Drospirenone-containing oral contraceptives and risk of venous thromboembolism

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Table of Contents

ABSTRACT

Combined oral contraceptives (COCs) are widely used by women to prevent unwanted pregnancies. The fourth generation of COCs, containing the progestin drospirenone, came on the market in 2000. In the last decade, there have been concerns regarding the potential venous thromboembolytic (VTE) risk of drospirenone-containing COCs. The many studies that assessed this relationship reported variable results which may be due to differences in their methodological quality. I aimed to synthesize the literature regarding drospirenone-containing COCs and the risk of VTE with a specific focus on its methodological quality. Subsequently, I aimed to describe and illustrate the methodological challenge of studying the risk of VTE among first-time users of drospirenone-containing COCs in a healthcare database.

In the first manuscript, I systematically searched seven databases from inception to November 2015 to identify all observational studies assessing the risk of VTE among users of drospirenone-containing COCs. I assessed the overall quality of each included study using the ACROBAT-NRSI and examined in detail four common sources of bias: prevalent user bias, inappropriate choice of comparator, VTE misclassification, and confounding. I identified 17 studies that met the inclusion criteria (11 cohort and 6 case-control). Based on the ACROBAT-NRSI, one study had low risk of bias, nine had a moderate risk, three had a serious risk, and four had a critical risk. Ten studies included prevalent user bias, five studies included inappropriate comparator groups, seven studies had VTE misclassification, and five failed to adjust for two or more important confounders.

In the second manuscript, I conducted an original research study that examined the VTE risk of drospirenone-containing COCs. I used data from the Clinical Practice Research Datalink

(CPRD) to create two cohorts. The first-time user cohort included all women aged 16 to 45 years who received a first ever prescription of drospirenone- or levonorgestrel-containing COCs between May 1st, 2002 and March 31st, 2015. The restarter cohort included all women aged 16 to 45 years who restarted a COC after a period of non-use of at least 6 months. For both cohorts, women were followed until VTE (defined by hospitalization for VTE or an outpatient diagnosis of VTE with subsequent prescription of warfarin, INR testing, or death within 90 days), discontinuation of COC use, switching to any other form of hormonal contraception (including the other study COC), pregnancy, arterial thromboembolism, death, departure from the CPRD, or the end of the study period, whichever occurred first. High-dimensional propensity scores (HDPS) were estimated to contrast users of drospirenone- and levonorgestrel-containing COCs. Cox proportional hazards models were used to estimate hazard ratios (HRs) and corresponding 95% confidence intervals (CIs). The final cohorts comprised 55,139 first-time ever users (3,582 drospirenone and 51,557 levonorgestrel) and 162,959 restarter users (23,191 drospirenone and 139,768 levonorgestrel). There were 25 cases of VTE during a mean follow-up of 1.0 years (crude incidence rate per 10,000 woman-years [IR]: 4.6, 95% CI: 3.0-6.8) among first-time users and 75 cases of VTE during a mean follow-up of 1.0 years (IR: 4.6, 95% CI: 3.6-5.7) among restarters. Among first-time ever users, drospirenone-containing COCs were associated with a substantially higher risk of VTE than levonorgestrel-containing COCs (adjusted HR: 3.19, 95% CI: 1.12-9.08). Among restarters, the adjusted HR was 1.96 (95% CI: 1.12-3.41). Both cohorts produced non-proportional hazards and all sensitivity analyses were consistent with the main findings.

Although previous studies have examined the association between drospirenone-containing COCs and the risk of VTE, this literature has several limitations, the most important

of which is likely the inclusion of prevalent users. To overcome these limitations, I examined two cohorts: a first-time ever user cohort and a restarter cohort, the latter of which represents a novel approach to studying the VTE risk of COCs. Although left truncation of healthcare databases is a concern for the identification of first-time users, the use of a well-defined restarter cohort suggests a doubling of VTE risk with drospirenone-containing COCs relative to levonorgestrel-containing COCs. Physicians and patients should be aware of this increased risk when considering the most appropriate choice of contraception.

RESUME

Les contraceptifs oraux combinés (COC) sont utilisés par la plupart des femmes pour prévenir les grossesses non désirées. La quatrième génération de COC, contenant le progestatif drospirénone, a été mise sur le marché au cours de l'année 2000. Dans la dernière décennie, des préoccupations ont été soulevées concernant le risque potentiel de thrombo-embolie veineuse (TEV) des COC contenant de la drospirénone. Les nombreuses études qui ont évalué cette relation ont rapporté des résultats variables qui peuvent être dus à leurs différences de qualité méthodologique. Mon étude vise à synthétiser la littérature concernant les COC contenant de la drospirénone et le risque de TEV, en me concentrant sur la qualité méthodologique. Elle vise secondairement à décrire et à illustrer les défis méthodologiques associés à l'étude du risque de TEV chez les nouvelles utilisatrices de COC contenant de la drospirénone dans une base de données de soins de santé.

Dans le premier manuscrit, j'ai cherché de façon systématique sept bases de données depuis leur création jusqu'en novembre 2015 afin d'identifier toutes les études observationnelles évaluant le risque de TEV chez les utilisatrices de COC contenant de la drospirénone. J'ai évalué la qualité méthodologique de chaque étude incluse en utilisant l'ACROBAT-NRSI et j'ai examiné en détail quatre sources fréquentes de biais: biais concernant les utilisateurs prévalents de COC, choix inapproprié du groupe de comparaison, mauvaise classification des TEV et biais de confusion. J'ai identifié 17 études qui répondaient aux critères d'inclusion (11 de cohorte et 6 cas-témoins). Basé sur l'ACROBAT-NRSI, une étude avait un faible risque de biais, neuf avaient un risque modéré, trois avaient un risque grave, et quatre avaient un risque critique. Dix études comportaient un biais en rapport avec les utilisateurs prévalents de COC, cinq études

comprenaient des groupes de comparaison inappropriés, sept études avaient des erreurs de classification de TEV, et cinq n'ont pu régler le biais lié à la présence d'au moins deux facteurs de confusion importants.

Dans le deuxième manuscrit, j'ai mené une étude de recherche originale qui a examiné le risque de TEV des COC contenant de la drospirénone. J'ai utilisé les données de la base Clinical Practice Research Datalink (CPRD) pour créer deux cohortes. La cohorte des nouvelles utilisatrices incluait toutes les femmes âgées de 16 à 45 ans ayant reçu une première prescription de COC contenant du drospirénone ou du lévonorgestrel entre le 1er mai 2002 et le 31 Mars 2015. La cohorte de femmes reprenant des COC incluait toutes les femmes âgées de 16 à 45 ans ayant utilisé des COC après une période de non-utilisation d'au moins 6 mois. Dans ces deux cohortes, les femmes ont été suivies jusqu'à la survenue d'une TEV (définie par l'hospitalisation pour TEV ou un diagnostic ambulatoire de TEV suivi d'une prescription de warfarine, de tests d'INR, ou d'un décès dans les 90 jours), l'arrêt de l'utilisation de COC, le passage à une autre forme de contraception hormonale (y compris l'autre COC d'étude), la grossesse, la thromboembolie artérielle, le décès, le départ du CPRD, ou la fin de la période d'étude, selon lequel de ces événement est survenu en premier. Les scores de propension de haute dimension ont été estimés pour contraster les utilisatrices de COC contenant du drospirénone et du lévonorgestrel. Les modèles Cox à risques proportionnels ont été utilisés pour estimer les rapports de risque (RR) et les intervalles de confiance (IC) à 95% correspondant. Les cohortes finales comprenaient 55139 nouvelles utilisatrices (3582 drospirénone et 51557 lévonorgestrel) et 162 959 utilisatrices redémarrant des COC (23191 de drospirénone et 139 768 lévonorgestrel). Vingt-cinq cas de TEV sont survenus au cours d'un suivi moyen de 1,0 année (IR: 4,6; IC à 95%: 3,0 à 6,8) chez les nouvelles consommatrices et 75 cas de TEV au cours d'un suivi moyen de 1,0

année (IR: 4,6; IC à 95%: 3,6 à 5,7) parmi les utilisatrices redémarrant les COC. Parmi les nouvelles utilisatrices, les COC contenant du drospirénone étaient associés à un risque plus élevé de TEV que les COC contenant du lévonorgestrel (RR ajusté: 3,19; IC à 95%: 1,12 à 9,08). Parmi les utilisatrices redémarrant les COC, le HR ajusté était de 1,96 (IC à 95%: 1,12 à 3,41). Les deux cohortes ont produit des risques non proportionnels.

Bien que des études antérieures aient examiné l'association entre les COC contenant de la drospirénone et le risque de TEV, cette littérature présente plusieurs limites, dont la plus importante est probablement l'inclusion d'utilisatrices fréquentes. Pour surmonter ces limites, j'ai étudié deux cohortes, une cohorte de nouvelles utilisatrices et une cohorte d'utilisatrices redémarrant les COC, cette dernière représentant une nouvelle approche pour étudier le risque de TEV des COC. Bien que la troncature à gauche des bases de données de santé représente un problème potentiel pour l'identification des nouvelles utilisatrices, l'étude d'une cohorte bien définie de femmes redémarrant les COC suggère un doublement du risque de TEV avec les COC contenant de la drospirénone par rapport aux COC contenant du lévonorgestrel. Les médecins et les patientes doivent prendre en considération ce risque accru lors du choix de la contraception la appropriée.

CONTRIBUTION OF AUTHORS

Natasha Larivée, M.Sc.

I contributed substantially to the study design, methodology, and analytical approach for both the systematic review and cohort study. For the systematic review, I wrote the protocol, designed and carried out the literature search, performed data extraction, assessed the quality of included studies, and drafted the manuscript. For the cohort study, I developed and submitted a protocol to the Independent Scientific Advisory Committee ("non-statutory expert advisory body established in 2006 by the Secretary of State to provide advice on research related requests to access data in the UK) of the Clinical Practice Research Datalink, I developed the study design and analytical approach, conducted several of the statistical analyses, and drafted the manuscript I presented my work as a finalist in the 3 Minute Thesis competition at McGill University and at the Annual McGill Biomedical Graduate Conference.

Finally, I obtained financial support for my graduate research in the form of a Masters bursary from the Fonds de Recherché Quebec Santé (Quebec Health Research Fund).

Samy Suissa, PhD

Dr. Suissa was my thesis supervisor. He conceived of the thesis topic, acquired the data, and contributed to the study design and interpretation of data. He attended thesis committee meetings. He reviewed the manuscripts and thesis for important intellectual content.

Kristian B Filion, PhD

Dr. Filion was my thesis co-supervisor. He conceived of the thesis topic and regularly provided insight on study design, analytical approach, and interpretation of data. He attended

thesis committee meetings. He reviewed the manuscripts and thesis for important intellectual content.

Vicky Tagalakis, MD MSc

Dr. Tagalakis was my thesis committee member. She regularly provided her clinical expertise and insight to all components of my thesis, including the development of several of the criteria used in bias assessment in the systematic review, outcome definition of the cohort study, and interpretation of data. She attended thesis committee meetings. She reviewed the manuscripts and thesis for important intellectual content.

Janie Coulombe, MSc

Ms. Coulomb performed data management and some of the statistical analyses for the cohort study. She assisted in the interpretation of data and critically reviewed the corresponding manuscript for important intellectual content.

Farzin Khosrow-Khavar, PhD

Mr. Khosrow-Khavar was the second extractor for the systematic review. He screened potentially relevant articles, performed quality assessment of the included studies, and performed data extraction. He assisted in the interpretation of data and critically reviewed the corresponding manuscript for important intellectual.

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CHAPTER 1: BACKGROUND

1.1 Oral contraceptives (OCs)

Contraception is an artificial method to prevent pregnancy. Common forms of contraception include the male condom, the intrauterine device (IUD) and the oral contraceptive (OC) pill. OCs include a myriad of other indications and benefits such as acne treatment, relief of symptoms associated with premenstrual dysphoric disorder, treatment of heavy or irregular menstruation, lower risk of ovarian and endometrial cancer, decreased risk of cyst formation, and endometriosis.[1] A recently completed national survey on contraception use found that 43.7% of women in the US claim to use oral contraceptives with 85.1% of women having ever used some form of contraception.[2]

Use and Trends in use of COCs

In the US, there are currently 65 million women of child-bearing age (15 to 44 years), of which 43 million are sexually active and do not wish to become pregnant.[3] These women are therefore candidates to use contraception. In fact, more than 99% of women of child-bearing age who have been sexually active have previously used at least one form of contraception and 62% of women of child-bearing age are currently using contraception.[3] A cross-sectional survey in 2012 in the US revealed that the OC pill has been one of the most popular contraceptive methods since 1982, with approximately 9,720,000 OC users in 2012[3] (Table 1.1).

Although OCs are commonly used worldwide, the type of OC being used varies greatly by region. In the US, OCs with norgestimate and those with drospirenone are the most commonly used OCs. In contrast, in Europe, the most commonly used pills are second generation OCs such as those that contain the progestin levonorgestrel. However, prescription

patterns also vary within Europe; in 2005 – 2010, levonorgestrel comprised 57% of all first-time OC prescriptions in Sweden but only 5% of those in Denmark.[4]

Table 1.1 Types of OCs and trends of use

Method	Number of users	% of women aged 15 – 44	% of total contraceptive users
Pill	9,720,000	16.0	25.9
Female sterilization	9,443,000	15.5	25.1
Intrauterine device (IUD)	3,884,000	6.4	10.3
Injectable	1,697,000	2.8	4.5
Vaginal ring	759,000	1.2	2.0
Implant	492,000	0.8	1.3
Patch	217,000	0.4	0.6
No method, at risk of pregnancy	4,175,000	6.9	N/A
No method, not at risk of pregnancy	19,126,000	31.4	N/A

* Includes diaphragm, female condom, foam, cervical cap, sponge, suppository, jelly/cream, and other methods.

Adapted from: Contraceptive Use in the United States. Guttmacher Institute, 2015. (Accessed June 2nd, 2016, at https://www.guttmacher.org/fact-sheet/contraceptive-use-united-states.)

Combined oral contraceptives (COCs) are a form of OCs that contain two female sex hormones, estrogen (*British spelling: oestrogen*) and progestin, which combine to prevent pregnancy by stabilizing the endometrium for better cycle control and preventing ovulation, respectively.[5] The first component of COCs is the estrogen component[6]. Estradiol (E2) is a potent, natural hormone secreted by the ovaries. However, when this hormone is ingested orally, its potency is substantially lower because of its absorption through the gut. However, its relative absorption increases dramatically when it's converted to its derivative ethinylestradiol (EE). (Figure 1) EE is therefore commonly used as the estrogen component in COC formulations. In addition to being absorption relative to E2 when ingested orally, EE possess many other

favorable qualities such as not binding to sex hormone-binding globulin, is resistant to enzymatic degradation by 17-beta-hydroxylas and has a higher affinity for the estrogen receptor.[7]

Figure 1.1 Estrogen (E2) Conversion to Ethinylestradiol (EE)

The second component of COCs is the progestin component. A progestin is a synthetic version of the natural occurring progestogen steroidal hormone family, with properties similar to those of progesterone. Progestins inhibit luteinizing hormone (LH), decreasing ovarian sensibility to follicle stimulating hormone (FSH) and decreasing E2 production. Progestins are classified based on their structure, and many progestins initially included in COCs were derivatives of testosterone (often referred to as "19-nortestosterone derivatives").[8] The main limitation of progestins is their androgenic properties, which has resulted in the development of new progestins over time.[4]

The hormonal composition of COCs has changed over time, with more recent generations containing smaller dosages of estrogen and larger dosages of progestins[9]. The current theory is that the major adverse effects associated with COC use (e.g., increased risk of thrombosis) are directly related to their corresponding estrogen dose.[1] The prothombotic effects of COCs seem to correlate with the dose of estrogen, whereas the progestins seem to reverse this effect[10]. The development of lower dose formulations with respect to the estrogen component has thus been an ongoing pursuit.

Types of COCs

COCs are classified by phase, regimen, preparation and generation. COCs are categorized by phase as monophasicor multiphasic, depending on the different levels of hormones contained in each pill per cycle[11]. The initial pill was monophasic, with biphasic and triphasic pills introduced in the 1980s. COCs are also classified by regimen. Traditional COC formulations contain 28 pills: 21 active pills with the same dose of estrogen and progestin and 7 placebo pills. This is referred to as a 21/7 regimen. Subsequent formulations included "three-phasic" or triphasic pills in which the estrogen component was gradually increased over the 3-week period; these formulations were introduced in order to mimic the *in utero* conditions and minimize unfavorable effects. A 24/4 regimen was then created to increase ovarian suppression while maintaining favorable androgenic properties.[12] Combined contraceptives are also prepared for non-oral use, such as a transdermal patch (EE/norelgestromin), a vaginal ring (EE/etonogestrel), and as injectables. Finally, COCs are classified by generation according to the time in which they entered the market and their corresponding progestin formulation (Table 1.2).

Table 1.2 Types of COCs by generation of progestin

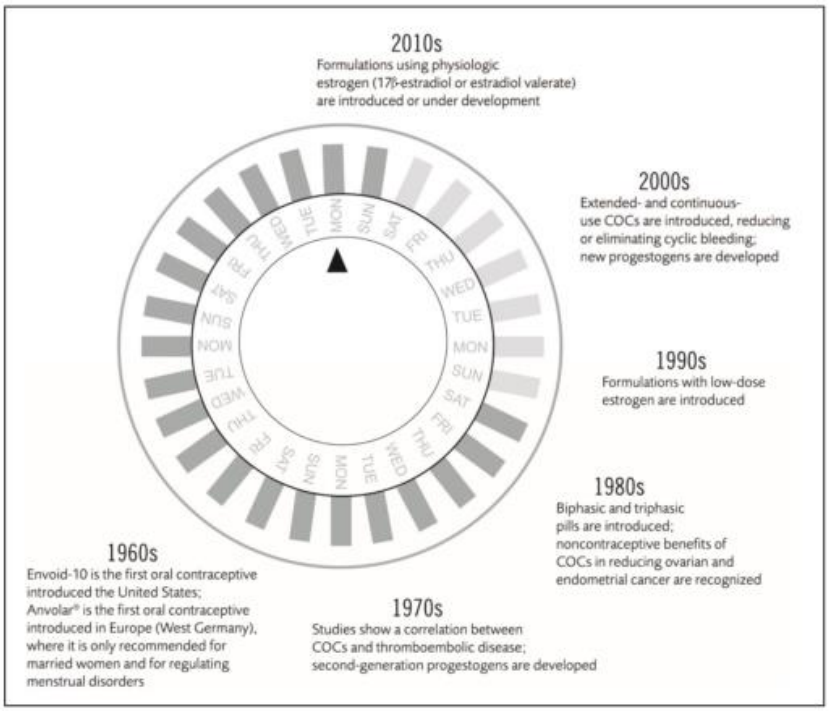
Generation*	Type of Progestin	Examples of Brand Names	Description
First	Norethynodrel, norethindrone, norethindrone acetate, ethynodiol diacetate, etc.	Camila, Errin, Heather, Jencycla, Jolivette, Nor-QD, Nora-BE, Ortho Micronor, etc.	Lowest potency and relatively short half-lives.
Second	Levonorgestrel, norgestrol, etc.	Aviane, Alesse, Enpresse, Lessina, Levora, Nordette, Portia, Tri-Levlen, Triphasil, Trivora, etc.	Significantly more potent and associated with androgen-related side effects.
Third	Desogestrel, norgestimate, gestodene, etc.	Apri, Cyclessa, Desogen, Ortho-Cept, Mononessa, Ortho Tri-Cyclen Lo, Sprintec	Maintain the potency but reduced androgenic side effects.
		Femoden, Lindynette, etc.	Associated with 1990s "pill scare".
Fourth	Dienogest, drospirenone, nestorone, etc.	Natazia, Yasmin, Yaz, etc.	Controversial reports with respect to thrombosis.

*Generation according to published studies on vascular disease.

COCs first entered the market in the 1960s as result of early OCs causing frequent side effects due to extremely high doses of estrogen[6] (e.g., up to 100 µg EE). It was thought that the inclusion of a progestin would create a more favorable safety-risk profile. This class of COCs is referred to as first generation COCs. Second generation COCs entered the market in the 1970s and included the hormones norgestrol and levonorgestrel[13]. These COCs had higher doses of progestins (e.g., more potent) than those of the first generation, which resulted in some androgen-related side-effects, such as increased lipid level, oily skin, acne, and facial hair growth.[14] Third generation COCs entered the market in the 1980's and 1990's with the goal of maintaining the potency of second generation COCs while reducing androgen-related side-

effects. These COCs contained the progestins desogestrel, norgestimate, and gestodene. Finally, in 2000, fourth generation COCs entered the market containing the progestin drospirenone[15] (Figure 1.2).

Figure 1.2 Evolution of OCs over time



<u>Reproduced from:</u> Szarewski A, Mansour D, Shulman LP. 50 Years of "The Pill": Celebrating a golden anniversary. Journal of Family Planning and Reproductive Health Care 2010;36:231-8.

Benefits and risks

As previously mentioned COCs have many benefits and may be prescribed for indications other than contraception, including treatment of acne, premenstrual dysphoric disorder, and heavy or irregular menstruation. COCs are almost 100% effective at preventing unwanted pregnancies if taken as directed. However, in practice there is a 9% failure rate within

the first year due to poor adherence[16]. Poor adherence to these agents is usually due to the occurrence of or fear of side effects such as mood disruptions, decreased libido, weight gain, poor bleeding control, and risk of venous thrombosis (VTE, a potentially fatal blood clot).[4] Risk of VTE has been an important and highly controversial risk of COCs[17].

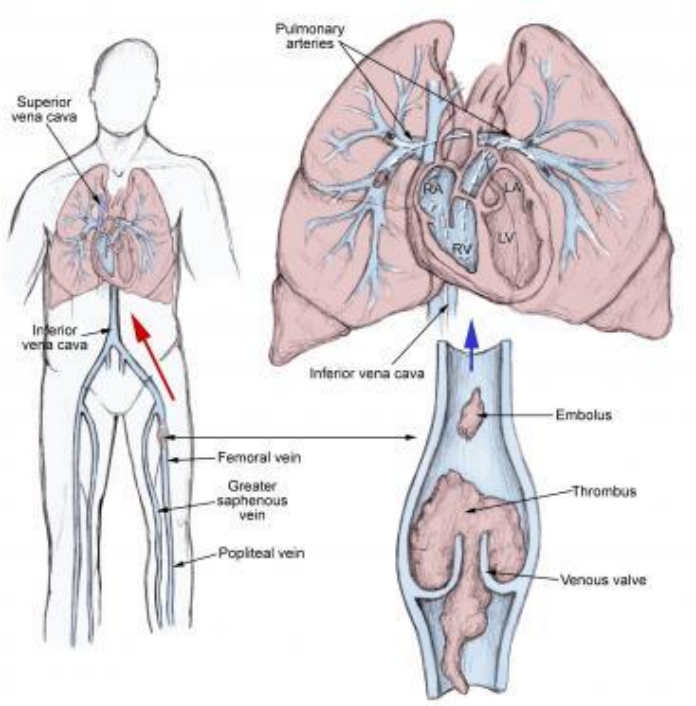
Regulatory response to VTE concerns

Based on a 2011 safety review, the Food and Drug Association (FDA) concluded that "drospirenone-containing birth control pills may be associated with a higher risk for blood clots than other progestin-containing pills". The FDA subsequently revised product labels to outline that some epidemiologic studies report increased risks as high as three-fold while others found no additional risk.[18] In contrast, a 2013 review by the European Medicines Agency (EMA) found that the benefits of drospirenone-containing COCs continue to outweigh the minimal risk of VTE.[19] Finally, Health Canada concluded that drospirenone-containing COCs may be associated with a risk of VTE that is 1.5 to 3 times higher than other COCs.[20] Despite these conclusions, drospirenone-containing COCs remain on the market.

1.2 Venous thrombosis

Venous thrombosis is defined by the formation of a blood clot inside a vein, resulting in obstructed blood flow[21]. A clot that breaks free and travels within the bloodstream is known as an *embolus*. A combination of venous thrombosis and embolism is termed VTE[22,23] (Figure 1.3).

Figure 1.3 An embolus in the blood stream causing VTE

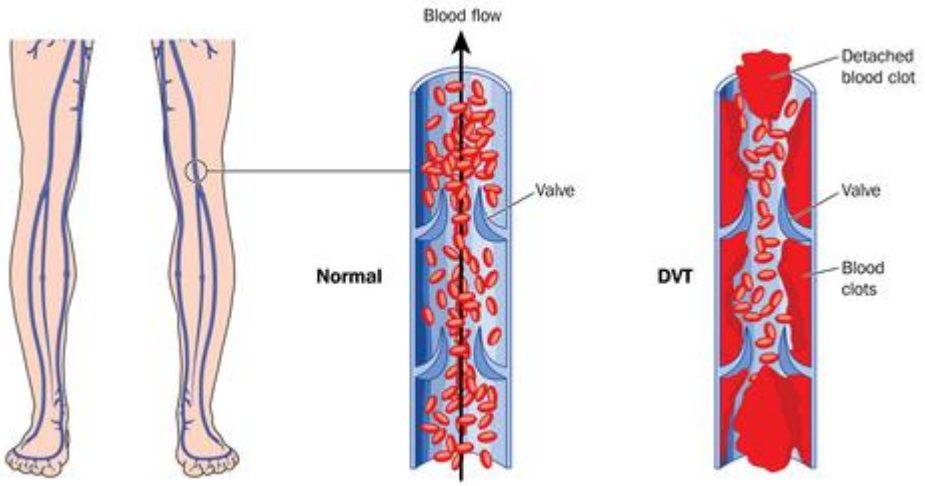


Reproduced from: Pulmonary embolism. 2015. (Accessed April 12th, 2016, at http://emedicine.medscape.com/article/300901-overview.)

