BJOG An International Journal of Obstetrics and Gynaecology

DOI: 10.1111/1471-0528.14358
www.bjog.org

Drospirenone-containing combined oral contraceptives and the risk of arterial thrombosis: a population-based nested case-control study

N Larivée,[a,b] S Suissa,[a,b,c] M Eberg,[a] L Joseph,[b,d] MJ Eisenberg,[a,b,e] HA Abenhaim,[a,f] KB Filion[a,b,c]

[a] Center for Clinical Epidemiology, Lady Davis Institute, Jewish General Hospital, Montreal, Quebec, Canada [b] Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, Quebec, Canada [c] Division of Clinical Epidemiology, Department of Medicine, McGill University, Montreal, Quebec, Canada [d] Division of Clinical Epidemiology, McGill University Health Centre, Montreal, Quebec, Canada [e] Division of Cardiology, Jewish General Hospital, McGill University, Montreal, Quebec, Canada [f] Department of Obstetrics and Gynecology, Jewish General Hospital, McGill University, Montreal, Quebec, Canada
Correspondence: KB Filion, Division of Clinical Epidemiology, Jewish General Hospital/McGill University, 3755 Cote Ste Catherine, Suite H416.1, Montreal, Quebec H3T 1E2 Canada. Email kristian.filion@mcgill.ca

Accepted 16 August 2016. Published Online 4 October 2016.

Objective To compare the rate of arterial thromboembolism (ATE) of drospirenone-containing COCs to that of levonorgestrel-containing COCs.

Design Population-based cohort study.

Setting United Kingdom's Clinical Practice Research Datalink (CPRD), which contains clinical records for >11 million patients.

Population Women aged 16–45 years prescribed a drospirenone- or levonorgestrel-containing COC between May 2002 and June 2012.

Methods We conducted nested case-control analyses using risk set sampling to randomly select up to 10 controls for each ATE case, matched on age, cohort entry year, CPRD registration year, COC user type (first-time ever, new, switcher, or prevalent users), duration of COC use, duration of progestin-only or implantable contraceptive use, pre-cohort entry duration of drospirenone and levonorgestrel use, and duration of follow up.

Main outcome measures We used conditional logistic regression to estimate hazard ratios and 95% confidence intervals (CIs), adjusted for high-dimensional propensity scores.

Results Our cohort included 339 743 women followed over a mean 4.4 years, during which 228 ATE cases occurred: 37 myocardial infarctions, 170 strokes, and 21 other ATEs; overall rate: 1.5 events per 10 000 person-years (PYs). After adjusting for potential confounders, the hazard ratio for ATE with current use of drospirenone-containing COCs versus current use of levonorgestrel-containing COCs was 0.89 (95% CI 0.35, 2.28), corresponding to a rate difference of −0.16 events per 10 000 PYs.

Conclusions The overall rate of ATE in this population is low regardless of which COC was taken. We found little evidence of a difference in the rate of ATE with drospirenone- versus levonorgestrel-containing COCs.

Keywords Arterial thromboembolism, drospirenone, drug safety, oral contraceptives.

Tweetable Abstract Little evidence was found of a greater incidence of arterial thrombosis with drospirenone versus levonorgestrel contraceptives.

Please cite this paper as: Larivée N, Suissa S, Eberg M, Joseph L, Eisenberg MJ, Abenhaim HA, Filion KB. Drospirenone-containing combined oral contraceptives and the risk of arterial thrombosis: a population-based nested case-control study. BJOG 2016; DOI: 10.1111/1471-0528.14358.

Introduction

Combined oral contraceptives (COCs) that contain the progestin drospirenone entered the market in 2000. As with other COCs, the use of these fourth generation COCs is associated with haemostatic changes[1] and thus may be associated with an increased risk of thrombosis. The U.S. Food and Drug Administration (FDA) conducted a 2012 safety review of drospirenone-containing COCs and concluded that drospirenone-containing COCs were associated with a relative risk of venous thromboembolism (VTE), including deep vein thrombosis and pulmonary embolism,

of between 1.3 and 3.0 relative to other COCs.[2] Similar conclusions were reached in a European Medicines Agency (EMA) review.[3]

