Drospirenone-containing Oral Contraceptive Pills and the Risk of Venous Thromboembolism: An Assessment of Risk in First-time Users and Restarters

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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 different underlying VTE risks, in healthcare databases.

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

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

KEY POINTS

- The identification of first-time users of oral contraceptives within databases can be challenging, and the results of a first-time user analysis are thus difficult to interpret.
- Our analysis of restarters suggests a doubling of venous thromboembolism risk with drospirenone versus levonorgestrel.

1. INTRODUCTION

The safety of fourth generation, drospirenone-containing combined oral contraceptives (COCs) remains controversial. Several observational studies have examined the association between use of drospirenone-containing COCs and the risk of venous thromboembolism (VTE)[1-17]. However, these studies have produced conflicting results, with some studies[1, 2, 4, 8, 17] suggesting no association and others[3, 5-7, 9, 11-16] 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[5, 7-10, 12-14, 16, 17], the use of inappropriate comparators[4, 5, 9, 13, 14, 16], misclassification of outcome[3, 5, 7, 10], and confounding[4-6, 9, 10]. Nonetheless, concerns regarding the VTE effects of drospirenone-containing COCs have resulted in safety reviews by the US Food and Drug Administration (FDA)[6] and the European Medicines Agency (EMA)[18]. While these agencies initially provided differing positions, they have both required labeling changes to reflect an increased risk of VTE for drospirenone-containing COCs.

One of 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. It has been suggested that the VTE risk of COCs may be greatest among first-time users, with the first year of use representing the highest risk period, and the risks gradually decreasing until the risk stabilizes[19]. Lower risks are observed among patients restarting COCs after a period of non-use[20]. Failure to account for these differences in underlying VTE risk may result in spurious associations[21, 22]. 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 and assess the association between drospirenone-containing COCs and the risk of VTE among identified first-time users and restarters of COCs.

2. 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).[23] 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[24, 25], and it has served as the data source for over 1,000 publications[23]. 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 International Statistical Classification of Diseases and Related Health Problems – 10th revision [ICD-10] codes) and procedures (based on Office of Population Censuses and Surveys – 4th revision [OCPS-4] codes), with HES linkage restricted to practices in England and available for approximately 58% of CPRD patients.

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 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] recorded in either the CPRD or HES). 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. In the restarter cohort, only 1 year of CPRD history was required for inclusion. 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.[26] Furthermore, all COCs increase the risk of thrombosis due to hemostatic changes[27]. Consequently, the use of an active comparator, as opposed to a "non-

use" comparator, overcomes a key limitation of many studies in this area[5, 9, 13, 14, 16]. It also provides the most clinically-relevant treatment comparison.

All women were 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 G08, I26, I67, I80, I81, I82, K64.5, O22, O87.3, O88); or 2) an outpatient VTE diagnosis (using Read codes; see Electronic Supplementary Material #1) 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[28, 29]. 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[16, 30-34] 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 (calculated using a 5-year assessment window prior but not including the date of cohort entry), and the variable was consequently not retained in our models. We imputed missing values for smoking status using multivariate regression with 5 different imputed databases. 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)[35]. We first used multiple logistic regression to create our propensity model, which had prescription of drospirenone-containing COCs as its dependent variable. This model included the pre-specified covariates described above as well as 500 covariates identified empirically using the HDPS algorithm. After trimming the areas of non-overlap of the HDPS distribution, we used a Cox proportional hazards model with VTE as the dependent variable as our outcome model, which included exposure, 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 idiopathic VTEs, with non-idiopathic VTEs considered an additional censoring criterion. Idiopathic 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 eight 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.[36] 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. The grace period is defined as the maximum number of days between recorded prescriptions to be considered a current oral contraceptive user. Women who had gaps longer than the duration of the grace period were considered to have discontinued current use. In the seventh, to better understand potential misclassification of outpatient events, we described the characteristics of possible VTE diagnoses (outpatient diagnosis of VTE without confirmation by anticoagulant prescription, INR testing, or death) versus probable VTE events (in-patient diagnoses and outpatient diagnoses accompanied by anticoagulant prescripton, INR testing, or death). In addition, we repeated our primary analysis with events defined using all recorded VTE diagnoses in CPRD and HES. 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).

3. 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 (Electronic Supplementary Material #2).

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: 1.1-9.1) (Table 2). Importantly, there was evidence of non-proportional hazards (p-value for exposure*time interaction <0.0001, Electronic Supplementary Material #3); the HRs for drospirenone versus levonorgestrel ranged from 7.4 (95% CI: 1.3-41.8) in the first 84 days of use to 1.0 (95% CI: 0.1-8.8) with ≥ 113 days of use. The reasons for cohort exit are described in Electronic Supplementary Material #4.

In secondary analyses, we found slightly attenuated HRs when restricting events to idiopathic VTE (3.7, 95% CI: 0.1-4.5; Table 2). In addition, the VTE risk with drospirenone-containing COCs appeared to be higher among ever smokers (HR: 10.5, 95% CI: 1.7-67.3) than among never-smokers (HR: 2.1, 95% CI: 0.6-7.7), though the interaction did not reach statistical significance (p-for-interaction: 0.15) (Table 2). The planned assessment of effect modification by thrombophilia was not performed as there were insufficient data to test the presence of effect modification.

The results of our sensitivity analyses of our cohort of first-time users were generally consistent with those of our primary analysis (Figure 2, Electronic Supplementary Material #5). Estimated HRs ranged from an adjusted HR of 2.0 (95% CI: 0.9-4.2) when exposure was defined in a time-dependent fashion to an adjusted HR of 5.2 (95% CI: 1.8-15.4) when defining exposure with a 30-day grace period. Finally, we observed similar characteristics at cohort entry when stratified on "possible" and "probable" VTE events (Electronic Supplementary Material #6).

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 (Electronic Supplementary Material #7).

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 2.0 (95% CI: 1.1-3.4) (Table 4). Hazards were, as expected, non-proportional (Electronic Supplementary Material #8). The reasons for cohort exit are described in Electronic Supplementary Material #9.

In secondary analyses, we found slightly higher risk of VTE when restricting events to idiopathic 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: 2.7, 95% CI: 1.2-6.0) than among never smokers (HR: 1.4, 95% CI: 0.6-3.3) but this did not reach statistical significance (p-for-interaction: 0.29) (Table 4). Again, the planned assessment of effect modification by thrombophilia was not performed as there were insufficient data to test the presence of effect modification.

