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Thrombosis risk with use of hormonal contraception among women with thrombophilia: an updated systematic review

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Abstract

Objectives: Thrombophilia is associated with an elevated risk of thrombosis, which may be further elevated with use of hormonal contraception. Our objective was to update a previously published systematic review on thrombosis risk with use of hormonal contraception among women with thrombophilia.

Study Design: We conducted a systematic review of five databases from database inception through December 8, 2022. We searched for articles that examined risk of venous thromboembolism (VTE) or arterial thromboembolism (ATE) in women with thrombophilia using hormonal contraception compared with women using non-hormonal or no contraception. We assessed risk of bias for each study and certainty of evidence for all outcomes.

Results: Eighteen articles met inclusion criteria; four had moderate risk of bias and 14 had high risk of bias. Odds of VTE in women with factor V Leiden (FVL) mutation or prothrombin (PT) gene mutation were elevated in combined oral contraception (COC) users vs non-users. Odds of VTE were elevated in COC users with FVL mutation, PT gene mutation, both FVL and PT mutations, antithrombin (AT) deficiency, or protein C deficiency compared with non-users without the mutation. Odds of stroke were elevated in COC users with FVL mutation compared with non-users without the mutation. Evidence was mixed on whether risk was elevated in women with protein S deficiency using COC compared with non-use. One study found elevated odds of

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VTE in women with FVL mutation but not women with PT gene mutation using progestin-only contraception (POC), compared with non-users without the mutation.

Conclusions: Overall, studies found elevated odds of VTE and ATE in women with thrombophilia using COC compared with non-users without thrombophilia. The certainty of evidence for all outcomes is low. Evidence is also limited by small numbers of women and minimal evidence on use of patch, ring, or POC, and is insufficient to assess differential risk by all thrombophilia types.

Implications: Use of estrogen-containing hormonal contraception might further elevate risk of thrombosis among women with thrombophilia. Further study is needed on safety of POC use in women with thrombophilia.

Keywords

Contraception; Factor V Leiden; Prothrombin gene mutation; Systematic review; Thromboembolism; Thrombophilia

1. Introduction

Thrombophilia, both inherited and acquired, increases risk of experiencing a thrombotic event. Among women of reproductive age, the relative risk of venous thromboembolism (VTE) ranges from 2–10 with factor V Leiden (FVL) mutation [1–7] and 2–6 with prothrombin (PT) mutation [1, 2, 4–6]. For women of reproductive age with both FVL and PT mutations, the relative risk of VTE is increased 15–46 fold [2, 5]. These estimates were obtained from mostly heterozygous carriers; relative risk would likely be higher for homozygous individuals. Evidence is mixed on whether thrombophilia is associated with arterial thromboembolism (ATE) among women of reproductive age [8, 9].

Pregnancy also confers an elevated risk of thrombosis, with relative risk of VTE increased 4–5 fold compared with nonpregnant women [10], and risk is further increased with thrombophilia. The percent who experience an initial VTE during pregnancy ranges from 2–14% if homozygous for FVL mutation and 2–4% if homozygous for PT mutation [10]. It is important that women with thrombophilia have access to the full range of contraceptive options to support their decisions about pregnancy planning. However, some methods of hormonal contraception also increase risk for thrombosis, although to a lesser degree than risk during pregnancy and the postpartum period. Combined hormonal contraception (CHC) contains estrogen and progestin, i.e., combined oral contraception (COC), transdermal patch, and transvaginal ring), and is associated with a 2–3-fold increased risk of VTE and ATE [11–14]. Some studies have found an elevated risk of VTE with use of depot medroxyprogesterone acetate (DMPA) [15–17]; however, evidence does not suggest an elevated risk with use of other progestin-only contraception (POC) (including levonorgestrel intrauterine devices [LNG-IUDs], etonogestrel implants, and progestin-only pills [POPs]) [15–17].

The U.S. Centers for Disease Control and Prevention (CDC) publishes the *U.S. Medical Eligibility Criteria for Contraceptive Use* (US MEC) [18], which provides evidence-based guidance on the safety of contraceptive methods for patients with certain characteristics or

medical conditions, including thrombophilia. As part of a process to update the US MEC, the objective of this systematic review was to identify evidence on risk of VTE or ATE among women with thrombophilia using hormonal contraception compared to women using non-hormonal contraception or no contraception. We sought to update a previous systematic review on inherited thrombophilia which included studies published through 2004 [19]. Given that the risk of thrombosis may differ among the thrombophilias, we sought to identify articles that reported on risk by thrombophilia type.

2. Methods

We conducted this systematic review according to an a priori protocol, which has been registered in the international prospective register of systematic reviews (PROSPERO) under the registration number CRD42019127163 [20] and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines [21].

