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ORIGINAL ARTICLE

Drospirenone and non-fatal venous thromboembolism: is there a risk difference by dosage of ethinyl-estradiol?

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Summary. *Background:* Previous studies concluded that there was an increased risk of non-fatal venous thromboembolism (VTE) with drospirenone. It is unknown whether the risk is differential by ethinyl-estradiol dosage. *Objectives:* To assess the risk of VTE with drospirenone and to determine whether drospirenone and ethinyl-estradiol 20 μg (DRSP/EE20) has a lower VTE risk than drospirenone and ethinyl-estradiol 30 μg (DRSP/EE30). *Methods:* Our cohort included women aged 18–46 years taking drospirenone or levonorgestrel (LNG)-containing combined oral contraceptives (COCs) in the IMS claims database between 2001 and 2009. VTE was defined using ICD-9-CM coding and anticoagulation. The hazard ratio (HR) from Cox proportional hazards models was used to assess the VTE relative risk (RR) with drospirenone compared with levonorgestrel, adjusted by a propensity score used to control for baseline co-morbidity and stratified by EE dosage and user-type (new/current). *Results:* The study included 238 683 drospirenone and 193 495 levonorgestrel users. Among new and current users, a 1.90-fold (95% CI, 1.51–2.39) increased VTE relative risk was observed for drospirenone (18.0 VTE/10 000 women-years) vs. levonorgestrel (8.9 VTE/10 000 women-years). In analysis of new users, DRSP/EE20 had a 2.35-fold (95% CI, 1.44–3.82) VTE RR versus LNG/EE20. New users of DRSP/EE30 observed an increased RR versus LNG/EE30 among women starting to use COCs between 2001 and 2006 (2.51, 95% CI, 1.12–5.64) but not between 2007 and 2009 (0.76, 95% CI, 0.42–1.39), attributable to an increased incidence rate with LNG/EE30 from 2007 to 2009. In direct comparison, DRSP/EE20 had an elevated risk of VTE compared with DRSP/EE30 (RR, 1.55; 95% CI, 0.99–2.41). *Conclusions:* We observed a modestly elevated risk of VTE with drospirenone, compared with levonorgestrel. The larger VTE incidence rate observed in DRSP/EE20 than in DRSP/EE30 and the increasing VTE incidence rate with levonorgestrel between 2007 and 2009 were unexpected.

Keywords: comparative study, contraception, drospirenone, Levonorgestrel, venous thromboembolism.

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Introduction

Venous thromboembolism (VTE) is a combined outcome that includes pulmonary embolism (PE) or deep vein thrombosis (DVT). The association between combined oral contraceptives (COCs) containing drospirenone and venous thromboembolism (VTE) has been a concern since their approval in 2001. Although initial observational studies did not find an increased VTE risk [1,2], seven observational studies subsequently published between 2007 and 2011 observed a 1.5–3.0-fold increased VTE relative risk associated with use of drospirenone compared with levonorgestrel-containing COCs [3–9].

This study evaluates two drospirenone products: drospirenone 3 mg with ethinyl-estradiol 30 μg (DRSP/EE30) and drospirenone 3 mg with ethinyl-estradiol 20 μg (DRSP/EE20). While both are approved for prevention of pregnancy, DRSP/EE20 contains a lower EE dosage and three additional days of active therapy. DRSP/EE20 has two additional FDA-approved indications for women seeking contraception: (i) treatment of emotional and physical symptoms of premenstrual dysphoric disorder

(PMDD) (added October 2006), and (ii) treatment of moderate acne vulgaris (added January 2007) [10].

The study's objective is to evaluate the non-fatal VTE relative risk with drospirenone compared with levonorgestrel at the comparable EE levels, additionally assessing whether DRSP/EE20 has a lower risk of VTE than DRSP/EE30.

Materials and methods

Data source

The IMS Lifelink™ database contains paid claims from 102 healthcare plans in the United States. It contains fully adjudicated medical and pharmacy claims for over 68 million patients, including inpatient and outpatient diagnoses and procedures (*International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) format*), in addition to retail and mail-order prescription records. The data are representative of US residents with private health insurance in terms of geography, age and gender. The Lifelink™ database is subject to quality checks to ensure data quality and minimize error rates [11].