VTE includes deep vein thrombosis [DVT] and pulmonary embolism [PE]). The world-wide annual incidence of VTE is approximately 1-2 per 1000[24], with approximately 60 to 70% of all VTE events being DVTs, 25% being PEs, and the remaining episodes being a combination of both DVT and PE. DVT occurs mostly in the veins of the lower extremities but can also occur in the veins of the upper extremities, cerebral sinuses, and those of the abdominal viscera. DVT of the lower extremity veins (e.g., popliteal, femoral, or iliac veins [Figure 1.4]) are associated with complications including PE, fatal PE, recurrence and the post-thrombotic syndrome[25-28]. Symptoms of DVT include limb pain, skin discoloration, and swelling, however, up to 50% of people with a diagnosis for DVT do not present with symptoms.[29] PE refers to a blood clot in the

artery of the lung, and is usually the result of a blood clot traveling from a vein in the leg. In the absence of prompt recognition and treatment, PE can be be fatal in up to 30% of patients presenting with symptoms.[30,31] PE is also the most common cause of inpatient mortality as well the leading cause of death in pregnant woman[32].

Figure 1.4 Deep vein thrombosis



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VTE diagnosis and treatment

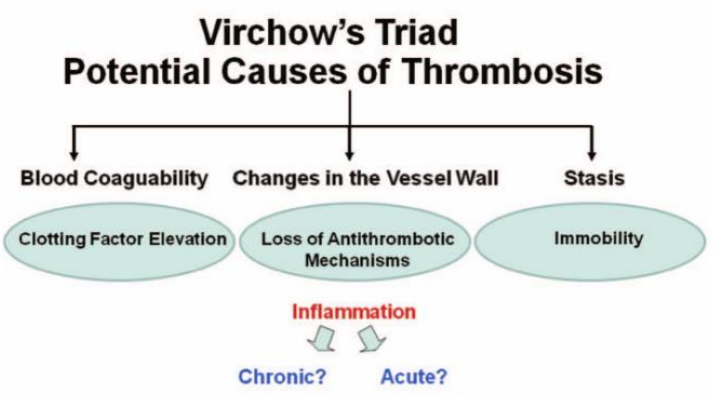
Diagnostic strategies for VTE usually combine a pretest probability score and a measured D-dimer level.[33] Depending on the pretest probability and the D-dimer level, a patient may or may not proceed to further diagnostic imaging tests (e.g. Doppler ultrasonography, venography, CT angiography of the chest).[31] A rule-in or rule-out approach is usually recommended, with the American Academy of Family Physicians and the American College of Chest Physicians providing 4 recommendations for the workup of patients with a suspected VTE.[34]

Treatment of VTE focuses on symptom relief and prevention of clot extension and embolization. However, an additional goal is to prevent post-thrombotic syndrome and reduce the risk of VTE recurrence.[31] Post-thrombotic syndrome is a condition developing in those patients with VTE and involves symptoms such as swelling, redness and ulcers[35]. Anticoagulation is the main form of therapy initially with 5-7 days of subcutaneous low molecular weight heparins followed by a minimum of 3 months of an oral vitamin K antagonist such as warfarin. New oral anticoagulants have recently been made available, including rivaroxaban and apixiban[36]. Thrombolysis or surgical interventions are typically reserved for those patients presenting with severe PE and/or DVT. The American College of Chest Physicians has recently released several recommendations regarding VTE diagnosis and subsequent anticoagulant therapy[37], as well as recommendations for duration of anticoagulant therapy including with aspirin[37].

Risk Factors for VTE

Risk factors for VTE are generally categorized according to Virchow's triad[38,39] (Figure 1.5). Virchow described thrombosis arising from abnormalities in the composition or viscosity of blood, vessel wall damage, and nature of blood flow. Subsequently, there are many known risk factors for VTE, including use of COCs[40,41] (Figure 1.6).

Figure 1.5 Virchow's triad of potential causes of thrombosis



Reproduced from: Esmon CT. Basic Mechanisms and Pathogenesis of Venous Thrombosis. Blood reviews 2009;23:225-9.

Figure 1.6 Risk factors for VTE

Table 1: Risk factors for VTE[1]

Strong risk factors (odds ratio > 10)
Fracture (hip or leg)
Hip or knee replacement
Major general surgery
Major trauma
Spinal cord injury
Moderate risk factors (odds ratio 2–9)
Arthroscopic knee surgery
Central venous lines
Chemotherapy
Congestive heart or respiratory failure
Hormone replacement therapy
Malignancy
Oral contraceptive therapy
Paralytic stroke
Pregnancy/postpartum
Previous venous thromboembolism
Inherited thrombophilia
Weak risk factors (odds ratio < 2)
Bed rest > 3 days
Immobility due to sitting, e.g. prolonged car or air travel
Increasing age
Laparoscopic surgery, e.g. cholecystectomy
Obesity
Pregnancy/antepartum
Varicose veins

Reproduced from: Anderson FA, Spencer FA. Four Topics in Venous Thromboembolism - Risk Factors for Venous Thromboembolism. Circulation 2003;107:I9.

1.3 Thrombotic risk of COCs

Biological mechanisms of VTE risk of COCs

All COCs are associated with an increased risk of thrombosis relative to non-use of COCs.[42,43] There are several hypothesized biological mechanisms by which COCs may induce thrombosis. Although these are generally viewed as competing mechanisms, some researchers argue that they may be complimentary. The most widely supported mechanism is that the use of COCs results in a number of hemostatic changes that activate or enhance the body's coagulation or clotting cascade (Figure 1.7, Figure 1.8). Specifically, COCs are associated with an increase in serum levels of pro-coagulant factors, a decrease in anti-coagulant proteins, an increase in markers of thrombin formation, and an increase in fibrinolytic factors.[43] The increase in coagulation factor VII results in the activation of the coagulation cascade and thrombin formation. During the same time, antithrombin is decreased, inhibiting anticoagulation, and further increasing thrombin formation.

Figure 1.7 Clotting cascade leading to thrombin formation

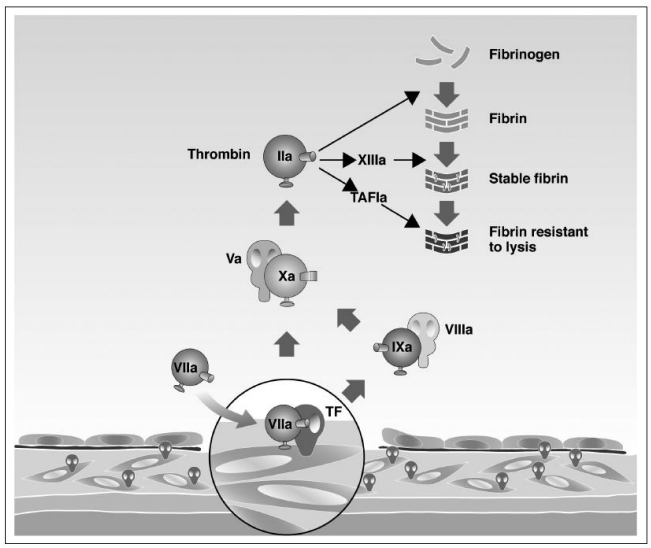


Figure 1 - Role of tissue factor (TF) and coagulation factor VII in the activation of the coagulation cascade leading to thrombin formation.
TAFI = thrombin activatable fibrinolysis inhibitor; "a" = "activated".

Reproduced from: Previtali E, Bucciarelli P, Passamonti SM, Martinelli I. Risk factors for venous and arterial thrombosis. Blood Transfus. 2011 Apr;9(2):120-38.

Figure 1.8 Clotting cascade leading to thrombin formation continued

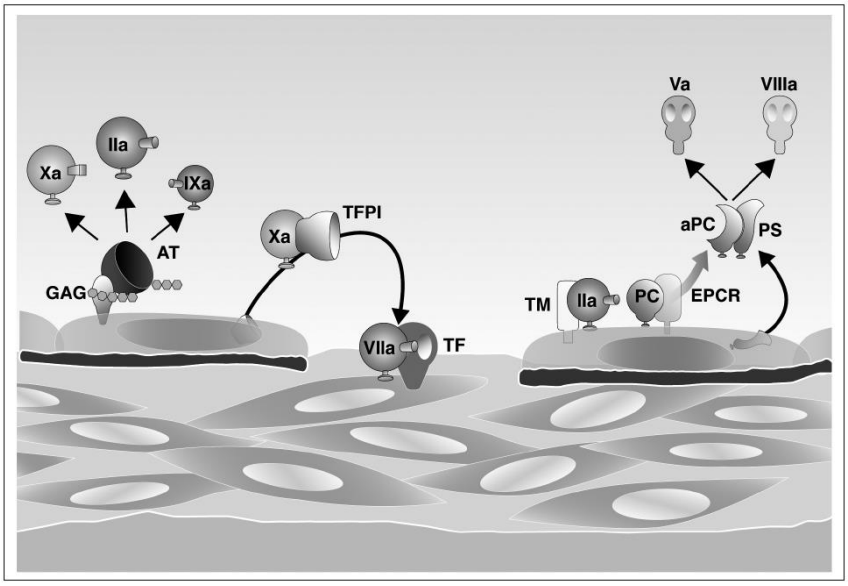


Figure 2 - Anticoagulant mechanisms of blood coagulation. Antithrombin (AT) inhibits mainly activated factors II (IIa) and X (Xa) through its binding to glycosaminoglycans (GAG); protein C (PC), with its co-factor protein S (PS), is activated by thrombomodulin (TM) and inhibits activated factors V (Va) and VIII (VIIIa) through its binding to endothelial protein C receptor (EPCR).
TFPI = tissue factor pathway inhibitor; "a" = "activated".

Reproduced from: Previtali E, Bucciarelli P, Passamonti SM, Martinelli I. Risk factors for venous and arterial thrombosis. Blood Transfus.2011Apr;9(2):120-38.

A second mechanism by which COCs increase the thrombotic risk is through activated protein C (APC). APC then decreases free protein TFPI and free protein S during COC; the plausibility of this mechanism relies on the capability of these proteins to increase risk of VTE.[44]

A third suggested mechanism involves the sex hormone binding globulin (SHBG), which binds testosterone and 17-β-estradiol. The plasma levels of SHBG are directly increased by estrogen and decreased by progestogen.[44] A Sweden study found a linear dose-response curve between the plasma levels of SHBG and risk of VTE during COC use.[45] According to Bradford-Hill's criteria, a dose-response relationship is indicative of causal inference[46]. However, this

proposed mechanism is consistent with the "total estrogenicity" hypothesis that differential effects of COCs are derived from distinct levels of estrogen and progestin which cause and reverse prothrombotic effects, respectively.[44]

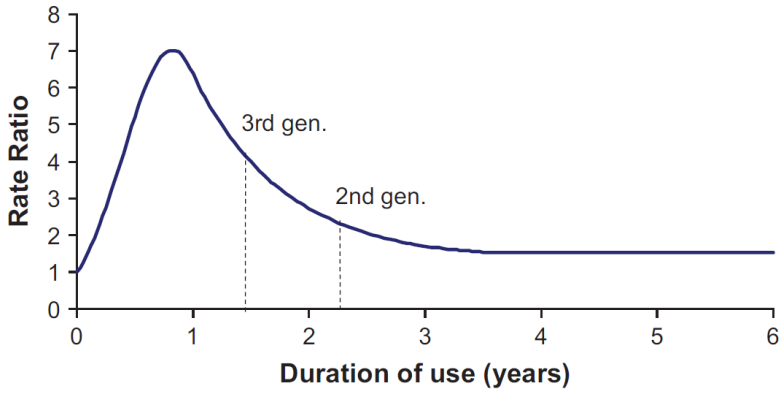
A fourth proposed mechanism is that carriers of F5 rs6025 polymorphism who sue COCs experience multiplicative effects of VTE risk relative to those exposed solely to COCs or the polymorphism alone.[10,47] Finally, it has been suggested that the thrombotic risk of COCs is unrelated to their progestin component but rather caused by the estrogen.[48] Although studies examining this theory are ongoing, some of the available evidence contradicts this theory. For instance, Bird et al. had an unexpected finding that drospirenone-containing COCs with 20 μg of EE had a higher risk of VTE compared with those containing 30 μg of EE (risk ratio: 1.55; 95% CI: 0.99–2.41).[49]

History of VTE risk of COCs

With their known thrombotic risks and high prevalence of use in women of child-bearing age, the VTE risk of COCs has been extensively investigated over the past two decades.[6,50-55] This field of research was especially active in the mid-1990s, when studies suggested that third generation COCs were associated with a higher risk of VTE relative to second generation COCs. These findings resulted in the Committee on Safety of Medicines (CSM) of the UK to issue a warning.[56] As a result of this warning, women began to discontinue use of third generation COCs, resulting in many unwanted pregnancies and abortions.[56] Subsequent analyses showed that the apparent increased risk was due to bias; the risk of VTE associated with COC use is greatest in the first year of use and gradually declines thereafter until a plateau is reached[57] (Figure 1.9). Given the differential timing of second and third generation COCs' entry into the market, women taking third generation COCs typically had a shorter duration of use than those

taking second generations COCs, resulting in a spurious increased risk with third generation COCs.

Fig 1.9 Effect of duration of exposure on studies of third generation COCs



Reproduced from: Suissa S, The Transnational study of oral contraceptive cardiovascular safety: history and science. J Clin Epidemiol. 2009 Jun;62(6):588-93. Epub 2009 Apr 5.

When analyses controlled for previous use of COCs, the apparent increased risk of VTE disappeared. Furthermore, many of these studies had large amounts of residual confounding due to baseline risk factors associated with VTE.[47] In 1999, CSM issued a revised statement recommending COCs be prescribed after considering all absolute (i.e. family history of VTE with confirmation of abnormal clotting factor, body mass index [BMI]>39, etc.) and relative (e.g., family history of VTE with normal clotting factors, BMI 30 -39) contraindications.[1]

Drospirenone-containing COCs and the risk of VTE

The thrombotic risk of fourth generation drospirenone-containing COCs is controversial, with several observational studies examining this issue[58] (discussed in detail in Chapter 2). In

addition, this potential adverse effect has been the subject of safety reviews conducted by the US FDA, the European Medicines Agency (EMA), and Health Canada (REFs) [59]. Despite a reported hazard ratio (HR) of 1.57 (95% CI 1.13-2.18) among new users and a HR of 1.45 (95% CI 1.15 – 1.83) among all users, the FDA chose to keep these agents on the market due to an overall favorable risk benefit ratio. Moreover, the EMA reported the highest incidence rates (IR) of VTE among fourth generation COCs. The reported IR of thrombosis were: women not taking a COC and are not pregnant: 2/10,000 women-years; users of levonorgestrel, norethisterone, or norgestimate: 5-7/10,000 women-years; user of etonogestrel or norelgestromin: 6-12/10,000 women-years; and users of drospirenone, gestodene, or desogestrel: 9-12/10,000 women-years.[4] Additionally, recent studies have shown that the risk of VTE may vary with the duration of drospirenone use[60], whereas some studies suggest that the prothombotic effects of COCs are correlated with estrogen dose rather than progestin[10]. Previously, a possible biological plausibility of the action of drospirenone-containing COCs in the risk of VTE has been suggested.[61] Aldosterone may be involved with hemostasis, which could lead to a decrease in coagulability. Therefore, the antimineralocorticoid properties of drospirenone could lead to hypercoagulability.

Current recommendation regarding drospirenone-containing COC prescription and VTE risk

The American College of Obstetricians and Gynecologists' Committee on Gynecologic Practice released an opinion piece in 2012 making the following recommendations[61]:

1) Decisions regarding COC choice should be left to clinicians and their patients, taking into account the following factors:

a. Possibly small increased risk of VTE in new users of drospirenone-containing OCs compared with users of other COCs. (10.22/10,000 woman-years compared with 3–9/10,000 woman-years);
b. Patient preference;
c. Available alternatives;

2) Women should have a wide range of contraceptive options.
3) If a patient is using a drospirenone-containing COC and is tolerating the regimen, then there is no need to discontinue that COC.
4) When prescribing, clinicians should consider a woman's risk factors for VTE and refer to the U.S. Medical Eligibility Criteria for Contraceptive Use.
5) Patient education materials, including product labeling, should place information regarding risks of VTE in context by also providing information about VTE risks, both overall and during pregnancy and the postpartum period.

1.4 Original thesis work

Thesis Objectives

This thesis contains two primary objectives:

1. To synthesize the available evidence on the effects of drospirenone-containing COCs on the risk of VTE, with a focus on methodological strengths and limitations of this literature.
2. To describe and illustrate the methodological challenge of studying the risk of VTE among first-time users of drospirenone-containing COCs in a healthcare database.

Thesis overview

Chapter 2, which includes the first manuscript of my thesis, is a systematic review of the existing literature of the association between drospirenone-containing COCs and the risk of VTE, with a particular focus on the methodological quality of this literature. Chapter 3 provides a transition based on the systematic review and provide clear motivation and rationale for the second manuscript. Chapter 4, which includes the second manuscript, describe and illustrates the methodological challenges of studying the risk of VTE among first-time users, contrasting the results obtained using this approach to those obtained using an explicit cohort of restarters. Chapter 5 provides a discussion of the main findings and implications of this research. Finally, Chapter 6 provides overall conclusions based on the research and provide future directions.

2.2 Systematic review manuscript

Drospirenone-containing Oral Contraceptive Pills and the Risk of Venous Thromboembolism: A Systematic Review of Observational Studies

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ABSTRACT

Introduction: The effects of fourth generation drospirenone-containing combined oral contraceptives (COCs) on the risk of venous thromboembolism (VTE) are controversial.

Objectives: To synthesize the available evidence on the VTE risk of these COCs, with a focus on the methodological strengths and limitations of this literature.

Methods: We searched CINAHL, the Cochrane Library, EMBASE, HealthStar, Medline, and the Science Citation Index for all cohort and case-control studies assessing the VTE risk of drospirenone-containing COCs. We assessed overall study quality using the ACROBAT-NRSI and assessed the presence of four common sources of bias: prevalent user bias, inappropriate choice of comparator, VTE misclassification, and confounding.

Results: Our systematic review included 17 studies. The relative risks of VTE associated with drospirenone- versus second generation levonorgestrel-containing COCs ranged from 1.0 to 3.3. Based on the ACROBAT-NRSI, 1 study had low risk of bias, 9 had a moderate risk, 3 had a serious risk, and 4 had a critical risk. Nine studies included prevalent users, 4 included inappropriate comparators, 4 had VTE misclassification, and 5 failed to account for 2 or more important confounders. The 3 highest quality studies had relative risks ranging from 1.0 to 1.57.

Conclusions: Due to the methodological limitations of the individual studies, the VTE risk of drospirenone-containing COCs remains unknown. The highest quality studies suggest no or slightly increased harmful effects, but their confidence limits do not rule out an almost doubling of the risk. Large, methodologically rigorous studies are needed to provide an accurate safety profile of these COCs.

INTRODUCTION

Oral contraceptives (OCs) are commonly prescribed to prevent unwanted pregnancies.[1] Estimates suggest that approximately 17.1% of women aged 15-44 in the US are currently using OCs.[2] Combined oral contraceptives (COCs) were first introduced in the 1960's and include both an estrogen and a progestin component. An increased risk of venous thromboembolism (VTE) has been associated with their use[3,4], but whether this risk is higher for more recent generations of COCs is controversial. This controversy stems, in part, from several observational studies published in the 1990s that suggested third generation COCs were associated with an increased risk of VTE compared with second generation COCs, resulting in the "pill scare".[5-8] However, it was subsequently shown that this apparent increased risk was largely due to important limitations in the design and analysis of several of these studies.[9]

The fourth generation of COCs contains the progestin drospirenone and was introduced to the market in 2000. Several observational studies have since assessed the VTE risk of drospirenone-containing COCs, with these studies producing heterogeneous results, as shown in previous systematic reviews and meta-analyses of this issue[10-13]. However, none of these previous reviews have adequately assessed the methodological strengths and limitations of the observational studies when synthesizing these data. We therefore conducted a systematic review of observational studies examining the VTE risk of drospirenone-containing COCs, with a particular focus on methodological strengths and limitations of the individual studies assessing this association.

METHODS

Our systematic review was conducted following a pre-specified protocol and is reported following the guidelines described in the PRISMA statement[14].

Search strategy

We systematically searched CINAHL, Cochrane Library Online, EMBASE, Healthstar, Medline, and Science Citation Index from inception to November 2015 to identify all studies examining the association between drospirenone-containing COCs and VTE, including deep vein thrombosis (DVT) and pulmonary embolism (PE). We also hand-searched the grey literature and the references of relevant articles, previous reviews, and meta-analyses on this topic. Our search strategy is reported in detail in Supplemental Appendix 1. Briefly, we used Medical Subject Heading terms for Medline, EMTREE terms for Embase, and keywords for all databases for drospirenone and all generic and trade names for drospirenone-containing COCs. The search was conducted with no restrictions on study design or language of publication.

Inclusion and exclusion criteria

Studies were included if they: 1) were comparative studies (cohort studies, case-control studies, and their derivatives) of women taking drospirenone-containing COCs; 2) reported at least one of the venous thrombotic outcomes (VTE, DVT, or PE); 3) had at least one comparator group; 4) reported at least one effect measure of the association of interest (odds ratio [OR], hazards ratio [HR], incidence rate ratio [IRR], risk ratio [RR]) or sufficient data for its calculation; and 5) were published in English or French. Cross-sectional studies, reviews, editorials, commentaries, conferences abstracts, and randomized controlled trials were excluded.

Title and abstract screening was performed independently by two reviewers (NL and FKK), with any article deemed potentially relevant by either reviewer carried forward for full-

text review. The full-texts of potentially relevant articles were reviewed by both reviewers, with any disagreements resolved by consensus or by a third reviewer (KBF).

Data Extraction

Data were independently extracted by two reviewers (NL and FKK), with disagreements resolved by consensus or by a third reviewer (KBF). The following information was extracted: study characteristics (study design, sample size for both drospirenone-containing COCs and comparator, data source, study period, patient population), VTE incidence rates (IR) with 95% confidence intervals (CI) overall and by exposure group, effect measures (OR, HR, IRR, RR) with 95% CIs, and approaches to control confounding (matching variables, exclusion criteria, confounders included in statistical models).

The results of analyses comparing drospirenone-containing COCs to the following comparator groups were extracted: levonorgestrel-containing COCs (main comparator of interest), other COCs, and non-use of OCs. We did not report comparisons made to third generation COCs as they are infrequently used due to the pill scare.

Quality Assessment

Overall study quality was assessed using the Cochrane Risk of Bias Tool for Non-randomized Studies of Interventions (ACROBAT-NRSI).[15] Seven domains were assessed: bias due to confounding, bias in selection of participants into study, bias in measurement of interventions, bias due to departure from intended interventions, bias due to missing data, bias in measurement of outcomes, and bias in selection of the reported results. Based on the assessment of each domain, an overall risk of bias was assigned as low, moderate, serious, or critical. Although the ACROBAT-NRSI is excellent for observational studies in general, it does not fully capture the methodological issues present in pharmacoepidemiologic studies. Consequently, we

conducted an in-depth assessment of 4 sources of biases that are particularly relevant to the study of VTE risk of COCs: prevalent user bias, inappropriate choice of comparator, VTE misclassification, and confounding. Using the ACROBAT-NRSI and pharmacoepidemiologic assessments, we then considered studies to be of high quality if the ACROBAT-NRSI yielded a low or moderate risk and none of the 4 pharmacoepidemiologic biases were present.

Prevalent user bias

Prevalent user bias occurs when history of use of the exposure (i.e., drospirenone-containing COCs) and/or its comparator) is not adequately considered when identifying the study cohort or analyzing the data. A COC user may be classified as any of following four user types: a first-ever user (a woman who has never used drospirenone-containing COCs or their comparator before), new user (either a first-ever user or a woman who is restarting use after a given period of non-use [often 6 months or 1 year]), a switcher (a woman who is switching from one COC to another at the time of cohort entry), or a prevalent user (a woman who was already using for some time the COC that resulted in cohort entry). The risk of thrombosis is greatest among first-ever users and during the first year of COC use and subsequently decreases.[9,16] Differences in the distribution of user types (and corresponding VTE risk) across exposure groups can therefore result in important bias, particularly when comparing different generations of COCs. Differences in history of COC use led to the spurious associations between third generation COCs and VTE[9]; given the differential timing of COC's entry into the market, participants taking third generation COCs typically had a shorter duration of use than those taking second generation COCs and were more likely to be first-ever users. In contrast, second generation users were more likely to include women who were restarting COCs and prevalent users and thus had necessarily survived the "high-risk" first year period; women in this group

who experienced a VTE during the high-risk period did so before cohort entry and were thus excluded due to their history of VTE. This resulted in a depletion of susceptibles among second-generation COC users and consequently, a spurious increased risk among third generation users (Figure 1). When analyses controlled for the differential duration of use, the apparent increased risk disappeared.[9] In addition, restarting after a period of non-use and, to a lesser degree, switching COCs also increase the risk of VTE, though these increased risks do not reach that observed among first-time users. [17]

Inappropriate choice of comparator

All COCs are associated with an increased risk of thrombosis relative to non-use of COCs due to hemostatic changes associated with their use.[3,4] The use of an inactive comparator is therefore expected to result in an observed increased risk. Although a comparison of the VTE risk of drospirenone-containing COCs to that of non-use of OCs is a valid comparison, it does not address the clinically relevant question that is the object of controversy, namely "Is the VTE risk of drospirenone-containing COCs greater than that of other commonly-prescribed COCs?"

VTE Misclassification

A common source of bias in studies examining the VTE risk of COCs is misclassification of VTE status. In our assessment, we considered the authors' VTE definition as well as any included validation processes and assigned a risk of VTE misclassification of low, moderate, or high. Low risk was given to studies where the event definition was based on objective, radiologic measures, to studies using a database for which VTE had been previously validated, and to studies in which the authors validated events. For example, studies that restricted to 'confirmed' events in which the VTE diagnosis was accompanied by a prescription for an anticoagulant were considered low risk. Moderate risk was assigned to studies with no requirement for anticoagulant

therapy prescriptions to supplement diagnoses or to those that did not consider outpatient events. Restriction to hospitalization codes results in the exclusion of VTEs treated in an outpatient setting, which may result in bias if differential between exposure groups. Serious risk was assigned to studies with both no requirement for anticoagulant therapy prescriptions to supplement diagnoses and no discussion of validity of data. Critical risk was assigned to studies using self-administered questionnaire and to those in which events were restricted to non-hospitalized VTEs (and thus excluded all inpatient events).