2.1. Eligibility criteria

Studies were eligible for inclusion if they examined risk of thrombosis with hormonal contraception use among women with thrombophilia. The population of interest was women with one or more of the following inherited or acquired thrombophilias (heterozygous or homozygous): FVL mutation, PT mutation, AT deficiency, protein C deficiency, protein S deficiency, or antiphospholipid syndrome (APS). We included studies of women with specific multiple thrombophilias (e.g., all study participants had FVL and PT mutations), but excluded studies that combined women with different thrombophilias and did not report results separately by thrombophilia type. The exposure of interest was use of any hormonal contraception, with results reported separately for CHC and POC. We excluded studies that focused on individual formulations of COCs and did not report risk estimates for all COCs combined. The comparison was use of non-hormonal or no contraception. The outcome of interest was ATE (including myocardial infarction [MI] or stroke) or VTE (including deep venous thrombosis or pulmonary embolism). We included randomized trials, non-randomized trials, cohort studies, or case-control studies. We excluded cross-sectional studies, non-comparative studies, case series, case reports, and review articles. We only included studies that reported statistical comparisons between appropriate exposure and comparison groups (e.g., risk ratio, odds ratio, comparison of incidence rates); we excluded studies that only reported crude numbers of events. We included studies in which the reference group was non-users with the thrombophilia and studies in which the reference group was non-users without the thrombophilia.

2.2. Literature search

We worked with a research librarian at the U.S. Centers for Disease Control and Prevention to develop the search strategy (Appendix 1). The search was conducted in MEDLINE, EMBASE, Cochrane, [ClinicalTrials.gov](https://www.clinicaltrials.gov), and CINAHL databases from database inception through December 8, 2022. We considered articles in all languages. We did not consider abstracts without full text articles.

2.3. Study selection and data extraction

Among articles identified by the search strategy, all titles and abstracts were screened independently by at least two co-authors, using the Covidence platform [22]. Two co-authors then reviewed full-text articles to determine if they met inclusion criteria. Any conflicts were resolved by discussion. We used standardized evidence tables to summarize information on each study.

2.4. Risk of bias assessment

We assessed risk of bias using a modified version of the Cochrane tool [23]. We considered selection bias (e.g., whether cases and controls were from the same population with the same inclusion criteria, was participation rate adequate, etc.), information bias for exposures and outcomes (e.g., whether thrombophilia diagnosis, contraceptive exposure, and thrombosis outcomes were assessed using valid and reliable measures), and confounding (e.g., whether the analysis accounted for important confounding factors). Two co-authors independently assessed the risk of bias for each included study and conflicts were resolved by discussion.

2.5. Data synthesis

We summarized descriptive statistics, unadjusted and adjusted point estimates, and results of significance tests. We did not conduct meta-analyses due to heterogeneity of study populations, exposures, and outcomes.

2.6. Certainty of evidence methods

We assessed the certainty of evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system [24–26]. For each outcome, we considered risk of bias, directness, precision, and consistency to be not serious, serious, or very serious. Based on these assessments, the certainty of evidence was rated as high, moderate, low, or very low. At baseline, randomized controlled trials are considered to have high certainty and observational studies are considered to have low certainty; ratings are then adjusted based on the criteria previously listed.

3. Results

We screened 5,707 articles through our database search, from which 742 articles were identified for full-text review (Figure 1). Among these articles, 724 were excluded (271 wrong study design, 178 abstract only, 89 no joint effect, 70 wrong outcomes, 47 wrong patient population, 40 wrong intervention, 13 wrong comparator, 10 pooled mutations without specification of mutation type, and 6 duplicates). Eighteen articles met inclusion criteria; seven [2, 5–7, 27–29] of these were included in the previous systematic review [19] and 11 were newly identified [1, 3, 4, 9, 30–36]. Six articles from the previous review did not meet inclusion criteria for this updated review because they did not separate results by thrombophilia type [37], did not include a comparison group [38], or did not include calculated risk estimates for the comparison of interest [39–42].

The included articles addressed women with the following thrombophilias: factor V Leiden mutation (13 articles [1–7, 9, 27, 29, 30, 33, 34]), PT gene mutation (11 articles [1–3, 5, 6, 9,

28, 30, 31, 33, 35]), AT deficiency (2 articles [32, 36]), protein C deficiency (2 articles [32, 36]), protein S deficiency (2 articles [32, 36]), and factor V Leiden plus PT gene mutation (2 articles [2, 5]). In the nine articles that reported zygosity, the vast majority of women were heterozygous carriers [1, 2, 5–7, 9, 28, 29, 32]; zygosity was not reported in nine articles [3, 4, 27, 30, 31, 33–36]. Two articles reported on retrospective cohort studies [32, 36] and 16 reported on case-control studies [1, 3, 4, 6, 7, 9, 27–36]. All studies examined CHC (COC, patch, or ring) or oral contraception (OC) (type unspecified, presumed to be mostly COC); one study additionally examined POC (LNG IUD, etonogestrel or LNG implant, DMPA, or POPs) [1]. Fifteen studies examined risk of VTE [1–7, 27–30, 32, 33, 35, 36], 2 studies examined risk of ATE [9, 34], and one study examined risk of VTE or ATE [31].