Study design

The study timeframe, 1 May 2001 to 31 December 2009, was selected to evaluate COC usage beginning with the initial approval of drospirenone. The exposure index date was the first prescription for a study COC after one full year of enrollment. Women with no hormonal contraception usage during this 1-year period were classified as new users, while those with prior hormonal contraceptive usage were classified as current users. Hormonal contraception was defined as a COC, hormonal injection, transdermal patch, hormonal ring or implanted device.

Inclusion criteria

Women were eligible for the study if they were between the ages of 18 and 46 years at the receipt of a COC containing ≤ 0.030 mg EE combined with the progestin drospirenone or levonorgestrel.

Exclusion criteria

Women were excluded if they did not have 1 year of total enrollment of if they had an ICD-9-CM code for a history of cancer, cerebrovascular disease, cardiovascular disease, prior VTE and prior anticoagulation (warfarin and heparins), assessed during the 1-year baseline period. Women contributed person-time to the analysis from their exposure index date until the first occurrence of: a study outcome, switching to another COC, a gap in possession of study COC therapy $\geq$ 30 days, discontinuation of enrollment, or the end of the study period.

Case ascertainment

Non-fatal VTE was defined as a combined outcome of PE (ICD-9-CM 415.1) or DVT (ICD-9-CM 453, 451.1). The event was required to occur during or within 30 days after cessation of COC therapy. If a patient discontinued COCs after a VTE, evaluating during this 30-day window prevented informative censoring bias, whereby the VTE claim may come after the patient has discontinued COC therapy [12]. As it was not possible for this study to validate the outcome with medical records or evaluate death in the hospital emergency room, all cases were required to have anticoagulant treatment, with the first dose administrated within 14 days of the VTE claim. Because women were required to survive 14 days post-discharge for anticoagulant assessment, our study outcome is non-fatal VTE, and the index date was 14 days after the VTE hospitalization. Identifying VTE cases using outpatient diagnoses and subsequent anticoagulation was shown to have an 83.3% positive predictive value in a study in Kaiser Permanente, Northern California [9].

Statistical analysis

We evaluated exposure to drospirenone (DRSP/EE20, DRSP/EE30) and levonorgestrel (LNG/EE20, LNG/EE30). Prescription and medical claims, demographics and healthcare utilization data, during the 365 days prior to the exposure index date (shown in Table 1), in addition to the calendar-year of treatment, were used to develop a propensity score to predict exposure to drospirenone. A propensity score is a summary score for the probability of receiving a given treatment that is based on a model that considers all measured baseline co-morbidity variables that potentially explain treatment selection. The score is an alternative to multivariate adjustment and can be used to balance treatment groups with regard to potential confounders. This technique is commonly used in large database studies to adjust for a large number of measured covariates without loss of statistical precision. Cox proportional hazards models were used to estimate the time to first occurrence of VTE with drospirenone compared with levonorgestrel-containing COCs, stratified by EE dosage and user type (new/current). Because DRSP/EE20 was first approved on 16 March 2006, women commencing COC therapy prior to this date were restricted from stratified analyses of DRSP/EE20 vs. LNG/EE20 to prevent against left censoring bias. Poisson regression was used to calculate age-specific incidence rates (IRs), reported as cases per 10 000 women-years (WY) for drospirenone and levonorgestrel and stratified by EE dosage and user type.

Strict VTE definition

We evaluated a stricter definition of VTE, limiting VTE cases to having a hospitalization, emergency room visit or

Table 1 Characteristics of the study population by combined oral contraceptive (COC), 2001–2009