Results of sensitivity analyses within the restarter cohort were consistent with our primary findings (Figure 4, Electronic Supplementary Material #10). Estimated HRs ranged from an adjusted HR of 1.6 (95% CI: 0.9-2.9) when exposure was based on an intention-to-treat approach to an adjusted HR of 2.6 (95% CI: 1.3-5.3) 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 “possible” and “probable” VTE events (Electronic Supplementary Material #11).

4. 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 and assess the risk among first-time users and 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: 3.2, 95% CI: 1.1-9.1). The increased risk was present soon after the initiation of drospirenone-containing COCs (HR for the first 84 days: 7.4, 95% CI: 1.3-41.8) and dissipated with time (HR for 113+ days: 1.0, 95% CI: 0.1-8.8). Among restarters, an elevated risk was observed with drospirenone-containing COCs (HR: 2.0, 95% CI: 1.1-3.4) 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 three possible 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. Previous studies have suggested that the risk of VTE is highest among first-time user[21]. The increased risk is attenuated among those with interrupted use (restarters and switchers) and lowest among prevalent users. This is also consistent with early risk among first-time users observed in the present study.

Second, it is possible that, despite our exhaustive efforts, our cohort of first-time users included some restarters, and that observed increased risk is an overestimate 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 possible that it is less likely for there to be a mixture of users within this group. First-time users may be more likely to use the most recent generation as restarters may return to a contraceptive that they had tolerated well previously. 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. It is also possible that, if some women did not take their previously prescribed COC, the restarter analysis may have contained some first-time users.

Third, it is possible that the difference occurred due to chance. Our analyses had relatively small numbers and our treatment effects are accompanied by relatively wide 95% CIs. While the point estimates differed, some overlap of the 95% CIs was present.

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[37, 38]. 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[39], 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[1-14, 16, 17]. 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.[1-4, 6, 11, 15] In addition, most previous studies either used an ITT analysis[3, 4, 10], 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[1, 2, 5-9, 11-17] 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 comparison of women with similar underlying risks of

VTE, and the use of an explicitly defined restarter cohort overcame 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. Fourth, with only 6 exposed events in the first-time user analysis, we were unable to conduct meaningful duration-response analyses. Fifth, we were unable to adjust for calendar year. Given its high correlation with exposure, it is a pseudo-instrument in our HDPS model, and we had too few exposed events to include it in the outcome model. Given the relative balance in the year of cohort entry across treatment groups and the similar VTE risk factor levels across groups, it is unlikely that calendar time was an important confounder in our study. Sixth, we have emphasized the results of our restarter analysis as it used an explicitly-defined cohort that included

patients with a similar VTE risk profile and was unlikely to be affected by the left truncation of the database. However, this estimate is lower than that obtained in the analysis of first-time users, and it is possible that it underestimates the VTE risk of drospirenone-containing COCs. Nonetheless, in both cohorts, drospirenone-containing COCs were associated with a clinically important increased risk. 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.

5. 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.

COMPLIANCE WITH ETHICAL STANDARDS

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Conflicts of Interest - Dr. Suissa has consulted for and received speaking fees from Novartis, Boehringer-Ingelheim, and AstraZeneca and research grants from Bayer Pharma AG, Boehringer-Ingelheim, Bristol-Myers Squibb, and Novartis. Ms. Larivée, Ms. Coulombe, Dr. Tagalakis, and Dr. Filion have no conflicts of interest to report.

Ethical Approval - 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.

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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 (<0.01)
Major general surgery	129 (3.6)	1113.0 (2.16)
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.
[†] For smoking, there were 26.3% missing for drospirenone users and 37.3% missing for levonorgestrel users. For BMI, there were 60.5% missing data for drospirenone users and 67.8% missing data for levonorgestrel users.

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)	1.0	1.0 (Reference)
Drospirenone	6	3,582	3,220.1	18.6 (6.8-40.6)	4.9	3.2 (1.1-9.1)
Idiopathic VTE						
Levonorgestrel	17	51,557	50,672.5	3.4 (2.0-5.4)	1.0	1.0 (Reference)
Drospirenone	6	3,582	3,220.1	18.6 (6.8-40.6)	4.5	3.2 (0.1-4.5)
Effect modification‡,§						
Smokers:						
Levonorgestrel	S	10,270	9,039.9	3.3 (0.7-9.7)	1.0	1.0 (Reference)
Drospirenone	S	642	474.7	63.2 (13.0-184.7)	14.8	10.5 (1.7-67.3)
Non-smokers:						
Levonorgestrel	S	41,287	41,632.7	3.8 (2.2-6.2)	1.0	1.0 (Reference)
Drospirenone	S	2,940	2,745.4	10.9 (2.3-31.9)	3.3	2.1 (0.6-7.7)

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.

† For smoking, there were 6.2% missing for drospirenone users and 12.3% missing for levonorgestrel users. For BMI, there were 23.1% missing for drospirenone users and 28.1% missing for levonorgestrel users.

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	1.0 (Reference)
Drospirenone	19	23,191	21,154.0	9.0 (5.4-14.0)	1.95	2.0 (1.1-3.4)
Idiopathic VTE						
Levonorgestrel	53	139,768	142,463.0	3.7 (2.8-4.9)	1.00	1.0 (Reference)
Drospirenone	18	23,191	21,154.0	8.5 (5.0-13.4)	2.46	2.3 (1.3-4.1)
Effect modification‡,§						
Smokers:						
Levonorgestrel	29	59,621	57,530.4	5.0 (3.4-7.2)	1.00	1.0 (Reference)
Drospirenone	9	9,080	7,840.6	11.5 (5.2-21.8)	2.75	2.7 (1.2-6.0)
Non-smokers:						
Levonorgestrel	37	80,147	84,932.6	4.4 (3.1-6.0)	1.00	1.0 (Reference)
Drospirenone	10	14,111	13,313.4	7.5 (3.6-13.8)	1.44	1.4 (0.6-3.3)

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.