Confounding

Confounding can occur due to 3 reasons: 1) confounding due to known confounders that were not adequately considered in a study's design or analysis, typically because they were poorly measured or not available; 2) confounding due to unknown confounders; or 3) time-varying confounding due to changes in confounder levels during follow-up. The first scenario is the most relevant to this review. Known confounders of the COC-VTE association include age, obesity or body mass index, previous history of thrombosis, and family history of thrombosis. Failure to account for these variables, either through study design (i.e., restriction, matching) or analytical approaches (i.e., stratification, regression analyses) may result in bias. Moreover, all of the included studies are observational in nature and thus susceptible to residual confounding due to unknown variables.

RESULTS

Literature Search

Our search identified 4,625 potentially relevant publications (Figure 2). After the removal of duplicates and the addition of 2 publications identified in the grey literature, 2,524 publications underwent title and abstract review. The full-texts of 20 studies were assessed, of which 17 studies (11 cohort[18-28] and 6 case-control[29-34]) were included in our systematic review.

Study and Patient Characteristics

The 17 studies examining the VTE risk of drospirenone-containing COCs included 2,246,361 women (cohort studies: 2,239,339 women; case-control studies: 2,230 cases and 4,792 controls) (Table 1). Although drospirenone-containing COCs only became available in 2000, the study periods ranged from 1995 to 2013; studies whose periods included pre-2000 examined the thrombotic risk of COCs in general and included drospirenone-containing COCs as a secondary exposure category. The studies included data from the USA, UK, Israel, Germany, and Denmark. Study populations were heterogeneous, with some studies including all women and others having several exclusion criteria, such as previous thrombotic events, serious illness, cancer, cardiovascular disease, risk factors for VTE, and gynaecological surgeries.

Drospirenone-containing COCs and the risk of VTE

Fifteen studies compared the risk of VTE between users of drospirenone- and levonorgestrel-containing COCs[18-20,22,23,25,26,28,30-36] (Table 2; Figure 3). One study used an approach analogous to an intention-to-treat, and 14 used a time-dependent exposure definition. The IR ranged from 2.3 to 13.7 VTEs per 10,000 woman-years among drospirenone-containing COC users and from 0.7 to 9.8 VTEs per 10,000 woman-years among levonorgestrel-containing

COC users. The RR for VTE associated with drospirenone- versus levonorgestrel-containing COCs ranged from 1.0 to 2.4 with the exception of one study, which reported an OR of 3.3[32].

Six studies compared the risk of VTE between users of drospirenone-containing COCs and users of other COCs[18,19,25,28,37,38] (Table 2; Figure S1). The IR ranged from 4.4 to 13.0 VTEs per 10,000 woman-years among drospirenone-containing COC users and from 0.7 to 14.0 VTEs per 10,000 woman-years among other COC users. The RRs ranged from 0.8 to 1.3 with the exception of one study, which reported a RR of 6.4[27].

Five studies compared the risk of VTE between users of drospirenone-containing COCs and non-users of OCs[22,26,30,31,33] (Table 2; Figure S2). The IR ranged from 7.8 to 13.7 VTEs per 10,000 woman-years among drospirenone-containing COC users and from 3.0 to 8.2 VTEs per 10,000 woman-years among non-users. The relative risks ranged from 1.8 to 8.4.

It should be noted that several studies[19,23,26,28,31,35] included additional analyses restricting to "confirmed" versus "not confirmed" VTE cases, 20 µg or 30-40 µg estrogen pills, and 21-day or 24-day pills. These analyses were considered in our bias assessments but the results of these additional analyses were not considered.

Overall Quality Assessment

Based on the ACROBAT-NRSI, 1 study was assigned a low risk of bias[34], 9 studies were assigned a moderate risk, 3 studies were assigned a serious risk, and 4 studies were assigned a critical risk (Table 3). The 2 domains that led to the greatest increase in the risk of bias were "risk of bias due to confounding" and "risk of bias in measurement of outcomes" (Table S2). For bias due to confounding, 1 study had a low risk[34], 6 studies a moderate risk[19-21,23,25,33], 6 studies a serious risk[18,24,26,28,31,32], and 4 studies a critical risk[22,27,29,30]. For bias in outcome measurement, 2

studies had a low risk[31,37], 9 studies a moderate risk[18,19,22,25,28,30,33-35], 5 studies a serious risk[20,23,32,36], and 1 study a critical risk[38].

In-depth assessment of COC-VTE specific biases

The results of the in-depth assessment of four biases specific to the study of the COC-VTE association are summarized in Table 3.

Prevalent user bias

There were 8 studies that restricted to new users and thus were less likely to have prevalent user bias[18,21,23,25,28,32,35,36]. However, given the left truncation of many databases and the corresponding challenges in identifying first-time use, the presence of prevalent user bias cannot be completely ruled out in many of these studies. In addition, 9 studies included all user types (first time users, new users, switchers, and prevalent users)[19,20,22,26,27,30,31,33,34] and were thus likely affected by prevalent user bias. While many studies acknowledged the need to adjust for history of COC use, none of these studies accounted for previous COC use, an important limitation in studies not restricted to first-time users.

Inappropriate choice of comparators

Five[22,26,30,31,33] of 17 studies included comparisons versus non-use of OCs, with 4 considering this as their primary analysis[22,26,30,31]. Given the known VTE risk associated with use of any COC, the use of such inactive comparators is not clinically relevant.

VTE Misclassification

VTE can be difficult to define, particularly when using administrative data. Consequently, without the use of a validated outcome definition, misclassification of VTE status can occur. Six studies had a low risk of bias for VTE misclassification[23,28,30,31,34,36], 7 had a

moderate risk[18,19,25,26,32,33,37], and 4 had a serious or critical risk[20,22,24,27] (Table S3). The 4 studies with the highest risk provided no information regarding their VTE definition and its validity.

Confounding

All of the included studies were observational and thus were likely affected by residual confounding due to unknown confounders. However, 5 studies[22,23,26,37,38] also failed to account for or consider 2 or more known confounders (Table S4). The omission of these known confounders typically occurred because they were not recorded in the study data source. One included study[21] used a clinically-derived propensity score to reduce residual confounding. Finally, none of the included studies attempted to adjust for time-varying confounding (i.e., changes in confounder levels during follow-up) through the use of techniques such as marginal structural models.

DISCUSSION

Our study was design to synthesize the available literature regarding the VTE risk of drospirenone-containing COCs, with a focus on the methodological strengths and limitations of this literature. We identified 17 studies that met our inclusion criteria. We found that all studies comparing drospirenone users to levonorgestrel users suggested some degree of increased VTE risk with drospirenone-containing COCs, with RRs ranging from 1.0 to 3.3. However, the literature examining the VTE effects of drospirenone-containing COCs has several limitations. Using the ACROBAT-NRSI to assess overall study quality, we found that 1 study had a low risk of bias[34], 9 had a moderate risk, 3 had a serious risk, and 4 had a critical risk. Furthermore, our assessment of four specific sources of bias revealed that these biases were highly prevalent across studies. Nine studies had prevalent user bias, 4 included inappropriate comparators, 4 had VTE misclassification, and 5 failed to account for 2 or more important confounders. Studies with the highest quality[18,19,25,28] suggest that drospirenone-containing COCs are either not associated with or slightly increase the risk of VTE relative to levonorgestrel-containing COCs. Some studies were considered to be at low or moderate risk of bias according to the ACROBAT-NRSI despite the presence of important pharmacoepidemiological biases,[19,39] underscoring the limited applicability of the ACROBAT-NRSI to pharmacoepidemiology.

The VTE risk of drospirenone-containing COCs has been the focus of several regulatory reviews. Following the completion of a 2011 US Food and Drug Association (FDA) funded study using the Kaiser Permanente and Medicaid databases, the FDA determined that drospirenone-containing COCs may increase the risk of VTE relative to other COCs[23]. The FDA subsequently revised the product labeling to indicate that some epidemiologic studies report increased risks as high as three-fold while others found no additional risk.[40] In addition, a 2013

European Medicines Agency review concluded that the benefits of all COCs (including drospirenone-containing ones), including preventing unwanted pregnancy, continue to outweigh the minimal risk of VTE.[41] In contrast, Health Canada concluded that drospirenone-containing COCs may be associated with a relative risk of VTE of 1.5 to 3 compared with other COCs.[42]

The identified limitations of the existing literature have important implications for knowledge users, including regulatory agencies, health care professionals, and patients. The consequences of methodological shortcomings in this area were well illustrated in the 'pill scare' of the 1990s[9], where as a result of methodologically flawed studies, women began to discontinue use of their third generation COCs, resulting in many unwanted pregnancies and abortions.[5] Given the number of women exposed to drospirenone-containing COCs and the clinical consequences of VTE, there remains a need for additional, methodologically-rigorous studies to determine the VTE risk of drospirenone-containing COCs relative to other COCs.

A more methodologically robust design would be a cohort study restricted to first-time users in which women are followed until VTE, or censoring due to discontinuation of use, switching to a different hormonal contraceptive, death, departure from the database, or end of the study period. By restricting to first-time users, the study would ensure that women are compared at a similar point on the COC-VTE risk curve and avoid the potential effects of prevalent user bias. In addition, this approach would avoid dilution of effects typically seen in intention-to-treat analyses. Given the known early risk of VTE with first-time use of COCs, studies with long follow-up may dilute the risk if hazards are, as expected, non-proportional. Moreover, it has been shown that COC users who interrupt or switch COC use have a different VTE risk profile than continuous COC users[9,16], making it difficult to interpret time-dependent or nested-case control analyses of this relationship. The reference category for such an analysis would be use of

levonorgestrel-containing COCs, a clinically relevant comparator and the most commonly used COC in the UK.[30,43] To avoid misclassification of VTE, outcome should be defined by an in-patient diagnosis or an outpatient diagnosis of VTE accompanied by a prescription for anticoagulant therapy, INR testing (indicative of monitoring anticoagulation), or death shortly after the event.[44,45] Finally, to minimize residual confounding, the use of approaches such as high-dimensional propensity scores should be considered.

Our study has many strengths. First, the study followed a pre-specified protocol. Second, our comprehensive systematic search included six databases. Third, our study included the use of the Cochrane Collaboration's ACROBAT-NRSI tool to assess overall study quality. Given the limited applicability of this tool to pharmacoepidemiology, we also considered 4 potential sources of bias related to the study of COCs and VTE. Finally, to our knowledge, this is the first systematic review to focus on the methodological strengths and limitations of the studies examining this relationship.

Our study also has some limitations. First, given the presence of several potential limitations in the included studies and the modest quality of this literature, there were few high quality studies on which to base substantive conclusions. Second, as is true for all systematic reviews, there is the potential for publication bias. Third, due to the presence of heterogeneity in study design, study definitions, and study populations, as well as the presence of several limitations in this literature, we were unable to pool results across studies. However, we believe that the thorough and systematic methodological assessment of this literature is needed to better understand the safety of drospirenone-containing COCs.

CONCLUSIONS

Although several observational studies have examined the association between drospirenone-containing COCs and the risk of VTE, the methodological limitations of this literature renders it difficult to interpret. Indeed, many of these studies had conclusion-altering biases, such as prevalent user bias, which was present in 9 of the 17 included studies. The highest quality studies of this association suggest no or slightly increased harmful effects, but their confidence limits do not rule out an almost doubling of the risk. Large, methodologically rigorous studies are needed to provide an accurate safety profile of these COCs.

Disclosures

Dr. Suissa has been a paid consultant for Bayer and Organon. The other authors have no conflicts to disclose.

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Table 1. Study characteristics of comparative studies evaluating venous thrombotic effects of drospirenone-containing COCs.

Study	Study design	n	Data origin	Study period	Population	Effect Measure
Dinger 2007[18]	Prospective cohort	58, 674	EURAS study	2000 – 2005	Women using OCs; first-ever users & switchers	HR
Seeger 2007[21]	Retrospective cohort	67,287	U.S. Health insurer database	2001 – 2004	Women aged 10 – 59 years; first-ever users, new users & switchers	RR
Lidegaard 2009[22]	Retrospective cohort	NR*	National Registry of Patients in Denmark	1995 – 2005	Women aged 15 – 49 years; excluded cancer, cardiovascular disease & pregnancy and related outcomes	IRR
Vlieg 2009[30]	Nested case-control	3,284	MEGA study	1999 – 2004	Women aged 18 – 50 years; excluded if severe psychiatric problems, inability to speak dutch, not premonopausal, using an IUD or depot contraceptive & pregnancy and related outcomes	OR
Dinger 2010[34]	Nested case-control	3,400	German primary care sector	2002 – 2008	Women aged 15 – 49 years; excluded if inability to speak German; required consent	OR
FDA 2011[23]	Retrospective cohort	835,826	Kaiser Permanente (North & South Carolina) & the Medicaid Program (Washington & Tennessee)	2001 – 2007	Women aged 10 – 55 years; excluded if suffering from serious illness or previous AMI, stroke or VTE & pregnancy	HR
Gronich 2011[24]	Retrospective cohort	329,995	Clalit clinical database	2002 – 2008	Women aged 12 – 50 years; excluded previous AMI, stroke or VTE	IRR
Jick 2011[29]	Nested case-control	867	PharMetrics database	2002 – 2008	Women aged 15 – 44 years; excluded if they have risk factors for VTE, cancer, cardiovascular disease & previous VTE	OR
LASS 2011[25]	Prospective cohort	47,799	EURAS study + 5 year LASS extension	2000 – 2010	Women using OCs; first-ever users & switchers; required consent	HR
Lidegaard	Retrospective	1,293,120	Four Danish registries	2001 – 2009	Women aged 15 – 49 years; excluded if	IRR

2011[26]	cohort				history of thrombosis, serious illness, cancer, gynaecological surgery, & coagulation disorder	
Parkin 2011[32]	Nested case-control	276	UK General Practice Research Database	2002 – 2009	Women aged 15 – 44 years; excluded risk factors for VTE, serious illness, cancer, cardiovascular disease, previous AMI, stroke or VTE & record of pregnancy, surgery, major injury, or prolonged immobility	OR
Leppee 2012[27]	Retrospective cohort	98,058	HALMED	2008 – 2010	Women aged 15 – 49 years	RR
Sidney 2013[28]	Retrospective cohort study	573,680	Kaiser Permante (North & South Carolina) & the Medicaid Program (Washington & Tennessee)	2001 – 2007	Women aged 10 – 55 years; new users; excluded previous thrombosis, serious illness, exposed to ≥ 2 OCs & pregnancy	HR
Bergendal 2014[31]	Nested case-control study	1,850	Thrombo Embolism Hormone Study	2003 – 2009	Women aged 18 – 54 years; excluded if did not initiate anticoagulant, previous thrombosis, malignancies	OR
Dinger 2014[19]	Prospective cohort	85,109	INAS-OC study	2005 – 2013	Women initiating OCs	HR
Ziller 2014[20]	Retrospective cohort	68,168	IMS HEALTH database	2005 – 2010	Women aged 16 – 45 years; excluded if previous thrombosis or antithrombotic use.	OR
Vinogradova 2015[33]	Nested case-control study	52,596	QResearch & CPRD	2001 – 2013	Women aged 15 – 49 years; excluded if prescriptions for anticoagulant before index date, exposed to ≥ 2 OCs , gynecological surgery & pregnancy.	OR

Abbreviations: CI: Confidence interval; HR: Hazards ratio; IR: Incidence rate; IRR: Incidence rate ratio; OR: Odds ratio; RR: Rate ratio; RD: Rate difference.

* Study reports woman year with 2045 cases.

Table 2. Effect estimates of VTE in comparative studies evaluating venous thrombotic effects of drospirenone-containing COCs

Study	Drospirenone (n)	Comparator (n)	Drospirenone users IR [*]	Drospirenone users 95% CI	Comparator users IR [*]	Comparator users 95% CI	Effect measure	Point estimate	95% CI
Drospirenone-containing COCs versus levonorgestrel-containing COCs									
Dinger 2007[†]	16,534	15,428	9.1	5.9 – 13.3	8.0	5.2 – 11.7	HR	1.0	0.6 – 1.8
Lidegaard 2009[†]	NR	NR	7.83	NR	5.47	NR	IRR	1.64	1.27 – 2.10
Vlieg 2009	33	858	NR	NR	NR	NR	OR	1.7	0.7 – 3.9
Dinger 2010[‡]	109	257	NR	NR	NR	NR	OR	1.0	0.5 – 1.8
FDA 2011 [†,§]	142,166	198,839	10.22	NR	6.64	NR	HR	1.45	1.15 – 1.83
Gronich 2011[†,‖]	56,429	16,500[¶]	8.62	NR	6.93	NR	IRR	1.65	1.02 – 2.65
Jick 2011[#]	434	433	3.08	2.56 – 3.68	1.25	0.961 – 1.59	OR	2.4	1.7 – 3.4
LASS 2011[†]	16,534	15,428	10.7	8.1 – 13.9	9.2	6.9 – 12.0	HR	1.1	0.8 – 1.7
Lidegaard 2011[†,**,††]	NR	NR	9.3	NR	7.5	NR	IRR	2.12	1.68 – 2.66
Parkin 2011[‡‡,§§]	43	233	2.3	1.34 – 3.69	0.91	0.66 – 1.22	OR	3.3	1.4 – 7.6
Sidney 2013[†]	109,070	137,311	13.7	10.0 – 18.6	NR	NR	HR	1.57	1.13 – 2.18
Bergendal 2014[‖‖]	66	173	NR	NR	NR	NR	OR	2.0	0.9 – 4.3
Dinger 2014[†,¶¶]	15,542	10,254	7.2	NR	9.8	NR	HR	1.3	0.63 – 2.5
Ziller 2014[##]	15,572	13,222	4	1 -8	3	0 - 6	OR	1.57	0.46 – 5.38
Vinogradova 2015[***]	611	3,923	NR	NR	NR	NR	OR	1.75	1.43 – 2.12
Drospirenone-containing COCs versus other OC users									
Dinger 2007[†]	16,534	26,341	9.1	5.9 – 13.3	9.9	7.4 – 13.0	HR	0.8	0.5 – 1.3
Seeger 2007[†††]	22,429	44,858	13	8 – 20	14	10 - 19	RR	0.9	0.5 – 1.6
LASS 2011[†]	16,534	26,341	10.2	8.1 – 13.9	13.6	11.4 – 16.0	HR	0.8	0.6 – 1.1
Leppee 2012	38,778	59,280	4.38	NR	0.68	NR	RR	6.4	NR
Sidney 2013	109,070	383,151	13.7	10.0 – 18.6	8.2	7.0 – 9.6	HR	1.77	1.33 – 2.35
Dinger 2014[†,¶¶]	15,542	60,190	7.2	NR	9.6	NR	HR	1.3	0.77 – 2.0
Drospirenone-containing COCs versus non-users of OCs									
Lidegaard 2009[†]	NR	NR	7.83	NR	3.01	NR	IRR	4.00	3.26 – 4.91
Vlieg 2009[‡‡‡]	33	1,523	NR	NR	NR	NR	OR	6.3	2.9 – 13.7
Lidegaard 2011[†,§§§]	NR	NR	9.3	NR	3.7	NR	IRR	6.37	5.43 – 7.47

Bergendal 2014	66	1118	NR	NR	NR	NR	OR	8.4	4.2 – 17
Vinogradova 2015[***]	611	NR	NR	NR	NR	NR	OR	4.12	3.43 – 4.96

Abbreviations: CI: Confidence interval; HR: Hazards ratio; IR: Incidence rate; IRR: Incidence rate ratio; NR: Not reported; OR: Odds ratio; RR: Rate ratio.

* Incidence rate differences are expressed as events per 10,000 person-years.

[†] Analysis is based on an as-treated approach (time-dependent).

[‡] Analysis is based on 25 VTE cases exposed to drospirenone, 84 controls exposed to drospirenone, 680 VTE cases unexposed to drospirenone, 2720 controls unexposed to drospirenone.

[§] Estimate reported for all users. Study also includes estimates reported for new users (HR: 1.57; 95% CI: 1.13-2.18).

[‖] Estimate reported for all users. Study also reports first-time ever users (IRR 1.67; 95% CI: 0.98-2.86).

[¶] Comparator is second-generation COCs which includes combination of norgestrel and levonorgestrel.

[#] Analysis is based on 28 VTE cases exposed to drospirenone, 72 controls exposed to drospirenone, 121 VTE cases unexposed to drospirenone, 313 controls unexposed to drospirenone.

[**] Estimate reported for drospirenone 30 – 40µg EE and confirmed VTE events. Study also includes drospirenone vs. levonorgestrel with adjustment for length of use (RR: 2.09; 95% CI: 1.55-2.82), estimates for drospirenone 20µg EE (RR: 2.22; 95% CI: 1.27-3.89) and by certainty of diagnosis.

[††] IRR presented is for confirmed VTE cases; among non-confirmed VTEs, the IRR is 1.78 (95% CI: 1.21-2.60).

[‡‡] OR is based on 17 VTE cases exposed to drospirenone, 26 controls exposed to drospirenone, 61 VTE cases unexposed to drospirenone, 189 controls unexposed to drospirenone.

[§§] OR is presented for multiple imputation analysis; for complete case analysis the OR is 2.9 (95% CI: 1.1-7.4).

[‖‖] OR is based on 55 VTE cases exposed to drospirenone,11 controls exposed to drospirenone, 498 VTE cases unexposed to drospirenone, 620 controls unexposed to drospirenone.

[¶¶] Estimate is shown for drospirenone$_{24\text{-}d}$ regimen.

[##] Estimate is based on an intention to treat (ITT) approach.

[***] OR is based pooled analysis of OR estimates from CPRD and QResearch databases.

[†††] Analysis is based on as-matched data (similar to ITT). For the as-treated approach (time-dependent) the corresponding RR is 1.0 (95% CI: 0.5-1.9).

[‡‡‡] OR is based on 19 VTE cases exposed to drospirenone, 14 controls exposed to drospirenone, 421 VTE cases unexposed to OCs, 1102 controls unexposed to OCs.

[§§§] RR is presented for drospirenone 30 – 40 ug EE and confirmed VTE events; for 20 ug EE, the RR is 6.95 (95% CI: 4.21-11.5).

Table 3. In-depth assessment of biases specific to the study of VTE risk of COCs.

Study	ACROBAT-NRSI bias assessment*	Pharmacoepidemiologic sources of bias				High Overall Quality
		Prevalent user bias	Inappropriate choice of comparators	VTE misclassification	Confounding	
Dinger 2007	Moderate					X
Seeger 2007	Moderate				X	
Lidegaard 2009	Critical	X	X	X	X	
Vlieg 2009	Critical	X	X			
Dinger 2010	Low	X				
FDA 2011	Moderate				X	
Gronich 2011	Moderate			X		
Jick 2011	Critical					
LASS 2011	Moderate					X
Lidegaard 2011	Serious	X	X		X	
Parkin 2011	Serious					
Leppee 2012	Critical	X		X	X	
Sidney 2013	Moderate					X
Bergendal 2014	Moderate	X	X			
Dinger 2014	Moderate	X				
Ziller 2014	Moderate	X		X		
Vinogradova 2015	Serious	X				

Abbreviations: X: Denotes bias was present

*Overall assessment derived from seven domains of ACROBAT-NRSI tool (bias due to confounding, bias in selection of participants into study, bias in measurement of interventions, bias due to departure from intended interventions, bias due to missing data, bias in measurement of outcomes, and bias in selection of the reported results). [15]

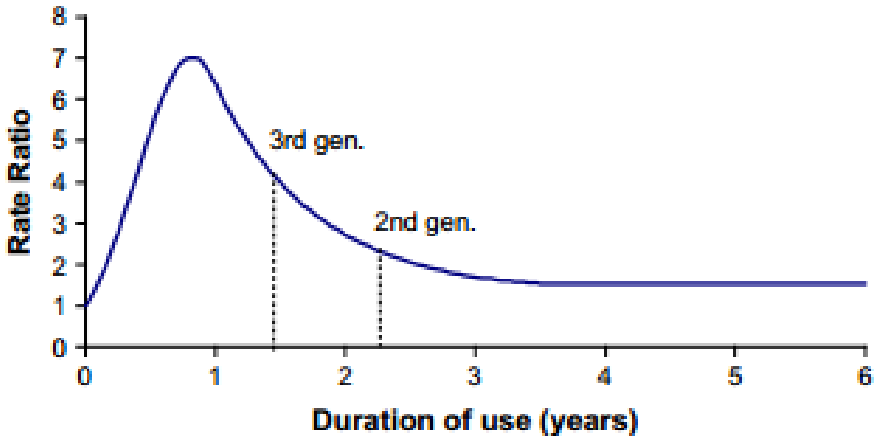
FIGURE LEGEND

Figure 1. Risk of venous thromboembolism as a function of duration of current use among first-time ever users of combined oral contraceptives. Reproduced from: Suissa S. The Transnational study of oral contraceptive cardiovascular safety: history and science. Journal of Clinical Epidemiology 2009;62:588-93

Figure 2. PRISMA flow diagram describing systematic literature search for observational studies examining the association between drospirenone-containing combined oral contraceptives and the risk of venous thromboembolism[46].

Figure 3. Forest plot describing the results of studies comparing drospirenone- and levonorgestrel-containing COCs, stratified by ACROBAT-NRSI-defined risk of bias.

Figure 1. Risk of venous thromboembolism as a function of duration of current use among first-time ever users of combined oral contraceptives.



Reproduced from: Suissa S. The Transnational study of oral contraceptive cardiovascular safety: history and science. Journal of Clinical Epidemiology 2009;62:588-93.[9]

Figure 2. PRISMA flow diagram describing systematic literature search for observational studies examining the association between drospirenone-containing combined oral contraceptives and the risk of venous thromboembolism[46].

