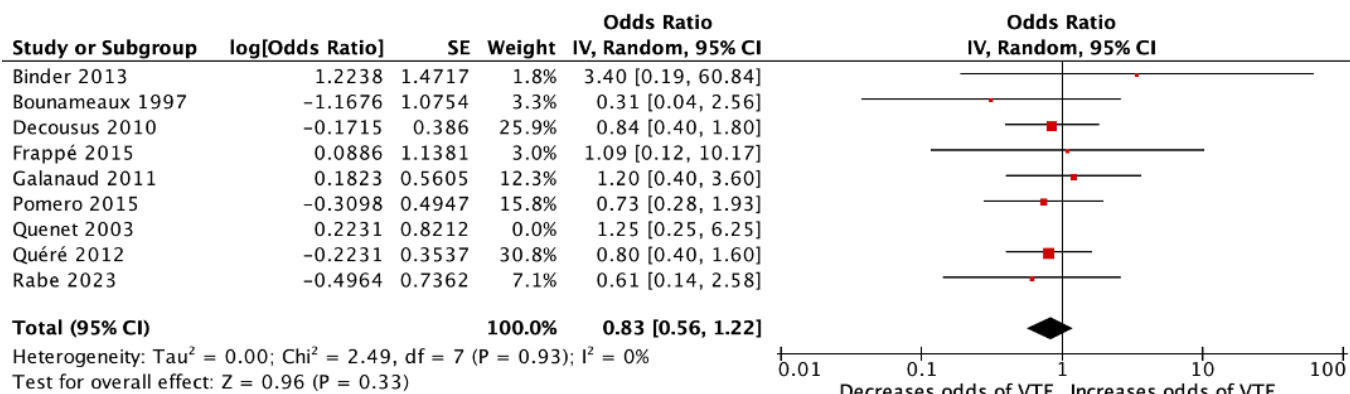


Supplement 9. Forest plot of the result after leave-one-out sensitivity analysis.

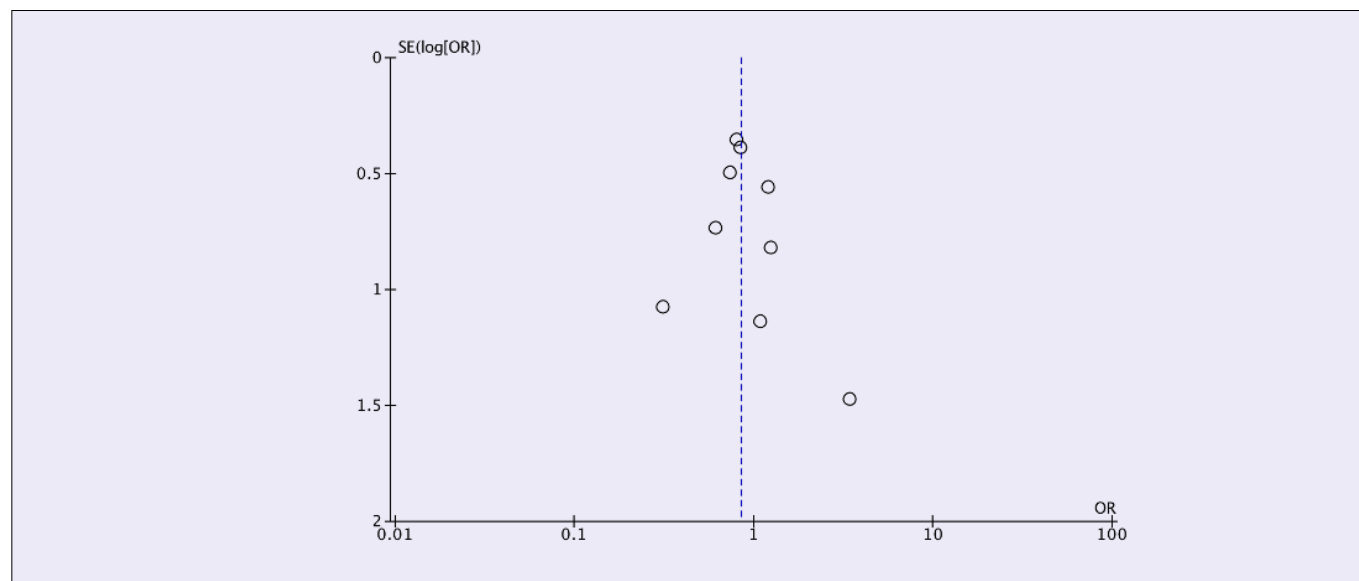
Studies	OR	Lower CI	Upper CI	P value	I ²
All included	0.85	0.58	1.23	0.38	0
Exclude Binder <i>et al.</i>	0.83	0.57	1.21	0.32	0
Exclude Bounameaux <i>et al.</i>	0.87	0.6	1.28	0.49	0
Exclude Decousus <i>et al.</i>	0.85	0.55	1.3	0.45	0
Exclude Frappé <i>et al.</i>	0.84	0.57	1.23	0.37	0
Exclude Galanaud <i>et al.</i>	0.81	0.54	1.2	0.29	0
Exclude Pomero <i>et al.</i>	0.87	0.58	1.3	0.49	0
Exclude Quenet <i>et al.</i>	0.83	0.56	1.22	0.33	0
Exclude Quéré <i>et al.</i>	0.87	0.55	1.35	0.53	0
Exclude Rabe <i>et al.</i>	0.87	0.59	1.28	0.47	0







Supplement 10. Funnel plot assessment on risk of VTE in women with SVT who use CHCs compared to non-CHC users. No asymmetries are observed hence publication bias is not present.



Supplement 11. GRADE assessment.

No of studies	Study design	Certainty assessment					Other considerations	Certainty assessment
		Risk of bias	Inconsistency	Indirectness	Imprecision			
9	Non-Randomised Studies	Not Serious	Not Serious	Serious ^a	Not Serious	All Plausible Residual Confounding Would Reduce The Demonstrated Effect	⊕⊕⊕⊕ High	

a. Indirectness is considered serious due to the use of secondary data from included studies.