	Ethinyl estradiol EE20 μg		Ethinyl estradiol EE30 μg	
	DRSP/EE20 μg	LNG/EE20 μg	DRSP/EE30 μg	LNG/EE30 μg
Number of women				
Total, # (%)	75 524	111 151	163 159	82 344
New users, # (%)	40 710 (53.9)	44 497 (40.0)	65 661 (40.2)	30 359 (36.9)
Current users, # (%)	34 814 (46.1)	66 654 (60.0)	97 498 (59.8)	51 985 (63.1)
Time on COC				
Mean, d	169.2	244.1	215.2	258.7
1–90 days, %	48.10	40.54	42.04	40.78
90–180 days, %	19.78	18.18	19.23	16.19
180–365 days, %	20.62	20.83	21.42	21.61
> 365 days, %	11.50	20.45	17.31	21.43
Age				
Mean, yr	30.0	28.1	28.2	30.0
18–22 years, %	6.0	19.7	17.5	10.9
23–27 years, %	34.3	29.4	30.9	27.2
28–32 years, %	24.6	22.1	23.0	23.6
33–37 years, %	17.7	16.7	17.3	20.9
38–42 years, %	13.0	10.0	9.9	14.2
43–46 years, %	4.4	2.1	1.4	3.2
Hospitalizations*				
1 prior, %	2.93	3.82	3.34	3.46
≥2 prior, %	0.28	0.34	0.29	0.37
ER visits*				
1 prior ER, %	2.27	2.93	2.65	2.87
≥2 prior ER, %	0.71	0.96	0.76	0.87
Office visits*				
1–4 prior visits, %	22.85	31.37	30.20	32.12
≥5 prior visits, %	20.44	23.01	25.46	26.52
Prior time on COC*				
1–90 days, %	13.56	12.12	12.89	11.14
91–180 days, %	9.64	9.62	10.83	10.24
181–270 days, %	10.21	11.68	13.45	13.17
271–365 days, %	12.35	26.37	22.33	28.42
Number prior COC*				
1 COC, %	12.29	8.21	10.58	11.73
≥2 COC, %	5.30	4.73	6.13	4.84
Medications, %				
ACEI/ARB	1.61	2.17	1.73	2.46
Beta blocker	4.28	4.72	4.28	5.38
Benzodiazepine	16.96	13.50	15.98	16.58
Calcium channel	1.09	1.46	1.14	1.60
Diabetes meds	4.27	2.89	5.23	3.04
SSRI/TCA	25.72	24.58	25.37	26.69
Spironolactone	2.93	1.38	3.07	1.33
Statin/Fibrate	1.97	2.26	2.08	2.82
Co-morbidities, %				
Acne	20.72	16.69	20.91	15.13
Allopecia	2.28	1.99	2.37	1.87
Anovulation	1.04	0.90	1.38	0.78
Asthma	9.39	10.17	10.38	10.75
COPD	6.39	7.60	6.94	7.55
Diabetes	3.07	3.46	3.69	3.39
Dysmenorrhea	9.95	9.43	10.26	9.99
Endometriosis	3.01	2.77	3.17	4.58
Hirsutism	2.12	1.07	2.60	0.89
Hyperlipidemia	12.50	11.81	13.04	13.39
Hypertension	7.27	7.89	7.72	8.89
Hypothyroid	8.56	7.23	8.39	7.99
Infertility	2.91	2.59	3.44	2.45
Ovarian inflammation	2.01	2.14	2.14	2.34
Vaginal inflammation	23.74	26.47	25.25	24.03

Table 1 (Continued)

	Ethinyl estradiol EE20 μg		Ethinyl estradiol EE30 μg	
	DRSP/EE20 μg	LNG/EE20 μg	DRSP/EE30 μg	LNG/EE30 μg
Uterine leiomyoma	3.64	3.29	3.16	3.80
Menstrual irregular	37.17	34.50	35.22	32.50
Migraine	10.77	10.65	10.65	12.69
Mood/anxiety disorder	26.44	25.07	25.07	26.22
Obesity	11.22	10.41	11.40	11.68
PUD	0.70	0.70	0.78	0.71
PCOS	4.72	2.16	6.05	2.09
PTS (PMS/PMDD)	6.21	2.85	3.81	3.07
Sleep disorder	1.31	0.96	0.98	1.36
Smoking	5.44	6.10	4.70	6.25

*Prior hospitalizations, prior ER visits, prior office visits, prior time on therapy (for current users) and number of prior COCs (for current users) were calculated during the 365-day period prior to initiating a COC.
DRSP, drospirenone; LNG, levonorgestrel; EE, ethinyl-estradiol; COC, combined oral contraceptive; ER, Emergency Room; ACE/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blocker; Diabetes meds, all available oral and injectable medications for the treatment of diabetes; SSRI/TCA, selective serotonin reuptake inhibitor/tricyclic antidepressant; Calcium channel, calcium channel blocker; COPD, chronic obstructive pulmonary disease; PUD, peptic ulcer disease; PCOS, polycystic ovary syndrome; PTS (PMS/PMDD), premenstrual tension syndrome (premenstrual syndrome/premenstrual dysphoric disorder); Vaginal inflammation, inflammation of cervix, vagina, vulva; Ovarian inflammation, inflammation of ovary, pelvic, peritoneum.

a diagnostic procedure (CPT4 code for venography, d-dimer or ultrasound/CT/MRI of upper/lower extremities). Cases were excluded during, or 4 weeks after, a normal delivery, Caesarean section, induced abortion, miscarriage or ectopic pregnancy. Prior studies have used a similar strict definition of VTE [5,6].