Although much attention has focused on the risk of VTE with drospirenone-containing COCs, their effects on the risk of arterial thromboembolism (ATE) remain understudied. The use of COCs increases pro-coagulant factors, decreases anti-coagulant proteins, and increases fibrinolytic factors, all risk factors for both VTE and ATE,[1] although the exact mechanism for COC-associated ATE is still a matter of debate.[4] These haemostatic changes can result in hypercoagulability, an important determinant of atherosclerosis and subsequent myocardial infarction (MI) and ischaemic stroke.[5] COC use is also associated with other risk factors of ATE, including increased triglyceride and low density lipoprotein cholesterol levels.[5,6] The review conducted by the FDA suggested that drospirenone-containing COCs may increase the risk of ATE compared with second generation COCs containing the progestin levonorgestrel [hazards ratio (HR) 1.64, 95% confidence interval (CI) 0.79, 3.40 among new users], but this analysis was inconclusive due to wide 95% CIs.[2] In contrast, the Long-term Active Surveillance Study for Oral Contraceptives (LASS)[7] found a strong protective effect (HR 0.4, 95% CI 0.2, 0.9). Given the conflicting nature of these results and the large number of women using drospirenone-containing COCs, there remains a need for additional studies to obtain a complete understanding of the safety profile of these COCs. We therefore conducted a nested case-control analysis of a retrospective cohort study to compare the rate of ATE of drospirenone-containing COCs with that of levonorgestrel-containing COCs.

Methods

Data source

This study was conducted using data extracted from the Clinical Practice Research Datalink (CPRD).[8] The CPRD is a population-based clinical database that contains detailed clinical records for more than 11 million patients seen at 674 general practitioner practices in the UK.[9] The CPRD contains detailed information regarding demographic characteristics and clinical diagnoses (using the Read coding system). The CPRD automatically records all prescriptions issued by the general practitioner, with prescriptions classified according to the British National Formulary. In the UK, the general practitioner is the gatekeeper to the healthcare system.[9] Consequently, specialists and other health care providers that are consulted are required to report back to the general practitioner.[8] In addition, the CPRD contains clinical information not found in many administrative databases, such as lifestyle variables [e.g. smoking, body mass index (BMI)], clinical measures (e.g. blood pressure), and laboratory test results. The validity of CPRD data has been studied extensively[8,10] and several quality assurance measures have been implemented to ensure that these data are of high quality.[9]

Study population

We identified all women aged 16–45 years who received a prescription for a drospirenone- or levonorgestrel-containing COC between May 2002 (drospirenone-containing COCs entered the UK market in April 2002[11]) and June 2012. The date of this prescription defined the date of cohort entry. Women with less than 3 years of recorded CPRD medical history at cohort entry, those with a recorded history of ATE prior to cohort entry, and those who received prescriptions for more than one COC on the day of cohort entry were excluded. Women were followed until a diagnosis of ATE (defined below) or censoring due to death, departure from the CPRD practice, the last date of data collection for the general practitioner practice, or the end of the study period (30 June 2012), whichever occurred first. Women with a follow-up duration of zero days were excluded.

Case-control selection

Cases were defined by a recorded diagnosis of ATE (based on Read codes and including stroke and other cerebrovascular events, MI, and other ATEs of unspecified location). The date of ATE diagnosis defined the index date. For each case, up to 10 controls were randomly selected using risk set sampling. Although it would have been ideal to restrict inclusion to first-time users of COCs, this was not feasible due to the low incidence of ATE in this population. Consequently, we developed a matching algorithm to account for pre-cohort entry history of COC use. This matching scheme, which is conceptually similar to one used previously,[12] was designed to ensure that cases and controls differed only by exposure to COCs prescribed during follow up. Using all available prescription data between 1988 and cohort entry, we defined history of COC use in terms of user type and duration of use. All women were classified as one of the following four mutually exclusive user types: (i) first-time ever user (no previous use of COCs); (ii) new user (unexposed to any COC in the 6 months prior to cohort entry); (iii) switcher (exposed to another COC in the 6 months prior to cohort entry); and (iv) prevalent user (exposed only to the cohort entry defining COC in the 6 months prior to cohort entry). Cases and controls were then matched on age (caliper: $\pm$ 1 year), year of cohort entry, year of CPRD registration, COC user type (first-time ever, new, switcher, or prevalent users), total duration of COC use at cohort entry ($\pm$ 1 year), total duration of non-COC use at cohort entry [including progestin-only contraceptives and intrauterine devices (IUDs)]

(±1 year), duration of previous drospirenone- and levonorgestrel-containing COC use at cohort entry (± 90 days), and duration of follow up. With this matching scheme, no suitable controls were identified for 50 cases. For those cases, the calipers for age (maximum caliper: ± 4 years), total duration of COC use (maximum caliper: ± 2.5 years), total duration of non-COC use (maximum caliper: ± 2.5 years), and duration of previous drospirenone- and levonorgestrel-containing COC use at cohort entry (maximum caliper: ± 180 days) were increasingly relaxed until all cases had at least one control. Controls were assigned the index date of their matched case.