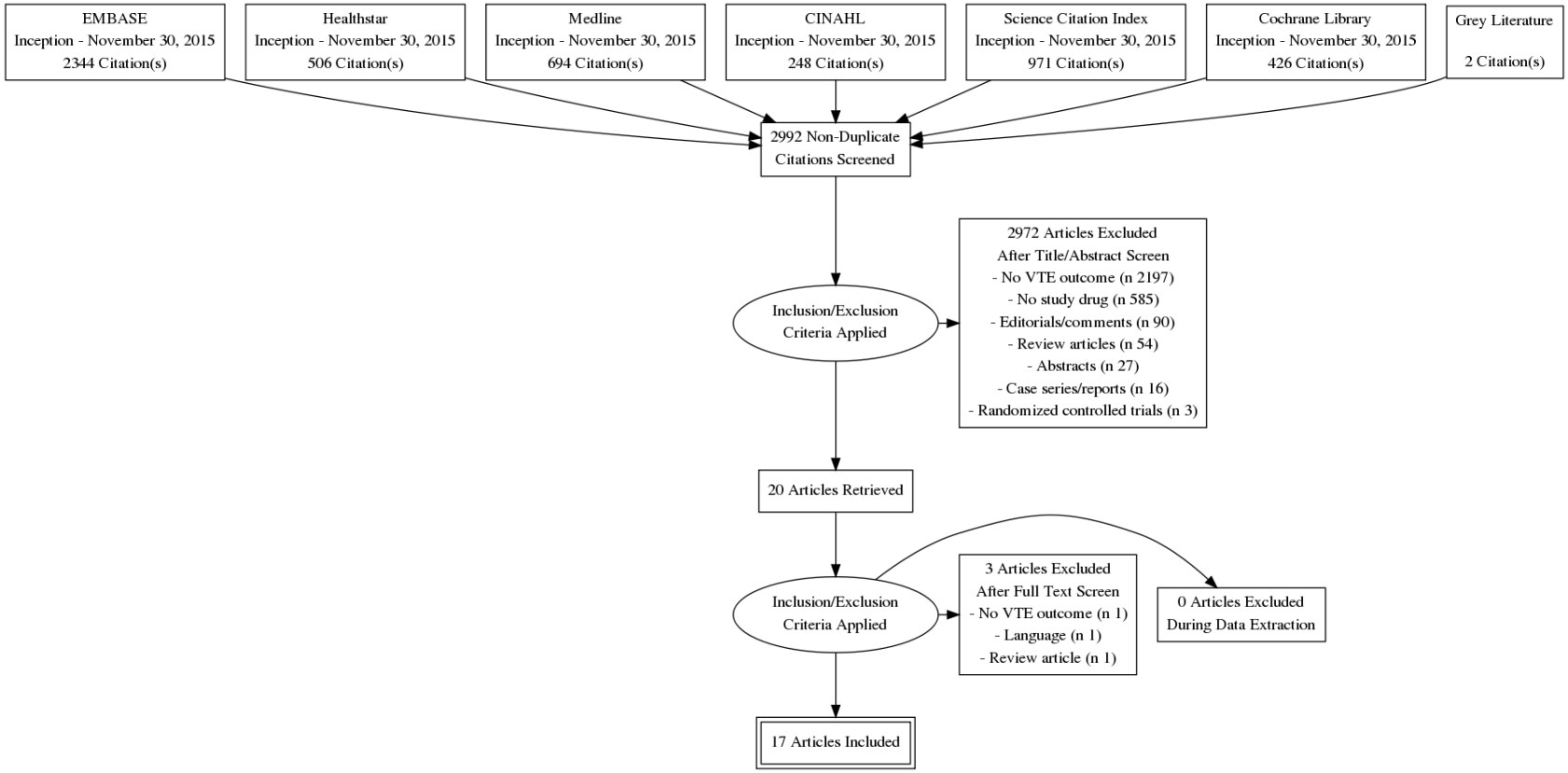
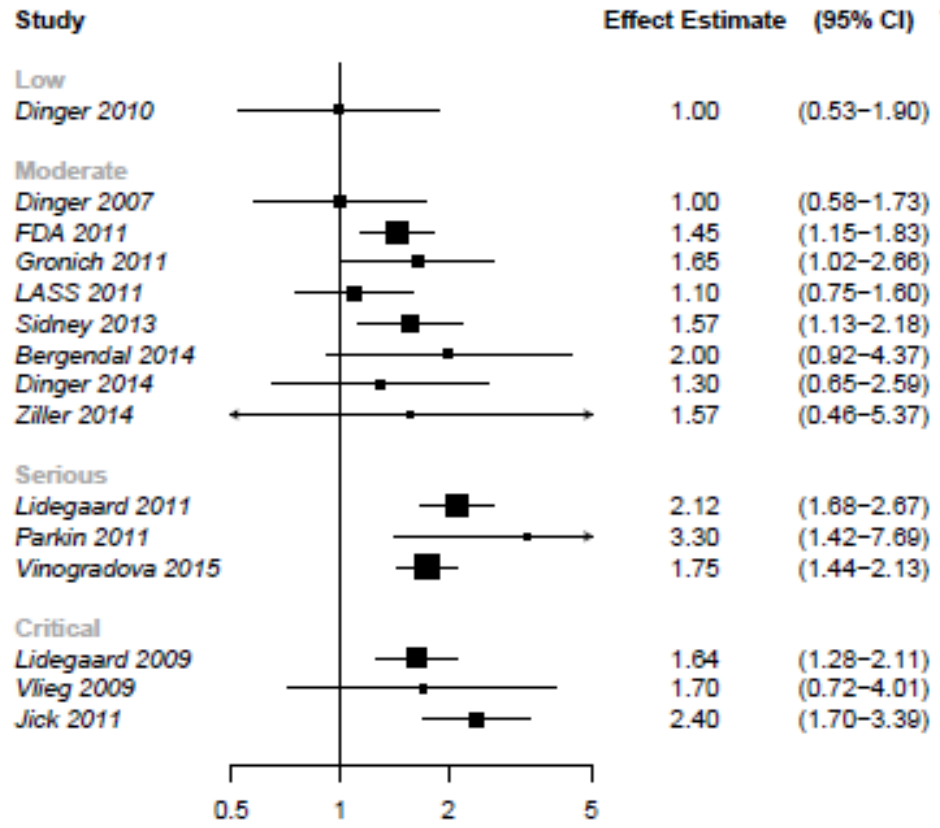


Figure 3. Forest plot describing the results of studies comparing drospirenone- and levonorgestrel-containing COCs, stratified by ACROBAT-NRSI-defined risk of bias.



Supplemental Material

Table S1. Search strategy for systematic review of thrombotic effects of drospirenone-containing oral contraceptives.

Database	Search Strategy
CINAHL	1. "Beyaz" 2. "Safyral" 3. "Yaz" 4. "Yasmin" 5. "drospirenone" 6. "gianvi or loryna or ocella or syeda or zarah or vestura" 7. 1 or 2 or 3 or 4 or 5 or 6
Cochrane Library Online	1. (yaz):ti,ab,kw 2. (yasmin):ti,ab,kw 3. (beyaz):ti,ab,kw 4. (safyral):ti,ab,kw 5. (gianvi or loryna or ocella or syeda or zarah or vestura):ti,ab,kw 6. (drospirenone):ti,ab,kw 7. (#1 OR #2 OR #3 OR #4 OR #5 OR #6) 8. limit #7 to Cochrane Reviews, Other Reviews, and Clinical Trials
EMBASE	1. Yaz.mp. 2. Yasmin.mp. 3. Beyaz.mp. 4. Safyral.mp. 5. (gianvi or loryna or ocella or syeda or zarah or vestura).mp. 6. exp drospirenone/ or dropirenone.mp. 7. 1 or 2 or 3 or 4 or 5 or 6
Healthstar	1. yasmin.mp. 2. yaz.mp. 3. beyaz.mp. 4. safyral.mp. 5. (gianvi or loryna or ocella or syeda or zarah or vestura).mp. 6. drospirenone.mp. 7. 1 or 2 or 3 or 4 or 5 or 6
Medline	1. beyaz.mp.

	2. Yasmin.mp. 3. yaz.mp. 4. safyral.mp. 5. (gianvi or loryna or ocella or syeda or zarah or vestura).mp. 6. drospirenone.mp. 7. 1 or 2 or 3 or 4 or 5 or 6
Science Citation Index	1. TS=yaz 2. TS=yasmin 3. TS=beyaz 4. TS=safyral 5. TS=(gianvi or loryna or ocella or syeda or zarah or vestura) 6. TS=drospirenone 7. 1 or 2 or 3 or 4 or 5 or 6

Table S2. Quality of included studies according to the ACROBAT-NRSI.

Study	Bias due to confounding	Bias in selection of participants into study	Bias in measurement of interventions	Bias due to departures from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall
Dinger 2007[18]	Serious	Moderate	Moderate	Moderate	Low	Moderate	Low	Moderate
Seeger 2007[21]	Moderate	Serious	Low	Unclear	Low	Low	Low	Moderate
Lidegaard 2009[22]	Critical	Serious	Low	Unclear	Low	Moderate	Low	Critical
Vlieg 2009[30]	Critical	Moderate	Critical	Low	No Information	Moderate	Low	Critical
Dinger 2010[34]	Low	Low	Moderate	Low	No Information	Moderate	Low	Low
FDA 2011[23]	Moderate	Moderate	Moderate	Unclear	Low	Serious	Low	Moderate
Gronich 2011[24]	Serious	Low	Moderate	Unclear	Low	Moderate	Low	Moderate
Jick 2011[29]	Critical	Moderate	Low	Low	Serious	Serious	Low	Critical
LASS 2011[25]	Moderate	Low	Serious	Unclear	Low	Moderate	Low	Moderate
Lidegaard 2011[26]	Serious	Serious	Moderate	Unclear	Low	Serious	Low	Serious
Parkin 2011[32]	Serious	Moderate	Moderate	Low	Low	Serious	Low	Serious
Leppee 2012[27]	Critical	No Information	Low	Unclear	Serious	Critical	Low	Critical
Sidney 2013[28]	Serious	Low	Low	Unclear	Low	Moderate	Low	Moderate
Bergendal 2014[31]	Serious	Moderate	Moderate	Low	Low	Low	Moderate	Moderate
Dinger 2014[19]	Moderate	Low	Serious	Unclear	Low	Moderate	Moderate	Moderate
Ziller 2014[20]	Moderate	Low	Low	Unclear	Low	Serious	Low	Moderate
Vinogradova 2015[33]	Moderate	Moderate	Low	Low	Moderate	Moderate	Moderate	Serious

Table S3. Assessment of validity of venous thromboembolism event definition used in included studies.

Study	VTE Definition	Validation of Outcome	Assessment
Dinger 2007	**Self-administered questionnaire:** Diagnosis confirmed if it included diagnostic measures with high specificity (i.e. venogram for DVT) or diagnosis plus a diagnostic test with low specificity (i.e. D-dimer). Unclear if included fatal cases.	All cases reviewed by 3 treatment-blinded adjudicators; Deemed confirmed if at least one adjudicator considered the event validated.	Moderate
Seeger 2007	**Claims database:** Diagnosis based on claims for a list of possible VTE codes. Received 90.1% of records which were reviewed by a blinded clinician. Included fatal cases.	Medical records extraction for 93% of DRSP initiators and 85% for other COC initiators; Adjudication by single blinded clinician; Only validated cases included.	Moderate
Lidegaard 2009	**Registry:** Diagnosis based on ICD 10 codes. Unclear if included fatal cases.	Authors have previously validated diagnoses of VTE in the national registry of patients and found 10% uncertain.	Serious
Vlieg 2009	**Clinics database:** Diagnosis based on code for VTE plus objective radiological measures. Did not include fatal cases.	Obtained hospital records and general practitioners; DVT confirmed with Doppler ultrasonography, PE confirmed by a ventilation perfusion lung scan, spiral computed tomography or angiogram.	Low
Dinger 2010	**Hospital database:** Diagnosis confirmed if it included imaging technique or clinical examination plus a positive result from a less specific diagnostic test and/or prescription for anticoagulant therapy. Did not include fatal cases.	Adjudication based on 3 blinded reviewers; Stratified based on definite VTE, probable VTE or no VTE. Classified as definite if one adjudicator classified VTE as confirmed.	Low
FDA 2011	**Administrative database:** Unclear if included fatal cases.	Hospitalized cases: All reviewed & blindly adjudicated by one physician. 10% sample of cases independently reviewed by a second blinded adjudicator; Outpatient cases: Medical records for 103 potential events at one site reviewed by PI; 89.3% validated by principal investigator, validated only at one site. Additional 128 outpatient events from other sites not reviewed or validated.	Low
Gronich 2011	**Administrative database:**	Not available.	Serious

	Diagnoses based on ICD-9 codes. Unclear if included fatal cases.		
Jick 2011	**Claims database:** Diagnosis based on a claim for a diagnosed DVT or hospitalized PE, a visit to the ER, or a positive diagnostic test plus a prescription for anticoagulant therapy. Unclear if included fatal cases.	Authors state that the database has been used for previous studies examining risk of VTE with OC use.	Low
LASS 2011	**Self-administered questionnaire:** Diagnosis confirmed if it included diagnostic measures with high specificity (i.e. venogram for DVT) or diagnosis plus a diagnostic test with low specificity (i.e. D-dimer). Unclear if included fatal cases.	All cases reviewed by 3 treatment-blinded adjudicators; Deemed confirmed if at least one adjudicator considered the event validated.	Moderate
Lidegaard 2011	**Registry:** Diagnosis based on code for VTE plus a prescription for anticoagulant therapy. Included fatal cases.	200/4246 randomly selected for validation by 2 treatment-blinded reviewers. 74% were considered validated; criteria: 1. Clinical signs of VTE; 2. Diagnostic confirmation; 3. Anticoagulation therapy	Moderate
Parkin 2011	**Administrative database:** Diagnosis based on READ and OXMIS codes. Required there to be no prescription of COC following diagnosis plus a prescription for anticoagulant therapy. Uncertain if included fatal cases.	48% cases reviewed: 4 cases excluded and 2 cases were minimal information; no other information	Moderate
Lepee 2012	**Claims database:** Diagnosis based on claim for VTE (including DVT, cerebral venous thrombosis, thrombophlebitis superficialis and basilar artery thrombosis, pulmonary embolism). Unclear if included fatal cases.	None	Critical
Sidney 2013	**Claims database:** Diagnosis based on claim for hospitalized PE or outpatient VTE (DVT plus prescription for anticoagulant therapy). Unclear if included fatal cases.	4 blinded adjudicators: obtained 92.3% of files and 87.4% considered validated	Low
Bergendal 2014	**Hospital database:** Diagnosis based on objective radiological measures. Fatal cases not included.	None	Low

Dinger 2014	**Self-administered questionnaire:** Diagnosis confirmed if it included diagnostic measures with high specificity (i.e. venogram for DVT) or diagnosis plus a diagnostic test with low specificity (i.e. D-dimer). Unclear if included fatal cases.	All cases reviewed by 3 treatment-blinded adjudicators.	Moderate
Ziller 2014	**Administrative database:** Diagnosis based on ICD-10 codes. Did not include fatal cases.	Authors state that the validity of the Disease Analyzer Database has been analyzed and the outcomes have been published.	Serious
Vinogradova 2014	**Administrative databases:** Diagnosis based on READ codes. Unclear if included fatal cases.	Based on previously validated CPRD and QResearch Databases used for research in risk of VTE with OC use.	Moderate

Table S4. Baseline characteristics included in matching, restriction, or statistical adjustment in the primary analyses of included studies.

Study	Age	BMI	Previous VTE	Family History of VTE	Calendar Time	Other variables included	Bias Assessment
Dinger 2007[18]	A	A	A	Unclear	-	-	Absent
Seeger 2007[21]	Unclear	-	Unclear	-	Unclear	Propensity score.	Present
Lidegaard 2009[22]	A	-	-	-	A	Education level, cancer, cardiovascular disease, and pregnancy related outcomes.	Present
Vlieg 2009[30]	A	*	-	*	A	Severe psychiatric problems, language, smoking and pregnancy related outcomes.	Absent
Dinger 2010[34]	M	A	A	A	-	Smoking, parity, educational level, chronic disease, concomitant medication, and area of residence.	Absent
FDA 2011[23]	A	-	E	-	A	Site of entry[†], serious illness, and pregnancy related outcomes.	Present
Gronich 2011[24]	A	A	E	-	-	Diabetes, hyperlipidemia, hypertension, cancer, smoking, and obesity.	Absent
Jick 2011[29]	M	-	-	-	M	Risk factors for VTE, cancer, and cardiovascular disease.	Absent
LASS 2011[25]	A	A	A	A	-	-	Absent
Lidegaard 2011[26]	A	-	A, E	-	A	Educational level, serious illness, cancer, gynaecological surgery, and coagulation disorders.	Present
Parkin 2011[32]	M	A	E	-	-	Risk factors for VTE, serious illness, cancer, cardiovascular disease, pregnancy, smoking, surgery, major injury, and prolonged immobility.	Absent
Leppee 2012[27]	-	-	-	-	-	-	Present
Sidney 2013[28]	A	-	E	-	A	Site of entry, serious illness, exposed to ≥ 2 OCs, and pregnancy related outcomes.	Absent
Bergendal 2014[31]	M	A	E	-	-	Smoking, immobilization, lack of prescription for anticoagulant, previous thrombosis, and malignancies.	Absent
Dinger 2014[19]	A	A	-	A	-	-	Absent
Ziller 2014[20]	A	A	E	-	-	Insurance status, region, history of COC use, history of hormone use, follow-up after surgery within 365 days,	Absent

						history of pregnancy related outcomes, and heart diseases.	
Vinogradova 2015[33]	M	A	-	-	M	Alcohol, ethnic group, chronic and acute conditions, use of other hormonal contraceptives, lack of prescription for anticoagulant, gynecological surgery, smoking, and pregnancy related outcomes.	Absent

Symbols: A: adjusted; M: matched; E: excluded; *: variable considered in secondary or sensitivity analyses; -: not accounted for or considered.

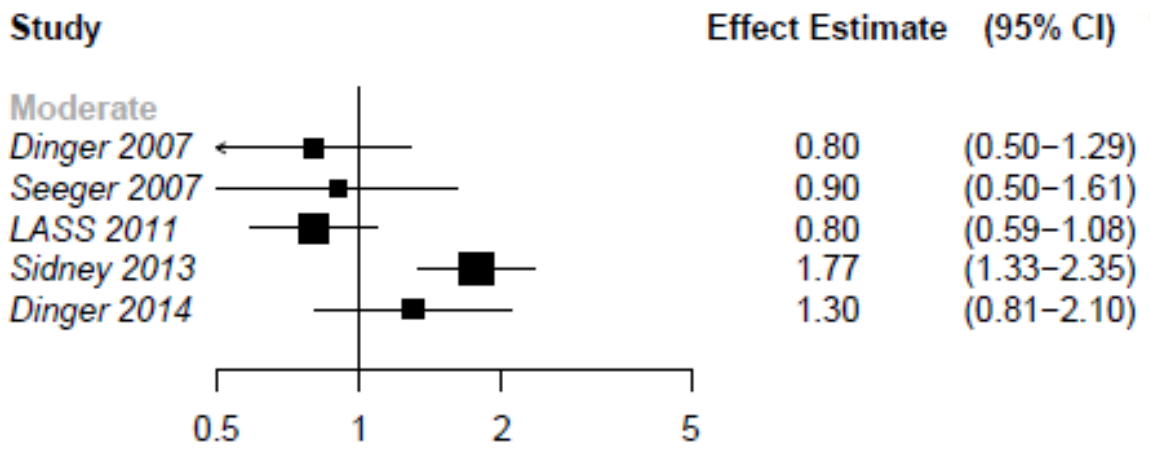
[†]Site of entry: site of clinic for databases using multiple sources.

FIGURE LEGEND

Figure S1. Forest plot describing the results of studies comparing drospirenone-containing COCs and other COCs, stratified by ACROBAT-NRSI-defined risk of bias*.

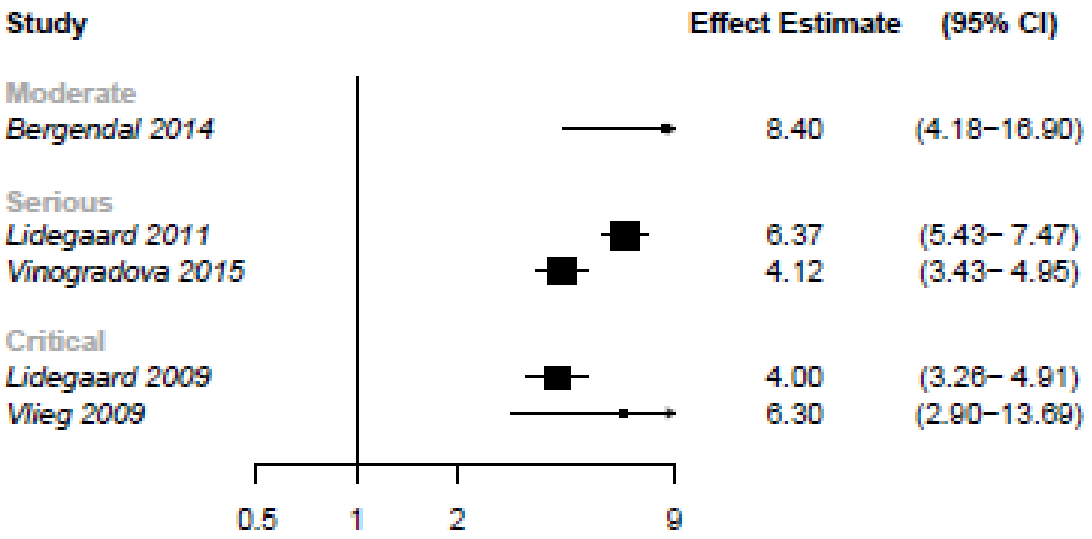
Figure S2. Forest plot describing the results of studies comparing drospirenone-containing COCs and no use, stratified by ACROBAT-NRSI-defined risk of bias.

Figure S1. Forest plot describing the results of studies comparing drospirenone-containing COCs and other COCs, stratified by ACROBAT-NRSI-defined risk of bias*.



* Leppee 2012 was omitted as 95% confidence intervals were not reported.

Figure S2. Forest plot describing the results of studies comparing drospirenone-containing COCs and no use, stratified by ACROBAT-NRSI-defined risk of bias.

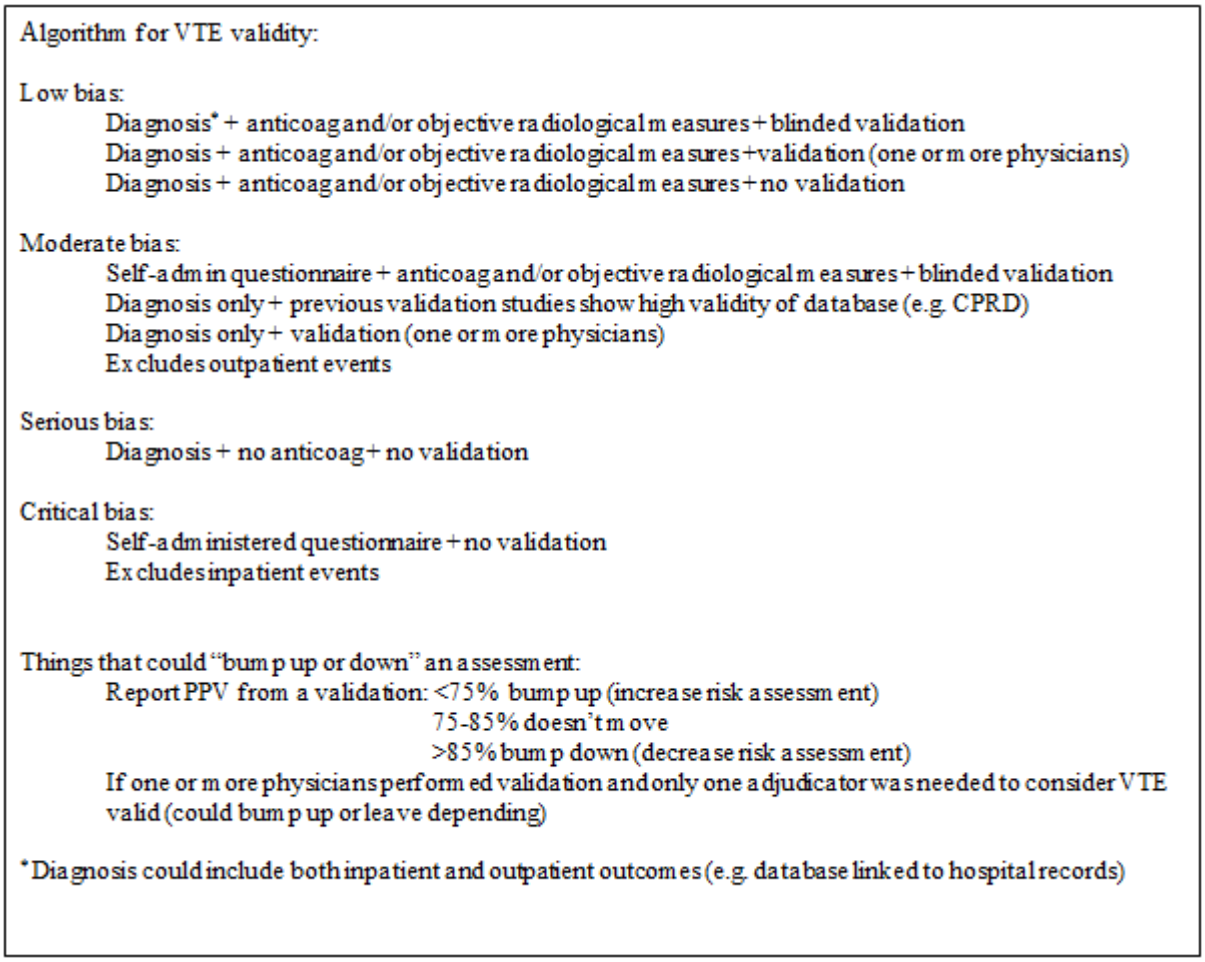


2.3 Supplementary material to systematic review

Outcome Misclassification

One of the main sources of bias within studies included in this review was outcome misclassification. However, to our knowledge, there exists no previously defined tool to evaluate misclassification of VTE within observational studies. I therefore decided to create an algorithm to assess misclassification of VTE. This algorithm was pilot-tested on two separate studies and then used by both independent reviewers to assess bias due to outcome misclassification within included studies. A low risk of bias (i.e. gold standard) was assigned to studies that included a diagnosis for VTE accompanied by a prescription for anticoagulant therapy or objective radiological measures (test confirmed event) plus a blinded validation (Figure 2.1). We also considered studies to have low risk of bias if they included a diagnosis for VTE accompanied by a prescription for anticoagulant therapy without the authors reporting any measure of validity. The presence of self-administered questionnaires for VTE ascertainment, low validity of data source, excluding inpatient or outpatient events, no requirement for anticoagulant therapy/objective radiological measures increased the potential for bias. In cases where a study reported a positive predictive value (PPV), there was a possibility to increase or decrease the initial assessment depending on its value. For instance, if a reported PPV was <75%, a low risk of bias would be increased to a moderate risk. In contrast, if a reported PPV was >85%, a serious risk of bias would be reduced to a moderate risk.