Proportionality of hazards was examined graphically by means of log-log survival curves, and no meaningful deviations from proportionality were observed after baseline. All analyses were conducted in SAS version 9.2. This study was approved by the University of Florida Institutional Review Board.

Results

Our study cohort included 238 683 drospirenone and 193 495 levonorgestrel users. Cohort formation is shown in Fig. 1 and baseline characteristics are provided in Table 1. The market share (percentage utilization) for each study COC by study year is shown in Fig. 2. Between 2001 and 2003, LNG/EE20 had the highest percent utilization of study COCs. DRSP/EE30 use increased rapidly following market availability in 2001, and it had the greatest percentage of COC prescriptions dispensed between 2004 and 2006. A similar pattern was seen for DRSP/EE20 following its initial approval in 2006, and it became the most prescribed study COC from 2007 to 2009.

We identified 354 VTE events during the study period, 236 events during 131 221 women-years exposed to drospirenone and 118 events during 132 681 women-years exposed to levonorgestrel. In an analysis of new and current users, including all EE dosages, use of levonorgestrel as a reference (IR 8.9/10 000 WY) showed a 1.90-fold (95% CI, 1.51–2.39) increased VTE relative risk (RR) with drospirenone (IR 18.0/10 000 WY).

Analysis restricted to new users identified 180 VTEs, 123 events during 50 284 women-years with drospirenone (24.5/10 000 WY) and 57 events during 40 478 women-years with levonorgestrel (14.1/10 000 WY), producing a slightly attenuated RR for VTE with drospirenone vs. levonorgestrel (RR, 1.63; (95% CI, 1.18–2.26). In stratified analyses of new users, DRSP/EE20 (RR, 2.50; 95% CI, 1.39–4.49) had a larger VTE RR than DRSP/EE30 (RR, 1.24; 95% CI, 0.79–1.94)] (Table 2). Among women commencing COC therapy between 2001 and 2006, DRSP/EE30 new users had a 2.51-fold (95% CI, 1.12–5.64) increased RR for VTE compared with LNG/EE30 new users, while analysis of women commencing COC therapy between 2007 and 2009 observed no risk difference (RR of 0.76; 95% CI, 0.42–1.39) (Table 3). The lack of a risk difference between 2007 and 2009 was driven by an unexpectedly high VTE IR with the LNG/EE30 comparator. Direct comparison of DRSP/EE20 new users with DRSP/EE30 new users observed a RR of 1.55 (95% CI, 0.99–2.41) (Table 4).

IRs for VTE increased with age as expected and were higher with DRSP/EE20 than DRSP/EE30 (Appendix S1). Comparing drospirenone with levonorgestrel, using a stricter definition of VTE that required additional clinical evidence resulted in a marginal increase in the magnitude of the effect found in the current study from HR 1.90 (95% CI, 1.51–2.39) to HR 1.95 (95% CI, 1.47–2.59).

Discussion

Analysis of all COC users found a 1.90-fold increased VTE RR with drospirenone compared with levonorgestrel-containing COCs, while analysis restricted to new users found a 1.63-fold increased RR. DRSP/EE30

