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Drospirenone and non-fatal venous thromboembolism: Is there a risk difference by dosage of Ethinyl-Estradiol?

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Abbreviations:

1. COC = Combined Oral Contraceptive (having both a progestin and estrogen component)
2. VTE = Venous Thromboembolism
3. DVT = Deep Vein Thrombosis
4. PE = Pulmonary Embolism
5. DRSP/EE20 = Drospirenone 3mg and Ethinyl Estradiol 20µg
6. DRSP/EE30 = Drospirenone 3mg and Ethinyl Estradiol 30µg
7. LNG/EE20 = Levonorgestrel 0.1mg and Ethinyl Estradiol 20µg
8. LNG/EE30 = Levonorgestrel 0.15mg and Ethinyl Estradiol 30µg
9. PMDD = Premenstrual dysphoric disorder
10. PCOS = Polycystic ovary syndrome

**Abstract:**

**Background:** Previous studies concluded increased risk for non-fatal venous thromboembolism (VTE) with drospirenone. It is unknown whether risk is differential by ethinyl-estradiol dosage.

**Objectives:** To assess VTE risk with drospirenone and to determine whether drospirenone and ethinyl-estradiol 20µg (DRSP/EE20) has a lower VTE risk than drospirenone and ethinyl-estradiol 30µg (DRSP/EE30).

**Methods:** Our cohort included women aged 18-46 years taking drospirenone or levonorgestrel (LNG)-containing combined oral contraceptives (COC) in the IMS claims-database between 2001-2009. 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 to levonorgestrel, adjusted by a propensity score used to control for baseline comorbidity and stratified by EE dosage and user-type (new/prevalent).

**Results:** The study included 238,683 drospirenone and 193,495 levonorgestrel users. Among new and prevalent-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) versus 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. DRSP/EE30 new-users observed an increased RR versus LNG/EE30 among women initiating COCs between 2001-2006 (2.51 95%CI: 1.12-5.64) but not 2007-2009 (0.76 95%CI: 0.42-1.39), attributable to an increased incidence-rate with LNG/EE30 from 2007-2009. In direct comparison, DRSP/EE20 had elevated VTE risk compared to DRSP/EE30 [RR 1.55 (95%CI: 0.99-2.41)].

**Conclusions:** We observed modestly elevated VTE risk with drospirenone, compared to levonorgestrel. The larger VTE incidence-rate observed in DRSP/EE20 than DRSP/EE30, and the increasing VTE incidence-rate with levonorgestrel between 2007-2009 were unexpected.

## INTRODUCTION

Venous thromboembolism (VTE) is a combined outcome that includes pulmonary embolism (PE) or deep vein thrombosis (DVT). The association between combined oral contraceptives (COC) containing drospirenone and venous thromboembolism (VTE) has been a concern since its 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 to 3.0-fold increased VTE relative risk associated with use of drospirenone compared to levonorgestrel-containing COCs [3-9].

This study evaluates two drospirenone products: drospirenone 3mg with ethinyl-estradiol 30µg (DRSP/EE30) and drospirenone 3mg with ethinyl-estradiol 20µg (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: 1) treatment of emotional and physical symptoms of premenstrual dysphoric disorder (PMDD) (added 10/2006), and 2) treatment of moderate acne vulgaris (added 1/2007) [10].

The study's objective is to evaluate the non-fatal VTE relative risk with drospirenone compared to levonorgestrel at the comparable EE levels, additionally assessing whether DRSP/EE20 has a lower risk for 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, 9<sup>th</sup> 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, May 1<sup>st</sup>, 2001 to December 31<sup>st</sup>, 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 one year period were classified as new-users, while those with prior hormonal contraceptive usage were classified as prevalent-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 COCs containing  $\leq 0.030$  mg EE combined with the progestin drospirenone or levonorgestrel.

### **Exclusion Criteria**

Women were excluded if they did not have one year of total enrollment or 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 one-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 against informative censoring bias, whereby the VTE claim may come after the patient has discontinued COC therapy [12]. Since 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 administered 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 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 comorbidity variables that potentially explain treatment selection. The score is an alternative to multivariate adjustment and can be used to balance treatment groups with regards 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 to levonorgestrel-containing COCs, stratified by EE dosage and user-type (new/prevalent). Because DRSP/EE20 was first approved on March 16<sup>th</sup>, 2006, women initiating COC therapy prior to this date were restricted from stratified analyses of DRSP/EE20 versus LNG/EE20 to prevent against left censoring bias. Poisson regression was used to calculate age-specific incidence rates (IR), 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 VTE definition, limiting VTE cases to having a hospitalization, emergency-room visit, or a diagnostic procedure (CPT4 code for venography, d-dimer, or ultrasound/CT/MRI of upper/lower extremities). Cases were excluded during, or four weeks