Fig. 1

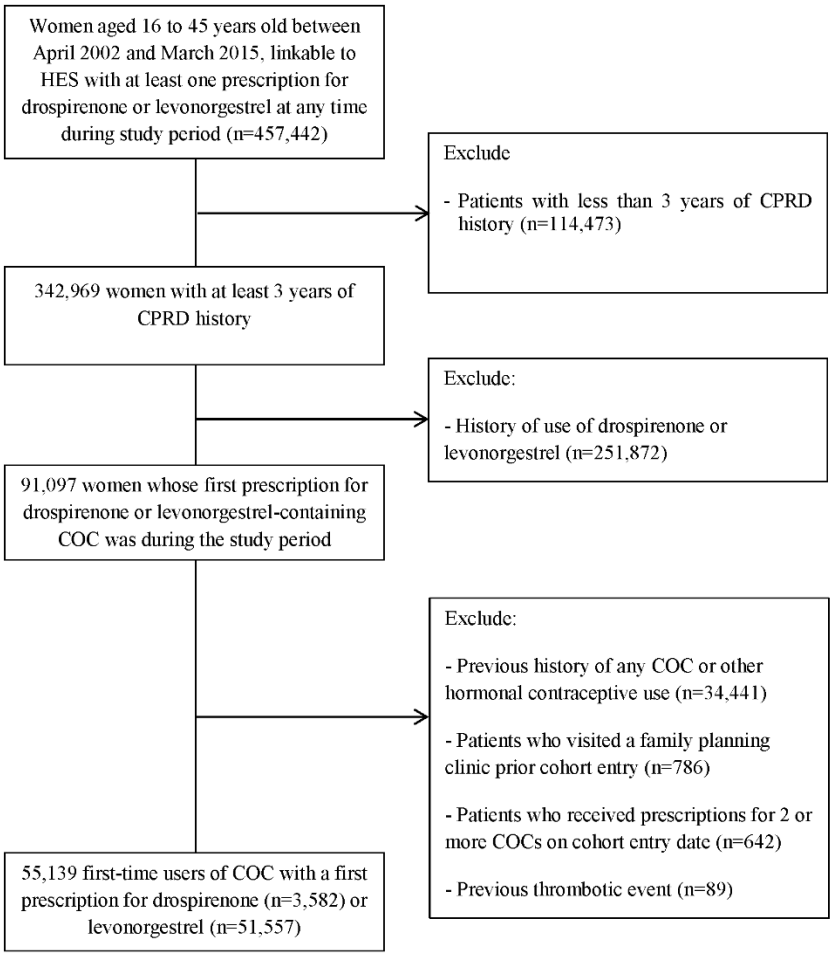

Women aged 16 to 45 years old between April 2002 and March 2015, linkable to HES with at least one prescription for drospirenone or levonorgestrel at any time during study period (n=457,442)
Exclude
- Patients with less than 3 years of CPRD history (n=114,473)
342,969 women with at least 3 years of CPRD history
Exclude:
- History of use of drospirenone or levonorgestrel (n=251,872)
91,097 women whose first prescription for drospirenone or levonorgestrel-containing COC was during the study period
Exclude:
- Previous history of any COC or other hormonal contraceptive use (n=34,441)
- Patients who visited a family planning clinic prior cohort entry (n=786)
- Patients who received prescriptions for 2 or more COCs on cohort entry date (n=642)
- Previous thrombotic event (n=89)
55,139 first-time users of COC with a first prescription for drospirenone (n=3,582) or levonorgestrel (n=51,557)

Figure 2

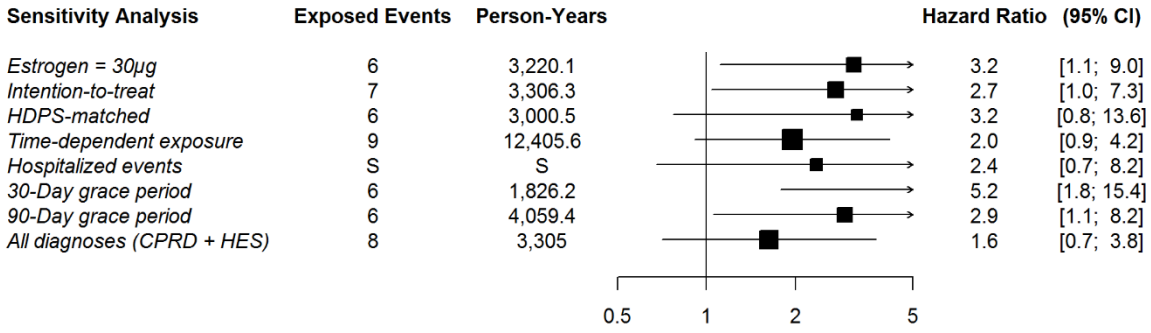

Sensitivity Analysis
Exposed Events
Person-Years
Hazard Ratio
(95% CI)
Estrogen = 30µg 6 3,220.1 3.2 [1.1; 9.0]
Intention-to-treat 7 3,306.3 2.7 [1.0; 7.3]
HDPS-matched 6 3,000.5 3.2 [0.8; 13.6]
Time-dependent exposure 9 12,405.6 2.0 [0.9; 4.2]
Hospitalized events S S 2.4 [0.7; 8.2]
30-Day grace period 6 1,826.2 5.2 [1.8; 15.4]
90-Day grace period 6 4,059.4 2.9 [1.1; 8.2]
All diagnoses (CPRD + HES) 8 3,305 1.6 [0.7; 3.8]
0.5
1
2
5

