Risk of venous thromboembolism in women taking the combined oral contraceptive: A systematic review and meta-analysis

Deborah Bateson, Belinda E Butcher, Catherine Donovan, Louise Farrell, Gab Kovacs, Tonia Mezzini, Camille Raynes-Greenow, Gino Pecoraro, Christine Read, Rod Baber

Background

Much scientific, media and patient interest surrounds the risk of venous thromboembolism (VTE) in women taking combined oral contraceptives (COCs).

Objectives

We conducted a systematic review and meta-analysis to assess VTE risk in women taking COCs, focusing on drospirenone.

Methods

Literature searches of clinical studies on COCs in which VTE was reported were undertaken in May 2015. No overall estimate of VTE risk between drospirenone-containing COCs and other COCs was produced because of heterogeneity of the study designs.

Results

The final review and meta-analysis included 15 studies. No increased risk of VTE with drospirenone was seen in prospective or case control studies, but the risk of VTE was increased in retrospective cohort and nested case control studies.

Discussion

The difference in risk of VTE based on the choice of progestin in COCs is, at worst, very small in absolute terms and should not be the sole factor considered when choosing the 'right' COC for each woman.

Combined oral contraceptives (COCs) remain a widely used contraceptive method.[1,2] General practitioners commonly see women for contraception-related consultations,[1] and therefore must provide evidence-based information about the risks and benefits within the context of the full range of contraceptive options. The rise of social media as a source of medical information makes it important for healthcare professionals to counterbalance emotive misinformation and misperceptions about the risks of COCs, in particular the risk of venous thromboembolism (VTE), with balanced, easy-to-understand facts.

The earliest COCs contained relatively high doses of the synthetic oestrogen, ethinyl oestradiol (EE), in combination with the progestin levonorgestrel or norethisterone. Changes in COC formulations over the past 50 years have included a reduction in EE dose, substitution of EE with oestradiol and use of newer, receptor-selective progestins including desogestrel, gestodene, drospirenone and nomegestrol acetate. These changes have been aimed at reducing cardiovascular risks and troublesome side effects while potentially enhancing desirable 'non-contraceptive' effects.

In Australia, the annual incidence of VTE in the general community is approximately 0.6 cases per 1000 population.[3] The incidence appears to be increasing in line with other high-income countries, which probably relates to an increase in diagnostic capability as well as increases in rates of modifiable risk factors such as obesity, smoking, long-distance travel and current COC use.[4] Major non-modifiable VTE risk factors include increasing age and inherited coagulopathies, in particular factor V Leiden mutation.[5] Current low-dose COC use (≤35 µg EE) is associated with an elevated VTE risk of twofold to threefold above baseline, which is highest in the first year of use. For most women of childbearing age, this translates into a very small absolute risk.[2,6,7] This absolute risk is also far less than that attributed to pregnancy

or the postpartum period (Table 1). An increasing body of international evidence points to the oestrogen component as the major contributor to VTE risk on the basis of the absence of an association for progestin-only contraceptives and an elevated risk for COCs containing more than 35 µg EE.[8] However, international controversy remains regarding the influence of different progestins on VTE risk. Conflicting results from several European and US-based studies have led to confusion about whether certain COC formulations can safely be prescribed.[9–13]

In this paper, we present a systematic review and meta-analysis of all available evidence relating to the risk of VTE associated with drospirenone-containing COCs. We aim to support best-practice prescribing for medically eligible women choosing an oral method of contraception.

Methods

Study

Methods of analysis and inclusion criteria were specified a priori and documented in a protocol. This systematic review was registered on PROSPERO (registration number CRD42014013589).

Data sources

We performed a systematic review of Medline, EMBASE, Derwent Drug File, Biosis, ISI – Current Contents, Chemical Abstracts and the International Pharmaceutical Abstracts, along with the Bayer internal company database. Searches were performed in August 2014 and updated in May 2015. We searched for all clinical studies (prospective or retrospective observational studies or randomised controlled trials) in women taking the COC that compared drospirenone with other progestins, and included information on VTE incidence. We included studies in all languages, but excluded case studies and case series. Searches were independently conducted by two librarians.