Exposure assessment

For cases and controls, exposure was assessed in a time-dependent manner; it was defined using the COC prescribed preceding the index date and categorised by both the timing and type of contraceptive prescribed. Prescription duration was defined using the duration and/or quantity prescribed, except for IUDs and progestogen-only implants, where durations were assumed to be 5 years and 3 years, respectively (except in the presence of a code indicating its removal). Current users were defined as women with a prescription for which the duration of the prescription included the index date. Recent users were defined as women whose prescription ended 1–90 days prior to the index date. Past users were defined as women whose prescription ended 91–365 days prior to the index date. In the case of overlapping prescriptions, the end of the earlier prescription was defined as the date of the new prescription. Users were then classified using the following five mutually exclusive exposure categories: (i) drospirenone-containing COCs (the primary exposure of interest); (ii) levonorgestrel-containing COCs (the reference category); (iii) other COCs (1st, 2nd, 3rd, 4th generation COCs that were not levonorgestrel- or drospirenone-containing COCs, the vaginal ring, or patch); (iv) non-CC (progestin-only oral contraceptives or IUD); and (v) no exposure to contraceptives in the previous year. We selected levonorgestrel-containing COCs as our comparator as it is the most frequently prescribed COC in the UK.[13] Furthermore, the use of an active comparator, as opposed to a non-use or an unexposed reference group, is essential, as it is well established that all COCs result in haemostatic changes that increase the risk of thrombosis.[1,14] In addition, a comparison of drospirenone-containing COCs with another COC prescribed for similar indications represents the most clinically relevant comparison. Data for patients in exposure categories other than current exposure to drospirenone- or levonorgestrel-containing COCs are not presented but were considered in the regression models (described below) for proper estimation of treatment effects.

Potential confounders

The present study is observational in nature and thus may be affected by confounding by indication and by other characteristics. Consequently, in addition to the patient characteristics considered as part of our matching algorithm, we considered several potential confounders. These confounders were lifestyle variables (e.g. smoking, BMI), comorbidities (e.g. chronic obstructive pulmonary disease, coronary artery disease, diabetes mellitus, dyslipidaemia, heart failure, hypertension, peripheral vascular disease, previous coronary revascularisation, alcohol-related disorders), and previous prescribed medications (e.g. aspirin, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, calcium-channel blockers, diuretics, fibrates, non-steroidal anti-inflammatory drugs, statins). In addition, we adjusted for family history of thrombosis as well as parity and pregnancy complications (e.g. gestational diabetes, gestational hypertension, pre-eclampsia), as these are cardiovascular stressors.[15–17] All potential confounders were measured at cohort entry, using assessment windows of 3 years for diagnoses and 1 year for medications. The values for BMI and smoking were defined using an assessment window of 5 years; in our primary analysis, patients with missing data for these variables were included through the use of an indicator variable.

Statistical analysis

Descriptive statistics were used to describe the baseline and clinical characteristics of our cases and matched controls. Categorical variables are presented as counts with corresponding proportions. Continuous variables are presented as means with standard deviations and, in the case of skewed distributions, medians with interquartile ranges. In addition, the overall rate of ATE and corresponding 95% CI was calculated based on the Poisson distribution.

In our primary analyses, we used conditional logistic regression to estimate the odds ratio for incident ATE with current use of drospirenone-containing COCs relative to current use of levonorgestrel-containing COCs. With our use of risk set sampling, these odds ratios are unbiased estimators of the HR.[18] In addition to our matching variables on which our models were conditioned, we adjusted for smoking, history of VTE, and high-dimensional propensity score (HDPS) deciles.[19] Our HDPS model, which modelled the probability of entering the cohort on drospirenone-containing COCs rather than levonorgestrel-containing COCs, included the prespecified covariates described above (other than smoking and VTE, which were included in our outcome model) as well as 500 covariates empirically identified by the HDPS algorithm. In addition, to help contextualise the results of our primary analysis, we used the adjusted HR and 95% CI obtained from our conditional

logistic model to estimate the adjusted rate difference (RD) using the approach described by Suissa.[20]

Sensitivity analyses

We conducted five sensitivity analyses to assess the robustness of our results. First, we stratified our analyses by COC user type. Secondly, we examined the impact of matching on history of COC use by repeating our primary analysis with matching on age, year of cohort entry, year of CPRD registration, and duration of follow up only. Thirdly, to examine the effect of our use of an indicator variable for missing data for smoking and BMI, we repeated our primary analysis using multiple imputation to address missing data. Fourthly, to examine the impact of residual confounding caused by relaxing our matching criteria for cases for whom no suitable controls were identified, we repeated our analyses excluding these cases and their corresponding controls. Finally, to examine potential effect modification by HDPS, we included an interaction term between exposure and HDPS in its continuous form.

Results

Study population

A total of 1 601 978 women had a recorded prescription for a drospirenone- or levonorgestrel containing COC in the CPRD database (Figure 1). Of these, 907 171 women were aged 16–45 years with at least 3 years of recorded medical history in the CPRD and 340 871 received a prescription for either a drospirenone- or levonorgestrel-containing COC between 1 May 2002 and 30 June 2012. The final cohort comprised 339 743 women (38 696 drospirenone users and 301 047 levonorgestrel users at cohort entry).