after, a normal delivery, cesarean section, induced abortion, miscarriage, or ectopic pregnancy. Prior studies have used a similar strict VTE definition [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 Figure 1 and baseline characteristics are provided in Table 1. The market share (percentage utilization) for each study COC by study year is shown in Figure 2. Between 2001-2003, 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 dispensings between 2004-2006. A similar pattern was seen for DRSP/EE20 following its initial approval in 2006, and it became the most prescribed study COC from 2007-2009.

We identified 354 VTE events during the study period, 236 events during 131,221 exposed women-years to drospirenone and 118 events during 132,681 exposed women-years to levonorgestrel. In an analysis of new and prevalent-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 VTE, 123 events during 50,284 women-years with drospirenone (24.5/10,000 WY) and 57 events during 40,478 exposed women-years with levonorgestrel (14.1/10,000 WY), producing a slightly attenuated RR for VTE with drospirenone versus 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 initiating COC therapy between 2001-2006, DRSP/EE30 new-users had a 2.51-fold (95%CI: 1.12-5.64) increased RR for VTE compared to LNG/EE30 new-users, while analysis of women initiating COC therapy between 2007-2009 observed no risk difference [RR of 0.76 (95%CI: 0.42-1.39)] (Table 3). The lack of a risk difference between 2007-2009 was driven by an unexpectedly high VTE IR with the LNG/EE30 comparator. Direct comparison of DRSP/EE20 new-users to 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 (online appendix). When comparing drospirenone to levonorgestrel, using a stricter VTE definition that required additional clinical evidence for VTE 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 to levonorgestrel-containing COCs, while analysis restricted to new-users found a

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

The largest RRs were observed for DRSP/EE30 between 2001-2006 and DRSP/EE20 between 2007-2009, 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 50µg EE have greater VTE risk than COCs containing <50ug EE. DRSP/EE20 does have three additional days of active drug therapy, although cumulative EE dosage per month is lower with the EE20 [0.02mg\*24days=0.48mg] than the EE30 formulation [0.03mg\*21days=0.63mg]. The DRSP/EE20 formulation also has 3 additional days [9mg] of drospirenone therapy each month which could explain this finding.

It is also possible 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 less pronounced hemostatic changes (including fibrinogen and Protein S activity) with DRSP/EE20, compared to 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 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 to levonorgestrel [15]. This study found the RR for VTE was greater after initial launch for 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. New-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 shown to reduce bias from depletion of susceptibles [16-17]. In our study, we stratified by a new-use covariate, defined using a one-year period prior to COC initiation. Similar results between new and prevalent-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% versus 40.2%), fewer women with a physician visit in the prior year (43.3% versus 55.7%), a shorter mean duration of therapy (169 days versus 214 days), and more women with premenstrual tension syndromes (PTS) including PMDD (6.2% versus 3.8%). Polycystic ovary syndrome (PCOS) codes were more common with DRSP/EE30 than DRSP/EE20 (6.1% versus 4.7%), likely 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 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 VTE risk with drospirenone, ranging from 0.9 to 3.3 when compared to 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 VTE risk with drospirenone, compared to 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 to low-dose estrogen comparators, finding increased VTE risk 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 versus LNG/EE30 (OR 2.22 95%CI:1.27-3.89) than with DRSP/EE30 versus LNG/EE30 (OR 2.09 95%CI: 1.55-2.82) when evaluating both new and prevalent-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 four 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, likely resulting from differences in included study populations.

### **Limitations and Selective Prescribing**

We conducted analysis 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 one-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 toward VTE risk with drospirenone compared to 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 [27-29]. It is possible that good publicity from these unique properties may have

channeled some women at high VTE risk 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 to levonorgestrel-containing COCs [1]. However, the authors conclude the absolute difference was small and this could only slightly increase the VTE incidence 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 has 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 [26]. Studies have also focused on the potentially beneficial antiandrogen properties of drospirenone to 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 VTE risk [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 PCOS signs. 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 to 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 2007-2009 was also unexpected, decreasing the significance for increased VTE risk with DRSP/EE30 during later study years. The marked shifts in COC utilization between 2001-2009, selective prescribing of drospirenone for conditions like PCOS and hyperandrogenism, and our inability to fully ascertain the indication for COC use increases the difficulty for interpreting VTE risk with drospirenone. Although risk is small, our study continues to suggest caution with use of drospirenone, especially in women at high VTE risk. Future research is needed to assess VTE risk by COC product in data that capture both the indication for use and baseline VTE risk.