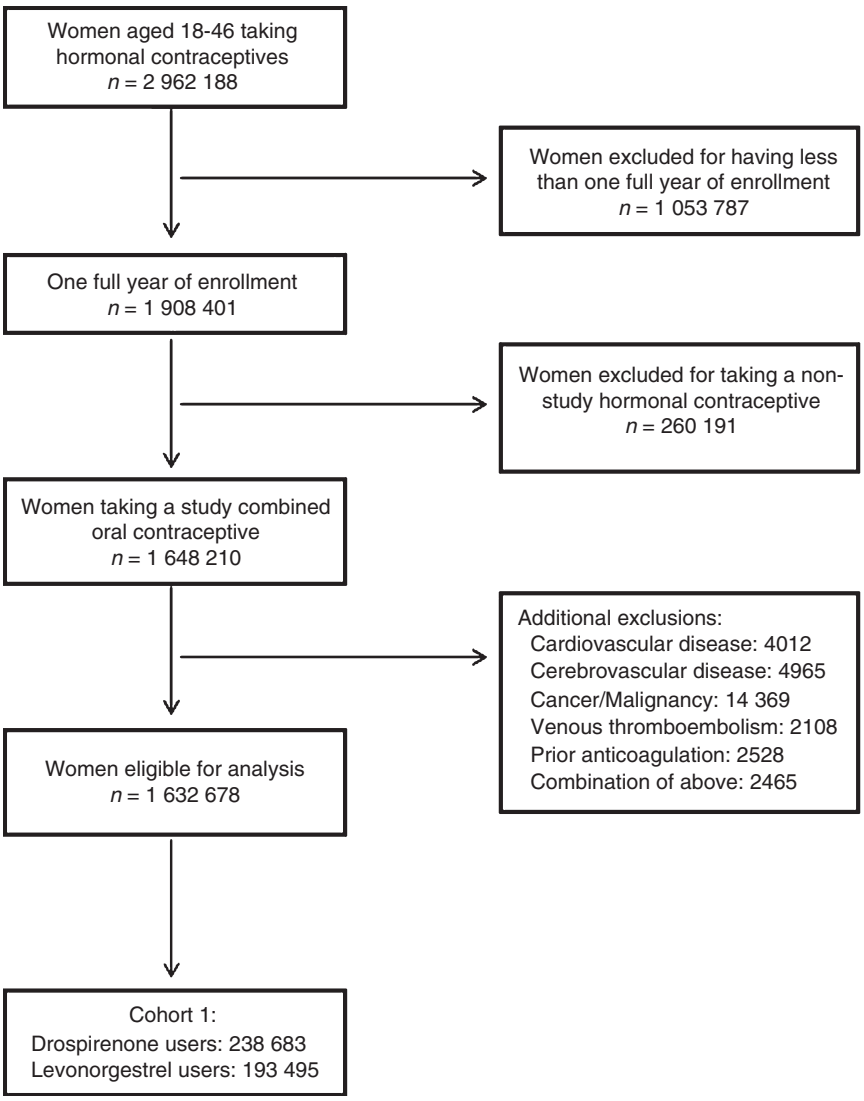

Fig. 1. Development of study cohorts.

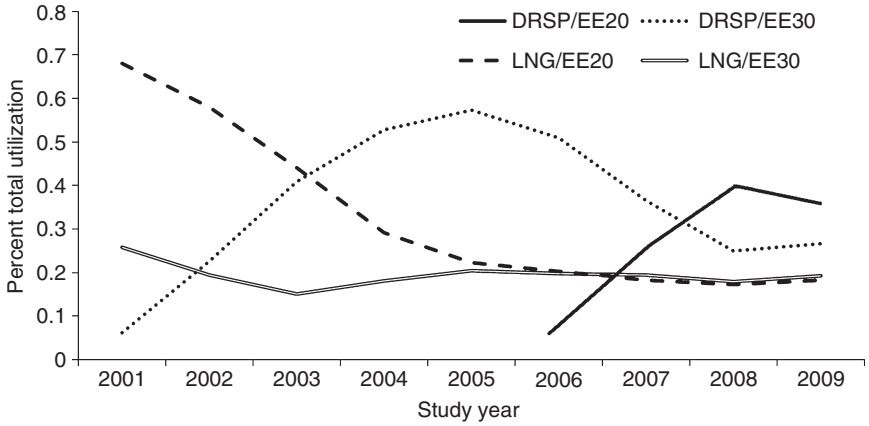

Fig. 2. Per cent total utilization of study combined oral contraceptives, 2001–2009.

showed an increased risk of VTE compared with LNG/EE30 between 2001 and 2006, but not 2007 and 2009. One likely explanation is that high-risk women were prescribed LNG/EE30 during these later study years after publicity that drospirenone was associated with an increased risk of VTE.

Table 2 Risk of venous thromboembolism with drospirenone compared with levonorgestrel, 2001–2009