Study selection

We identified 43 studies in our search, of which five were duplicates and were excluded. Of the remaining 38 studies, 22 were excluded following abstract review (Figure 1). The included studies underwent quality appraisal using the MERGE criteria.[14] One author completed the MERGE assessment, and a second author reviewed the assessment. A third author resolved disagreements between authors. Papers with a high risk of bias (MERGE category 'C') were excluded from the narrative review (one paper[15] was excluded). The remaining 15 studies were included.[9–13,16–25] Additional information for one study was obtained from a Food and Drugs Administration (FDA) briefing document.[26] Characteristics of the included studies are reported in Table 2 (available online only).

Data extraction

Data extraction forms were piloted by two authors and modifications were made before sending to all authors for analysis. One author completed data extraction using the pre-defined data fields and a second author reviewed the extraction. A third author resolved disagreements between authors. We extracted information on participant demographics, study setting, comparators and relative risks of VTE. Given an anticipated high level of heterogeneity between the retrieved studies, we did not combine all studies meta-analytically to form one overall pooled risk estimate. We instead combined studies of similar type using Mantel-Haenszel fixed effects meta-analysis to give a pooled estimate for each study type. As some studies reported odds ratios (OR) or relative risks (RR), while others reported hazard ratios (HR), methodological issues may arise with combining these different types of measures, leading to potential bias of the estimate by study group.[27] Therefore, a sensitivity analysis was conducted excluding the HR or the OR/RR measure (depending on study type) to explore whether the study type estimates were stable. Heterogeneity was assessed using I^2 measures.

Results (data synthesis)

Studies were grouped by type with a pooled estimate for each: prospective cohort (n = 4), retrospective cohort (n = 6), case-control (n = 2), nested case control (n = 3, including non-fatal idiopathic VTE (n = 2), and all VTE (n = 1)).

In the prospective cohort studies, there were no differences in VTE risk between those taking drospirenone-containing COCs, compared with those taking levonorgestrel[10,11,18] or other COCs[21] (combined RR = 0.94, 95% confidence interval [CI] = 0.75,1.18; Figure 2). This lack of difference remained when excluding the INGENIX study,[21] which reported an RR (combined HR = 0.95, 95% CI = 0.74,1.21; Figure 3). No difference in risk was observed in the case control studies[9,23] either (combined RR = 1.21, 95% CI = 0.72, 2.02; Figure 2).

The retrospective cohort studies[12,13,16,17,22,24] showed a significant increase in risk of VTE in women taking drospirenone-containing COC, compared with women taking levonorgestrel or other COCs (combined RR = 1.82, 95% CI = 1.60, 2.06; Figure 2). This increased

Table 1. Risk of VTE in women at various life stages[5,6]

Population	Risk of VTE per 10,000 women per year
Women of childbearing age non-OC users	4
Women taking COC	7–10
Pregnant and postpartum women	20–30*

**Postpartum rates for the first 12 weeks postpartum have been quoted as 40–65 per 10,000 women per year,[35] and approximately 300–400 per 10,000 women per year during the two days before and the day after delivery[36]*
COC, combined oral contraceptive; OC, oral contraceptive; VTE, venous thromboembolism

risk was still observed when the Sidney study,[22] which reported an HR, was excluded (combined RR = 1.83, 95% CI = 1.59, 2.10). An increased risk was also observed in the nested case control studies of idiopathic VTE[19,20] (combined RR = 2.51, 95% CI = 1.82, 3.46; Figure 2) and all VTE[25] (OR = 1.80, 95% CI = 1.49, 2.18; Figure 2).

Discussion

While current evidence supports a twofold to threefold increase in the risk of VTE for low-dose oestrogen-containing COCs (≤35 µg EE)[6] over non-use, the difference in risk between COC types on the basis of the progestin content remains controversial. Our systematic review of all available studies has found consistent differences in VTE outcomes for drospirenone-containing COCs when compared with levonorgestrel and other COCs between studies with a retrospective or nested case control design, but not in case control and prospective cohort studies.