3.1. Risk of bias

The overall risk of bias for each study was deemed to be moderate or high (Figure 2). Four studies had moderate risk of bias because cases and controls may have been from different populations [3, 4], cases and controls had different participation rates [1, 43], hormonal contraceptive methods were retrospectively self-reported soon after index event [1, 3, 4, 33], the comparison group may have included current or recent hormonal contraception users [33], or minimal adjustment for confounders was reported [3, 4]. Fourteen studies had high risk of bias because cases and controls may have been derived from different populations or not stated [2, 5, 7, 31, 32, 36], OC type was not specified [2, 7, 32, 35], hormonal contraceptive methods were retrospectively self-reported and timing of interview was remote (≥ 1 year) from event or not stated [5, 6, 9, 28, 30, 34], contraceptive method reporting and validation was not described [31], or crude estimates were reported without adjustment for confounders [2, 27, 29, 31, 32, 36].

3.2. Factor V Leiden mutation

Thirteen studies examined women with FVL mutation [1–7, 9, 27, 29, 30, 33, 34] (Table 1, Figure 3, and Appendix 2). All were case-control studies and examined women using CHC ($>95\%$ COC), COC, or OC (type not specified but presumed mostly COC); one study additionally examined women using POC (LNG IUD, implant, DMPA, or POPs) [1]. Among women with FVL mutation, two studies found increased odds of VTE when comparing OC users with non-users (adjusted odds ratio [aOR] 5.0, 95% confidence interval [CI] 0.8–31.8; aOR 6.5, 95% CI 1.6–26.9) [7, 29]. When comparing women with FVL mutation using COC or OC compared with women without FVL mutation not using hormonal contraception, ten studies reported statistically significant increased odds of VTE, with odds ratios ranging from 10–65 [1–7, 27, 30, 33]. Two studies of ischemic stroke among women with FVL mutation using OC compared with women without FVL mutation not using hormonal contraception found statistically significant increased odds ratios (aOR 11.3, 95% CI 4.3–29.0; aOR 12.9, 95% CI 1.3–133.7) [9, 34]. One study reported increased odds of VTE among women with FVL mutation using POC compared with women without the mutation not using hormonal contraception (aOR 5.4, 95% CI 2.5–13) [1].

3.3. PT gene mutation

Eleven studies examined women with PT gene mutation [1–3, 5, 6, 9, 28, 30, 31, 33, 35] (Table 1, Figure 4, and Appendix 3). All were case-control studies and examined women

using CHC (>95% COC), COC, or OC (type not specified but presumed mostly COC); one study additionally examined women using POC [1]. Among women with PT gene mutation, one study found increased odds of VTE or ATE when comparing CHC users with non-users (OR 4.7, 95% CI 1.9–11.5) [31]. When comparing women with PT gene mutation using CHC, COC, or OC compared with women without PT gene mutation not using hormonal contraception, eight studies reported statistically significantly increased odds of VTE, with odds ratios ranging from 7–149 [1–3, 5, 6, 28, 30, 35]; one study found an elevated odds ratio that was not statistically significant (aOR 5.1, 95% CI 0.8–31.2) [33]. One study of ischemic stroke among women with PT gene mutation using OC compared with women without PT gene mutation not using hormonal contraception found that odds of stroke were elevated but not statistically significant (aOR 3.1, 95% CI 0.4–23.3) [9]. One study of VTE among women with PT gene mutation using POC compared with women without PT gene mutation not using hormonal contraception found that odds of VTE were not increased [1].

3.4. AT deficiency

Two studies examined women with AT deficiency [32, 36] (Table 1 and Appendix 4). Both were retrospective cohort studies and reported risk of VTE with use of COC or OC. Both studies found a higher incidence of VTE in women with AT deficiency when comparing COC or OC users with non-users (27.5% vs. 3.4% per patient year, $p=0.005$; 5.1% [95% CI 1.1–15.0] vs 1.8% [95% CI 0.7–3.9] annual incidence) [32, 36]. No studies were identified examining POC, and no studies reported risk of ATE.

3.6. Protein C deficiency

Two studies examined women with protein C deficiency [32, 36] (Table 1 and Appendix 5). Both were retrospective cohort studies and reported risk of VTE with use of COC or OC. Both studies found incidence of VTE was higher but not statistically significantly so in women with protein C deficiency when comparing COC or OC users with non-users (12.0% vs. 6.9% per patient year, $p=0.5$; 7.1% [95% CI 2.8–14.5] vs. 2.2% [95% CI 0.7–5.2] annual incidence) [32, 36]. No studies were identified examining POC, and no studies reported risk of ATE.