Fig. 3

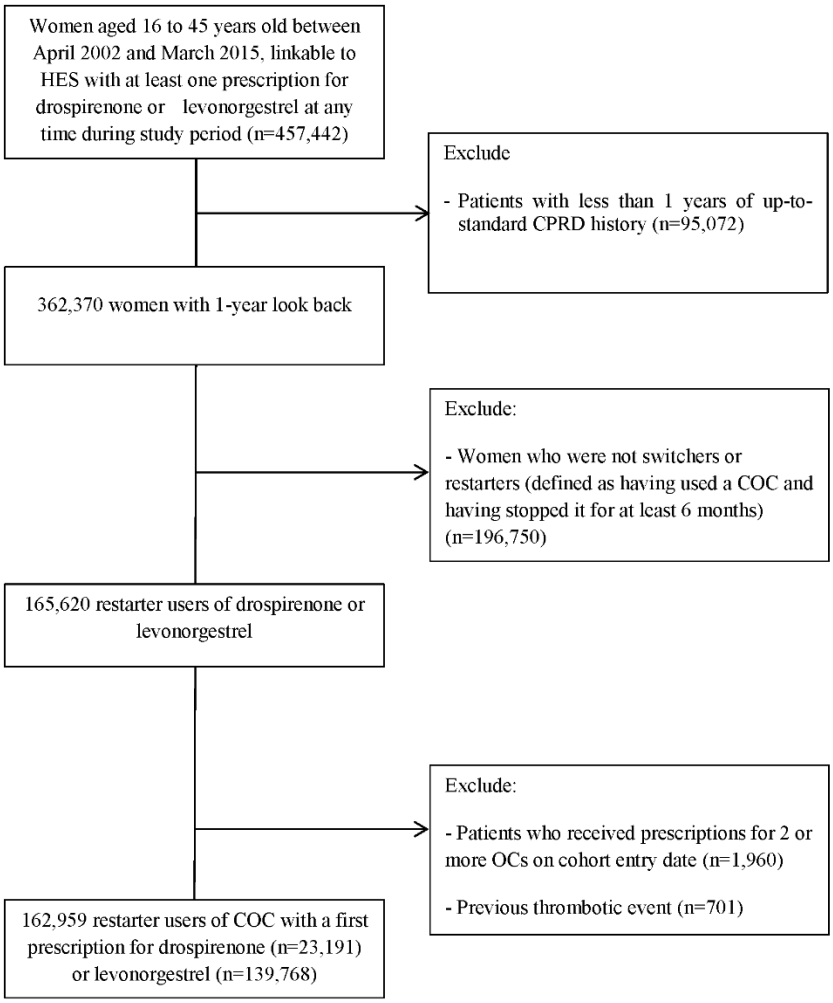
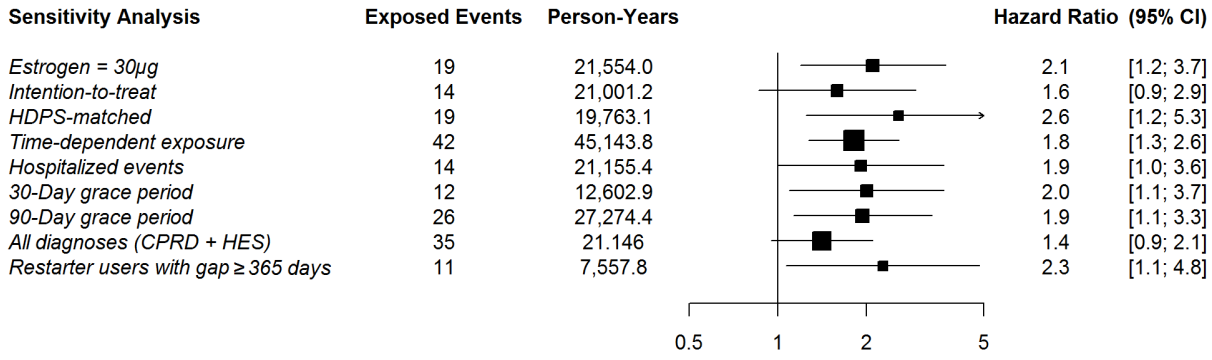

Women aged 16 to 45 years old between April 2002 and March 2015, linkable to HES with at least one prescription for drospirenone or levonorgestrel at any time during study period (n=457,442)
Exclude
- Patients with less than 1 years of up-to-standard CPRD history (n=95,072)
362,370 women with 1-year look back
Exclude:
- Women who were not switchers or restarters (defined as having used a COC and having stopped it for at least 6 months) (n=196,750)
165,620 restarter users of drospirenone or levonorgestrel
Exclude:
- Patients who received prescriptions for 2 or more OCs on cohort entry date (n=1,960)
- Previous thrombotic event (n=701)
162,959 restarter users of COC with a first prescription for drospirenone (n=23,191) or levonorgestrel (n=139,768)

Figure 4


Sensitivity Analysis
Exposed Events
Person-Years
Hazard Ratio
(95% CI)
Estrogen = 30µg 19 21,554.0 2.1 [1.2; 3.7]
Intention-to-treat 14 21,001.2 1.6 [0.9; 2.9]
HDPS-matched 19 19,763.1 2.6 [1.2; 5.3]
Time-dependent exposure 42 45,143.8 1.8 [1.3; 2.6]
Hospitalized events 14 21,155.4 1.9 [1.0; 3.6]
30-Day grace period 12 12,602.9 2.0 [1.1; 3.7]
90-Day grace period 26 27,274.4 1.9 [1.1; 3.3]
All diagnoses (CPRD + HES) 35 21.146 1.4 [0.9; 2.1]
Restarter users with gap ≥ 365 days 11 7,557.8 2.3 [1.1; 4.8]
0.5
1
2
5

ELECTRONIC SUPPLEMENTAL MATERIAL

Title: Drospirenone-containing Oral Contraceptive Pills and the Risk of Venous Thromboembolism: An Assessment of Risk in First-time Users and Restarters

Authors: Natasha Larivée MSc, Samy Suissa PhD, Janie Coulombe MSc, Vicky Tagalakis MD MSc, and Kristian B. Filion PhD