Our cohort was followed over a mean 4.4 years. During this follow up, a total of 228 ATE cases occurred (37 MIs, 170 strokes, and 21 other ATEs), resulting in an overall event rate of 1.5 ATEs per 10 000 person-years (PYs).

Demographic and clinical characteristics

Although both cases and their matched controls were relatively healthy, there were several differences in demographic and clinical characteristics between the two (Tables 1 and S1). Compared with controls, cases had higher BMI, a higher percentage of ever smoking, and were more likely to have been hospitalised in the year before cohort entry. In addition, cases had a higher prevalence of comorbidities (including diabetes, dyslipidaemia, and hypertension) and greater use of medications in the year before cohort entry (including beta-blockers, diuretics, and statins).

There were also some differences between baseline characteristics of women currently exposed to drospirenone-containing COCs and those currently exposed to levonorgestrel-containing COCs (Tables 2 and S2). Compared with controls currently exposed to levonorgestrel-containing COCs (n = 366), those currently exposed to drospirenone-containing COCs (n = 51) had lower BMIs and a greater prevalence of ever smoking. They were also less likely to have been hospitalised in the year before cohort entry, had a higher number of pregnancies before cohort entry, and used a greater number of distinct drug classes in the year before cohort entry. Despite these differences, there was good overlap in HDPS distributions between those prescribed drospirenone- and levonorgestrel-containing COCs (Figure S1).

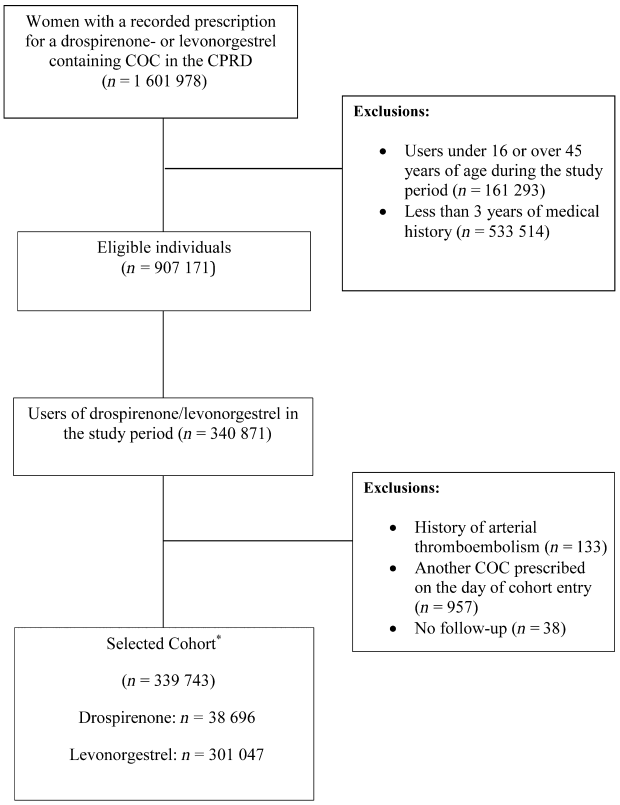

Figure 1. Flow diagram describing cohort construction. *A total of six drospirenone-containing COC and 22 levonorgestrel-containing COC users were subsequently trimmed by the high-dimensional propensity score (HDPS) algorithm due to non-overlap of the HDPS distribution.

Drospirenone-containing COCs and the rate of ATE

After adjusting for potential confounders, the HR for ATE with current use of drospirenone-containing COCs versus current use of levonorgestrel-containing COCs was 0.89 (95% CI 0.35, 2.28) (Table 3). An HR of 0.89 corresponds to an adjusted rate difference of −0.16 ATEs per 10 000 PYs.

Table 1. Baseline demographic and clinical characteristics of cases of arterial thromboembolism and corresponding matched controls

Characteristic*	Cases (*n* = 228)	Controls (*n* = 1385)
Age (years), mean (SD)**	30.6 (7.8)	30.4 (7.8)
Duration of follow up, mean (SD)**	3.8 (2.6)	3.8 (2.4)
Hospitalisation in the year before cohort entry, *n* (%)	21 (9.2)	71 (5.8)
Smoking status, *n* (%)		
Never	68 (29.8)	654 (46.7)
Ever	104 (45.6)	448 (34.7)
Unknown	56 (24.6)	283 (21.2)
Body mass index, *n* (%)		
<30 kg/m^2	128 (56.1)	760 (55.3)
≥30 kg/m^2	29 (12.7)	137 (10.0)
Unknown	71 (31.1)	488 (34.7)
Comorbidities *n* (%)		
Alcohol-related disorders, *n* (%)	7 (3.1)	16 (1.3)
COPD	S	7 (0.7)
Coronary artery disease	S	0 (0.0)
Diabetes	6 (2.6)	15 (1.1)
Dyslipidaemia	S	S
Heart failure	0 (0.0)	0 (0.0)
Hypertension	S	S
Peripheral vascular disease	S	S
Previous coronary revascularisation	S	0 (0.0)
Pregnancy history*, *n* (%)**		
Number of pregnancies, median (IQR)	2 (1, 2)	2 (1, 2)
No pregnancy before cohort entry	145 (63.6)	874 (63.1)
History of gestational diabetes	0 (0.0)	0 (0.0)
History of hypertensive disorders during pregnancy	S	S
Prothrombotic disorders, *n* (%)		
History of VTE	S	7 (0.5)
Family history of VTE	0 (0.0)	S
Anti-phospholipid Syndrome	0 (0.0)	0 (0.0)