3.7. Protein S deficiency

Two studies examined women with protein S deficiency [32, 36] (Table 1 and Appendix 6). Both were retrospective cohort studies and reported risk of VTE with use of COC or OC. One study found annual incidence of VTE was higher but not statistically significantly so in women with protein S deficiency when comparing COC users with non-users (2.4% [95% CI 0.5–7.1] vs 0.5% [95% CI 0.01–2.5]) [36]. The other study found that VTE incidence was similar in women with protein S deficiency using OC and not using hormonal contraception (6.5% vs. 8.6% per patient year, $p=0.4$) [32]. No studies were identified examining POC, and no studies reported risk of ATE.

3.8 Multiple mutations

Two studies examined women with FVL and PT gene mutations [2, 5] (Table 1 and Appendix 7). Both were retrospective cohort studies and reported risk of VTE with

use of COC or OC. When comparing women with both mutations using COC or OC compared with women without either mutation not using hormonal contraception, both studies reported statistically significant increased odds ratios (OR 17.0, 95% CI 4.0–72.8; aOR 86.5, 95% CI 10.0–747) [2, 5]. No studies were identified examining POC, and no studies reported risk of ATE.

3.9 Certainty of evidence

The certainty of evidence was deemed to be very low for all outcomes [44]. For all outcomes, the risk of bias was considered serious or very serious. For some outcomes, inconsistency was considered serious due to varying results among studies. For all outcomes, imprecision was considered serious or very serious due to small numbers of women with thrombophilia and lack of power calculations. For most outcomes, indirectness was considered serious because risk estimates were not calculated for hormonal contraception use versus non-use among women with the thrombophilia, rather, the analyses compared hormonal contraception users with the thrombophilia to non-users without the thrombophilia.

4. Discussion

This updated systematic review identified new studies examining risk of thrombosis among women with thrombophilia using hormonal contraception. For CHC use, risk of VTE was elevated among women with FVL mutation, PT mutation, AT deficiency, and protein C deficiency in studies comparing CHC users and non-users among those with the thrombophilia, as well as studies comparing CHC use and thrombophilia with no CHC use and no thrombophilia. Evidence was mixed on whether CHC use increased VTE risk among women with protein S deficiency. Risk of stroke was elevated with CHC use among women with FVL mutation but not PT mutation. For POC use, one study found elevated risk of VTE among women with FVL mutation but not PT mutation, compared with non-users without thrombophilia. Newly identified evidence was consistent with evidence included in the previously published systematic review [19]. No evidence was identified examining women with APS. One study was identified that did not meet inclusion criteria for the systematic review because women had lupus anticoagulant (LAC) but not necessarily APS [45]. This study found that women with LAC who used COCs had increased odds of MI or stroke compared with non-users without LAC [45]; these results may provide some indirect evidence on risk of MI and stroke associated with COC use among those with APS.

Mechanisms of thrombosis related to thrombophilia result from alterations which generally lead to loss of function or gain of function [46, 47]. Mutations in the genes for antithrombin, protein C, and protein S lead to reduced function of these anticoagulants and subsequent increased coagulation. Mutations in the genes for factor V Leiden and prothrombin result in increased function of these procoagulants. Antiphospholipid antibodies increase thrombosis risk likely through a variety of mechanisms including inhibition of natural anticoagulant and fibrinolytic systems, activation of endothelial cells and platelets, and production of proinflammatory cytokines [48].

Hormonal contraceptives can have effects on multiple components of the hemostatic system, although the mechanism for increased thrombosis is not fully understood [49]. CHC can cause procoagulant changes, such as decreased protein S levels, resistance to activated protein C, and elevated levels of coagulation factors [49]. These effects are largely related to the estrogen component of CHC. Progestins can counteract estrogen effects, but this effect differs by progestin type [49]. Progestins may also have certain procoagulant effects, such as increased platelet aggregation and upregulation of thrombin receptors in vessel walls, and these effects may be more pronounced at higher progestin doses [49–51]. Given the complexity of mechanisms for thrombosis, it is not clear whether hormonally-associated effects might interact with thrombophilia-related changes and whether those effects might be additive or multiplicative. Few studies formally assessed the presence of multiplicative interaction between the thrombophilia and the contraceptive method on thrombosis risk, and those that did generally found no interaction [3, 6, 29, 33]. In some studies that did not formally assess interaction, the odds of thrombosis were higher among those with both the mutation and CHC use than would be expected from the odds for the individual risk factors alone, suggesting the possibility of a synergistic effect.