Journal: Drug Safety

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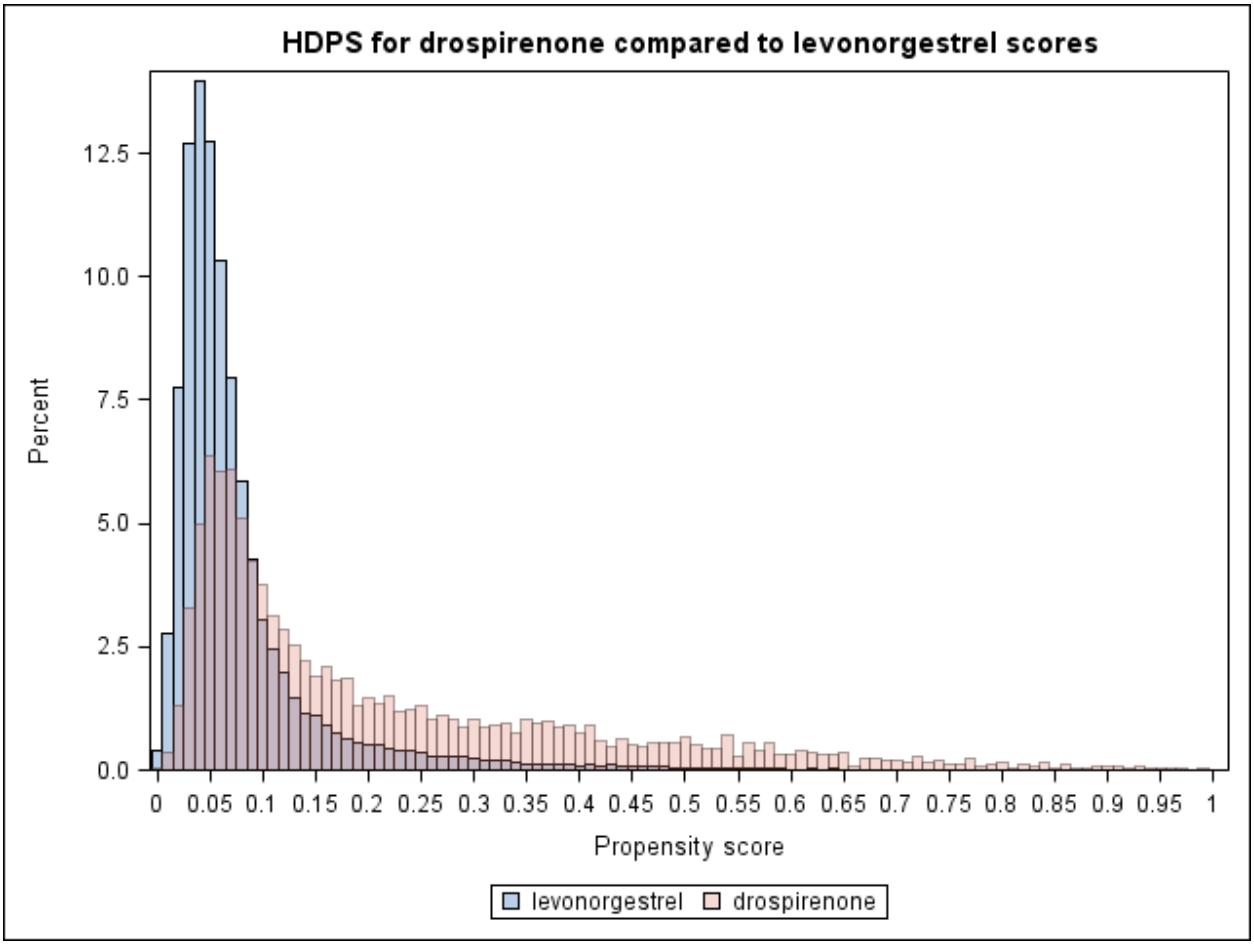
Electronic Supplementary Material #1. List of READ codes used to define VTE.

Read code	Read term
G401100	Recurrent pulmonary embolism
G801G00	Recurrent deep vein thrombosis
G401.00	Pulmonary embolism
G401.12	Pulmonary embolus
G401000	Post operative pulmonary embolus
G676.00	Nonpyogenic venous sinus thrombosis
G740.14	Saddle embolus
G80..00	Phlebitis and thrombophlebitis
J420200	Thrombus of the superior mesenteric veins
G801.00	Deep vein phlebitis and thrombophlebitis of the leg
G801.11	Deep vein thrombosis
G801.12	Deep vein thrombosis, leg
G801.13	DVT - Deep vein thrombosis
G801000	Phlebitis of the femoral vein
G801100	Phlebitis of the popliteal vein
G801200	Phlebitis of the anterior tibial vein
G801400	Phlebitis of the posterior tibial vein
G801600	Thrombophlebitis of the femoral vein
G801700	Thrombophlebitis of the popliteal vein
G801800	Thrombophlebitis of the anterior tibial vein
G801A00	Thrombophlebitis of the posterior tibial vein
G801B00	Deep vein thrombophlebitis of the leg unspecified
G801C00	Deep vein thrombosis of leg related to air travel
G801D00	Deep vein thrombosis of lower limb
G801E00	Deep vein thrombosis of leg related to intravenous drug use
G801F00	Deep vein thrombosis of peroneal vein
G801z00	Deep vein phlebitis and thrombophlebitis of the leg NOS
G802.00	Phlebitis and thrombophlebitis of the leg NOS
G802000	Thrombosis of vein of leg
G80y.00	Other phlebitis and thrombophlebitis
G80y.11	Phlebitis and/or thrombophlebitis of iliac vein
G80y400	Thrombophlebitis of the common iliac vein
G80y500	Thrombophlebitis of the internal iliac vein
G80y600	Thrombophlebitis of the external iliac vein
G80y700	Thrombophlebitis of the iliac vein unspecified
G80y800	Phlebitis and thrombophlebitis of the iliac vein NOS