Understanding the difference in VTE risk between COC preparations as well as between studies and study types is challenging for the clinician, and has been the subject of much debate. A randomised controlled trial might settle this issue, but given the rarity of VTE events, it is unlikely that one would ever be completed given the very large sample size that would be required. Restrictive inclusion criteria may also limit the generalisability of the data to everyday clinical practice. There are several known non-modifiable and modifiable VTE risk factors including older age, genetic predisposition, obesity and smoking,[28] and it would be important to be able to adjust for these factors when making comparisons between progestins. In line with best-practice prescribing guidelines,[2,29] COCs are contraindicated in women with known VTE risk factors, and non–oestrogen-containing alternative methods of contraception should be provided instead.[28]

Interpretation of the evidence has also been made more complex by phenomena such as an early user effect, reported in some studies, with increased risk of VTE events reported in new users of COCs.[11,16,30] The mechanism for this increased risk in new users is poorly understood, but may be due to differential effects on sex hormone binding globulin or activated protein C resistance in early use, or by an unmasking of an underlying inherited coagulation disorder. The effects on coagulation parameters may explain the higher incidence of clotting after a COC break of four weeks or more.[31] As user status may be more difficult to determine in retrospective database studies than in studies capturing this information prospectively from patients, it may result in unbalanced comparisons between groups. It should be noted that all of the included studies had limitations in design, including