Despite these potential interactions, routine screening for thrombophilia is not recommended before initiating hormonal contraception. The overall prevalence of thrombophilia in the general population is low, ranging from 0.02% to 5% depending on the mutation [47]. If all women in the general population were screened for thrombophilia before initiating COC and avoided COC if thrombophilia diagnosed, there would be an estimated 0.26 fewer VTE events per 1,000 women per year [52]. Given the low prevalence in the general population and the lack of clear benefit for routine screening, the *U.S. Medical Eligibility Criteria for Contraceptive Use* (US MEC) and the American Society of Hematology do not recommend screening for thrombophilia in the general population before starting contraception [18, 52].

The body of evidence on thrombosis risk in women with thrombophilia using hormonal contraception has several limitations. Most of the studies were deemed to have a serious or very serious risk of bias and the certainty of evidence was rated as very low. Most studies had poor generalizability because they included small numbers of women with thrombophilia or the study group was not representative of the general population. For most outcomes, there were serious concerns for indirectness related to the comparator group, given that the analysis compared users with thrombophilia to non-users without thrombophilia. Given the indirectness of some of the comparisons and that interactions between thrombophilia and hormonal contraception were not formally assessed in modeling, it is difficult to assess the risk of thrombosis that is attributable to hormonal contraception. Few studies were found examining women with AT deficiency, protein C deficiency, and protein S deficiency, and no studies were identified which examined women with APS. Only one study examined use of POC. Few studies examined risk of MI and stroke. No studies compared homozygous to heterozygous carriers or compared individuals with different mutations; therefore the evidence was insufficient to assess whether thrombosis risk differs between those homozygous or heterozygous for specific mutations or between those with different mutations.

In conclusion, risk of VTE and ATE is generally elevated among women with certain thrombophilias who use COC compared to non-users without the thrombophilia. However, risk is also elevated with thrombophilia alone, regardless of HC use, and evidence remains limited that directly compares use and non-use among women with thrombophilia. In addition, more studies are needed on HC use and thrombosis risk among women with specific thrombophilias and on women with thrombophilia using non-oral CHC or POC.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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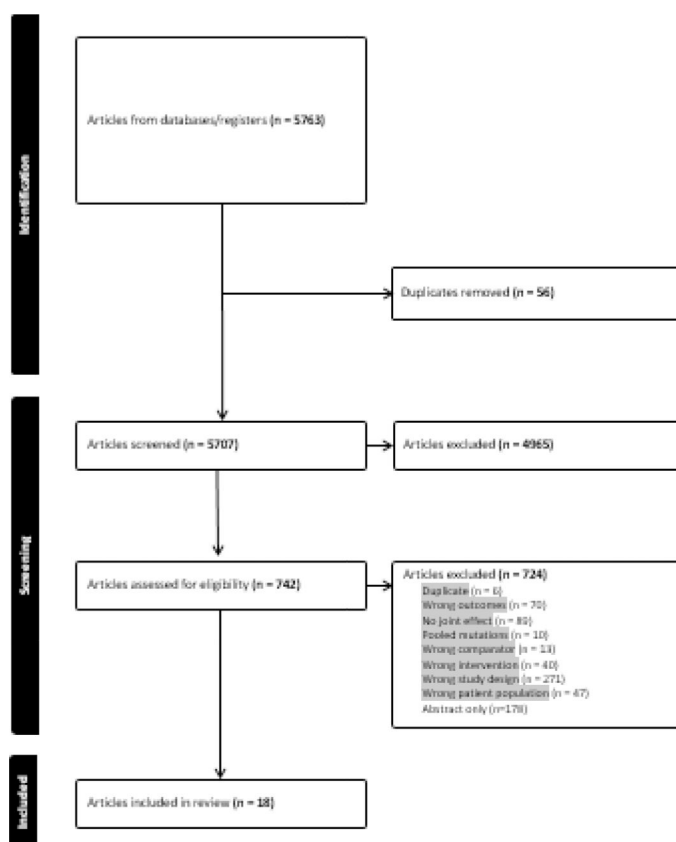


Figure 1.
PRISMA flow chart for the search process for evidence on thrombosis risk with use of hormonal contraception among women with thrombophilia

Non-randomized, comparative studies				
	Selection Bias	Information Bias	Confounding	Overall Risk of Bias
Anderson 1998 [26]	?	?	-	-
Bergendal 2014 [1]	?	?	+	?
Emmerich 2001 [2]	-	-	-	-

Khialani 2020 [3]	?	?	?	?
Kuipers 2009 [4]	?	?	?	?
Legnani 2002 [5]	-	-	?	-
Martinelli 1998 [27]	+	-	?	-
Martinelli 1999 [6]	+	-	?	-
Martinelli 2003 [29]	+	-	+	-
Martinelli 2006 [9]	+	-	+	-
Momot 2019 [30]	-	-	-	-
Pabinger 1994 [31]	-	-	-	-
Sidney 2004 [32]	+	?	+	?
Slooter 2005 [33]	?	-	+	-
Spannagl 2000 [7]	-	-	+	-
Tufano 2014 [34]	-	-	?	-
Van Vlijmen 2007 [35]	-	?	-	-
Vandenbroucke 1994 [28]	+	?	-	-

Figure 2.