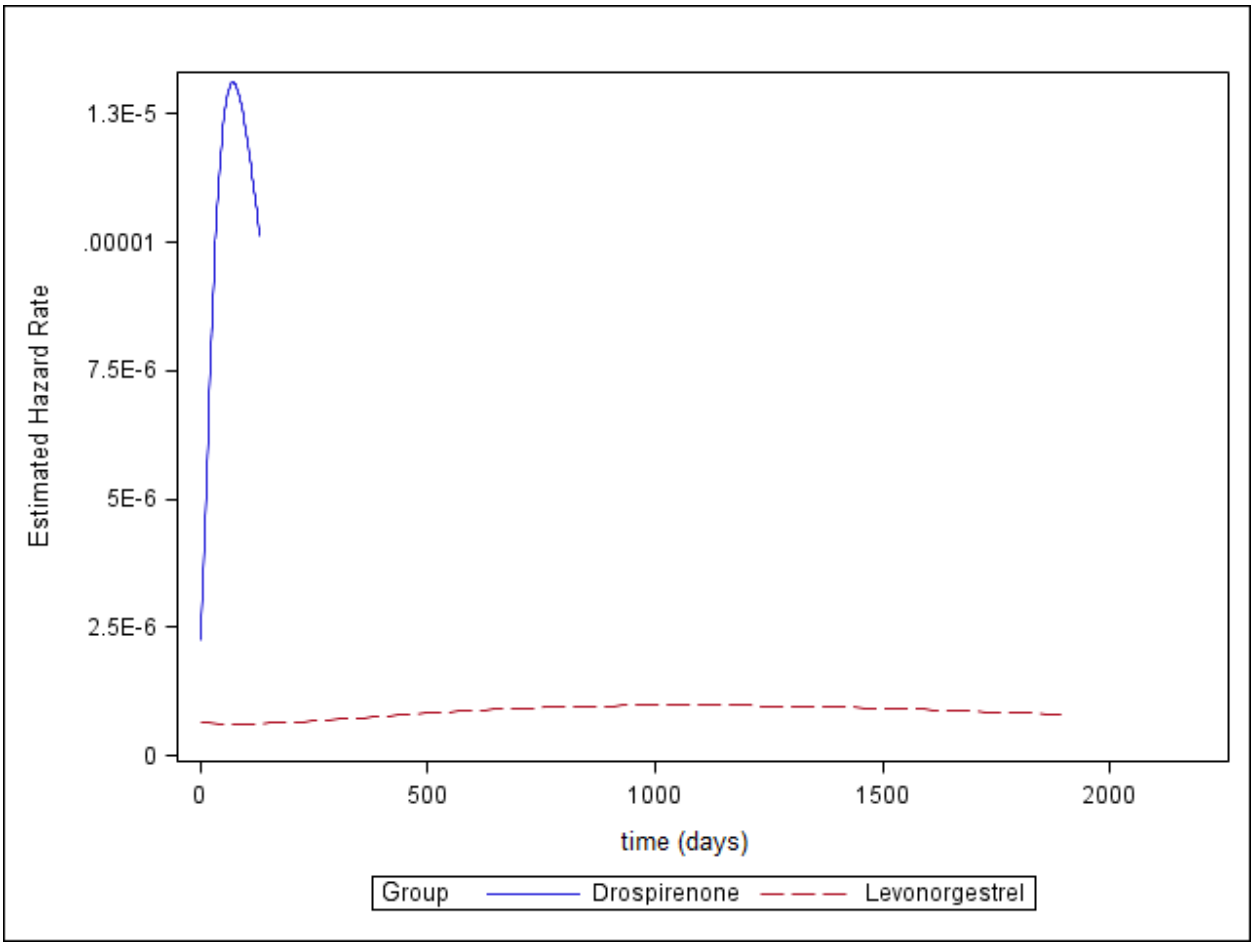
G80yz00	Other phlebitis and thrombophlebitis NOS
G80z.00	Phlebitis and thrombophlebitis NOS
G80z100	Thrombophlebitis NOS
G80zz00	Phlebitis and thrombophlebitis NOS
G822.00	Embolism and thrombosis of the vena cava
G822000	Thrombosis of inferior vena cava
G824.00	Axillary vein thrombosis
G825.00	Thrombosis of subclavian vein
G82y.00	Other embolism and thrombosis
G82z.00	Embolism and thrombosis NOS
G82z100	Thrombosis of vein NOS
G82zz00	Embolism and thrombosis NOS
Gyu8000	[X]Phlebitis+thrombophlebitis/oth deep vessls/low extremites
F423800	Central retinal vein occlusion
F423811	Retinal vein thrombosis
F423911	Branch retinal vein occlusion
G800.12	Saphenous vein thrombophlebitis
G800300	Thrombophlebitis of the long saphenous vein
G800400	Thrombophlebitis of the short saphenous vein
G801900	Thrombophlebitis of the dorsalis pedis vein
G80y900	Thrombophlebitis of the breast - Mondor's disease
L044200	Incomplete inevitable abortion complicated by embolism
L045211	Complete inevitable miscarriage complicated by embolism
L096.00	Embolism following abortive pregnancy
L096400	Pulmonary embolism following abortive pregnancy
L0A3.00	Failed medical abortion, complicated by embolism
L412511	Thrombophlebitis of legs in pregnancy
L413.00	Antenatal deep vein thrombosis
L413.11	DVT - deep venous thrombosis, antenatal
L413000	Antenatal deep vein thrombosis unspecified
L413100	Antenatal deep vein thrombosis - delivered
L413200	Antenatal deep vein thrombosis with antenatal complication
L413z00	Antenatal deep vein thrombosis NOS
L414.00	Postnatal deep vein thrombosis
L414.11	DVT - deep venous thrombosis, postnatal
L414000	Postnatal deep vein thrombosis unspecified
L414200	Postnatal deep vein thrombosis with postnatal complication
L414z00	Postnatal deep vein thrombosis NOS
L415.00	Other phlebitis and thrombosis in pregnancy and puerperium

L415000	Other phlebitis/thrombosis in pregnancy/puerperium unsp
L415100	Other phlebitis/thrombosis in pregnancy/puerperium - deliv
L415300	Other phlebitis/thrombosis in preg/puerperium + a/n comp
G82..00	Other venous embolism and thrombosis
G823.00	Embolism and thrombosis of the renal vein
G826.00	Thrombosis of internal jugular vein
L41z513	Gestational thrombosis NOS
L41z613	Puerperal thrombosis NOS
L43..00	Obstetric pulmonary embolism
L43..11	Obstetric pulmonary embolus
L432.00	Obstetric blood-clot pulmonary embolism
L43z.00	Obstetric pulmonary embolism NOS
L43z000	Obstetric pulmonary embolism NOS, unspecified
L43z100	Obstetric pulmonary embolism NOS - delivered
L43z400	Obstetric pulmonary embolism NOS with postnatal complication
L43zz00	Obstetric pulmonary embolism NOS
G827.00	Thrombosis of external jugular vein
G82z000	Embolus of vein NOS
G82z011	Embolism of vein NOS
Gyu8200	[X]Embolism and thrombosis of other specified veins
L417.00	Obstetric cerebral venous thrombosis
L417000	Cerebral venous thrombosis in pregnancy
L417100	Cerebral venous thrombosis in the puerperium
SP12100	Thrombophlebitis as a complication of care
SP12200	Post operative deep vein thrombosis
SP32100	Thromboembolism after infusion
SP32200	Thrombophlebitis after infusion

Electronic Supplementary Material #2. High-dimensional propensity score distributions among first-time users of drospirenone- and levonorgestrel-containing COCs.



Electronic Supplementary Material #3. Hazard function among first-time users of drospirenone- and levonorgestrel-containing COCs.



Electronic Supplementary Material #4. 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.