Figure 2.1 Algorithm for assigning bias assessment based on VTE misclassification



CHAPTER 3: TRANSITION

Based on our systematic review, all studies examining the VTE risk of drospirenone-containing COCs had important limitations, with prevalent user bias affecting the majority of these studies. Consequently, there remains a need for large, population-based, methodologically-rigorous studies to obtain a complete understanding of the safety profile of these agents.

I used my systematic assessment of the literature to inform the design of my original research study. Using the Clinical Practice Research Database (CPRD), linked to Hospital Episode Statistics (HES; inpatient and outpatient), we created two parallel study designs to study the methodological challenge of studying the drospirenone-containing COC associated risk of VTE among first-time users. We created a cohort of first-time users, as well as a cohort of restarter users and conducted a retrospective cohort study of drospirenone users versus levonorgestrel users. This study design allows us to both describe and illustrate the methodological challenges of this literature, but also to overcome the main limitation seen in my systematic review which is to the need to compare users of similar underlying risk profiles. Moreover, the use of restarter cohort will allow us to overcome any left truncation issues traditionally seen within health care databases.

CHAPTER 4: ORIGINAL RESEARCH ARTICLE

4.1 Preface to second manuscript

Based on our systematic review, we have outlined an improved study design to assess this association. Our study will have some important qualities: (1) It will use two parallel study designs to assess the methodological challenge of assessing the risk of VTE associated with drospirenone-containing COCs. We will use both a first-time user cohort as well as a restarter user cohort; (2) We will use an novel approach to avoid dilution of risk typically associated with intention-to-treat analyses and dilution of risks if hazards are non-proportional in studies with long follow-up; (3) We will use levonorgestrel-containing COCs as the comparator group as it is the most frequently prescribed COC in the UK and we are unlikely to observe depletion of susceptibles in this population; (4) VTE outcome will be defined as an in-patient diagnosis or an outpatient diagnosis of VTE accompanied by a prescription for anticoagulant therapy, INR testing, or death within 90 days of the event; (5) We will use HDPS scores to minimize residual confounding.

4.2 Cohort study manuscript

Drospirenone-containing Oral Contraceptive Pills and the Risk of Venous Thromboembolism: The Methodological Challenges in the Identification of First-Time Users in Healthcare Databases

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ABSTRACT

Introduction: The effects of drospirenone-containing combined oral contraceptives (COCs) on the risk of venous thromboembolism (VTE) remain controversial due to the challenge in distinguishing between first-time users and restarters, and their differences in underlying VTE risk, in healthcare databases.

Objectives: To describe the methodological challenge of studying the risk of VTE among first-time users of drospirenone-containing COCs in a healthcare database.

Methods: We used data from the Clinical Practice Research Datalink (CPRD) to construct two cohorts. The first-time user cohort included all women aged 16 to 45 years who received a first ever prescription of drospirenone- or levonorgestrel-containing COCs between May 2002 and March 2015. The restarter cohort included all women who were restarting a COC after a period of non-use of at least 6 months. Cox proportional hazards models adjusted for high dimensional propensity scores were used to estimate hazard ratios (HRs) and corresponding 95% confidence intervals (CIs).

Results: The final cohorts included 55,139 first-time users (3,582 drospirenone and 51,557 levonorgestrel) and 162,959 restarters (23,191 drospirenone and 139,768 levonorgestrel). The adjusted HR of incident VTE associated with drospirenone versus levonorgestrel was 3.19 (95% CI: 1.12-9.08) for first-time users and 1.96 (95% CI: 1.12-3.41) for restarters.

Conclusions: We found an elevated risk of VTE associated with drospirenone-containing COCs in comparison to levonorgestrel-containing COCs in both cohorts. While left truncation of healthcare databases is a concern for the identification of first-time users, the use of a more explicit cohort of restarters suggests a doubling of VTE risk with drospirenone-containing COCs.

INTRODUCTION

Combined oral contraceptives (COCs), which include both an estrogen and progestin, are primarily used to prevent unwanted pregnancies. Other indications for their use include acne treatment, relief of symptoms associated with premenstrual dysphoric disorder, treatment of heavy or irregular menstruation[1]. A cross-sectional survey in 2012 in the US revealed that the oral contraceptive pill has been one of the most popular contraceptive methods since 1982, with approximately 9,720,000 users in 2012[2]. The fourth generation of COCs entered the market in 2000 and contains the progestin drospirenone.

The safety of drospirenone-containing COCs remains controversial. Several observational studies have examined the association between use of drospirenone-containing COCs and the risk of venous thromboembolism (VTE)[3-19]. However, these studies have produced conflicting results, with some studies[3,4,6,10,19] suggesting no association and others[5,7-9,11,13-18] suggesting a substantially increased risk relative to use of second generation levonorgestrel-containing COCs. Some of this heterogeneity can be explained by the presence of several important methodological limitations, including prevalent user bias[7,9-12,14-16,18,19], the use of inappropriate comparators[7,11,15,16,18], misclassification of outcome[5,7,9,12], and confounding[6-8,11,12]. Nonetheless, concerns regarding the VTE effects of drospirenone-containing COCs have resulted in safety reviews by the US Food and Drug Administration (FDA)[8] and the European Medicines Agency (EMA)[20], which resulted in differing conclusions.

The main methodological challenge in studying the VTE risk of drospirenone-containing COCs is distinguishing between first-time users and restarters, and their differences in underlying VTE risk, in routine healthcare databases. The VTE risk of COCs is greatest among first-time users, with the first year of use representing the highest risk period, and the risks

gradually decreasing until a plateau is reached[21]. Lower risks are observed among patients restarting COCs after a period of non-use[22]. It is well established that failure to account for these differences in underlying VTE risk can result in spurious associations[23,24] but the difficulty in identifying first-time users in healthcare databases is not well understood. Our objective was therefore to describe and illustrate the methodological challenge of studying the risk of VTE among first-time users of drospirenone-containing COCs.

METHODS

Data source

We conducted a retrospective cohort study using data from the Clinical Practice Research Datalink (CPRD), a clinical database that contains the medical records of over 11.3 million patients seen at more than 674 general practitioner practices in the United Kingdom (UK).[25] It contains demographic, lifestyle (e.g., body mass index [BMI], smoking), recorded symptoms and clinical diagnoses (based on the Read coding system), clinical measures (e.g., blood pressure), laboratory test results, and prescriptions (based on the British National Formulary). The CPRD has been validated extensively[26,27], and it has served as the data source for over 1,000 publications[25]. It can also be linked to other National Health Service data sources, including Hospital Episode Statistics (HES) data. HES contains detailed hospitalization data, including diagnoses (based on ICD-10 codes) and procedures (based on OCPS-4 codes), with HES linkage restricted to practices in England and available for approximately 58% of CPRD patients.

This study was approved by the Independent Scientific Advisory Committee (ISAC) of the CPRD (ISAC protocol 16_009A, which was made available to journal reviewers) and the Research Ethics Board of the Jewish General Hospital in Montreal, Canada.

Study population: First-time user cohort

Using the CPRD linked to HES, we created two separate cohorts to study the VTE risk of drospirenone-containing COCs: a cohort of first-time users and a cohort of restarters. The cohort of first-time users included all women who received a first ever prescription for a drospirenone-containing or levonorgestrel-containing COC between May 1st 2002 and March 31st, 2015. To ensure that inclusion was restricted to first-time users of COC, we restricted inclusion to women with at least three years of CPRD history and at least one year of HES history before their first COC

prescription. We excluded women with a previous prescription or Read code indicating a history of hormonal contraceptive use, including COCs, progestin-only oral contraceptives, and combined contraceptives administered via other routes such as the vaginal ring, transdermal patch, and intrauterine devices (IUD). In the UK, COCs are also available from family planning clinics. We thus excluded women with Read codes indicating previous use as well as those previously seen at family planning clinics or fertility clinics. In addition, we excluded women who received prescriptions for two or more oral contraceptives on the day of their first ever COC prescription and those with a recorded history of thrombosis (either VTE or arterial thrombosis [ATE]). The date of the first ever prescription for a drospirenone-containing or levonorgestrel-containing COC defined the date of cohort entry.

Study population: Restarter cohort

The restarter cohort included all women who received a prescription for drospirenone- or levonorgestrel-containing COCs between May 1st, 2002 and March 31st, 2015 who had previously received a prescription for hormonal contraceptives and had a period of non-use of at least 6 months prior to this new prescription. The date of this new drospirenone- or levonorgestrel-containing COC prescription defined the date of cohort entry. All other inclusion and exclusion criteria for the restarter cohort were the same as those of the first-time user cohort and were applied to the date of cohort entry.

Exposure definition

In both cohorts, women were classified into two, mutually-exclusive exposure categories defined by the COC that resulted in cohort entry: users of drospirenone-containing COCs (the main exposure of interest) and users of levonorgestrel-containing COCs (the reference group). Levonorgestrel-containing COCs were chosen as the comparator as they are the most frequently

prescribed COC in the UK.[28] Furthermore, all COCs increase the risk of thrombosis due to hemostatic changes[29]. Consequently, the use of an active comparator, as opposed to a "non-use" comparator, overcomes a key limitation of many studies in this area[7,11,15,16,18]. It also provides the most clinically-relevant treatment comparison.

All women followed until VTE (defined below) or censoring due to discontinuation of use (defined as a 60-day gap between the end of one COC prescription and the next COC prescription), switching to any other form of hormonal contraception (including study COCs), ATE, pregnancy, death, departure from the CPRD or HES, the last date of data collection for the general practitioner practice, or the end of the study period (March 31st, 2015), whichever occurred first.

VTE definition

The primary outcome was incident VTE (including deep vein thrombosis [DVT] and pulmonary embolism [PE]). An event was defined by either 1) an inpatient diagnosis of VTE (using ICD-10 codes); or 2) an outpatient VTE diagnosis (using Read codes) accompanied by a prescription for anticoagulant therapy, INR testing (indicative of anticoagulation), or death within 90 days of VTE diagnosis. This outcome definition has been shown to be the most accurate method of VTE ascertainment in administrative databases[30,31]. The event date was defined as the date of admission for HES-defined inpatient events or the date of diagnosis for CPRD-defined events.

Potential confounders

Several risk factors for VTE[18,32-36] were pre-specified as potential confounders. These risk factors included age, family history of VTE, lifestyle characteristics (smoking, alcohol use), comorbidities (asthma, heart failure, respiratory failure, inflammatory bowel disease,

malignancy, polycystic ovary syndrome [PCOS], renal disease, rheumatic disease, stroke, systemic lupus erythematosus, thrombophilia, and varicose veins), and hospital events and procedures (hospitalization with length of stay > 3 days, central venous catheters, major general surgery [cardiac, abdominal, gynecological, genitourinary, neurological], orthopedic surgery [hip/knee replacement], parity, spinal cord injury, and trauma [leg/hip/pelvis fracture]), prescribed medications (antiplatelet therapy, aspirin, and non-steroidal anti-inflammatory drugs [NSAIDs]). BMI is a well-known risk factor for VTE; however, BMI data for approximately 50% of women were missing, and the variable was consequently not retained in our models. Comorbidities were defined using diagnosis codes (Read or ICD-10) recorded any time before cohort entry, hospital events and procedures were defined using ICD-10 codes or OPCS-4 codes in the 90 days before cohort entry, and medications were defined using prescriptions recorded in the year before cohort entry. The values for smoking were defined using an assessment window of five years, and missing smoking data were imputed using multiple imputation.

Statistical analysis

All analyses were repeated in both the first-time user and restarter cohorts. Descriptive statistics were used to describe demographic and clinical characteristics by exposure group at cohort entry. Categorical variables are presented as counts with corresponding proportions, and continuous variables are presented as means with standard deviations (SD). VTE rates and corresponding 95% confidence intervals (CIs) were calculated using the Poisson distribution, both overall and by exposure category.

For the primary analysis, we used Cox proportional hazards models to estimate hazard ratios (HRs) and corresponding 95% CIs of VTE associated with drospirenone-containing COCs compared with levonorgestrel-containing COCs. To minimize potential confounding, we

adjusted for high-dimensional propensity score (HDPS)[37], which included the pre-specified covariates described above as well as up to 500 empirically-identified covariates; models included HDPS decile, as well as an interaction term between HDPS decile and HDPS as a continuous variable to minimize potential residual confounding within each HDPS decile. We tested the assumption of proportionality of hazards by including an interaction term between time and exposure in the Cox proportional hazards model; given the presence of non-proportional hazards, the primary analysis of each cohort was repeated with follow-up time stratified by quartile based on the distribution of the first-time user cohort.

Secondary analyses

In each cohort, we conducted three secondary analyses. In the first, we restricted events to unprovoked VTEs, with provoked VTEs considered an additional censoring criterion. Provoked VTE was defined as any VTE in which any of the following occurred in the 90 days before the event: hospitalization with length of stay >3 days, central venous catheters, major general surgery, orthopedic surgery, pregnancy, cancer, spinal cord injury, and trauma [leg/hip/pelvis fracture]). In the second and third secondary analyses, we examined the possible presence of effect modification of the drospirenone-VTE association by smoking and by thrombophilia status, respectively.

Sensitivity analyses

We conducted seven sensitivity analyses to examine the robustness of our results. In the first, we repeated our primary analyses restricting inclusion to COCs with an estrogen dose of 30µg to ensure that results were not confounded by differences in estrogen dosage.[38] In the second, we examined the potential impact of informative censoring by repeating our analyses using an approach analogous to an intention-to-treat (ITT) in which patients were followed until an event or censoring

due to ATE, death, departure from the CPRD or HES, the end of the study period (March 31st, 2015), or a maximum follow-up of one year, whichever occurred first. In the third, we conducted an HDPS-matched analysis to assess the impact of adjusting for HDPS by decile. In the fourth, we employed a time-dependent exposure definition in which we did not censor on discontinuation of OC use. This analysis resulted in the inclusion of three exposure categories: drospirenone-containing COCs, levonorgestrel-containing COCs, and other (including women exposed to other forms of hormonal contraception as well as those no longer currently exposed to hormonal contraception). In the fifth, we restricted analyses to hospitalized events. In the sixth, we repeated our primary analysis with grace periods of 30 days and 90 days. In the seventh, to better understand potential misclassification of outpatient events, we described the characteristics of unconfirmed VTE diagnoses(outpatient diagnosis of VTE without confirmation by anticoagulant prescription, INR testing, or death) versus confirmed VTE events (in-patient diagnoses and outpatient diagnoses accompanied by anticoagulant prescripton, INR testing, or death). Finally, we included a separate sensitivity analysis for the restarter user cohort only in which we restricted to those users who had a gap of ≥ 365 days in COC use. All analyses were performed in SAS Statistical Software version 9.4 (The SAS Institute, Cary, NC).

RESULTS

First-time users

There were 457,442 women aged 16 to 45 years old between April 2002 and March 2015 with at least one prescription for a drospirenone- or levonorgestrel-containing COC (Figure 1). After applying our inclusion and exclusion criteria, 3,582 first-time users of drospirenone-containing COCs and 51,557 first-time users of levonorgestrel-containing COCs were included in our study cohort.

The demographic and clinical characteristics of first-time users of drospirenone- and levonorgestrel-containing COCs are described in Table 1. Drospirenone users were slightly older at cohort entry compared to levonorgestrel users (21.1 [SD: 6.6] years versus 19.8 [SD: 5.5] years). Drospirenone users also had lower values for parity compared to levonorgestrel users. Characteristics were otherwise similar between groups. There was good overlap in the HDPS distribution between groups (Online Appendix Figure S1).

In our cohort of first-time users, 25 VTE events occurred in 53,892.6 person-years (PYs) of follow-up, resulting in an overall incidence rate of 4.6 per 10,000 PY (95% CI: 3.0-6.8). Among drospirenone users, the incidence rate was 18.6 events per 10,000 PYs (95% CI: 6.8-40.6) whereas among levonorgestrel users, the incidence rate was 3.8 events per 10,000 PYs (95% CI: 2.3-5.9) (Table 2). After adjusting for HDPS, the HR of incident VTE with drospirenone compared to levonorgestrel was 3.19 (95% CI: 1.12-9.08) (Table 2). Importantly, there was evidence of non-proportional hazards (p-value for exposure*time interaction <0.0001, Online Appendix Figure S2); the HRs for drospirenone versus levonorgestrel ranged from 8.59 (95% CI: 1.59-46.4) in the first 84 days of use to 0.98 (95% CI: 0.11-8.75) with ≥ 113 days of use. The reasons for cohort exit are described in Online Appendix S1.

In secondary analyses, we found slightly attenuated HRs when restricting events to unprovoked VTE (2.03, 95% CI: 0.65-6.37; Table 2). In addition, the VTE risk with drospirenone-containing COCs appeared to be higher among ever smokers (HR: 10.53, 95% CI: 1.65-67.26) than among never-smokers (HR: 2.07, 95% CI: 0.55-7.73), though the interaction did not reach statistical significance (p-for-interaction: 0.15) (Table 2).

The results of our sensitivity analyses of our cohort of first-time users were generally consistent with those of our primary analysis (Figure 2, Online Appendix S2). Estimated HRs ranged from an adjusted HR of 1.95 (95% CI: 0.91-4.20) when exposure was defined in a time-dependent fashion to an adjusted HR of 5.24 (95% CI: 1.78-15.42) when defining exposure with a 30-day grace period. Finally, we observed similar characteristics at cohort entry when stratified on "unconfirmed" and "confirmed" VTE events (Online Appendix S3).

Restarter cohort

From the cohort of 457,442 potentially eligible women aged 16 to 45 years old between April 2002 and March 2015 with at least one prescription for a drospirenone- or levonorgestrel-containing COC, we identified 162,959 women who were restarting COC use after a period of at least 6 months of non-use of hormonal contraceptives (Figure 3). These women included 23,191 users of drospirenone-containing COCs and 139,768 users of levonorgestrel-containing COCs.

Table 3 describes the demographic and clinical characteristics of restarters of drospirenone-and levonorgestrel-containing COCs. As with the first-time user cohort, users of drospirenone and levonorgestrel had similar demographic and clinical characteristics. In addition, there was large overlap in the HDPS distribution between exposure groups (Online Appendix Figure S3).

In our cohort of restarter users, 85 VTE events occurred in 163,617 PYs of follow-up, resulting in an overall incidence rate of 5.2 per 10,000 PYs (95% CI: 4.1-6.4). Among drospirenone users, the incidence rate was 9.0 events per 10,000 PYs (95% CI: 5.4-14.0) whereas among levonorgestrel users, the incidence rate was 3.8 events per 10,000 PYs (95% CI: 2.3-5.9) (Table 4). After adjusting for HDPS, the HR of incident VTE with drospirenone compared to levonorgestrel was 1.96 (95% CI: 1.12-3.41) (Table 4). Hazards were, as expected, non-proportional (Online Appendix Figure S4). The reasons for cohort exit are described in Online Appendix S4.

In secondary analyses, we found slightly higher risk of VTE when restricting events to unprovoked VTE (2.28, 95% CI: 1.26-4.14; Table 4). In addition, we found some evidence of a higher VTE risk with drospirenone among ever-smokers (HR: 2.68, 95% CI: 1.19-6.02) than among never smokers (HR: 1.39, 95% CI: 0.59-3.25) but this did not reach statistical significance (p-for-interaction: 0.29) (Table 4).

Results of sensitivity analyses within the restarter cohort were consistent with our primary findings (Figure 4, Online Appendix S5). Estimated HRs ranged from an adjusted HR of 1.59 (95% CI: 0.86-2.94) when exposure was based on an intention-to-treat approach to an adjusted HR of 2.57 (95% CI: 1.25-5.30) when defining exposure according to an HDPS-matched analysis. As with the first-time user cohort, we observed similar characteristics at cohort entry when stratified on “unconfirmed” and “confirmed” VTE events (Online Appendix S6).

DISCUSSION

This study was designed to describe and illustrate the methodological challenge of studying the risk of VTE among first-time users of drospirenone-containing COCs. To do this, we created two distinct cohorts of COC users: a cohort of first-time users and a cohort of restarters. Among first-time users, we found that drospirenone-containing COCs were associated with a substantially higher risk of VTE than levonorgestrel-containing COCs (HR: 3.19, 95% CI: 1.12-9.08). The increased risk was present soon after the initiation of drospirenone-containing COCs (HR for the first 84 days: 8.59, 95% CI: 1.59-46.40) and dissipated with time (HR for 113+ days: 0.98, 95% CI: 0.11-8.75). Among restarters, an elevated risk was observed with drospirenone-containing COCs (HR: 1.96, 95% CI: 1.12-3.41) but this increased risk was attenuated relative to that observed with first-time users. Importantly, in this analysis of an explicitly-defined cohort of women with a similar underlying risk of VTE, drospirenone-containing COCs were associated with a clinically important increased risk. In both cohorts, several sensitivity analyses produced results that were consistent with those of our cohort-specific primary analyses.

There are two likely explanations of the observed heterogeneity between the VTE risk of drospirenone-containing COCs among first-time users and among restarters. First, it is possible that the observed difference in the VTE risk with drospirenone-containing COCs is due to the increased risk of VTE among first-time users of COCs relative to restarters. The literature currently suggests that the risk of VTE is highest among first-time user, then those with interrupted use (restarters and switchers) and finally prevalent users.[23] This is also consistent with early risk among first-time users observed in the present study. The importance of restricting analyses to those with a similar underlying VTE risk (i.e., comparing first-time users

to first-time users) became evident in the 1990s, when a comparison of first-time users of third generation COCs to a population of users of second generation COCs that included both first-time users and restarters resulted in a spurious increased risk with third generation COCs. This resulted in a 'pill scare' in which women quickly stopped using their third generation COCs, resulting in dramatically increased rates of abortions and unwanted pregnancies.[39] Subsequent analyses that compared women at similar points on the VTE risk curve revealed no difference in the risk of VTE with second and third generation COCs.[21]

Second, it is possible that, despite our exhaustive efforts, our cohort of first-time users included some restarters, and that observed increased risk is spuriously high due to the comparison of first-time users of drospirenone-containing COCs to a mixture of first-time users and restarters of levonorgestrel-containing COCs. As drospirenone-containing COCs were introduced in the 2000s, it is less likely for there to be a mixture of users within this group. There are two potential sources of misclassification of restarters as first-time users. As is true with most healthcare databases, data are left truncated, resulting in the incomplete capture of medical history and previous use of medications. This issue is particularly important in insurance databases, where no information is available outside of the coverage period, and databases such as US Medicare, which only cover patients aged 65 years or older. This truncation is partially mitigated in the CPRD by the transfer of patient records from one practice to another when patients change practices, but such transfers are only feasible between practices that use the same software and it is not possible to link patient records across practices.

Restarters of COCs can also be misclassified as first-time users in UK databases as oral contraceptives are commonly prescribed at family planning clinics (i.e., community contraception clinics, genitourinary medicine clinics, sexual health clinics). In England,

approximately 7.9% of women aged under 16 attended a family planning clinic from 2009 to 2010 and 21.5% of women aged 16 to 19 years visited a family planning clinic from 2008 to 2009[40,41]. The CPRD only captures prescriptions issued by the general practitioner, and the availability of oral contraceptives at family planning clinics makes the identification of first-time users difficult. To attempt to overcome this issue, we applied several exclusion criteria, such as the exclusion of all women with previous prescriptions for hormonal contraception issued by the general practitioner and those with diagnostic codes indicating previous use of hormonal contraception. In addition, we excluded all women with a diagnostic or referral code indicating previous visits to a family planning clinic any time before cohort entry. The number of women excluded for previously attending family planning clinics was substantially lower than expected based on previous reports of family planning clinic usage[42], suggesting that the use of family planning clinics is not well recorded in the CPRD. Thus, despite our best efforts at restricting this cohort to first-time users, we cannot rule this out as explanation for the observed increased risk in the first-time user cohort.

Previous observational studies comparing the VTE effects of drospirenone- and levonorgestrel-containing COCs have reported relative risks ranging from 1.0 to 3.3, with most studies reporting relative risk between 1.0 and 2.4[3-16,18,19]. The adjusted HR of 3.19 observed in our first-time user analysis is thus somewhat higher than previous reported estimates while the adjusted HR of 1.96 in our restarter analysis is consistent with these previous estimates. Importantly, only 7 of 17 previous studies on this topic were restricted to first-time users, and those that did restrict to first-time use often had insufficient database history to do so accurately.[3-6,8,13,17] In addition, most previous studies either used an ITT analysis[5,6,12], which can result in a dilution of effect, or a time-dependent exposure definition (in either a cohort or nested

case-control analysis), which can result in comparing women at different underlying VTE risks[3,4,7-11,13-19] due to the switching, interrupting, and restarting of CCOs that occurs during follow-up.

Our study had many strengths. First, the analysis of two distinct cohorts, one of first-time users and one of restarters, allowed for the investigation of the methodological challenges associated with distinguishing these two types of COC users. In addition, by comparing women with similar underlying risks of VTE, the use of an explicitly defined restarter cohort overcomes many of the challenges in assessing the VTE risk of COCs due to the left truncation of healthcare databases. Second, to our knowledge, this is the first study to assess the association of drospirenone-containing COCs on the risk of VTE with respect to levonorgestrel-containing COCs with follow-up restricted to the period in which women were exposed to their cohort-entry defining COC. This approach offers several advantages over the ITT and time-dependent exposure definitions used in previous studies. Third, we employed HDPS and an active comparator to minimize potential confounding and conducted several sensitivity analyses to test the robustness of our results.

Our study also has several limitations. First, this study is observational by nature and thus prone to biases such as confounding by indication or contraindication. Although this should be greatly reduced by our use of an active comparator, preferential prescribing of one COC over another due to perceived VTE risk is possible. Second, although available in the CPRD, family history of VTE was infrequently recorded; although we included this variable in our HDPS model, some residual confounding is likely. In addition, due to the amount of missing BMI, we were unable to include it as a covariate in the HDPS model. Third, the CPRD records prescriptions written and not dispensing or use of COCs. Consequently, some misclassification

of exposure is possible. Finally, COCs are used in relatively young women, resulting in a relatively healthy study population. Therefore, relatively few events were observed, resulting imprecise treatment effects.