COPD, chronic obstructive pulmonary disease; S, data suppressed to comply with CPRD privacy restrictions; SD, standard deviation; VTE, venous thromboembolism.
*Final results are weighted by the number of controls per case.
**Variable on which cases and controls were matched.
***For pregnancy counts the median (IQR) are derived using data from those patients who had at least one pregnancy; patients with no previous pregnancies were thus excluded.

Table 2. Baseline characteristics of current users of drospirenone-containing COCs and current users of levonorgestrel-containing COCs among controls

Characteristic	Drospirenone users (*n* = 51)	Levonorgestrel users (*n* = 366)
Age (years), mean (SD)	27.0 (7.8)	28.3 (8.0)
Duration of follow up, mean (SD)	2.5 (2.1)	2.7 (2.3)
Hospitalisation in the year before cohort entry, *n* (%)	S	18 (4.9)
Smoking status, *n* (%)		
Never	23 (45.1)	199 (54.4)
Ever	19 (37.2)	101 (27.6)
Unknown	9 (17.7)	66 (18.0)
Body mass index, *n* (%)		
<30 kg/m^2	38 (74.5)	222 (60.7)
≥30 kg/m^2	S	33 (9.0)
Unknown	S	111 (30.3)
Comorbidities, *n* (%)		
Alcohol-related disorders, *n* (%)	S	S
COPD	0 (0.0)	0 (0.0)
Coronary artery disease	0 (0.0)	0 (0.0)
Diabetes	0 (0.0)	S
Dyslipidaemia	0 (0.0)	S
Heart failure	0 (0.0)	0 (0.0)
Hypertension	0 (0.0)	S
Peripheral vascular disease	S	S
Previous coronary revascularisation	0 (0.0)	0 (0.0)
Pregnancy history*, *n* (%)		
Number of pregnancies, median (IQR)	1 (0,2)	0 (0, 1)
No pregnancy before cohort entry	31 (60.8)	242 (66.1)
History of gestational diabetes	0 (0.0)	0 (0.0)
History of hypertensive disorders during pregnancy	0 (0.0)	0 (0.0)
Prothrombotic disorders, *n* (%)		
History of VTE	0 (0.0)	S
Family history of VTE	0 (0.0)	0 (0.0)
Anti-phospholipid Syndrome	0 (0.0)	0 (0.0)

COPD, chronic obstructive pulmonary disease; S, data suppressed to comply with CPRD privacy restrictions; SD, standard deviation; VTE, venous thromboembolism.
*For pregnancy counts, the median (IQR) are derived using data from those patients who had at least one pregnancy; patients with no previous pregnancies were thus excluded.

Sensitivity analyses

Sensitivity analyses that examined the association between drospirenone-containing COCs and the rate of ATE by user type were inconclusive due to the small number of exposed events in each strata (first-time ever users: HR 0.64, 95% CI 0.06, 6.80; new users: HR 0.62, 95% CI 0.07, 5.69; switchers: HR 1.24, 95% CI 0.19, 8.20; prevalent users: HR 1.04, 95% CI 0.12, 8.92) (Table S3). Our sensitivity analysis comparing our results with or without matching on previous contraceptive use suggests that the use of this matching approach removed some confounding (with matching: HR 0.89, 95% CI 0.35, 2.28, without matching: HR 1.02, 95% CI 0.41, 2.54), although both estimates are accompanied by wide 95% CIs (Table S4). The use of multiple imputation produced results that were similar to those

Table 3. Drospirenone-containing combined oral contraceptives and the rate of arterial thrombosis

Exposure category*	Cases (*n* = 228) *n* (%)	Controls (*n* = 1385) *n* (%)	Crude HR (95% CI)**	Adjusted HR (95% CI)**,***
Current Levonorgestrel COC	56 (24.6)	366 (26.4)	1.00 (Reference)	1.00 (Reference)
Current Drospirenone COC	6 (2.6)	51 (3.7)	0.92 (0.36, 2.35)	0.89 (0.35, 2.28)