Electronic Supplementary Material #5. 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)	1.0 (Reference)	1.0 (Reference)
Drospirenone	6	3,582	3,220.1	18.6 (6.8-40.6)	4.8	3.2 (1.1-9.0)
Intention-to-treat analysis‡						
Levonorgestrel	25	51,557	47,507.1	5.3 (3.4-7.8)	1.0 (Reference)	1.0 (Reference)
Drospirenone	7	3,582	3,306.3	21.2 (8.5-43.6)	4.0	2.7 (1.0-7.3)
HDPS-matched analysis§						
Levonorgestrel	S	3,363	S	5.1 (1.1-15.0)	1.0 (Reference)	1.0 (Reference)
Drospirenone	6	3,363	3,000.5	20.0 (0.7-4.4)	3.4	3.3 (0.8-13.6)
Time-dependent exposure definition‖						
Levonorgestrel	34	51,557	95,195.5	3.6 (2.5-5.0)	1.0 (Reference)	1.0 (Reference)
Drospirenone	9	3,582	12,405.6	7.3 (3.3-13.8)	2.3	2.0 (0.9-4.2)
Restricted to hospitalized events						
Levonorgestrel	16	51,557	50,673.3	3.2 (1.8-5.1)	1.0 (Reference)	1.00 (Reference)
Drospirenone	S	3,582	S	12.4 (3.4-31.8)	3.89	2.36 (0.7-8.2)
30-Day grace period						
Levonorgestrel	14	51,557	28,780.0	4.9 (2.7-8.2)	1.0 (Reference)	1.0 (Reference)
Drospirenone	6	3,582	1,826.2	3.3 (12.1-71.5)	6.7	5.2 (1.8-15.4)
90-Day grace period						
Levonorgestrel	22	51,557	63,273.0	3.5 (2.2-5.3)	1.0 (Reference)	1.0 (Reference)
Drospirenone	6	3,582	4,059.4	14.8 (5.4-32.2)	4.3	2.9 (1.1-8.2)
All VTE diagnoses (CPRD + HES)						
Levonorgestrel	51	51,557	47,495	1.1 (0.8-1.4)	1.0 (Reference)	1.0 (Reference)
Drospirenone	8	3,582	3,305	2.4 (1.0-4.8)	2.3	1.6 (0.7-3.8)

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

Electronic Supplementary Material #6. Baseline characteristics of the events stratified by probable and possible VTE among first-time users.

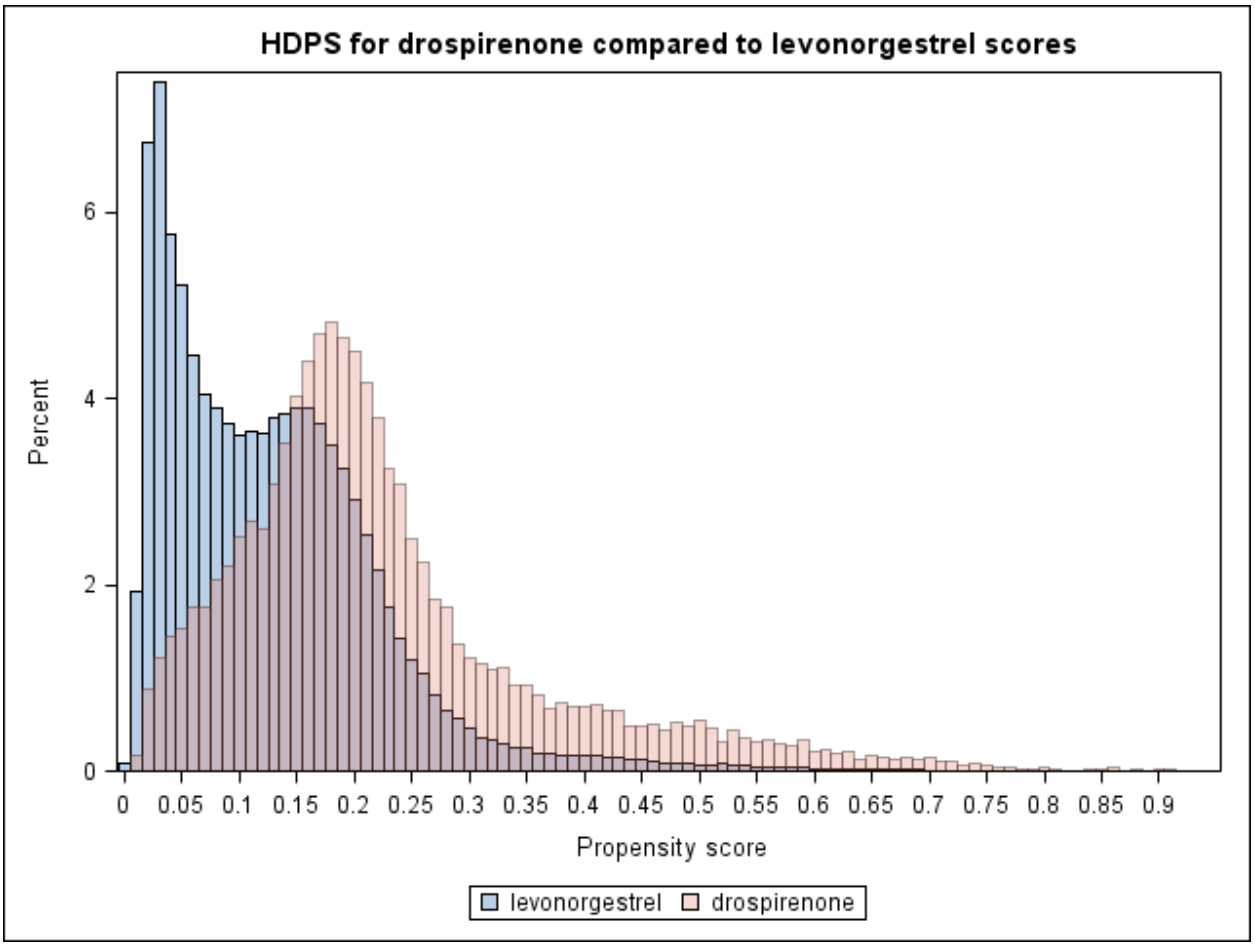
Characteristic	Possible VTE (n=139)	Probable VTE (n=25)
	n (%)	n (%)
Drug defining cohort entry		
Drospirenone	7 (5.0)	6 (24.0)
Levonorgestrel	132 (95.0)	19 (76.0)
Age, mean (SD)		
16-25	104 (74.8)	18 (72.0)
26-35	23 (16.6)	S
36-45	12 (8.6)	S
Year of cohort entry		
2002	10 (7.2)	S
2003	23 (16.6)	S
2004	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