Drug name	# VTE/# women	Women-years (WY)	IR/10 000 WY	HR (95% CI)†
All combined oral contraceptive users				
All EE doses				
Drospirenone	236/238 683	131 221	18.0	1.90 (1.51–2.39)
Levonorgestrel (ref)	118/193 495	132 681	8.9	—
EE30 stratification				
DRSP/EE30 μg	151/163 159	96 217	15.7	1.82 (1.34–2.49)
LNG/EE30 μg (ref)	56/82 344	58 356	9.6	—
EE20 stratification*				
DRSP/EE20 μg	85/75 524	35 004	24.3	2.38 (1.55–3.65)
LNG/EE20 μg (ref)	30/45 225	28 782	10.4	—
New combined oral contraceptive users				
All EE doses				
Drospirenone	123/106 371	50 284	24.5	1.63 (1.18–2.26)
Levonorgestrel (ref)	57/74 856	40 478	14.1	—
EE30 stratification				
DRSP/EE30 μg	62/65 661	32 907	18.8	1.24 (0.79–1.94)
LNG/EE30 μg (ref)	29/30 359	16 735	17.3	—
EE20 stratification*				
DRSP/EE20 μg	61/40 710	17 377	35.1	2.50 (1.39–4.49)
LNG/EE20 μg (ref)	14/19 467	9 524	14.7	—

*Restricted Post 3/16/2006, the initial approval date of the DRSP/EE20 μg formulation (i.e. LNG dispensed prior to this date not included in reference).
†Adjusted by a propensity score to predict exposure to drospirenone.
VTE, venous thromboembolism; WY, women-years; IR, incidence rate (calculated per 10 000 WY); HR (95% CI), hazard ratio (95% confidence interval); EE, ethinyl estradiol; DRSP, drospirenone; LNG, levonorgestrel; ref, reference comparator.

Table 3 Venous thromboembolism risk with DRSP/EE30 compared with LNG/EE30, stratified by the year of COC initiation (2001–2006 and 2007–2009)

Drug name	# VTE/# women	Women-years (WY)	IR/10 000 WY	HR (95% CI)*
All combined oral contraceptive users				
2001–2006				
DRSP/EE30 μg	82/98 484	55 785	14.7	2.70 (1.60–4.56)
LNG/EE30 μg (ref)	18/41 648	31 022	5.8	—
2007–2009				
DRSP/EE30 μg	69/64 675	40 432	17.1	1.35 (0.90–2.01)
LNG/EE30 μg (ref)	38/40 696	27 334	13.9	—
New combined oral contraceptive users				
2001–2006				
DRSP/EE30 μg	41/43 867	22 386	18.3	2.51 (1.12–5.64)
LNG/EE30 μg (ref)	7/15 392	9 055	7.7	—
2007–2009				
DRSP/EE30 μg	21/21 794	10 521	20.0	0.76 (0.42–1.39)
LNG/EE30 μg (ref)	22/14 967	7 680	28.6	—

*Adjusted by a propensity score to predict exposure to drospirenone.
VTE, venous thromboembolism; WY, women-years; IR, incidence rate (calculated per 10 000 WY); HR (95% CI), hazard ratio (95% confidence interval); EE, ethinyl estradiol; DRSP, drospirenone; LNG, levonorgestrel; ref, reference comparator.

The largest RRs were observed for DRSP/EE30 between 2001 and 2006 and DRSP/EE20 between 2007 and 2009, corresponding to the first years of marketing for each product. A larger IR with DRSP/EE20 than DRSP/EE30 was a paradoxical finding. There is a known dose-response relationship between EE dosage and VTE [13], where COCs containing 50 μg EE have greater VTE risk than COCs containing < 50 ug EE. DRSP/EE20 does have three additional days of active drug therapy, although cumulative EE dosage per month is lower with the EE20 (0.02 mg*24 days = 0.48 mg) than the EE30 formulation (0.03 mg*21 days = 0.63 mg). The DRSP/EE20 formulation also has 3 additional days (9 mg) of drospirenone therapy each month, which could explain this finding.

It is also possible that the larger IR with DRSP/EE20 resulted from heavy marketing of this formulation (Yaz®) and its approved secondary indications, which could lead to selective prescribing to women with different VTE risk profiles. An open-label randomized study in 2006 found

Table 4 Direct comparison of venous thromboembolism risk between DRSP/EE20 and DRSP/EE30, after DRSP/EE20 approval (post 3/16/2006)

Drug name	# VTE/# women	Women-years (WY)	IR/10 000 WY	HR (95% CI)*
All combined oral contraceptive users				
Direct comparison				
DRSP/EE20	85/75 524	35 004	24.3	1.21 (0.88–1.68)
DRSP/EE30 (ref)	86/81 464	50 411	17.1	–
New combined oral contraceptive users				
Direct comparison				
DRSP/EE20	61/40 710	17 377	35.1	1.55 (0.99–2.41)
DRSP/EE30 (ref)	32/30.370	15 155	21.1	–