CI, confidence interval; HR, hazard ratio.
*Current users of other COCs (including current users of 1st, 2nd, 3rd, 4th generation of COC, Nuvaring, and combined-contraceptive patch), current users of other non-COCs (including current users of non-combined oral contraceptives as well as IUD, progestin-only implant and progestin-only injection), recent users, past users, and non-users (representing 166 cases and 968 controls) were considered in the regression model for proper estimation of treatment effects but are not presented in the table above.
**Cases and controls were matched on age, year of cohort entry, year of first registration in CPRD, user type, total duration of COC use, total duration of non-COC use, duration of exposure use.
***Adjusted for smoking, history of venous thromboembolism (VTE), and high-dimensional propensity score deciles.

of our primary analysis (HR 0.88, 95% CI 0.34, 2.26; Table S5). Similarly, the exclusion of the 50 cases for which we could not find suitable controls using our primary matching algorithm produced results that were consistent with those of our primary analysis (HR 1.01, 95% CI 0.39, 2.62) (Table S6). Finally, we found no evidence of interaction between exposure and HDPS in its continuous form (β 0.05, 95% CI −0.31, 0.42).

Discussion

Main findings

The overall rate of ATE in this population is low regardless of which COC was taken. We found little evidence of a difference in the rate of ATE with drospirenone-containing COCs relative to levonorgestrel-containing COCs, although results were inconclusive owing to wide 95% CIs (HR 0.89, 95% CI 0.35, 2.28). These estimates correspond to a rate difference of –0.16 ATEs per 10 000 PYs. Any increased risk is small and unlikely to be of clinical importance.

Although COCs are typically prescribed to prevent unwanted pregnancies, they have several other approved indications, including for acne treatment, relief of symptoms associated with premenstrual dysphoric disorder, treatment of heavy or irregular menstruation, and lower risks of ovarian and endometrial cancer, cyst formation, and endometriosis.[21] However, drospirenone-containing COCs offer some advantages relative to previous generations. This is largely because each successive generation of COC aims to mimic endogenous steroids in a way that maximises uptake and tolerability while lowering harmful side-effects; drospirenone-containing COCs exhibit strong anti-mineralocorticoid activity and anti-androgenic activity.[22] Moreover, drospirenone is the preferred treatment for polycystic ovary syndrome (PCOS).[23] Given these benefits and our findings, the evidence supports the FDA and EMA decisions that the benefits of drospirenone-containing COCs likely outweigh any potential risk associated with their use relative to other COCs.[2,3]

Strengths and limitations

Our study has several strengths. First, several previous studies[2,7,24–26] did not account for history of COC use, which may introduce bias. To overcome this potential limitation, we matched cases and controls on COC user type as well as duration of previous contraceptive use. Secondly, the CPRD contains population-based data that are representative of the age and sex distribution of the UK and thus highly generalisable.[9] Thirdly, previous studies suggest that CPRD data are valid.[8,10] Finally, through the use of an active comparator, our matching algorithm, and rigorous adjustment, we minimised potential confounding.

Our study also has some potential limitations. First, this study is observational in nature and some residual confounding is therefore possible. Secondly, ATE remains a relatively rare event among women of reproductive age. With few exposed events, our study produced estimates that were accompanied by wide 95% CIs. However, this study was sufficiently large to rule out HRs greater than 2.28. Thirdly, although many Read codes included in our endpoint definition were very specific, some were more general (e.g. 'stroke'), and it is therefore possible that some haemorrhagic strokes were included. However, with over 85% of all strokes having an ischaemic etiology, the expected number of included haemorrhagic strokes is expected to be minimal. Fourthly, although we adjusted for 'family history of thrombosis', the validity of this code in the CPRD is unknown, especially under the age of 50. Fifthly, although we accounted for a history of COC use to avoid bias, there were insufficient data to conclusively examine effect modification by history of use. Finally, in the UK, drospirenone-containing COCs are not the hormonal contraceptives of first choice and are only reimbursed under certain circumstances. Moreover, women are

able to receive prescriptions for COCs from both family planning clinics and general practitioners. However, the misclassification of exposure due to prescriptions from family planning clinics is likely to be small, as it is unlikely that women would receive prescriptions from family planning clinics after first receiving them from their general practitioner. Prescriptions from family planning clinics may also have resulted in some residual confounding due to misclassification of COC history. There is the possibility of selection bias if the risk of ATE is differential between women receiving prescriptions from family planning clinics and those receiving them from general practitioners.