CONCLUSIONS

With their differences in underlying risk, it is essential to distinguish between first-time users and restarters when examining the VTE risk of COCs. We found an elevated risk of VTE associated with drospirenone-containing COCs in comparison to levonorgestrel-containing COCs in both first-time users and restarters. However, the left truncation of healthcare databases and the corresponding challenge of identifying first-time users of COCs render the results of our first-time user analysis difficult to interpret. The examination of a more explicit cohort of restarters, which compares patients with a similar underlying risk of VTE and overcomes the potential consequences of left truncation of healthcare databases, suggests a doubling of VTE risk with drospirenone-containing COCs relative to levonorgestrel-containing COCs.

Disclosures

Dr. Suissa has been a paid consultant for Bayer and Organon. The other authors have no conflicts of interest to report.

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Table 1. Baseline characteristics of first-time users of drospirenone-containing COCs and levonorgestrel-containing COCs.

Characteristic	**Drospirenone users (n=3,582)**	**Levonorgestrel users (n=51,557)**
	n (%)	n (%)
Age (years), mean (SD)	21.1 (6.6)	19.8 (5.5)
Year of cohort entry		
2002	86 (2.4)	2,196 (4.3)
2003	113 (3.2)	3,635 (7.1)
2004	138 (3.9)	4,119 (8.0)
2005	173 (4.8)	4,331 (8.4)
2006	250 (7.0)	4,578 (8.9)
2007	313 (8.7)	4,671 (9.1)
2008	406 (11.3)	4,821 (9.4)
2009	426 (11.9)	4,382 (8.5)
2010	473 (13.2)	4,310 (8.4)
2011	370 (10.3)	3,929 (7.6)
2012	294 (8.2)	3,722 (7.2)
2013	292 (8.2)	3,269 (6.3)
2014	208 (5.8)	2,867 (5.6)
2015	40 (1.1)	727 (1.4)
Family history of VTE	S	S
Lifestyle characteristics		
Alcohol abuse	40 (1.1)	531 (1.0)
Smoking*	480 (18.2)	6,432 (19.9)
Comorbidities		
Asthma	623 (17.4)	9,713 (18.8)
Heart failure	0 (0.0)	0 (0.0)
Inflammatory bowel disease	12 (0.3)	72 (0.1)
Malignancy	122 (3.4)	1485 (2.9)
Renal disease	17 (.5)	150 (0.3)
Respiratory failure	0 (0.0)	S
Rheumatoid arthritis	49 (1.4)	371 (0.7)
Systemic lupus erythematosus	9 (0.3)	67 (0.1)
Thrombophilia	S	S
Varicose veins	26 (0.7)	180 (0.4)
Hospital events		
Hospital length stay > 3 days	289 (8.1)	3377 (6.6)
Central venous catheters	S	10 (<0.1)
Major general surgery	129 (3.6)	2.16 (1113.0)
Orthopedic surgery (Hip/knee replacement)	S	10 (<0.01)
Pregnancy	1,281 (35.8)	21,252 (41.2)

Spinal cord injury	S	77 (0.2)
Trauma (Leg/hip/pelvis fracture)	79 (2.2)	1139 (2.2)
Parity		
0	2,301 (64.2)	30,305 (58.8)
1	766 (21.4)	12,528 (24.3)
2	307 (8.6)	5,573 (10.8)
3	136 (3.8)	2,037 (4.0)
4	52 (1.5)	732 (1.4)
5	S	237 (0.5)
6+	S	88 (0.2)
Medications		
Antiplatelet therapy	0 (0.0)	0 (0.0)
Aspirin	6 (0.2)	72 (0.1)
NSAIDs	414 (11.6)	6,383 (12.4)
Polycystic ovary syndrome	198 (5.5)	593 (1.2)

Abbreviations: NSAIDs: non-steroidal anti-inflammatory drugs; S: suppressed data in order to comply with CPRD privacy restrictions; SD: Standard deviation; VTE: Venous thromboembolism.

* Estimates reported prior to multiple imputation of missing data.

Table 2. Drospirenone-containing combined oral contraceptives and the rate of venous thromboembolism among first-time users.

Exposure	No. of Events	No. of patients	Person-Years (PYs)	IR (95% CI)*	Crude HR	Adjusted HR (95% CI) [†]
Levonorgestrel	19	51,557	50,672.5	3.7 (2.3-5.9)	1.00	1.00 (Reference)
Drospirenone	6	3,582	3,220.1	18.6 (6.8-40.6)	4.88	3.19 (1.12-9.08)
0-84 days	S	3,582	763.9	39.3 (8.1-114.8)	10.98	7.35 (1.29-41.83)
85-112 days	S	2,637	807.4	24.8 (3.0-89.5)	7.57	5.40 (0.87-33.38)
113+ days	S	2,595	3,051.0	3.3 (0.1-18.3)	1.46	0.98 (0.11-8.75)
Unprovoked VTE						
Levonorgestrel	17	51,557	50,672.5	3.4 (2.0-5.4)	1.00	1.00 (Reference)
Drospirenone	6	3,582	3,220.1	18.6 (6.8-40.6)	4.47	3.16 (0.12-4.47)
Effect modification[‡,§]						
Smokers:						
Levonorgestrel	S	10,270	9,039.9	3.3 (0.7-9.7)	1.00	1.00 (Reference)
Drospirenone	S	642	474.7	63.2 (13.0-184.7)	14.80	10.53 (1.65-67.26)
Non-smokers:						
Levonorgestrel	16	41,287	41,632.7	3.8 (2.2-6.2)	1.00	1.00 (Reference)
Drospirenone	S	2,940	2,745.4	10.9 (2.3-31.9)	3.32	2.07 (0.55-7.73)

Abbreviations: CI: Confidence interval; COC: Combined oral contraceptive; HR: Hazard ratio; IR: Incidence Rate; S: suppressed data in order to comply with CPRD privacy restrictions.

*Rate differences are expressed as events per 1,000 person-years.

[†] Adjusted for HDPS decile (including several prespecified confounders) and an interaction term between HDPS decile and HDPS as a continuous variable.

[‡] The planned assessment of effect modification by thrombophilia was not performed as there were insufficient data to test the presence of effect modification.

[§] P value for interaction between exposure and smoking was 0.15.

Table 3. Baseline characteristics of restarters of drospirenone-containing COCs and levonorgestrel-containing COCs.

Characteristic	**Drospirenone users (n=23,191)**	**Levonorgestrel users (n=139,768)**
	n (%)	n (%)
Age (years), mean (SD)	26.2 (6.2)	26.5 (6.9)
Year of cohort entry		
2002	599 (2.6)	20,671 (14.8)
2003	1,018 (4.4)	18,448 (13.2)
2004	1,142 (4.9)	13,066 (9.4)
2005	1,430 (6.2)	11,529 (8.3)
2006	1,751 (7.6)	10,709 (7.7)
2007	2,011 (8.7)	10,120 (7.2)
2008	2,375 (10.2)	9,952 (7.1)
2009	2,603 (11.2)	9,105 (6.5)
2010	2,686 (11.6)	8,245 (5.9)
2011	2,339 (10.1)	7,566 (5.4)
2012	1,942 (8.4)	7,381 (5.3)
2013	1,691 (7.3)	6,385 (4.6)
2014	1,337 (5.8)	5,418 (3.9)
2015	267 (1.2)	1,173 (0.8)
Family history of VTE	13 (0.1)	59 (0.0)
Lifestyle characteristics		
Alcohol abuse	665 (2.9)	3,956 (2.8)
Smoking*		
Comorbidities		
Asthma	4,167 (18.0)	25,261 (18.1)
Heart failure	0 (0.0)	10 (0.0)
Inflammatory bowel disease	102 (0.4)	675 (0.5)
Malignancy	1,105 (4.8)	5,828 (4.2)
Renal disease	106 (0.5)	521 (0.4)
Respiratory failure	S	16 (0.0)
Rheumatoid arthritis	271 (1.2)	1,455 (1.0)
Systemic lupus erythematosus	57 (0.3)	272 (0.2)
Thrombophilia	S	18 (0.0)
Varicose veins	364 (1.6)	1,960 (1.4)
Hospital events		
Hospital length stay > 3 days	2,712 (11.7)	19,056 (13.6)
Central venous catheters	S	20 (0.0)
Major general surgery	1,408 (6.1)	7,523 (5.2)
Orthopedic surgery (Hip/knee replacement)	12 (0.1)	56 (0.0)
Pregnancy	11,372 (49.0)	85,381 (61.1)

Spinal cord injury	30 (0.1)	168 (0.1)
Trauma (Leg/hip/pelvis fracture)	292 (1.3)	1,579 (1.1)
Parity		
0	11,819 (51.0)	54,387 (38.9)
1	4,785 (20.6)	29,317 (21.0)
2	3,654 (15.8)	29,550 (21.1)
3	1,775 (7.7)	15,691 (11.2)
4	733 (3.2)	6,542 (4.7)
5	273 (1.2)	2,571 (1.8)
6+	110 (0.5)	1,045 (0.8)
Medications		
Antiplatelet therapy	0 (0.0)	S
Aspirin	25 (0.1)	276 (0.2)
NSAIDs	2,557 (11.0)	15,522 (11.1)
Poly cystic ovary syndrome	1,749 (7.5)	2,930 (2.1)

Abbreviations: NSAIDs: non-steroidal anti-inflammatory drugs; S: suppressed data in order to comply with CPRD privacy restrictions; SD: Standard deviation; VTE: Venous thromboembolism.

* Estimates reported from before data imputation

Table 4. Drospirenone-containing combined oral contraceptives and the rate of venous thromboembolism among restarters of COCs.

Exposure	No. of Events	No. of patients	Person-Years (PYs)	IR (95% CI)*	Crude HR	Adjusted HR (95% CI) †
Levonorgestrel	66	139,768	142,463.0	4.6 (3.6-5.9)	1.00	1.00 (Reference)
Drospirenone	19	23,191	21,154.0	9.0 (5.4-14.0)	1.95	1.96 (1.12-3.41)
0-84 days	S	23,191	5,235.0	7.6 (2.1-19.6)	1.61	1.97 (0.61-6.37)
85-150 days	S	22,286	8,764.2	3.4 (0.7-10.0)	1.87	1.68 (0.42-6.78)
150+ days	12	17,136	19,317.6	6.2 (3.2-10.9)	2.12	1.97 (0.97-4.00)
Unprovoked VTE						
Levonorgestrel	53	139,768	142,463.0	3.7 (2.8-4.9)	1.00	1.00 (Reference)
Drospirenone	18	23,191	21,154.0	8.5 (5.0-13.4)	2.46	2.28 (1.26-4.14)
Effect modification‡,§						
Smokers:						
Levonorgestrel	29	59,621	57,530.4	5.0 (3.4-7.2)	1.00	1.00 (Reference)
Drospirenone	9	9,080	7,840.6	11.5 (5.2-21.8)	2.75	2.68 (1.19-6.02)
Non-smokers:						
Levonorgestrel	37	80,147	84,932.6	4.4 (3.1-6.0)	1.00	1.00 (Reference)
Drospirenone	10	14,111	13,313.4	7.5 (3.6-13.8)	1.44	1.39 (0.59-3.25)

Abbreviations: CI: Confidence interval; COC: Combined oral contraceptive; HR: Hazard ratio; IR: Incidence Rate; S: suppressed data in order to comply with CPRD privacy restrictions.

*Rate differences are expressed as events per 1,000 person-years.

† Adjusted for HDPS decile (including several prespecified confounders) and an interaction term between HDPS decile and HDPS as a continuous variable.

‡ The planned assessment of effect modification by thrombophilia was not performed as there were insufficient data to test the presence of effect modification.

§ P value for interaction between exposure and smoking was 0.29.

FIGURE LEGEND

Figure 1. Flow chart describing the creation of the first-time user cohort.

Figure 2. Forest plot describing results of sensitivity analyses of the first-time user cohort.

Figure 3. Flow chart describing the creation of the restarter cohort.

Figure 4. Forest plot describing the results of sensitivity analyses of the restarter cohort.

Figure 1. Flow chart describing the creation of the first-time user cohort.

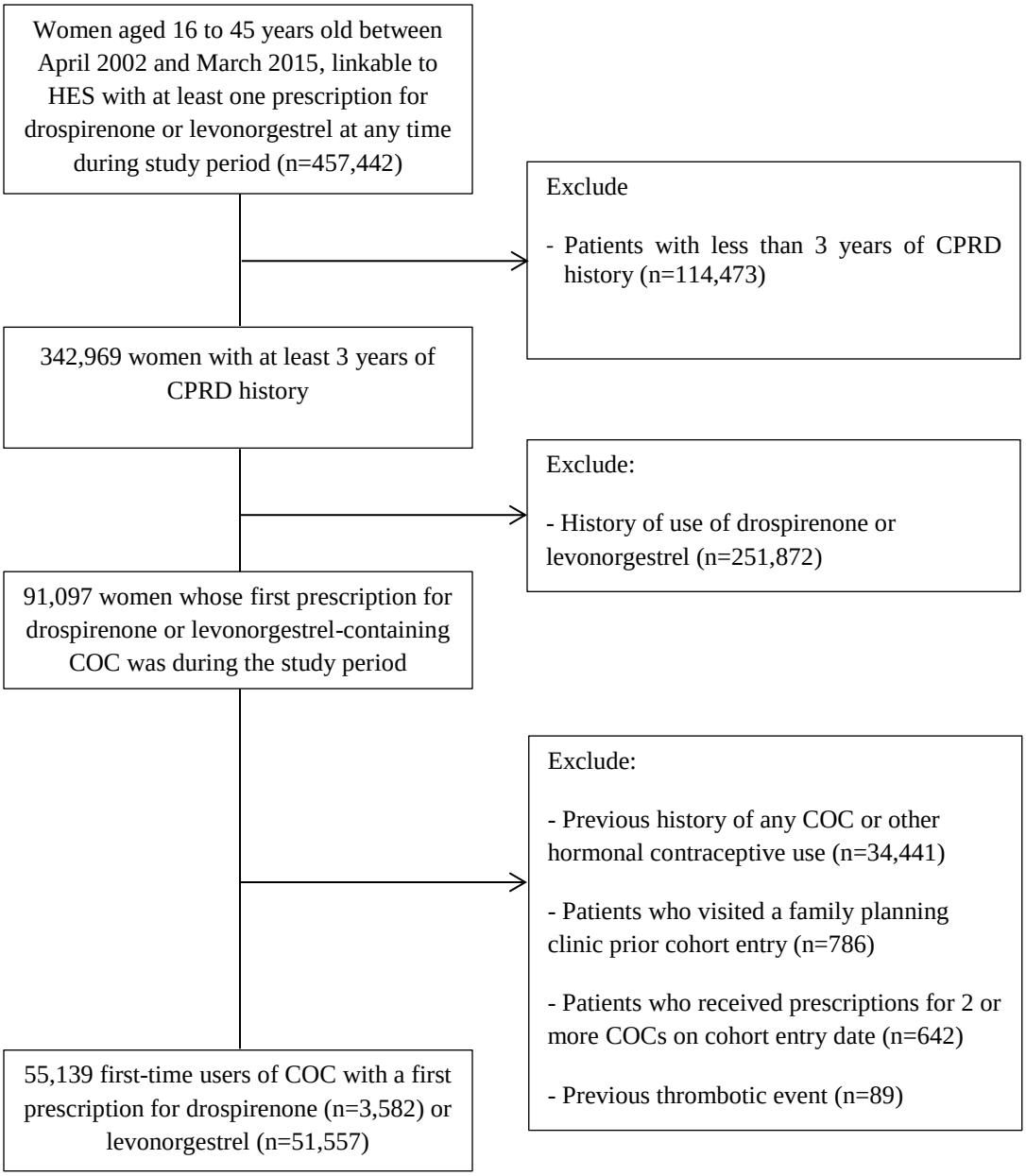


Figure 2. Forest plot describing results of sensitivity analyses of the first-time user cohort.

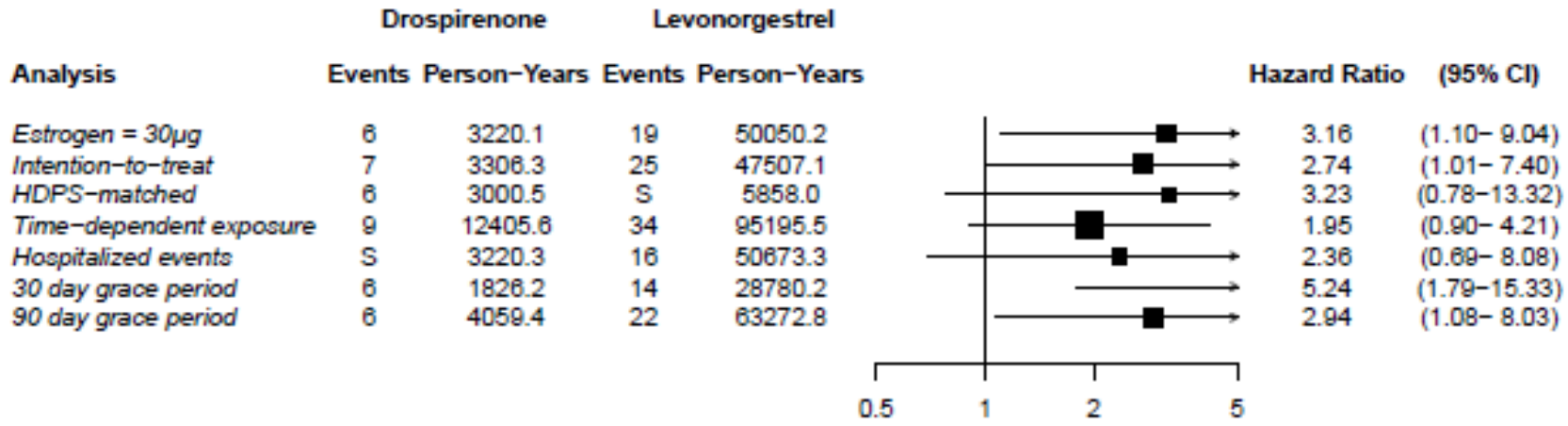


Figure 3. Flow chart describing the creation of the restarter cohort.

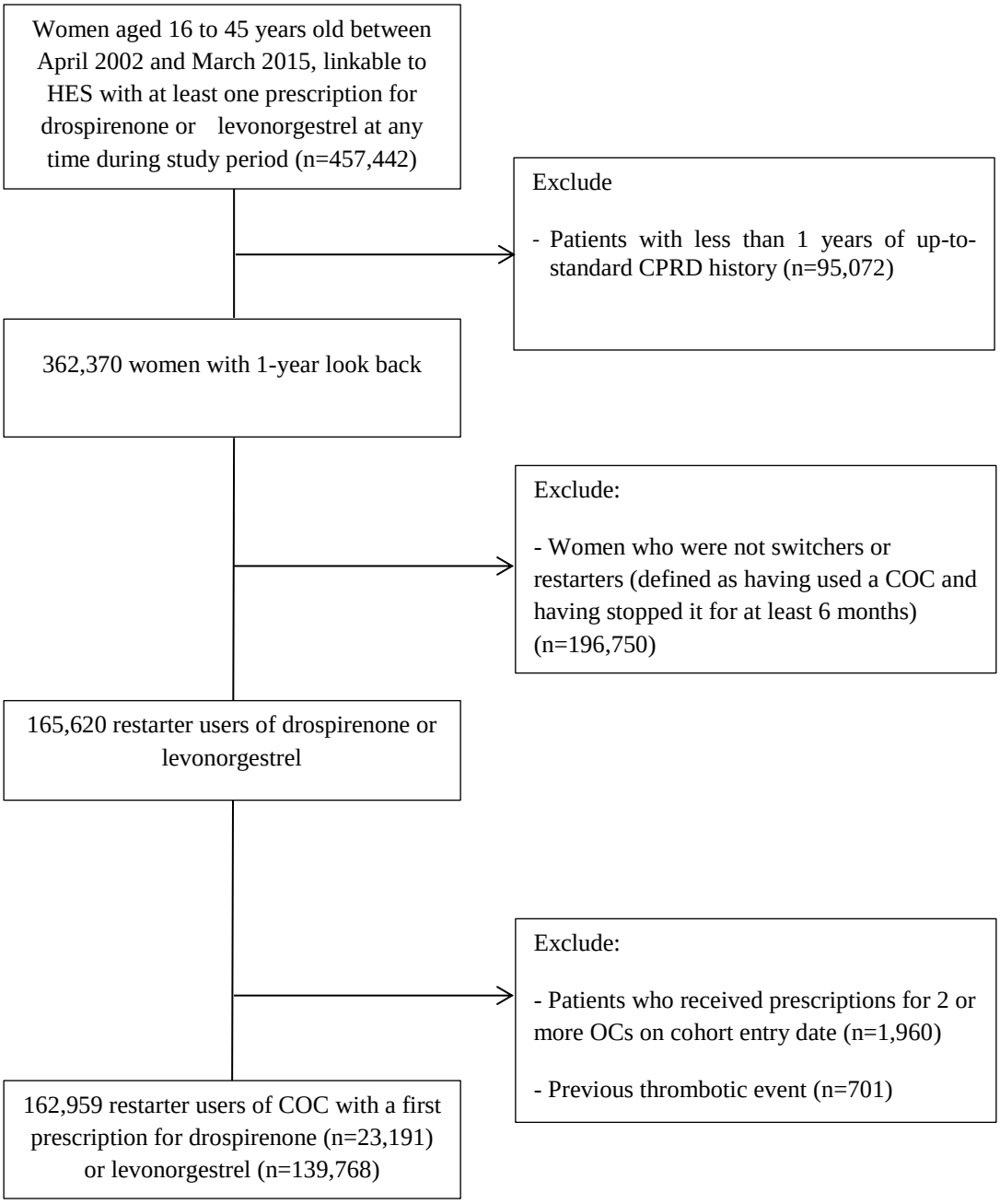
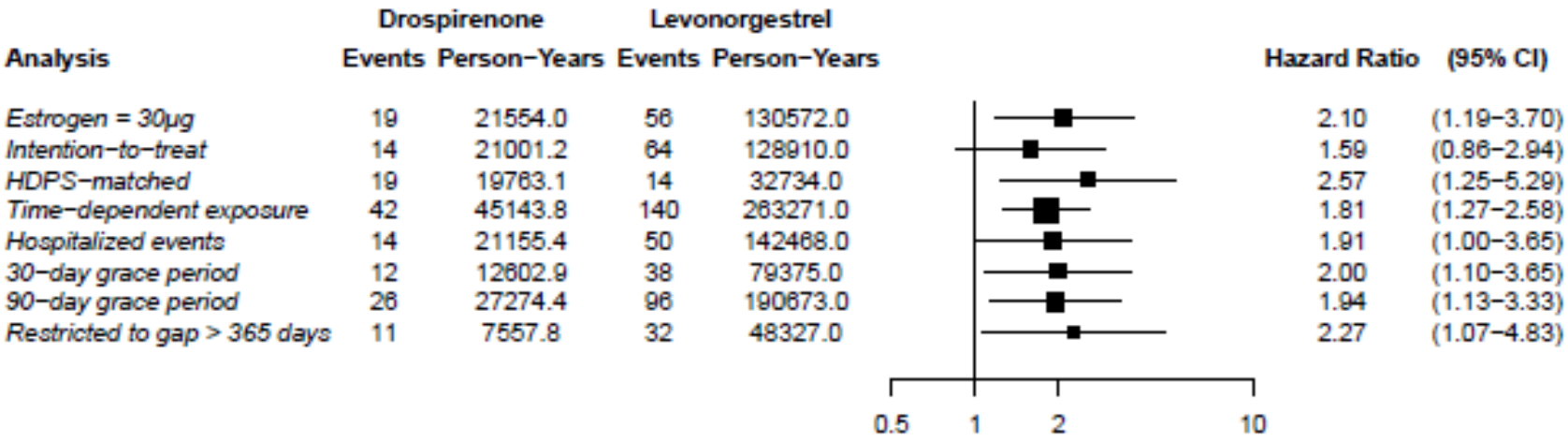


Figure 4. Forest plot describing the results of sensitivity analyses of the restarter cohort.



SUPPLEMENTAL

Table S1. Reasons for cohort exit by exposure group among first-time users.

Reason for cohort exit	**Drospirenone n (%)**	**Levonorgestrel n (%)**
VTE	6 (0.2)	19 (0.1)
Censoring:		
ATE	S	S
Pregnancy	S	S
End of registration in CPRD/end of study period	432 (12.1)	6,583 (12.8)
Switching	1,897 (53.0)	26,279 (51.0)
Discontinuation of study drug	1,243 (34.7)	18,584 (36.1)

S: suppressed data in order to comply with CPRD privacy restrictions.

Table S2 –Sensitivity analyses of drospirenone-containing COCs and rates of venous thromboembolism among first-time users.

Exposure Category	Events n (%)	No. of patients	Person-Years	IR (95% CI)*	Crude HR	Adjusted HR (95% CI) †
Restricted to estrogen doses = 30µg						
Levonorgestrel	19	50,905	50,050.2	3.8 (2.3-5.9)	1.00 (Reference)	1.00 (Reference)
Drospirenone	6	3,582	3,220.1	18.6 (6.8-40.6)	4.815	3.16 (1.11-8.98)
Intention-to-treat analysis‡						
Levonorgestrel	25	51,557	47,507.1	5.3 (3.4-7.8)	1.00 (Reference)	1.00 (Reference)
Drospirenone	7	3,582	3,306.3	21.2 (8.5-43.6)	4.02	2.74 (1.03-7.25)
HDPS-matched analysis§						
Levonorgestrel	S	3,363	S	5.1 (1.1-15.0)	1.00 (Reference)	1.00 (Reference)
Drospirenone	6	3,363	3,000.5	20.0 (0.7-4.4)	3.37	3.23 (0.77-13.57)
Time-dependent exposure definition‖						
Levonorgestrel	34	51,557	95,195.5	3.6 (2.5-5.0)	1.00 (Reference)	1.00 (Reference)
Drospirenone	9	3,582	12,405.6	7.3 (3.3-13.8)	2.31	1.95 (0.91-4.20)
Restricted to hospitalized events						
Levonorgestrel	16	51,557	50,673.3	3.2 (1.8-5.1)	1.00 (Reference)	1.00 (Reference)
Drospirenone	S	3,582	S	12.4 (3.4-31.8)	3.89	2.36 (0.67-8.24)
30-Day grace period						
Levonorgestrel	14	51,557	28,780.0	4.9 (2.7-8.2)	1.00 (Reference)	1.00 (Reference)
Drospirenone	6	3,582	1,826.2	3.3 (12.1-71.5)	6.72	5.24 (1.78-15.44)
90-Day grace period						
Levonorgestrel	22	51,557	63,273.0	3.5 (2.2-5.3)	1.00 (Reference)	1.00 (Reference)
Drospirenone	6	3,582	4,059.4	14.8 (5.4-32.2)	4.28	2.94 (1.05-8.19)

Abbreviations: CI: Confidence interval; COC: Combined oral contraceptive; HR: Hazard ratio; IR: Incidence Rate; S: suppressed data in order to comply with CPRD privacy restrictions.