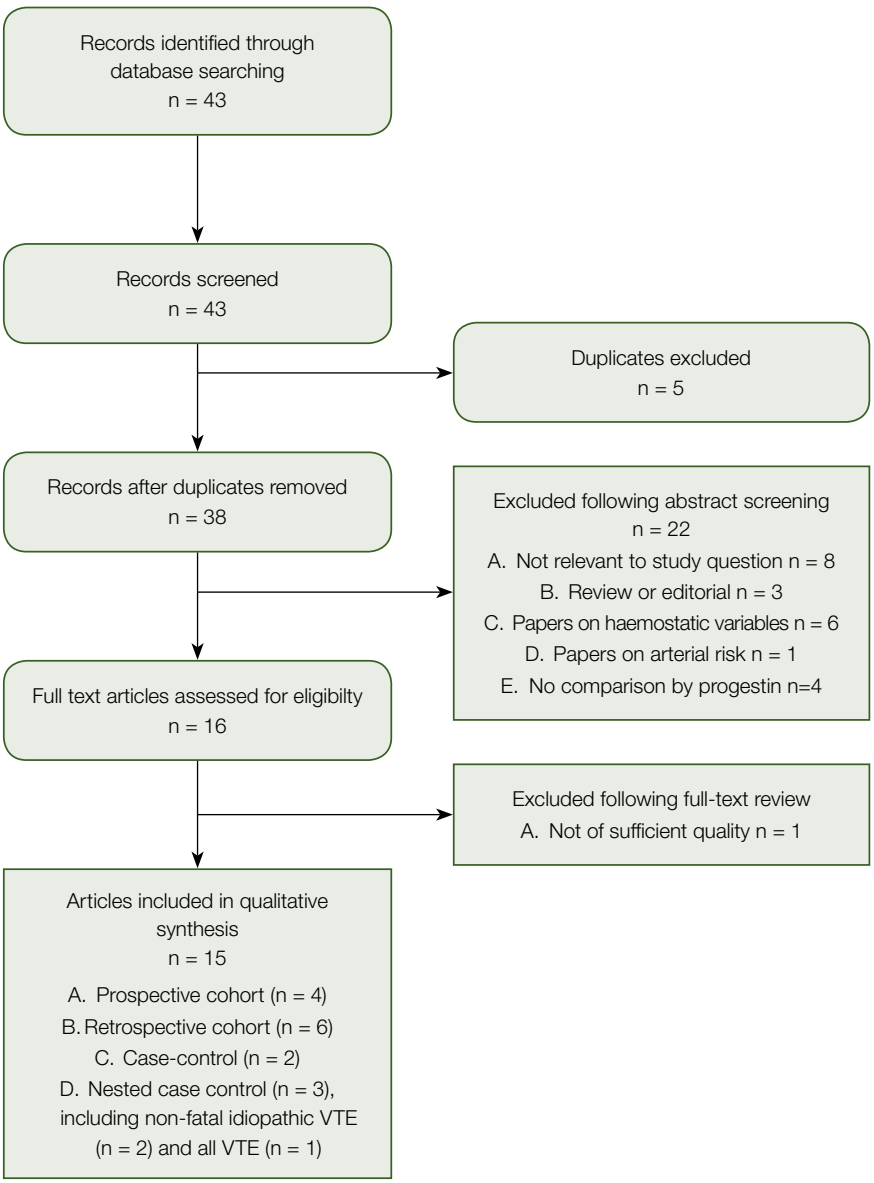

Figure 1. PRISMA flowchart

differences in the inclusion criteria. The two large prospective observational studies (INAS-OC and EURAS)[10,11] were sponsored by Bayer Healthcare as a requirement of the regulatory bodies. These studies had minimal inclusion/exclusion criteria and any woman who was seeking a new COC or switching COCs was eligible, which meant that some women with higher risk of thrombotic events were prescribed a COC despite not meeting current medical eligibility criteria. Many studies also had significant data limitations in relation to VTE-related risk factors. For example, many of the retrospective studies did not collect information about a current or previous history of VTE, or a family history of VTE.[25,28] Studies also did not report the presence of factor V Leiden mutation, which shows marked regional variation. It is estimated to affect 5% of the Australian population.[32] Despite the association with VTE, there is no indication for routinely screening women for factor V Leiden mutations prior to COC prescription. The COC is contraindicated in women with a known thrombogenic mutation,[33] while caution is needed in those with a first-degree relative who experienced a VTE of any cause before the age of 45 years, as the risks are thought to outweigh the benefits.[28,33]

The applicability of the study outcomes to the global population is difficult to ascertain. The women in the large prospective observational INAS-OC study were recruited from Europe and the US and, overall, were relatively young (mean age 26.3 years), had a mean body mass index (BMI) of 24.9 kg/m^2 and were mainly non-smokers; only 16.9% of the cohort were obese (BMI ≥30 kg/m^2) and 22% were smokers. It is difficult to know whether these demographics can be generalised to other COC-taking populations such as Australian women. Unfortunately, information about BMI, obesity and smoking status was not routinely collected in many of the other included studies, particularly in the retrospective cohort studies, or was not captured in the database for all patients in nested case control studies.

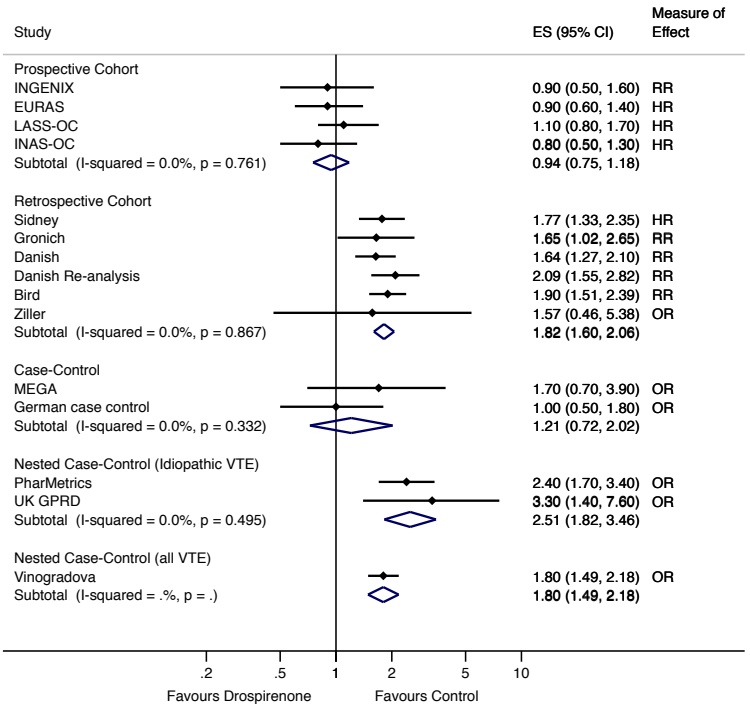

Figure 2. VTE risk in drospirenone users compared to other oral contraceptive users by study type
ES, effect size (relative risk, odds ratio or hazard ratio)