*Adjusted by a propensity score to predict exposure to drospirenone.
VTE, venous thromboembolism; WY, women-years; IR, incidence rate (calculated per 10 000 WY); HR (95% CI), hazard ratio (95% confidence interval); EE, ethinyl estradiol; DRSP, drospirenone; LNG, levonorgestrel; ref, reference comparator.

less pronounced hemostatic changes (including fibrinogen and Protein S activity) with DRSP/EE20, compared with DRSP/EE30 [14], and knowledge of this study may have influenced prescribing practice. Although we do not have data on hemostatic parameters, it is important to note that most measured cardiovascular risk factors in our data (aside from polycystic ovary syndrome, PCOS) do not indicate the presence of this selective prescribing among study COCs.

In a previous study, a similar paradoxically larger VTE risk was observed with the EE20 formulation of desogestrel (RR, 2.8; 95% CI, 1.3–6.5) than the EE30 formulation (RR, 1.5; 95% CI, 0.9–2.5), both compared with levonorgestrel [15]. This study found that the RR for VTE was greater after the initial launch of several COC products. The effect was attributed to depletion of women susceptible to VTE with levonorgestrel, resulting from an increased capture of new users taking more recently approved products. Commencing use of COCs is known to be a time period of greater VTE risk, and adjusting for a full history of prior COC use has been shown to reduce bias due to depletion of susceptible patients [16,17]. In our study, we stratified subjects by a new-use covariate, defined using a 1-year period prior to COC initiation. Similar results between new and current users suggest this bias should be minimal in our data.

There is some evidence for selective prescribing to specific subpopulations in Table 1. DRSP/EE20 had a larger percentage of new users than DRSP/EE30 (53.9% vs. 40.2%), fewer women with a visit to a physician in the prior year (43.3% vs. 55.7%), a shorter mean duration of therapy (169 days vs. 214 days), and more women with premenstrual tension syndromes (PTS), including PMDD (6.2% vs. 3.8%). Polycystic ovary syndrome (PCOS) codes were more common with DRSP/EE30 than DRSP/EE20 (6.1% vs. 4.7%), probably because studies have evaluated the DRSP/EE30 formulation for improvement of hirsutism and hyperandrogenism in women with PCOS [18–20]. More drospirenone than levonorgestrel users in this database, regardless of EE dose, had ICD-9-CM codes for PCOS, premenstrual tension syndrome, hirsutism and spironolactone treatment (see Table 1). It is important to note that the measurable differences noted above are adjusted for in the statistical analysis; however, use of ICD-9-CM coding may have resulted in under-reporting of these covariates due to the confusion surrounding diagnosis of PCOS for different age groups.

Prior studies

The literature provides a wide range of estimates for risk of VTE with drospirenone, ranging from 0.9 to 3.3 when compared with other COC formulations [1–9,21–23]. The EURAS study, commissioned by Bayer in coordination with the European Medicines Agency, prospectively identified users of drospirenone, levonorgestrel and other COCs. It did not find increased risk of VTE with drospirenone compared with levonorgestrel in its main analysis (HR, 1.0; 95% CI, 0.6, 1.8) [1], evaluation of idiopathic cases (HR 1.0; 95% CI, 0.7–1.6) [22] or long-term follow-up (HR, 1.1; 95% CI, 0.8–1.7) [23]. However, identification of VTE through prescriber referral and patient interview could lead to recall bias. The FDA study, like the EURAS study, evaluated only DRSP/EE30, compared with low-dose estrogen comparators, finding increased risk of VTE among new users of drospirenone (HR, 1.77; 95% CI, 1.33–2.35] [9]. Only one prior study evaluated drospirenone's VTE risk by EE dosage, finding non-significantly higher VTE risk with DRSP/EE20 vs. LNG/EE30 (OR, 2.22; 95% CI,1.27–3.89) than with DRSP/EE30 vs. LNG/EE30 (OR, 2.09; 95% CI, 1.55–2.82) when evaluating both new and current users [8]. This study was conducted in Denmark, where physicians may have different prescribing practices, supported by the fact that 8% of their drospirenone users took DRSP/EE20, while 31.6% of our drospirenone users took DRSP/EE20.