*Rate differences are expressed as events per 1,000 person-years.

† Adjusted for HDPS decile (including several prespecified confounders) and an interaction term between HDPS decile and HDPS as a continuous variable.

‡ Maximum follow-up of one year. Users' follow-up censored on discontinuation, pregnancy, ATE, death, departure from the CPRD or HES, and end of the study period.

[§]Based on a 1:1 HDPS match.
[‖] This analysis resulted in the inclusion of three exposure categories: drospirenone-containing COCs, levonorgestrel-containing COCs, and no current use. Users censored on discontinuation, pregnancy, ATE, death, departure from the CPRD or HES, and end of the study period

Table S3 – *First-time user analysis:* Baseline characteristics of the events stratified by confirmed and unconfirmed VTE

Characteristic	**Unconfirmed VTE (n=139)**	**Confirmed VTE (n=25)**
	n (%)	**n (%)**
Drug defining cohort entry		
Drospirenone	7 (5.0)	6 (24.0)
Levonorgestrel	132 (95.0)	19 (76.0)
Age, mean (SD)		
16-25	104 (74.8)	18 (72.0)
26-35	23 (16.6)	S
36-45	12 (8.6)	S
Year of cohort entry		
2002	10 (7.2)	S
2003	23 (16.6)	S
2004	21 (15.1)	0 (0.0)
2005	23 (16.6)	S
2006	14 (10.1)	S
2007	12 (8.6)	S
2008	13 (9.4)	6 (24.0)
2009	7 (5.0)	S
2010	5 (3.6)	6 (24.0)
2011	5 (3.6)	S
2012	S	0 (0.0)
2013	S	S
2014	0 (0.0)	S
Family history of VTE	0 (0.0)	0 (0.0)
Lifestyle characteristics		
Alcohol abuse	S	0 (0.0)
BMI*, mean (SD)	23.6 (4.3)	30.3 (10.7)
Smoker†	47 (33.8)	6 (24.0)
Non smoker†	92 (66.2)	19 (76.0)
Comorbidities and inflammatory conditions		
Asthma	27 (19.4)	S
Congestive heart failure	0 (0.0)	0 (0.0)
Respiratory failure	0 (0.0)	0 (0.0)
Inflammatory bowel disease	0 (0.0)	0 (0.0)
Malignancy	S	S
Renal disease	0 (0.0)	0 (0.0)

Rheumatoid arthritis	S	0 (0.0)
Systemic lupus erythematosus	0 (0.0)	0 (0.0)
Thrombophilia	0 (0.0)	0 (0.0)
Varicose veins	5 (3.6)	0 (0.0)
Hospital events		
Central venous catheters	0 (0.0)	0 (0.0)
Hospital length stay > 3 days	17 (12.2)	S
Major general surgery	S	0 (0.0)
Orthopedic surgery (Hip/knee replacement)	S	0 (0.0)
Pregnancy	90 (64.8)	8 (32.0)
Spinal cord injury	0 (0.0)	0 (0.0)
Trauma (Leg/hip/pelvis fracture)	S	S
Medications		
Antiplatelet therapy	0 (0.0)	0 (0.0)
Aspirin	S	0 (0.0)
NSAIDs	20 (14.4)	S
Poly cystic ovary syndrome	0 (0.0)	S

Abbreviations: NSAIDs: non-steroidal anti-inflammatory drugs; S: suppressed data in order to comply with CPRD privacy restrictions; SD: Standard deviation; VTE: Venous thromboembolism.

* Estimates reported before data imputation.

† Estimates reported after data imputation.

Table S4. Reasons for cohort exit by exposure group among restarters.

Reason for censoring	**Drospirenone n (%)**	**Levonorgestrel n (%)**
VTE	19 (0.08)	66 (0.05)
Censoring:		
ATE	S	16 (0.01)
Pregnancy	S	651 (0.47)
End of registration in CPRD/end of study period	4175 (18.00)	21112 (15.11)
Switching	10340 (44.59)	59006 (42.22)
Discontinuation of study drug	8568 (36.95)	58917 (42.15)

S: suppressed data in order to comply with CPRD privacy restrictions.

Table S5 – *Restarter user analysis:* Sensitivity analyses of rates of venous thromboembolism

Exposure Category	Events n (%)	No. of patients	Person-Years	IR (95% CI)*	Crude HR	Adjusted HR (95% CI) †
Restricted to estrogen doses = 30µg						
Levonorgestrel	56	129,137	130,572.0	4.3 (3.2-5.6)	1.00 (Reference)	1.00 (Reference)
Drospirenone	19	23,191	21,554.0	8.8 (5.3-13.8)	2.11	2.10 (1.19-3.70)
Intention-to-treat analysis‡						
Levonorgestrel	64	139,768	128,910.0	5.0 (3.8-6.3)	1.00 (Reference)	1.00 (Reference)
Drospirenone	14	23,191	21,001.2	6.7 (3.6-11.2)	1.34	1.59 (0.86-2.94)
HDPS-matched analysis§						
Levonorgestrel	14	21,752	32,734.0	4.3 (2.3-7.2)	1.00 (Reference)	1.00 (Reference)
Drospirenone	19	21,752	19,763.1	9.6 (5.8-15.0)	2.63	2.57 (1.25-5.30)
Time-dependent exposure definition‖						
Levonorgestrel	140	139,768	263,271.0	5.3 (4.5-6.3)	1.00 (Reference)	1.00 (Reference)
Drospirenone	42	23,191	45,143.8	9.3 (6.7-12.6)	1.74	1.81 (1.27-2.58)
Hospitalized events						
Levonorgestrel	50	139,768	142,468.0	3.5 (2.6-4.6)	1.00 (Reference)	1.00 (Reference)
Drospirenone	14	23,191	21,155.4	6.6 (3.6-11.1)	1.91	1.91 (1.00-3.65)
30-day grace period						
Levonorgestrel	38	139,768	79,375.0	4.8 (3.4-6.6)	1.00 (Reference)	1.00 (Reference)
Drospirenone	12	23,191	12,602.9	9.5 (4.9-16.6)	1.96	2.00 (1.10-3.66)
90-day grace period						
Levonorgestrel	96	139,768	190,673.0	5.0 (4.1-6.1)	1.00 (Reference)	1.00 (Reference)
Drospirenone	26	23,191	27,274.4	9.5 (6.2-14.0)	1.95	1.94 (1.13-3.33)
Restarter users with gap ≥ 365 days						
Levonorgestrel	32	57,459	48,327.0	6.6 (4.5-9.3)	1.00 (Reference)	1.00 (Reference)
Drospirenone	11	9,250	7,557.8	14.6 (7.3-26.0)	2.22	2.27 (1.07-4.84)

Abbreviations: CI: Confidence interval; COC: Combined oral contraceptive; HR: Hazard ratio; IR: Incidence Rate; S: suppressed data in order to comply with CPRD privacy restrictions.
*Rate differences are expressed as events per 1,000 person-years.
† Adjusted for HDPS decile (including several prespecified confounders) and an interaction term between HDPS decile and HDPS as a continuous variable.
‡ Maximum follow-up of one year. Users' follow-up censored on discontinuation, pregnancy, ATE, death, departure from the CPRD or HES, and end of the study period.
§Based on a 1:1 HDPS match.
‖ This analysis resulted in the inclusion of three exposure categories: drospirenone-containing COCs, levonorgestrel-containing COCs, and no current use. Users censored on discontinuation, pregnancy, ATE, death, departure from the CPRD or HES, and end of the study period.

Table S6 – *Restarter user analysis*: Baseline characteristics of the events stratified by confirmed and unconfirmed VTE

Characteristic	**Unconfirmed VTE (n=332)**	**Confirmed VTE (n=85)**
	n (%)	**n (%)**
Drug defining cohort entry		
Drospirenone	78 (12.2)	19 (22.4)
Levonorgestrel	564 (87.9)	66 (77.7)
Age, mean (SD)		
16-25	222 (34.6)	26 (30.6)
26-35	341 (53.1)	41 (48.2)
36-45	79 (12.3)	18 (21.2)
Year of cohort entry		
2002	154 (24.0)	11 (12.9)
2003	120 (18.7)	12 (14.1)
2004	76 (11.8)	8 (9.4)
2005	69 (10.8)	8 (9.4)
2006	59 (9.2)	S
2007	39 (6.1)	S
2008	36 (5.6)	11 (12.9)
2009	25 (3.9)	8 (9.4)
2010	25 (3.9)	9 (10.6)
2011	15 (2.3)	S
2012	9 (1.4)	S
2013	12 (1.9)	S
2014	S	S
Family history of VTE	0 (0.0)	0 (0.0)
Lifestyle characteristics		
Alcohol abuse	21 (3.3)	1 (1.2)
BMI*, mean (SD)	26.0 (5.6)	26.6 (6.8)
Smoker*	313 (48.8)	38 (44.7)
Non smoker	329 (51.3)	47 (55.3)
Comorbidities and inflammatory conditions		
Asthma	138 (21.5)	16 (18.8)
Congestive heart failure	0 (0.0)	0 (0.0)
Respiratory failure	0 (0.0)	0 (0.0)
Inflammatory bowel disease	S	S
Malignancy	33 (5.1)	6 (7.1)
Renal disease	0 (0.0)	0 (0.0)
Rheumatoid arthritis	10 (1.6)	S
Systemic lupus erythematosus	S	0 (0.0)

Thrombophilia	0 (0.0)	0 (0.0)
Varicose veins	68 (10.6)	S
Hospital events		
Central venous catheters	0 (0.0)	0 (0.0)
Hospital length stay > 3 days	142 (22.1)	19 (22.4)
Major general surgery	51 (7.9)	10 (11.8)
Orthopedic surgery (Hip/knee replacement)	0 (0.0)	0 (0.0)
Pregnancy	497 (77.4)	55 (64.7)
Spinal cord injury	S	0 (0.0)
Trauma (Leg/hip/pelvis fracture)	7 (1.1)	0 (0.0)
Medications		
Antiplatelet therapy	0 (0.0)	0 (0.0)
Aspirin	0 (0.0)	0 (0.0)
NSAIDs	108 (16.8)	15 (17.7)
Poly cystic ovary syndrome	21 (3.3)	S

Abbreviations: NSAIDs: non-steroidal anti-inflammatory drugs; S: suppressed data in order to comply with CPRD privacy restrictions; SD: Standard deviation; VTE: Venous thromboembolism.

* Estimates reported from before data imputation.

FIGURE LEGEND

Figure S1. High-dimensional propensity score distributions among first-time users of drospirenone- and levonorgestrel-containing COCs.

Figure S2. Hazard function among first-time users of drospirenone- and levonorgestrel-containing COCs.

Figure S3. High-dimensional propensity score distributions among restarter users of drospirenone- and levonorgestrel-containing COCs.

Figure S4. Hazard function among restarter users of drospirenone- and levonorgestrel-containing COCs.

Figure S1. High-dimensional propensity score distributions among first-time users of drospirenone- and levonorgestrel-containing COCs.

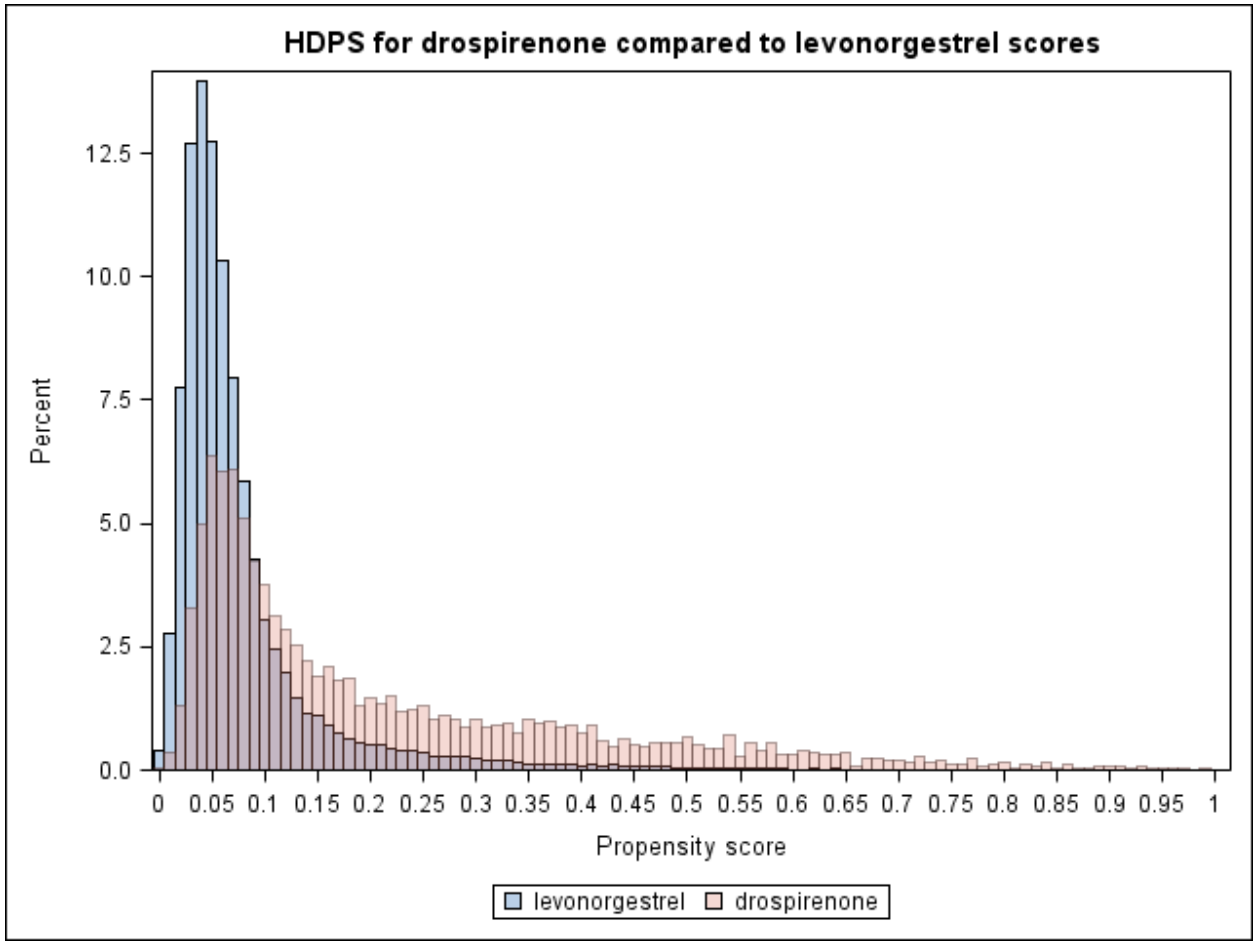


Figure S2. Hazard function among first-time users of drospirenone- and levonorgestrel-containing COCs.

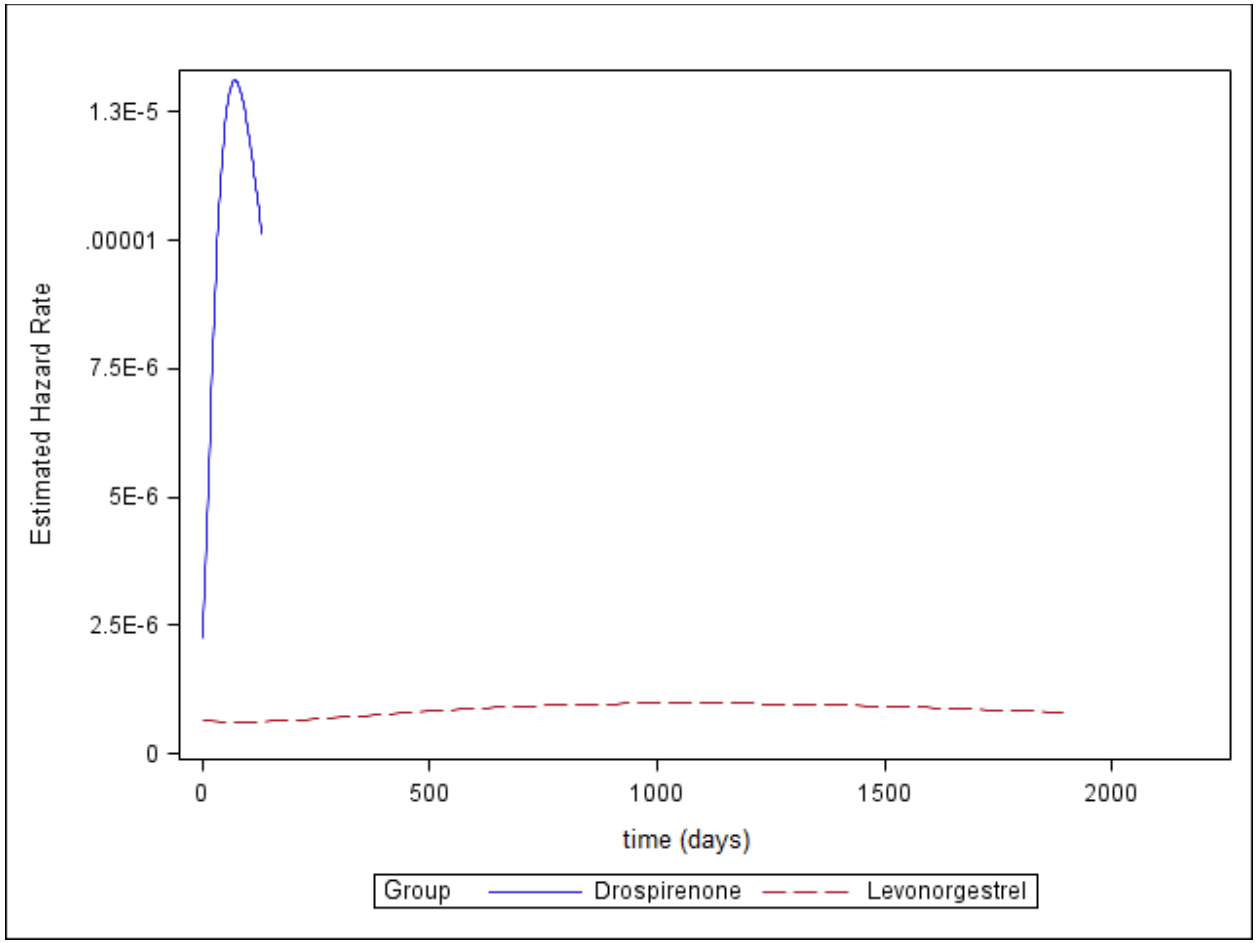


Figure S3. High-dimensional propensity score distributions among restarter users of drospirenone- and levonorgestrel-containing COCs.

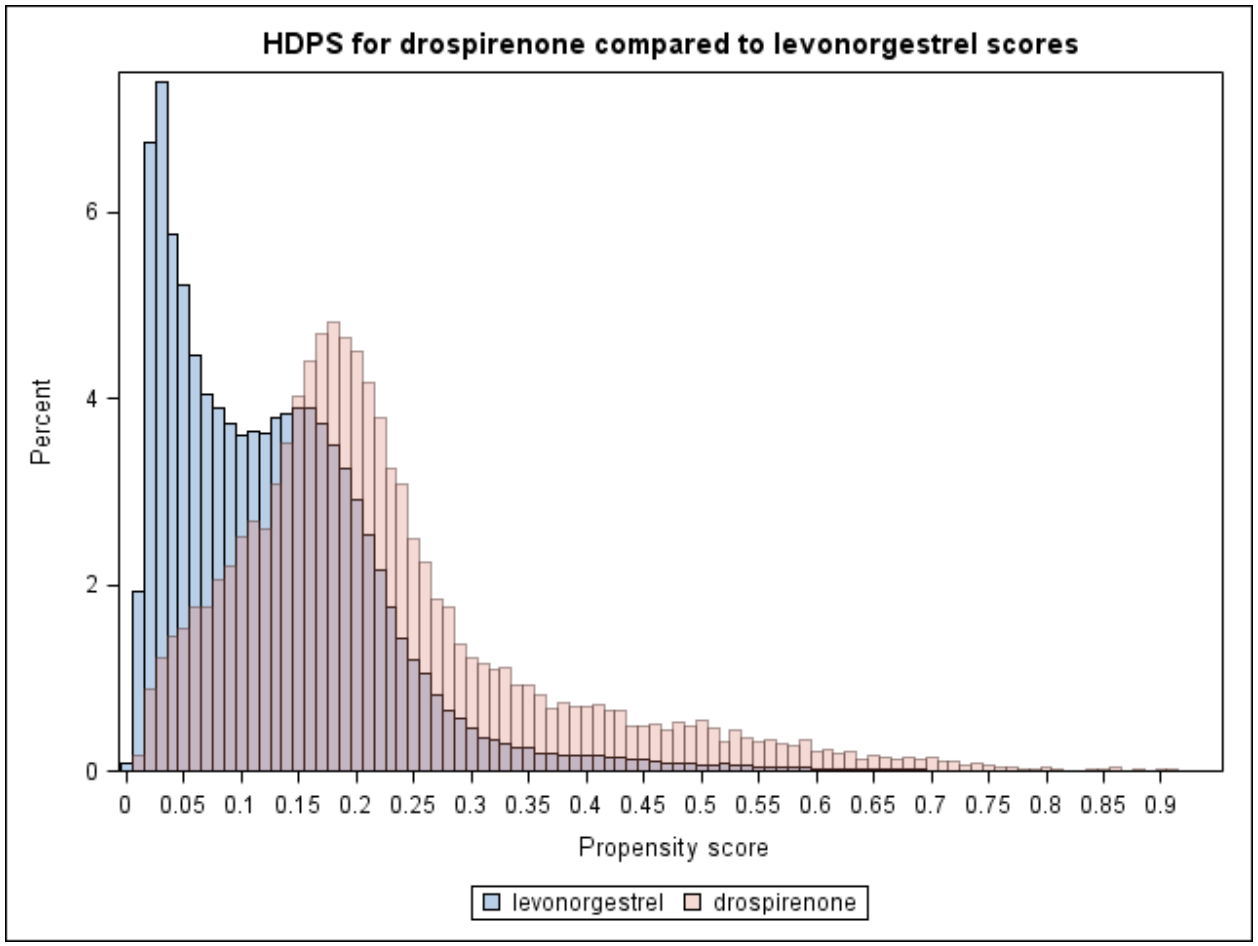
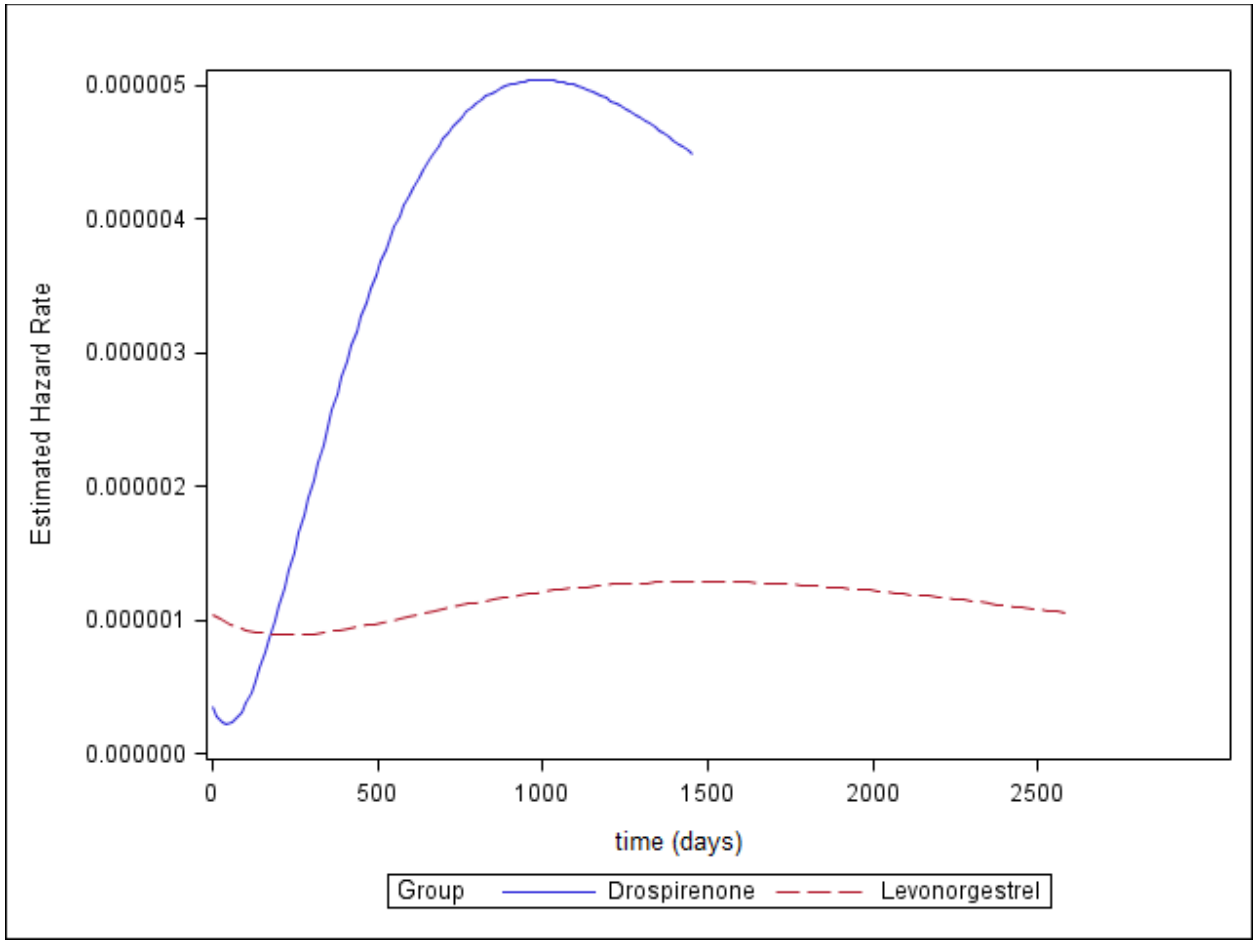


Figure S4. Hazard function among restarter users of drospirenone- and levonorgestrel- containing COCs.