Risk of bias of studies included in systematic review on thrombosis risk with use of hormonal contraception among women with thrombophilia

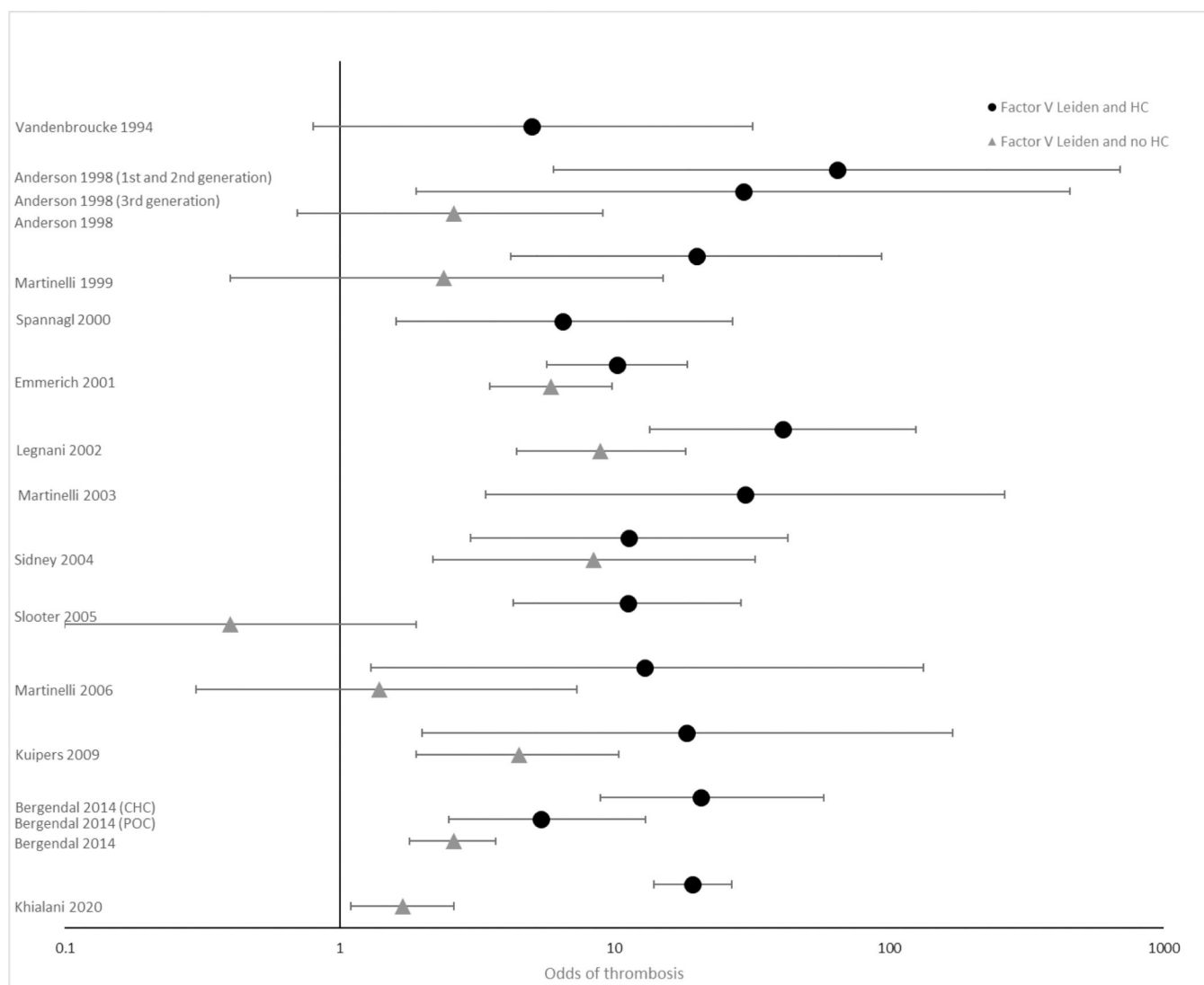


Figure 3.

Odds¹ of thrombosis among women with factor V Leiden mutation using and not using hormonal contraception

CHC, combined hormonal contraception; HC, hormonal contraception; POC, progestin-only contraception.

¹Reference group for most studies is women without the mutation using non-hormonal or no contraception.