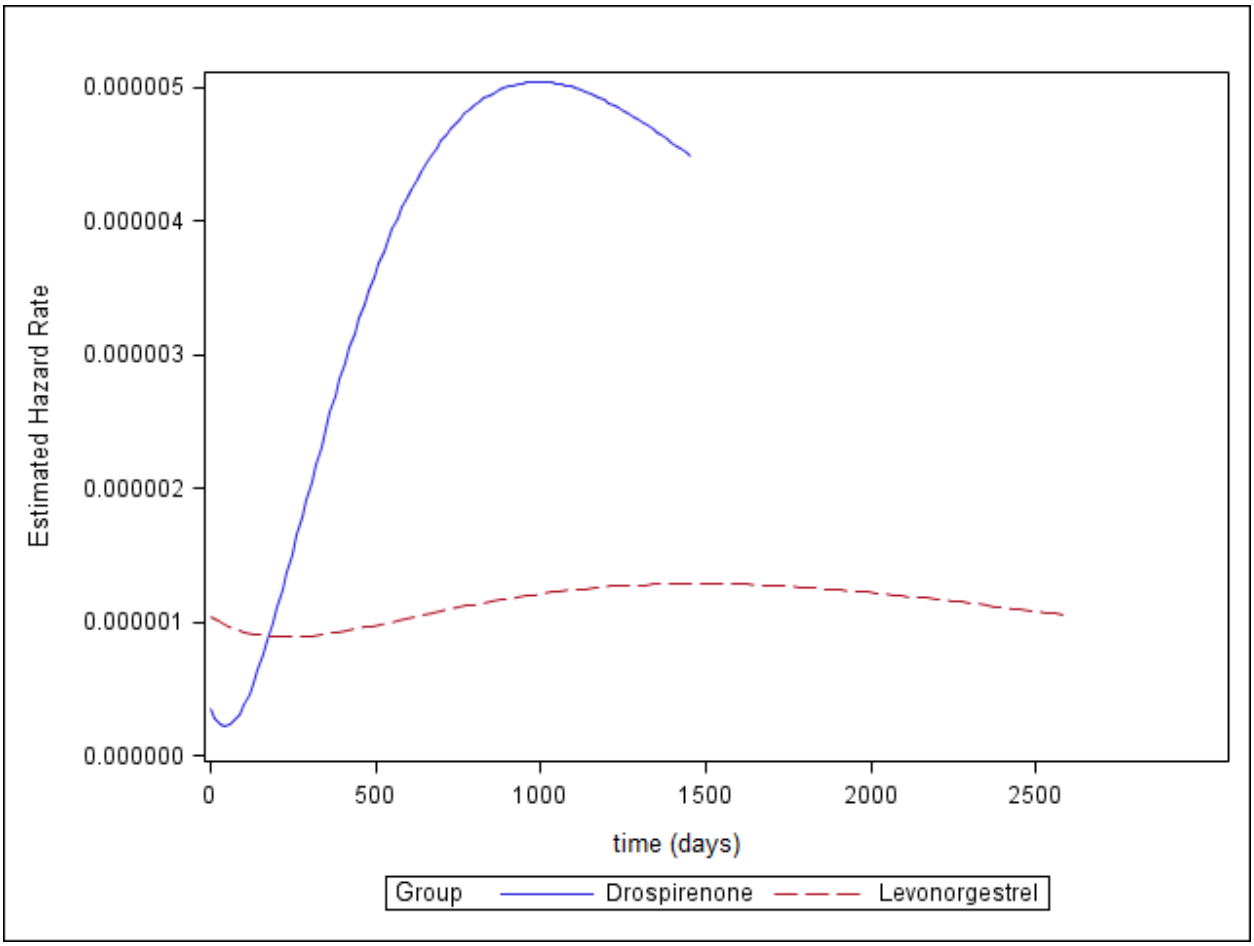
Abbreviations: NSAIDs: non-steroidal anti-inflammatory drugs; S: suppressed data in order to comply with CPRD privacy restrictions; SD: Standard deviation; VTE: Venous thromboembolism.

* Estimates reported after data imputation.

Electronic Supplementary Material #7. High-dimensional propensity score distributions among restarter users of drospirenone- and levonorgestrel-containing COCs.



Electronic Supplementary Material #8. Hazard function among restarter users of drospirenone- and levonorgestrel- containing COCs.



Electronic Supplementary Material #9. 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 (0.5)
End of registration in CPRD/end of study period	4,175 (18.0)	21,112 (15.1)
Switching	10,340 (44.6)	59,006 (42.2)
Discontinuation of study drug	8,568 (37.0)	58,917 (42.2)

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

Electronic Supplementary Material #10. Sensitivity analyses of drospirenone-containing COCs and rates of venous thromboembolism among restarters.

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)	1.0 (Reference)	1.0 (Reference)
Drospirenone	19	23,191	21,554.0	8.8 (5.3-13.8)	2.1	2.1 (1.2-3.7)
Intention-to-treat analysis‡						
Levonorgestrel	64	139,768	128,910.0	5.0 (3.8-6.3)	1.0 (Reference)	1.0 (Reference)
Drospirenone	14	23,191	21,001.2	6.7 (3.6-11.2)	1.3	1.6 (0.9-2.9)
HDPS-matched analysis§						
Levonorgestrel	14	21,752	32,734.0	4.3 (2.3-7.2)	1.0 (Reference)	1.0 (Reference)
Drospirenone	19	21,752	19,763.1	9.6 (5.8-15.0)	2.6	2.6 (1.3-5.3)
Time-dependent exposure definition‖						
Levonorgestrel	140	139,768	263,271.0	5.3 (4.5-6.3)	1.0 (Reference)	1.0 (Reference)
Drospirenone	42	23,191	45,143.8	9.3 (6.7-12.6)	1.7	1.8 (1.3-2.6)
Hospitalized events						
Levonorgestrel	50	139,768	142,468.0	3.5 (2.6-4.6)	1.0 (Reference)	1.0 (Reference)
Drospirenone	14	23,191	21,155.4	6.6 (3.6-11.1)	1.9	1.9 (1.0-3.7)
30-day grace period						
Levonorgestrel	38	139,768	79,375.0	4.8 (3.4-6.6)	1.0 (Reference)	1.0 (Reference)
Drospirenone	12	23,191	12,602.9	9.5 (4.9-16.6)	2.0	2.0 (1.1-3.7)
90-day grace period						
Levonorgestrel	96	139,768	190,673.0	5.0 (4.1-6.1)	1.0 (Reference)	1.0 (Reference)
Drospirenone	26	23,191	27,274.4	9.5 (6.2-14.0)	2.0	1.9 (1.1-3.3)
All VTE diagnoses (CPRD + HES)						
Levonorgestrel	160	139,768	142,395	1.1 (1.0-1.3)	1.0 (Reference)	1.0 (Reference)
Drospirenone	35	23,191	21,146	1.7 (1.2-2.3)	1.5	1.4 (1.0-2.1)

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)	2.2	2.3 (1.1-4.8)

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.

Electronic Supplementary Material #11. Baseline characteristics of the events stratified by probable and possible VTE among restarters.

Characteristic	Possible VTE (n=332)	Probable 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 after data imputation.