4.3 Supplementary materials for methods of substantive paper

Pre-specified confounder selection

All of the covariates were included on the basis of being a risk factor for VTE and/or influencing the probability of exposure to oral contraceptives. In general, there are several risk factors that are capable of independently increasing the risk of VTE (i.e., age, family history of VTE, previous VTE, obesity) but risk factors also act cumulatively[40], increasing risk substantially with each additional risk factor[62]. In Table 4.1, I provide the rationale for the potential confounders included as covariates in the statistical models.

Table 4.1. Summary of rationale for pre-specified confounder selection

Risk factor	**Rationale**	**References**
Lifestyle characteristics		
Age	Associated with decreased mobility and an increase in age-related changes in clotting tendency of the blood and veins themselves. Incidence of VTE increases from approximately 1 in 100,000 in females aged 0 to 25 years to 1 in 100 in woman aged > 80 years.	63,64
Calendar year	A marker for changes in prescription patterns over time and VTE diagnostic time-trends.	63,64
Family history of VTE	A proxy for genetic risk factors for VTE, including defects in the coagulation cascade that have been linked to a higher incidence of VTE such as thrombophilia, antithrombin deficiency, protein C and S deficiencies, APC resistance, factors VIII, IX, and XI, and hyperhomocysteinemia.	41,65
Prior VTE	Risk of recurrence of VTE is strongest in the first 6-12 months, decreasing thereafter. Cumulative recurrence rates are 25% and 30% at 5 and 10 years, respectively, which increase without anticoagulation prophylaxis for unprovoked VTE.	26
Smoking, alcohol, obesity	Have been cited as controversial risk factors, with evidence suggesting that attributable diseases or other predisposing factors are essential for them to be independent risk factors of VTE. Patients with a BMI >30 having a four-fold higher incidence than patients with BMI <30.	41,51,66-71
Comorbidities		

Asthma, renal disease, stroke	Increase risk of VTE due to the periods of immobility that occur during hospitalization for such conditions (e.g., asthma and its associated oral corticosteroid use are independent risk factors for PE (HR: 3.33, 95% CI: 1.16-9.93 and HR: 2.82, 95% CI: 1.09-7.30, respectively) due to activated coagulation in the airways)	[40,72]
Heart failure, respiratory failure	Associated with increased age and prolonged immobility.	[73]
Malignancy	Associated with pathways of prolonged immobility and procedure-related hypercoagulability. Patients with malignancy who receive chemotherapy have been shown to be at a 2-3 times higher risk of VTE.	[41]
Polycystic ovary syndrome (PCOS)	Mechanism is still controversial but may be a pre-disposing factor for VTE.	[69,74]
Rheumatic disease, inflammatory bowel disease, systemic lupus erythematosus	Associated with reduced size of veins and increased risk of vein wall damage that occurs with inflammation.	[40]
Thrombophilia	A genetic condition that increases risk of thrombosis.	[75]
Varicose veins	Associated with increasing age.	[76]
Hospital events and procedures		
Hospitalization, spinal cord injury, and central venous catheters	Hospitalization with length of stay > 3 days, spinal cord injury inducing paralysis, and central venous catheters introduce long periods of immobility and subsequent increases in coagulability of blood.	[41,77,78]
Parity	Pregnancy is a hypercoagulable state with known increases in characterized procoagulant factors and simultaneous decrease of other anticoagulant factors (e.g., protein C and protein S. Moreover, multiple pregnancies are associated with thrombotic risk factors such as increased venous capacitance, vein mechanical obstruction due to the uterus, etc.	[79]
Major general surgery	Cardiac, abdominal, gynecological, genitourinary, neurological are all major surgeries and thus are associated with long periods of immobilization. Inactivity of the muscles causes blood to accumulate in the lower regions of the body and increase risk of DVT.	[40,41]
Orthopedic surgery	Hip/knee replacement are associated with long periods of immobilization and thus increase risk of VTE.	
Trauma	Leg/hip/pelvis fractures are associated with long periods of immobilization and thus increase risk of VTE.	

Prescribed medication		
Antiplatelet therapy, aspirin, non-steroidal anti-inflammatory drugs (NSAIDs)	Drugs used to treat inflammatory conditions increase the risk for VTE by nature of treating conditions that are associated with reduced size of veins and increased risk of vein wall damage that occurs with inflammation.	[40]

Creation of operationalized variable definitions

One of the major endeavors in conducting the CPRD study was the creation of all operationalized variable definitions. While some variable definitions were already available from other members of the research team, definitions for exposure, outcome, and many of the covariates needed to be created (Table 4.2).

Table 4.2. Summary of creation of operationalized variable definitions

Variable	Previously defined	Needed to define
Exposure		
Drospirenone-containing COCs		X
Levonorgestrel-containing COCs		X
Outcome		
VTE outcome		X
INR	X	
Anticoagulation	X	
Censoring Events		
Other hormonal contraceptives		X
Arterial thromboembolism		X
Pregnancy		X
Covariates		
Smoking	X	
Alcohol use	X	
BMI	X	
Family history of VTE		X
Asthma		X
Heart failure	X	
Respiratory failure	X	
Inflammatory Bowel disease (IBD) (Including crohn's)		X
Malignancy (cancer)	X	

Renal disease	X	
Rheumatoid arthritis		X
Stroke	X	
Systemic lupus erythematosus		X
Thrombophilia	X	
Varicose veins		X
Central venous catheters		X
Hospitalization (admission resulting in bed rest > 3 days)	X	
Trauma (hip/pelvis/long bone fracture)	X	
Orthopedic surgery (hip/knee replacement)	X	
Major general surgery (cardiac, abdominal, gynecological, genitourinary, neurological)		X
Spinal cord injury		
Parity	X	
Antiplatelet therapy	X	
Polycystic ovary syndrome (PCOS)	X	

In general, the creation of definitions involved an iterative process of identifying all of the possible synonyms for each variable. Next, all synonyms would be searched within the CPRD browser tool for Read codes (for diagnoses) or product codes (for drugs), within the ICD10 code lookup[80] for HES diagnoses, or within the OPCS procedural codes for surgical and procedural codes. For instance, in creating the variable "thrombosis", the following synonyms were searched within the CPRD browser tool (with wildcards included before and after the tem): 'thromboembolism' or 'thrombosis' or 'thromboses' or 'thrombolytic' or 'thrombolysis' or 'thrombus' or 'thrombosed' or 'thrombocytic' or 'thrombocythaemia' or 'thrombocytopenic' or 'thrombophilia' or 'clot' or 'blood clot' or 'thrombus' or 'embolectomy' or 'embolisation' or 'embolic' or 'thrombophlebitis' or 'embolus' or 'thrombocytopenia' or 'thromboangiitis' or 'thromboplastin'. Each variable definition was then cross-referenced with a previously created or validated definition, cross-referenced with a publicly available definition[81], or approved by a physician in general internal medicine.

Creation of VTE and ATE definitions

Although VTE typically includes DVT and PE, venous thrombosis of atypical veins sites (e.g., the eyes, kidney, spleen, liver, and gut vessels) was also included. Therefore, the search focused on the term "thrombosis", with identified codes subsequently classified as VTE, ATE, or unclear. ATE describes thromboses that occur in the arterial circulation, including stroke and myocardial infarction. Although the pathophysiology of arterial thrombosis differs from that of VTE, COC use has also been linked to ATE[58]. A diagnostic code for thrombosis would be considered to fall in the unclear category if, for example, it was a mesenteric (involving a gut vessel) thromboembolism but did not specify whether it was in an artery or a vein. As such, variables were defined with high specificity.

Creation of contraceptive variables

Three contraceptives variables needed to be defined: drospirenone-containing COCs, levonorgestrel-containing COCs, and all other OCs. To do this, I adopted two approaches. First, I defined all types of progestin (Table 4.3). By definition, a hormonal contraceptive contains a progestin.

Table 4.3. Progestins included in hormonal contraception by generation

Generation	**Progestin**
First	Ethisterone, norethisterone, norethisterone acetate, noretynodrel, etynodiol diacete, medroxyprogesterone acetate, megestrol acetate
Second	Norgestrel, levonorgestrel
Third	Norgestimate, norelgestromin, desogestrel, etonogestrel, gestodene
Fourth	Dienogest, drospirenone, nestorone, nomegestrol acetate, trimegestone

I searched for all of these progestins in the browser tool. The second approach was to determine all possible generic and brand names of available contraceptives in the UK[82]: Cilest®, Microgynon 30 ED®, Microgynon 30®, BiNovum®, Brevinor®, Katya® 30/75, Levest®, Loestrin 20®, Loestrin 30®, Logynon ED®, Logynon®, Micronor®, Norgeston®, Noriday®, Norimin®, Norinyl-1®, Ovranette®, Ovysmen®, Rigevidon®, Synphase®, TriNovum®, TriRegol®, Cerazette®, Femodene®, Femodene® ED, Femodette®, Gedarel® 20/150, Gedarel® 30/150, Marvelon®, Mercilon®, Millinette® 20/75, Millinette® 30/75, Sunya® 20/75, Yasmin®, Qlaira®. After searching for this list using the browser tool, I then sorted the resulting codes into 10 mutually exclusive groups: 1) drospirenone COCs, 2) levonorgestrel COCs, 3) other COCs (1st, 2nd, 3rd, 4th generation COCs that did not contain drospirenone or levonorgestrel), 4) non-COC (progestin-only oral contraceptives), 5) the vaginal ring, 6) the transdermal patch, 7) the IUD, 8) intramuscular injection/implant, 9) the cervical cap, and 10) other hormonal pills that were not for inclusion in our list of hormonal contraceptives (e.g., emergency contraceptive, hormone replacement therapy). The first two groups were used to define the main exposure and reference groups, respectively, while groups 3-9 were used to define "other hormonal contraceptives".

Creation of pregnancy variable

A pregnancy variable was created to censor patients no longer at risk of receiving a COC. Because the beginning of pregnancy is sometimes unknown and is not recorded in the CPRD, I estimated the beginning of pregnancy from the date of delivery by assuming a gestational age of 12 weeks for pregnancies with an abortive/ectopic outcome, 245 days for a preterm delivery, 280 days for a term delivery, and 294 days for post-term deliveries. Pregnancies were considered to end in term delivery unless otherwise specified.

Creation of major general surgery

Surgery is a well-known risk factor for VTE.[41] I sub-classified surgery into three categories: trauma (hip/pelvis/long bone fracture/reduction), orthopedic surgery (hip/knee replacement), and major general surgery. Major general surgery was classified into five main categories: gynaecological surgery, thoracic surgery (including cardiac surgery and coronary artery bypass grafting [CABG]), general abdominal surgery, neurosurgery, and genitourinary surgery. To create this variable, I began by consulting the protocol for surveillance of surgical site infection supplement for the operating procedure codes (OPCS)[83] (Table 4.4). This was created as part of the Surgical Site Infection Surveillance Service (SSISS). Thus, I was able to use existing definitions for several types of surgery.

Table 4.4. OPCS codes available through the SSISS

Our surgical category	**SSISS defined procedures**
Gynaecological surgery	Abdominal hysterectomy, breast surgery
Thoracic surgery	Cardiac surgery (non-CABG), CABG, vascular surgery
General abdominal surgery	Bile duct, liver or pancreatic surgery, cholecyctectomy (non-laproscopic), gastric surgery, large bowel surgery, small bowel surgery, limb amputation
Neurosurgery	Cranial surgery, spinal surgery
Genitourinary	None available

However, there were several types of surgery for which definitions were not available: kidney, bladder, adrenal, ureter, urethral surgery, ovarian, cervix, fallopian tube surgery, and pulmonary surgery. These surgical variables were defined and included as part of the major general surgery variable.

CHAPTER 4: DISCUSSION

Main findings

In my systematic review, I aimed to assess the exiting literature on the association of drospirenone-containing COCs and the risk of VTE with a particular focus on its methodological quality. I found that, although a total of 17 observational studies had assessed this association, with reported relative risks ranging from 1.0 to 3.3, all had important methodological limitations, including prevalent user bias, inappropriate comparator groups, VTE misclassification, and confounding. The results of this systematic review underscored the need for additional, methodologically-rigorous studies assessing the VTE risk of drospirenone-containing COCs.

My cohort study was designed to describe and illustrate the methodological challenge of studying the risk of VTE among first-time users of drospirenone-containing COCs. To do this, I used two parallel study designs to study this risk: a cohort of first-time users and a cohort of restarters. Among first-time users, I found that drospirenone-containing COCs were associated with a substantially higher risk of VTE than levonorgestrel-containing COCs (HR: 3.19, 95% CI: 1.12-9.08). The risk was highest soon after the initiation of use of drospirenone-containing COCs and dissipated with time. Among restarters, an elevated risk was observed with drospirenone-containing COCs (HR: 1.96, 95% CI: 1.12-3.41) but this increased risk was attenuated relative to that observed with first-time users. It is unclear if the differences in observed risk between cohorts are true differences between first-time users and restarters of COCs or the result of some restarters being inappropriately included in the first-time user analysis. Nonetheless, in the analysis restricted to restarters of COCs, a group with a similar underlying risk of VTE, drospirenone-containing COCs were associated with a doubling of VTE risk relative to levonorgestrel-containing COCs. With this analysis explicitly excluding first-time users, the

COC users with the highest underlying VTE risk, the analysis represents a conservative estimate of the VTE risk of drospirenone-containing COCs. This restarter analysis also represents a novel methodological approach to studying the VTE risk of COCs given the challenging in distinguishing first-time users from restarters given the left truncation of most healthcare databases.

Individual issues

COCs increase hemostatic parameters and therefore pose a risk of developing VTE outcomes. Due to the nature of this drug, observational studies examining the association of COCs and VTE are particularly susceptible to time-related biases. One factor to consider when studying the association of COCs and risk of VTE is the importance of comparing users of similar profiles and underlying VTE risks. In order to do so, history of use must be fully captured by both pattern and duration of OC use. Risk varies depending on patterns of first-time ever use, interrupted use (restarters, switchers), and prevalent use, which was shown to account for large margins of bias as seen with the transnational data from the 1995 UK pill scare.[84] Although, significantly large relative risks of VTE were reported for users of third generation COCs with respect to second generation COCs, when pattern and duration of use were accounted for, there were similar risk profiles among third generation and second generation groups. Specifically, the risk increases sharply to 10 relative to non-use and decreases to approximately 2 thereafter, for both groups. It is therefore only valid to compare associations of COCs and VTE among subjects with similar durations and profiles of history of COC use. Duration of use, when not accounted for, can also be a principle source of bias.[84,85] In fact, when duration of use is stratified by <1, 1-2, 2-5, and >5 years, risks between second and third generation pills disappear.[85]

Despite the differing underlying VTE risks of different user types, studies continue to address this issue inadequately. In my systematic review, I have shown that studies to date have been unable to fully account for such time related biases. There were 7 studies that restricted to first-time ever users and thus were unlikely to have prevalent user bias[29,86-91]. However, 10 of the 17 included studies included all user types (first time users, new users, switchers, and prevalent users)[52,54,59,69,92-97] and were thus likely affected by prevalent user bias. While many studies acknowledged the need to adjust for history of COC use, none of the included studies accounted for previous COC use, an important limitation in studies not restricted to first-time ever users.

The second manuscript of this thesis used observational data from the the Clinical Practice Research Datalink (CPRD)[98]. Although there are several advantages to the CPRD as highlighted previously, this administrative database also introduced a few issues. Left truncation of healthcare databases, such as the CPRD, poses many difficulties for the creation of a first-time user cohort. In the UK, women are able to receive prescriptions to COCs from family planning clinics as well as general practitioners. Given that some women may have been seen at a family planning clinic and this was not recorded in the CPRD, some women included in our first-time user cohorts may have actually been restarter user or switchers. We used several measures to try and minimize user type misclassification. First, we required three years of CPRD history to ensure no prescriptions in the three years prior. We then developed three separate codes lists: a list of Product codes for all possible prescriptions of any OC, a list of Read codes for all possible prescriptions for any OC, and a list of Read codes for being seen at a family planning/fertility clinic. We then excluded women with any of these codes prior to cohort entry. Despite our best efforts, we are still unable to say for certain that we have a first-time user cohort. However, most effective in overcoming this issue, was our inclusion of a restarter cohort. These women were

required to have a previous COC prescription and thus left truncation was not an issue for this cohort.

Despite every effort to overcome the limitations identified in the first manuscript of this thesis, some of the identified limitations remain present in my cohort study (manuscript #2). Using the same quality assessment used in the systematic review, my cohort study would be considered to have a low risk of bias according to the ACROBAT-NRSI. In addition, it would be considered to have a low risk of prevalent user bias, a low risk of bias due to inappropriate comparator groups, a moderate risk of VTE misclassification, and a moderate risk of confounding.

There are several areas for future research regarding the association of drospirenone-containing COCs and the risk of VTE. First, it would interesting to repeat this study in a database with lifetime drug exposure (such as some of those in Scandinavian countries) to determine if the observed difference in the first-time user analysis and restarter analysis is a true difference in the effect of drospirenone-containing COCs in first-time users versus restarters or whether it is due to the difficulty in identifying first-time users in the setting of left truncation and the availability of COCs from family planning clinics. It also may be helpful to have a network such as CNODES investigate this issue to have the sample size required to obtain precise treatment effects.

Implications of this thesis

In the first manuscript of this thesis, I synthesized the existing literature to provide knowledge users with a better understanding of the available evidence regarding the VTE risk of drospirenone-containing COCs. I also explained some of the heterogeneity in this literature,

providing examples of four common sources of bias. In the second manuscript of this thesis, I described and illustrated the methodological challenges in distinguishing between first-time users and restarters given the left truncation of healthcare databases. In doing so, I developed a novel approach to studying the VTE risk of COCs that overcomes the limitations of the existing literature. Using this novel approach, I was able to show that drospirenone- containing COCs double the risk of VTE versus levonorgestrel-containing COCs, even in the most conservative estimates. This finding has important implications for regulatory agencies, physicians, and women taking COCs.

CHAPTER 5: CONCLUSIONS

This thesis contained two objectives: (1) To synthesize the available evidence on the effects of drospirenone-containing COCs on the risk of VTE, with a focus on methodological strengths and limitations of this literature; (2) To describe and illustrate the methodological challenge of studying the risk of VTE among first-time users of drospirenone-containing COCs. To address the first, I conducted a systematic review that focused on methodological quality of the existing literature. I found that many studies included important limitations, such as prevalent user bias, inappropriate comparator, misclassification of VTE and confounding. Although the studies considered at lowest risk for bias suggested there may be an increased risk of VTE associated with drospirenone-containing COCs, the evidence remained inconclusive. This methodological assessment of the existing literature helped inform the design of my retrospective cohort study, which addressed the second objective. This study included two cohorts: a first-time ever user cohort and a restarter cohort, the latter of which represents a novel approach to studying the VTE risk of COCs. Although left truncation of healthcare databases is a concern for the identification of first-time users, the use of a well-defined restarter cohort suggests a doubling of VTE risk with drospirenone-containing COCs relative to levonorgestrel-containing COCs. Physicians and patients should be aware of this increased risk when considering the most appropriate choice of contraception.

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APPENDICES

Appendix A. Rates of VTE of comparative studies examining the thrombotic effects of drospirenone-containing combined oral contraceptives

Study	DRSP N*	Comparator N	Comparator Definition	IR DRSP Users†	95% CI	IR Comparator†	95% CI	Effect Measure	Point Estimate	95% CI
Dinger 2007	16,534	26,341	Levonorgestrel/ Ethinyl Estradiol	91	59, 133	80	52, 117	Hazard ratio	3.3	0.9, 10
Seeger 2007	22,429	44,858	Other OCs	130	80, 200	NR	NR	Rate ratio	0.9	0.5, 1.6
Lidegaard 2009	NR	NR	Non-users of COCs	78.3	NR	54.7	NR	Rate ratio	4.0	3.3, 4.9
Vlieg 2009	NR‡	NR	Non-users of COCs	NR	NR	NR	NR	Odds ratio	6.3	2.9, 13.7
Dinger 2010	NR§	NR	Levonorgestrel/ Ethinyl Estradiol	NR	NR	NR	NR	Odds ratio	1.0	0.5, 1.8
Parkin 2011	NR‖	NR	Levonorgestrel/ Ethinyl Estradiol	23.0	13.4, 36.9	9.1	6.6, 12.2	Odds ratio	3.3	1.4, 7.6
Jick 2011	NR¶	NR	Levonorgestrel/	30.8	25.6, 36.8	9.6	9.6, 15.9	Odds ratio	2.4	1.7, 3.4

Lidegaard 2011	NR	NR	Ethinyl Estradiol Levonorgestrel/ Ethinyl Estradiol	93	NR	75	NR	Rate ratio	2.12	1.68, 2.66
FDA 2011	142,166	198,839	Levonorgestrel/ Ethinyl Estradiol	76.1	NR	65.8	NR	Rate ratio	1.49	1.19, 1.87
Gronich 2011	73,629	21,546	Levonorgestrel/ Ethinyl Estradiol	63.3	NR	NR	NR	Rate ratio	1.65	1.02, 2.65
LASS 2011	NR	NR	Levonorgestrel/ Ethinyl Estradiol	107	81, 13.9	92	69, 120	Hazard ratio	1.1	0.8, 1.7

Abbreviations: CI = Confidence interval; COC = Combined oral contraceptive; DRSP = Drospirenone; DRSP N = Sample size of the group of patients on drospirenone-containing COCs; NR = Not reported; OC = Oral contraceptive; Comparator N = Sample size of the control group, those unexposed to drospirenone-containing COCs; VTE = Venous thromboembolism.

*Patients were given COCs containing dropirenone and ethinyl estradiol in combination. †Incidence rate per 100,000 women years. ‡Report 19 VTE cases exposed to drospirenone, 14 controls exposed to drospirenone, 421 VTE cases unexposed to drospirenone, 1,102 controls unexposed to drospirenone. §Report 25 VTE cases exposed to drospirenone, 84 controls exposed to drospirenone, 60 VTE cases unexposed to drospirenone, 197 controls unexposed to drospirenone. ||Report 17 VTE cases exposed to drospirenone, 26 controls exposed to drospirenone, 44 VTE cases unexposed to drospirenone, 189 controls unexposed to drospirenone. ¶Report 121 VTE cases exposed to drospirenone, 313 controls exposed to drospirenone, 65 VTE cases unexposed to drospirenone, 368 controls unexposed to drospirenone.

Appendix B. Ethics approval for Protocol #16_024

Centre intégré universitaire de santé et de services sociaux du Centre-Ouest-de-l'Île-de-Montréal
Québec
Hôpital général juif

CENTRE GÉRIATRIQUE DONALD BERMAN MAIMONIDES GERIATRIC CENTRE
CENTRE D'HÉBERGEMENT FATHER-DOWD RESIDENTIAL CENTRE
CENTRE D'HÉBERGEMENT HENRI-BRADET RESIDENTIAL CENTRE
CENTRE D'HÉBERGEMENT ST-ANDREW RESIDENTIAL CENTRE
CENTRE D'HÉBERGEMENT ST-MARGARET RESIDENTIAL CENTRE
CENTRE MIRIAM HOME AND SERVICES
CENTRE DE RÉADAPTATION CONSTANCE-LETHBRIDGE REHABILITATION CENTRE
CENTRE DE RÉADAPTATION MAB-MACKAY REHABILITATION CENTRE
SLD JUIF DE MONTRÉAL JEWISH ELDERCARE CENTRE
CLSC DE BENNY FARM
CLSC DE CÔTE-DES-NEIGES
CLSC MÉTRO
CLSC DE PARC-EXTENSION
CLSC RENÉ-CASSIN
HÔPITAL CATHERINE BOOTH HOSPITAL
HÔPITAL GÉNÉRAL JUIF JEWISH GENERAL HOSPITAL
HÔPITAL MOUNT SINAI HOSPITAL
HÔPITAL RICHARDSON HOSPITAL

Integrated Health and Social Services University Network for West-Central Montreal

COMITÉ D'ÉTHIQUE DE LA RECHERCHE
RESEARCH ETHICS COMMITTEE

Dr. Vasiliki Bessy Bitzas, N, PhD, CHPCN(C).
Chair, Research Ethics Committee
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February 18, 2016

Dr. Samy Suissa
Centre for Clinical Epidemiology
Jewish General Hospital

SUBJECT: **Protocol #16-024** entitled "Drospirenone-containing combined oral contraceptives and risk of venous thromboembolism"

Dear Dr. Suissa,

Thank you for submitting the following documents pertaining to the above-mentioned protocol to the Research Ethics Office for review:

- Protocol
- ISAC Evaluation of Protocols for Research Involving CPRD Data feedback to Applicants – 16_009 – Approval letter (10th February 2016)

The Research Ethics Committee of the Jewish General Hospital (Federalwide Assurance Number: 0796) is designated by the province (MSSS) and follows the published guidelines of the TCPS 2 - Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (2014), in compliance with the "Plan d'action ministériel en éthique de la recherche et en intégrité scientifique" (MSSS, 1998), the membership requirements for Research Ethics Boards defined in Part C Division 5 of the Food and Drugs Regulations; acts in conformity with standards set forth in the United States Code of Federal Regulations governing human subjects research, and functions in a manner consistent with internationally accepted principles of good clinical practice.

As this study involves no more than minimal risk in accordance with TCPS 2 article 6.12, this protocol received a delegated research ethics review. We are pleased to inform you that the above-mentioned documents are granted Delegated Approval for the period of one year.

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Delegated Approval Date:	**February 18, 2016**
Expiration date of Delegated Approval:	**February 17, 2017**

For your information, the above-mentioned protocol will be presented for corroborative approval at the next meeting of the Research Ethics Committee to be held on March 11, 2016.

Your "Continuing Review Application" must be received by the Research Ethics Committee **one month** before the expiration date above in order to ensure timely review. Otherwise, the study will be terminated.

Respectfully,

Dr. Vasiliki Bessy Bitzas, N, PhD, CHPCN(C)
Chair, Research Ethics Committee

VBB/kb
16-024DelegatedApprovalSecondaryResearch.doc