Interpretation (in light of other evidence)

The association between the use of drospirenone-containing COCs and ATE has been examined previously. Those observational studies produced inconsistent results, with some reporting an increased risk[2,26,28] and others finding a null or protective association.[7,24,25] Several of those studies had important methodological limitations, including inadequate control for previous COC use or COC user type,[2,24,26] the use of an inactive comparator,[26] and residual confounding.[2,7,24–26,28] The importance of considering user type was well illustrated by the FDA analysis,[2] where the hazard ratio for drospirenone- versus levonorgestrel-containing COCs was 0.81 (95% CI 0.45,1.44) among all users, but 1.64 (95% CI 0.79, 3.40) when restricted to new users.[29] With the use of an active comparator, matching on previous contraceptive history, and rigorous statistical adjustment, the present study has overcome many of the limitations in the existing literature.

Conclusions

The overall rate of ATE in this population was low, regardless of which COC was taken. Therefore, although our comparative results between drugs was inconclusive due to wide 95% CIs, this potential adverse drug effect is unlikely to be of clinical or population health importance. Further studies are still needed to examine this potential adverse drug effect due to the limited number of events in this population, but the present study provides some reassurance regarding the benefit–harm profile of drospirenone-containing COCs relative to levonorgestrel-containing COCs.

Disclosure of interests

Full disclosure of interests available to view online as supporting information.

Details of ethics approval

This study was approved by the Independent Scientific Advisory Committee of the CPRD (protocol number: 13_038R) and the Research Ethics Board of the Jewish General Hospital in Montreal, Canada (reference number: 14–011; approved 15 January 2014, re-approved 16 January 2016).

Contribution to authorship

KBF conceived of the study idea and supervised the study. NL drafted the manuscript. ME conducted the statistical analyses. NL, SS, ME, LJ, MJE, HAA, and KBF interpreted study results and critically reviewed the manuscript for important intellectual content. KBF is the guarantor.

Acknowledgements

This study is supported by an operating grant from the Canadian Institutes of Health Research (CIHR; MOP-123588). Ms Larivée holds a Masters bursary from the *Fonds de recherche du Québec* - Santé (Quebec Health Research Fund). Dr Filion holds a CIHR New Investigator Award. This study was presented as a poster at the Society of Epidemiologic Research annual meeting in Denver, Colorado, in 2015 and as an oral presentation at the International Conference on Pharmacoepidemiology in Boston, Massachusetts, in August 2015.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Additional baseline demographic and clinical characteristics of cases of arterial thromboembolism and corresponding matched controls.

Table S2. Additional baseline characteristics of current users of drospirenone-containing COCs and current users of levonorgestrel-containing COCs among controls.

Table S3. Drospirenone-containing combined oral contraceptives and the rate of arterial thrombosis by user type.

Table S4. Drospirenone-containing combined oral contraceptives and the rate of arterial thrombosis, with and without matching on contraceptive history.

Table S5. Drospirenone-containing combined oral contraceptives and the rate of arterial thrombosis using multiple imputation to handle missing BMI and smoking data.

Table S6. Drospirenone-containing combined oral contraceptives and the rate of arterial thrombosis excluding cases for which the matching caliper was increased.

Figure S1. Distributions of high dimensional propensity scores among women receiving prescriptions for drospirenone- and levonorgestrel-containing oral contraceptives. ■

References

1 Previtali E, Bucciarelli P, Passamonti SM, Martinelli I. Risk factors for venous and arterial thrombosis. *Blood Transfus* 2011;9:120–38.

2 Food and Drug Administration. *FDA Drug Safety Communication: Updated Information About the FDA-Funded Study on Risk of Blood*