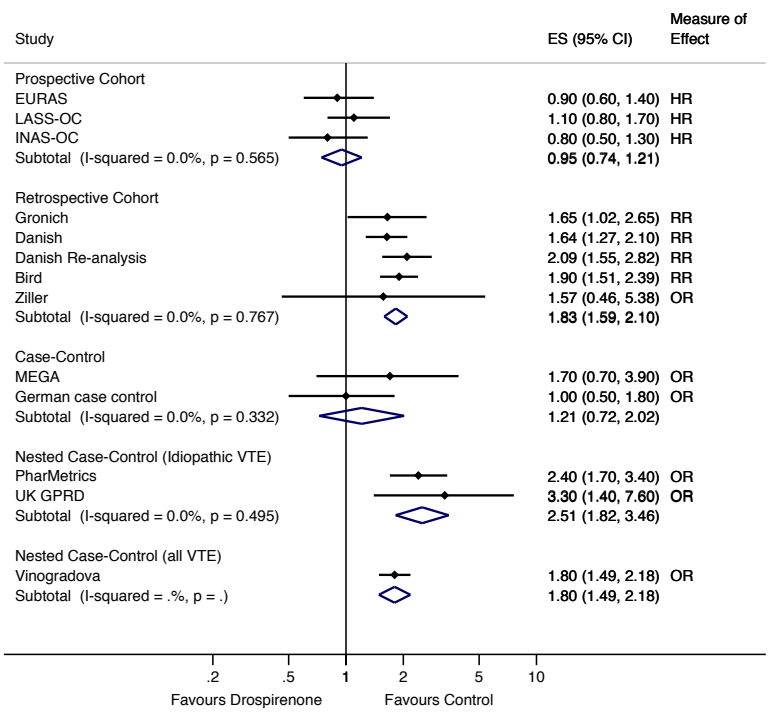

Figure 3. Sensitivity analysis of VTE risk in drospirenone users compared to other oral contraceptive users by study type. ES, effect size (relative risk, odds ratio or hazard ratio)

Given the differences in results and study methods observed between the prospective and retrospective studies, it is difficult to determine the 'truth' in relation to VTE risk between different COC preparations. The retrospective studies had issues such as no validation of reported VTE events, insufficient risk factor data and possible provider bias due to selective prescribing of drospirenone-containing COC in higher risk women. The prospective cohort studies, especially those published more recently, may also suffer from prescriber bias in either direction, possibly due to the media influencing prescribing behaviour. Additionally, one might consider the lack of difference in studies funded by pharmaceutical companies as 'evidence of influence', although we note that on investigation these studies appear to be scientifically robust and independent. We cannot, therefore, exclude the possibility that the relative risk of VTE in women taking drospirenone-containing COC lies somewhere between the estimates of the prospective and retrospective analyses.

A strength of our study was the inclusion of the larger prospective studies and the use of adjusted risks where these were available. A recent network meta-analysis by de Bastos and colleagues[34] examined VTE risk in women taking COCs. However, their analysis excluded the larger prospective studies (INAS, INGENIX, EURAS or LASS-OC; Table 2, available online only), as they restricted their focus to studies analysing the first VTE event, and the data entered into network meta-analysis was not adjusted for possible confounders. While excluding the prospective studies that included women who had experienced a previous VTE (in whom, therefore, COC use should have been contraindicated) may be seen as a strength of the meta-analysis by de Bastos and colleagues, it also potentially results in a loss of data from the vast majority of women who had not suffered a previous VTE event who were also included in these studies.

When making treatment decisions about prescribing COCs, consistent with evidence-based practice, individual risk factors for each woman must be carefully considered. Prescribers are encouraged to prescribe according to medical eligibility criteria and patient preferences. We believe those women who are eligible for COCs can use any COC with 35 µg of ethinyl oestradiol or less, or the newer oestradiol/oestradiol valerate COCs (which are not included in this review because of lack of data). Those who are ineligible for an oestrogen-containing method due to VTE risk factors, including women with a high BMI and factor V Leiden mutation, should not be prescribed any COC.