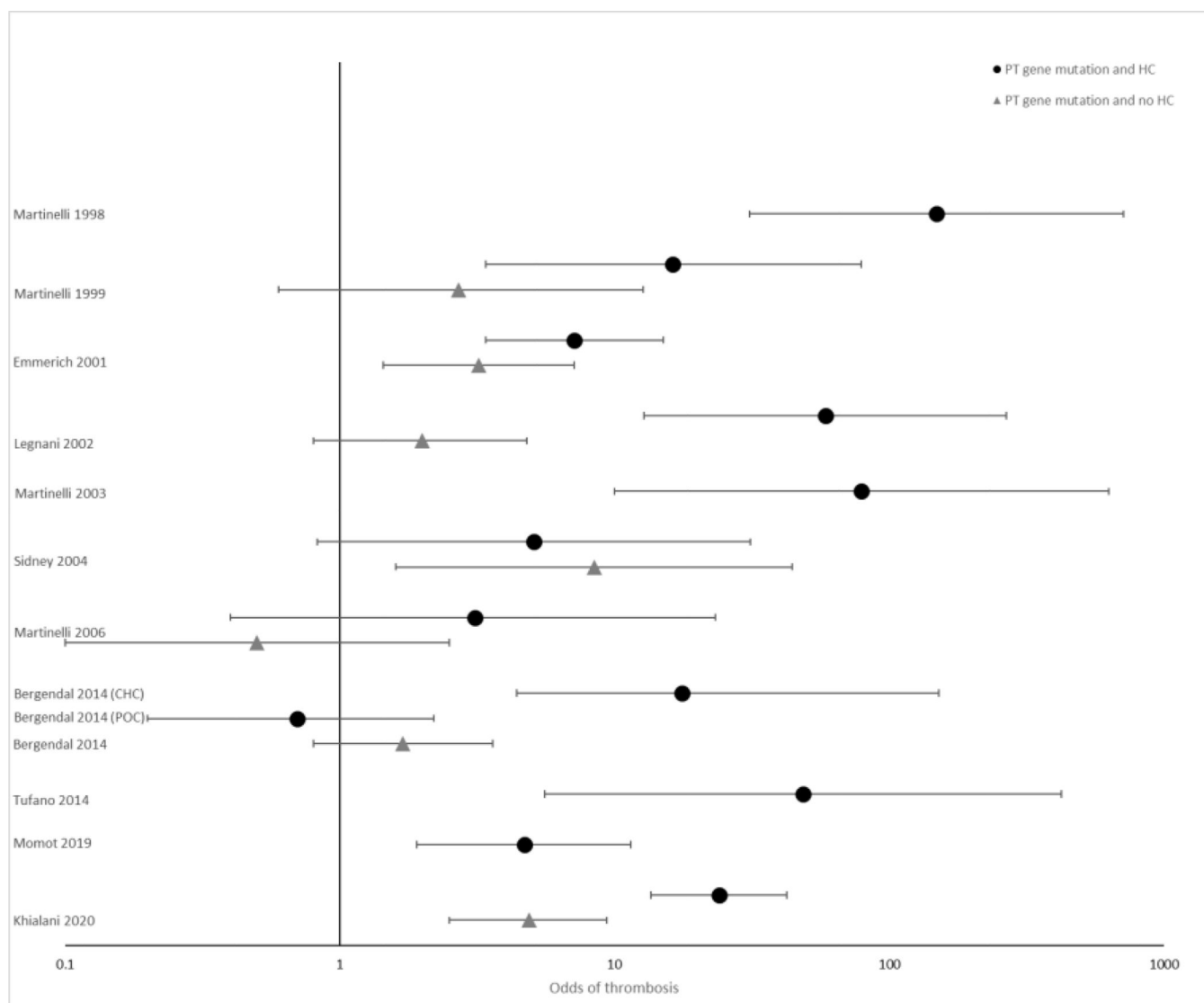


Figure 4.
 Odds¹ of thrombosis among women with prothrombin gene mutation using and not using hormonal contraception
 CHC, combined hormonal contraception; HC, hormonal contraception; POC, progestin-only contraception.
¹Reference group for most studies is women without the mutation using non-hormonal or no contraception.

Table 1.

Summary of evidence on thrombosis risk with use of hormonal contraception among women with thrombophilia