Clots in Women Taking Birth Control Pills Containing Dorspirenone. Food and Drug Administration, 2011 [www.fda.gov/Drugs/DrugSafety/ucm277346.htm]. Accessed 2 February 2012.
3 European Medicines Agency. *Benefits of Combined Hormonal Contraceptives (CHCs) Continue to Outweigh Risks*. European Medicines Agency, 2013 [www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Combined_hormonal_contraceptives/human_referral_prac_000016.jsp&mid=WC0b01ac05805c516f]. Accessed 7 October 2015.
4 Tanis BC, van den Bosch MA, Kemmeren JM, Cats VM, Helmerhorst FM, Algra A, et al. Oral contraceptives and the risk of myocardial infarction. *N Engl J Med* 2001;345:1787–93.
5 Roach REJ, Helmerhorst FM, Lijfering WM, Stijnen T, Algra A, Dekkers OM. Combined oral contraceptives: the risk of myocardial infarction and ischemic stroke. *Cochrane Database Syst Rev* 2015;CD011054.
6 Kemmeren JM, Tanis BC, van den Bosch MA, Bollen EL, Helmerhorst FM, van der Graaf Y, et al. Risk of Arterial Thrombosis in Relation to Oral Contraceptives (RATIO) study: oral contraceptives and the risk of ischemic stroke. *Stroke* 2002;33:1202–8.
7 Dinger J, Mohner S, Heinemann K. Cardiovascular risks associated with the use of drospirenone-containing combined oral contraceptives. *Contraception* 2016;93:378–85.
8 Herrett E, Thomas SL, Schoonen WM, Smeeth L, Hall AJ. Validation and validity of diagnoses in the General Practice Research Database: a systematic review. *Br J Clin Pharmacol* 2010;69:4–14.
9 Herrett E, Gallagher AM, Bhaskaran K, Forbes H, Mathur R, van Staa T, et al. Data resource profile: Clinical Practice Research Datalink (CPRD). *Int J Epidemiol* 2015;44:827–36.
10 Khan NF, Harrison SE, Rose PW. Validity of diagnostic coding within the General Practice Research Database: a systematic review. *Br J Gen Practice* 2010;60:e128–36.
11 Parkin L, Sharples K, Hernandez RK, Jick SS. Risk of venous thromboembolism in users of oral contraceptives containing drospirenone or levonorgestrel: nested case-control study based on UK General Practice Research Database. *Br Med J* 2011;342:d2139.
12 Suissa S, Azoulay L, Dell'Aniello S, Evans M, Vora J, Pollak M. Long-term effects of insulin glargine on the risk of breast cancer. *Diabetologia* 2011;54:2254–62.
13 Brynhildsen J. Combined hormonal contraceptives: prescribing patterns, compliance, and benefits versus risks. *Ther Adv Drug Saf* 2014;5:201–13.
14 CDC. *Centers for Disease Control and Prevention*. CDC, 2010 [www.cdc.gov/reproductivehealth/UnintendedPregnancy/USMEC.htm]. Accessed 3 June 2015.
15 Di Cianni G, Ghio A, Resi V, Volpe L. Gestational diabetes mellitus: an opportunity to prevent type 2 diabetes and cardiovascular disease in young women. *Womens Health (Lond)* 2010;6:97–105.
16 Robbins CL, Dietz PM, Bombard J, Valderrama AL. Gestational hypertension: a neglected cardiovascular disease risk marker. *Am J Obstet Gynecol* 2011;204:336.e1–9.
17 McDonald SD, Malinowski A, Zhou Q, Yusuf S, Devereaux PJ. Cardiovascular sequelae of preeclampsia/eclampsia: a systematic review and meta-analyses. *Am Heart J* 2008;156:918–30.
18 Szklo M, Nieto FJ. *Epidemiology: Beyond the Basics*, 3rd edn. Sudbury: Aspen Publishers, 1999.
19 Schneeweiss S, Rassen JA, Glynn RJ, Avorn J, Mogun H, Brookhart MA. High-dimensional propensity score adjustment in studies of treatment effects using health care claims data. *Epidemiology* 2009;20:512–22.
20 Suissa S. The quasi-cohort approach in pharmacoepidemiology. *Epidemiology* 2015;26:242–6.
21 Slabbert DR, Kruger TF, Steyn PS. Oral contraception: Five important issues. *South Afr Fam Practice* 2005;47:22–4.
22 Szarewski A, Mansour D, Shulman LP. 50 Years of 'The Pill': Celebrating a golden anniversary. *J Fam Plan Reprod Health Care* 2010;36:231–8.
23 Mathur R, Levin O, Azziz R. Use of ethinylestradiol/drospirenone combination in patients with the polycystic ovary syndrome. *Ther Clin Risk Manage* 2008;4:487–92.
24 Gronich N, Lavi I, Rennert G. Higher risk of venous thrombosis associated with drospirenone-containing oral contraceptives: a population-based cohort study. *Can Med Assoc J* 2011;183:E1319–25.
25 Dinger J, Bardenheuer K, Heinemann K. Cardiovascular and general safety of a 24-day regimen of drospirenone-containing combined oral contraceptives: final results from the International Active Surveillance Study of Women Taking Oral Contraceptives. *Contraception* 2014;89:253–63.
26 Lidegaard O, Lokkegaard E, Jensen A, Skovlund CW, Keiding N. Thrombotic stroke and myocardial infarction with hormonal contraception. *N Engl J Med* 2012;366:2257–66.
27 FDA Drug Safety Communication: Safety review update of Chantix (varenicline) and risk of cardiovascular adverse events, 2012 [www.fda.gov/Drugs/DrugSafety/ucm330367.htm]. Accessed 7 October 2015.
28 Sidney S, Cheetham TC, Connell FA, Ouellet-Hellstrom R, Graham DJ, Davis D, et al. Recent combined hormonal contraceptives (CHCs) and the risk of thromboembolism and other cardiovascular events in new users. *Contraception* 2013;87:93–100.
29 Food and Drug Administration Office of Surveillance and Epidemiology. *Combined Hormonal Contraceptives (CHCs) and the Risk of Cardiovascular Disease Endpoints*. Food and Drug Administration Office of Surveillance and Epidemiology, 2011 [www.fda.gov/downloads/Drugs/DrugSafety/UCM277384.pdf]. Accessed 18 February 2012.