Implications for general practice

The risk of VTE for any woman taking a low-dose COC (≤35 µg EE) is approximately two to three times higher than for non-users. In absolute terms, risk of VTE is often quoted in the literature as 4/10,000 women-years for non-pregnant non-users and 7–10/10,000 women years for COC users, which translates to a very low, acceptable absolute risk for any user when appropriate prescribing guidelines are applied. The question of whether or not the risk of VTE among users of drospirenone-containing COCs is higher again cannot be definitively answered by the available scientific literature as the retrospective studies suggest an increased risk, whereas the prospective studies show no difference. However, this does, of itself, suggest that any change in absolute risk in drospirenone-containing COCs must remain extremely small in absolute terms. The choice of contraceptive method should always be made together with the patient, on the basis of the evidence using appropriate medical eligibility criteria. We do not believe the available scientific evidence supports selective prescribing of COC based on 'differential' VTE risk alone. COC choice should be based on other factors, including the side effect profile, potential additional benefits and cost. Ultimately, however, the choice of COC type is up to the woman herself with, ideally, expert, up-to-date evidence-based advice from her clinician.

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Author declaration

All authors were involved in critical review of included papers and extraction of data for inclusion in the study. All authors critically reviewed the manuscript and approved it for submission.

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Table 2. Characteristics of included studies

Source	Study type	Setting	Number of eligible patients	Age, years; mean (SD) or (min to max)	BMI	Obese (%)*	Ever used OC pill (%)	Current users of OC pill (%)	Family history of VTE (%)	Personal history of VTE (%)	Comparisons considered	Follow-up or study period	MERGE
INGENIX[20]	P-CS	US claims database	DRSP: 22,429 Comparator: 44,858	28.4 (NR) 28.4 (NR)	NR NR	NR NR	100 100	100 100	NR NR	0.1 0.1	DRSP versus other COC	14,081 women-years	B1
EURAS[11]	P-CS	Europe & UK community	DRSP: 16,534 LNG: 15,428 OCOC: 26,341 NOHC: 371	25.9 (8.1) 25.1 (8.7) 24.8 (7.8) 27.5 (8.0)	22.9 (4.4) 22.0 (4.0) 21.7 (3.8) 21.7 (3.7)	8.2 5.2 4.5 NR	NR NR NR NR	100 100 100 NR	0.8† 0.6† 0.8† 1.6†	NR NR NR NR	DRSP versus LNG/OCOC	142,475 women-years	B1
LASS-OC[18,26‡]	P-CS	Europe community	47,799	NR	NR	NR	NR	NR	NR	NR	LNG versus DRSP versus OCOC	2000–10; 318,784 women-years	B1
INAS-OC[10]	P-CS	US and Europe community	85,109	26.3 (7.7)	24.9 (5.9)	16.4	100	100	2.45	0.12 (DVT) 0.03 (PE)	LNG versus DRSP 24d or 21d versus OCOC	2002–11; 206,296 women-years	B1
Sidney[22]	R-CS		DRSP: 109,070 Comparator: 383,151	26.4§ 27.2	NR NR	NR NR	100 100	100 100	NR NR	NR NR	DRSP versus other COC‖	2001–07	B1

**Where not explicitly stated, a BMI over 30 kg/m² was considered obese*
†VTE-like conditions
‡The LASS-OC study is an extension of EURAS, so the demographics between the two studies would be very similar
§Mean age at initiation for all users (including comparator, norelgestromin-containing transdermal patch and tonogestrel vaginal ring)
‖LNG10-20; LNG15-30; norethindrone 1mg/ethinyl estradiol 20 µg; and nogestimate (0.18–0.25 mg)/ethinyl estradiol 35 µg