Study	Contraception	Outcome	Comparison group	Risk of thrombosis (95% CI)
Factor V Leiden mutation				
Vandenbroucke, 1994 [28]	OC	DVT	+ FVL mutation, - HC	RR 5.0 (0.8–31.8) Incidence per 10,000 PY: 28.5 (OC use); 5.7 (non-use)
Anderson, 1998 [26]	COC	DVT +/- PE	- thrombophilia, - HC	OR 2.6 (0.7–9.1)
Martinelli, 1999 [6]	COC	DVT	- thrombophilia, - HC	OR 20.0 (4.2–94.3)
Spannagl, 2000 [7]	OC	DVT +/- PE	+ FVL mutation, - HC	aOR 6.5 (1.6–26.9)
Emmerich, 2001 [2]	OC	DVT +/- PE	- thrombophilia, - HC	OR 10.25 (5.69–18.45)
Legnani, 2002 [5]	COC	DVT +/- PE	- thrombophilia, - HC	aOR 41.0 (13.5–125)
Martinelli, 2003 [29]	OC	CVT	- thrombophilia, - HC	OR 30.0 (3.4–263.0)
Sidney, 2004 [32]	COC	DVT +/- PE	- thrombophilia, - HC	aOR 11.32 (3.00–42.81)
Slooter, 2005 [33]	OC	Ischemic stroke	- thrombophilia, - HC	aOR 11.2 (4.3–29.0)
Martinelli, 2006 [9]	OC	Ischemic stroke	- thrombophilia, - HC	aOR 12.9 (1.3–133.7)
Kuipers, 2009 [4]	OC	DVT +/- PE	- thrombophilia, - HC	aOR 18.3 (2.0–171)
Bergendal, 2014 [1]	CHC	DVT +/- PE	- thrombophilia, - HC	OR 20.6 (8.9–58)
	POC			OR 5.4 (2.5–13)
Khialani, 2020 [3]	COC	DVT +/- PE	- thrombophilia, - HC	aOR 19.3 (13.9–26.8)
Prothrombin gene mutation				
Martinelli, 1998 [27]	OC	CVT	- thrombophilia, - HC	OR 149.3 (31.0–711.0)
Martinelli, 1999 [6]	COC	DVT	- thrombophilia, - HC	OR 16.3 (3.4–79.1)
Emmerich, 2001 [2]	OC	DVT +/- PE	- thrombophilia, - HC	OR 7.14 (3.39–15.04)
Legnani, 2002 [5]	COC	DVT +/- PE	- thrombophilia, - HC	aOR 58.6 (12.8–267)
Martinelli, 2003 [29]	OC	CVT	- thrombophilia, - HC	OR 79.3 (10.0–629.4)
Sidney, 2004 [32]	COC	DVT +/- PE	- thrombophilia, - HC	aOR 5.10 (0.83–31.18)
Martinelli, 2006 [9]	OC	Ischemic stroke	- thrombophilia, - HC	aOR 3.1 (0.4–23.3)
Bergendal 2014 [1]	CHC	DVT +/- PE	- thrombophilia, - HC	OR 17.6 (4.4–152)
	POC			OR 0.7 (0.2–2.2)
Tufano, 2014 [34]	OC	CVT	- thrombophilia, - HC	OR 48.53 (5.57–422.56)
Momot, 2019 [30]	CHC	VTE or ATE	+ PT gene mutation, - HC	OR 4.7 (1.89–11.54)
Khialani, 2020 [3]	COC	DVT +/- PE	- thrombophilia, - HC	aOR 24.0 (13.6–42.3)
Antithrombin deficiency				
Pabinger, 1994 [31]	COC	VTE	+ AT deficiency, - HC	Incidence per PY: 27.5% (OC use), 3.4% (non-use) (p=0.005)
Van Vlijmen, 2007 [35]	COC	VTE	+ AT deficiency, - HC	Annual incidence: 5.14% (1.1–15.0) (COC use), 1.77% (0.7–3.9) (non-use)
Protein C deficiency				
Pabinger, 1994 [31]	OC	VTE	+ protein C deficiency, - HC	Incidence per PY: 11.95% (OC use), 6.9% (non-use) (p=0.5)
Van Vlijmen, 2007 [35]	COC	VTE	+ protein C deficiency, - HC	Annual incidence: 7.06% (2.8–14.5) (COC use), 2.23% (0.7–5.2) (non-use)
Protein S deficiency				

Study	Contraception	Outcome	Comparison group	Risk of thrombosis (95% CI)
Pabinger, 1994 [31]	OC	VTE	+ protein S deficiency, - HC	Incidence per PY: 6.5% (OC use), 8.6% (nonuse) (p=0.4)
Van Vlijmen, 2007 [35]	COC	VTE	+ protein S deficiency, - HC	Annual incidence: 2.42% (0.5–7.1) (COC use), 0.46% (0.01–2.5) (non-use)
Multiple thrombophilias				
Emmerich, 2001 [2]	OC	DVT +/- PE	- thrombophilia, - HC	OR 16.97 (3.95–72.80)
Legnani, 2002 [5]	COC	DVT +/- PE	- thrombophilia, - HC	aOR 86.5 (10.0–747)

aOR, adjusted odds ratio; AT, antithrombin; ATE, arterial thromboembolism; CHC, combined hormonal contraception; CI, confidence interval; COC, combined oral contraception; CVT, cerebral vein thrombosis; DVT, deep venous thrombosis; FVL, factor V Leiden; HC, hormonal contraception; OC, oral contraception; OR, odds ratio; PE, pulmonary embolism; POC, progestin-only contraception; PT, prothrombin; PY, person-year; VTE, venous thromboembolism.