The IR for VTE with COC products has varied by study, which may be partially due to differences between the selected populations, diagnostic practices for VTE by country and study year, underlying population-based

VTE risk factors, definition of new users, case ascertainment methodologies, and insurance formularies. Requiring 4 months of anticoagulation therapy [8] and limiting identification to non-fatal idiopathic cases in some recent studies [5,6] provide less comparable IRs to our current study. The recent FDA study found an IR for DRSP/EE30 of 13.7/10 000 WY and an IR for comparator COCs of 8.2/10 000 WY [9], which are smaller than our study IRs, probably resulting from differences in the included study populations.

Limitations and selective prescribing

We conducted analyses on drospirenone and VTE in a population-based cohort and improved on previous studies by providing an in-depth look at risk by EE dosage, including data from 2008-2009, and using a 1-year period to assess baseline covariates. However, use of ICD-9-CM coding to identify smoking and obesity is known to under-ascertain these covariates, and we did not have information on immobility, travel or family history of blood clots. Media attention focusing on the risk of VTE with drospirenone compared with levonorgestrel could increase monitoring in these women, although it could also result in prescribing levonorgestrel to higher risk women during later study years.

It is important to address the unique antiandrogen and antimineralocorticoid activity of drospirenone. Antimineralocorticoid activity is known to increase renal elimination of sodium and water [24], and one clinical trial found a reduction in both body weight and blood pressure with drospirenone, but not with levonorgestrel [25]. Other published studies have found similar results [26–28]. It is possible that good publicity from these unique properties may have channeled some women at high risk of VTE to drospirenone during earlier study years. With regards to unmeasured BMI, the EURAS study found that obesity (BMI $\geq$ 30) was 1.6 times more common in users of drospirenone-containing compared with levonorgestrel-containing COCs [1]. However, the authors conclude that the absolute difference was small and this could only slightly increase the incidence of VTE with drospirenone. The EURAS study, and several others having access to BMI, did not find this covariate to be a confounder [1,3,5,7,21]. Although claims data have a poor capture of obesity, the percentage of women taking each of our four study COCs with a claim for obesity was similar.

Among commonly used COCs, levonorgestrel and norgestrel have high androgenic activity, norethindrone and norethindrone acetate have medium androgenic activity, desogestrel and norgestimate have no androgenic activity, and drospirenone has antiandrogenic activity [29]. Studies have also focused on the potentially beneficial antiandrogen properties of drospirenone for women with PCOS [18–20]. Although recent PCOS consensus treatment guidelines recommend that all COCs appear to have equal efficacy for PCOS [30], recent studies have shown selective prescribing of drospirenone to women with PCOS [31] and hyperandrogenism [32]. PCOS has also been shown by two studies to confer an approximate 2-fold increased risk of VTE [33,34]. This is further complicated by the FDA approval of DRSP/EE20 for acne vulgaris because androgenic acne is often one of the first clinical signs of PCOS. Although some women with endometriosis benefit from antiandrogen therapy, and recent treatment guidelines recommend hormonal therapy for suppression of ovarian function, there is no evidence to suggest selective prescribing by COC product for endometriosis [35]. While we adjusted for the above conditions, ICD-9-CM coding resulted in a poor capture of these covariates.

Conclusions

Overall, we found modestly increased RR for non-fatal VTE with drospirenone compared with levonorgestrel. The higher VTE IR with DRSP/EE20 than DRSP/EE30 was a paradoxical finding. A trend toward an increased VTE IR with levonorgestrel between 2007 and 2009 was also unexpected, decreasing the significance of increased VTE risk with DRSP/EE30 during later study years. The marked shifts in COC utilization between 2001 and 2009, selective prescribing of drospirenone for conditions such as PCOS and hyperandrogenism, and our inability to fully ascertain the indication for COC use, increases the difficulty in interpreting the risk of VTE with drospirenone. Although the risk is small, our study continues to recommend caution with the use of drospirenone, especially in women at high risk of VTE. Future research is needed to assess risk of VTE by COC product in data that capture both the indication for use and baseline risk of VTE.

Competing interests

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

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FDA/CDER disclaimer

S. Bird is employed by the Food and Drug Administration. This study represents the opinions of the authors and not those of the Food and Drug Administration.

Addendum

All the authors took part in the study design and the analysis and interpretation of the data. The manuscript was drafted by S. Bird and critically revised for important intellectual content by all authors. The statistical analysis was completed by S. Bird and the study guarantor is B. Hartzema.

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Disclosure of Conflict of Interest

The authors state that they have no conflicts of interest.

Supporting Information

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

Appendix S1. Venous thromboembolism incidence rates by combined oral contraceptive and age, 2001–2009.

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