Table 2. Characteristics of included studies

Source	Study type	Setting	Number of eligible patients	Age, years; mean (SD) or (min to max)	BMI	Obese (%)*	Ever used OC pill (%)	Current users of OC pill (%)	Family history of VTE (%)	Personal history of VTE (%)	Comparisons considered	Follow-up or study period	MERGE
Gronich[14]	R-CS	Israel Clalit medication database	329,995	NR (12 to 50)	NR	NR	NR	100	NR	NR	2nd generation versus 3rd generation versus DRSP versus gestodene versus chlormadinone	2002–08; 819,749 women-years	
Danish[12]	R-CS	Danish census (community)	NR	NR, but most WY of exposure in 35–39 year olds	NR	NR	52.9#	31.1#	NR	?**	LNG versus DRSP versus OCOC	1995–2005; 10.4 million women-years	B2
Danish re-analysis[13]	R-CS	Danish census (community)	1,296,120	15 to 49	NR	NR	68.3	NR	NR	NR	DRSP versus LNG and 3rd generation COC	2001–09; 8.0 million women-years	B1
Bird[16]	R-CS	US community	DRSP/EE20: 75,524	30.0 (NR)	NR	11.22	100	100	NR	NR	DRSP/EE20 versus LNG/EE20	2001–09	B1
			LNG/EE20: 111,151	28.1 (NR)	NR	10.41	100	100	NR	NR			
			DRSP/EE30: 163,159	28.2 (NR)	NR	11.40	100	100	NR	NR	DRSP/EE30 versus LNG/EE30		
			LNG/EE30: 82,344	30.0 (NR)	NR	11.68	100	100	NR	NR			

#Proportion of women-years of follow-up

***Women with malignancy and CVD ICD codes were excluded, although it is unclear whether these exclusions would have captured all women with a personal history of VTE*

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Source	Study type	Setting	Number of eligible patients	Age, years; mean (SD) or (min to max)	BMI	Obese (%)*	Ever used OC pill (%)	Current users of OC pill (%)	Family history of VTE (%)	Personal history of VTE (%)	Comparisons considered	Follow-up or study period	MERGE
Ziller[24]	R-CS	SP	68,168	29.6	23.5	NR	100	100	NR	0	LNG versus DRSP	2005–10	B2
MEGA[23]	C-CS	Anticoagulation clinics Netherlands	Case: 1,524 Control: 1,760	37.1 (18 to 49) 37.4 (18 to 49)	26.8 (16 to 57.8) 24.4 (15.7 to 50.7)	NR NR	NR NR	72.4 37.4	26.4 14.3	NR NR	COC versus NCOC Progestogen type; estrogen type	1999–2004	B2
German case control[9]	C-CS	German community	Case: 680 Control: 2,720	36.1 (9.0) 36.1 (9.0)	NR NR	21.2 13.3	84.7 80.8	40.1 29.9	30.6 12.9	7.4 2.1	LNG versus DRSP	2002–08;	B1
Vinogradova[25]	N-CC All VTE	CPRD database QResearch database	Cases UK: 5,062 Control UK: 19,638 Cases QR: 5,500 Control QR: 22,396	15 to 49	15 to ≥30	12.5 16.3 19.3 21.6	NR	32.6 20.3 33.4 19.7	NR	NR	LNG versus DRSP	2001–13	B1
PharMetrics[19]	N-CC I	US claims database	Case: 681 Control: 186	15 to 44 15 to 44	NR NR	13 6	100 100	100 100	NR NR	NR†† NR	LNG versus DRSP	2002–08	B1
UK GPRD[20]	N-CC I	UK GP database	Case: 61 Control: 215	32.2 (7.2) 31.8 (7.4)	26.1 (19.1 to 45.7) 23.3 (17.3 to 43.2)	25 7	100 100	100 100	excl. excl	0 0	LNG versus DRSP	2002–09	B1

C-CS, case-control study; COC, combined oral contraceptive; DRSP, drospirenone containing COC; excl, excluded; GP, general practitioner; I, idiopathic VTE study; NCC, nested case-control; NCOC, no combined oral contraceptive; NOHC, non-oral hormonal contraceptive; NR, not reported; OCOC, other COC; P-CS, prospective cohort study; R-CS, retrospective cohort study; SP, specialist practice

††Women were excluded if they had important risk factors, including major surgery, lower limb injury, trauma and pregnancy