**Competing Interests:** All authors have completed the Unified Competing Interest form at [www.icmje.org/coi\\_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf) (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations 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:** Steven 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. The authors have no other conflicts of interest to declare.

**Addendum:** All 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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#### Figure 1. Development of Study Cohorts

[Figure attached separately]

#### Figure 2: Percent Total Utilization of Study Combined Oral Contraceptives, 2001-2009

[Figure attached separately]

**Table 1. Characteristics of the Study Population by Combined Oral Contraceptive (COC), 2001-2009**

|                        | Ethinyl Estradiol EE20 $\mu$ g |                   | Ethinyl Estradiol EE30 $\mu$ g |                  |
|------------------------|--------------------------------|-------------------|--------------------------------|------------------|
|                        | DRSP/ EE20 $\mu$ g             | LNG/ EE20 $\mu$ g | DRSP/EE30 $\mu$ g              | LNG/EE30 $\mu$ g |
| <b>Number of Women</b> |                                |                   |                                |                  |
| 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)    |
| Prevalent Users, # (%) | 34,814 (46.1)                  | 66,654 (60.0)     | 97,498 (59.8)                  | 51,985 (63.1)    |
| <b>Time on COC</b>     |                                |                   |                                |                  |
| 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 |
| <b>Age</b>                |       |       |       |       |
| <i>Mean, yr</i>           | 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   |
| <b>Hospitalizations*</b>  |       |       |       |       |
| 1 Prior Hospital, %       | 2.93  | 3.82  | 3.34  | 3.46  |
| ≥2 Prior Hospital, %      | 0.28  | 0.34  | 0.29  | 0.37  |
| <b>ER Visits*</b>         |       |       |       |       |
| 1 Prior ER, %             | 2.27  | 2.93  | 2.65  | 2.87  |
| ≥2 Prior ER, %            | 0.71  | 0.96  | 0.76  | 0.87  |
| <b>Office Visits*</b>     |       |       |       |       |
| 1-4 Prior visits, %       | 22.85 | 31.37 | 30.20 | 32.12 |
| ≥5 Prior visits, %        | 20.44 | 23.01 | 25.46 | 26.52 |
| <b>Prior time on COC*</b> |       |       |       |       |
| 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 |
| <b>Number Prior COC*</b>  |       |       |       |       |
| 1 COC, %                  | 12.29 | 8.21  | 10.58 | 11.73 |
| ≥2 COC, %                 | 5.30  | 4.73  | 6.13  | 4.84  |
| <b>Medications, %</b>     |       |       |       |       |
| 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  |
| <b>Comorbidities, %</b>   |       |       |       |       |
| 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 |
| 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 Dis.  | 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  |

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, Mood / Anxiety Dis=Mood or Anxiety Disorder, 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

\* Prior Hospitalizations, prior ER visits, prior office visits, prior time on therapy (for prevalent users), and number of prior COCs (for prevalent users) were calculated during the 365 day period prior to initiating a COC.

**Table 2. Risk for Venous Thromboembolism with Drospirenone compared to Levonorgestrel, 2001-2009**

| Drug Name                                    | All Combined Oral Contraceptive Users |                  |              |                  |
|--|---------------------------------------|------------------|--------------|------------------|
|  | # VTE / # Women                       | Women-Years (WY) | IR/10,000 WY | HR (95% CI)**    |
| <b>All EE doses</b>                          |                                       |                  |              |                  |
| Drospirenone                                 | 236/238,683                           | 131,221          | 18.0         | 1.90 (1.51-2.39) |
| Levonorgestrel (ref)                         | 118/193,495                           | 132,681          | 8.9          | ---              |
| <b>EE30 Stratification</b>                   |                                       |                  |              |                  |
| DRSP/EE30µg                                  | 151/163,159                           | 96,217           | 15.7         | 1.82 (1.34-2.49) |
| LNG/EE30µg (ref)                             | 56/82,344                             | 58,356           | 9.6          | ---              |
| <b>EE20 Stratification*</b>                  |                                       |                  |              |                  |
| DRSP/EE20µg                                  | 85/75,524                             | 35,004           | 24.3         | 2.38 (1.55-3.65) |
| LNG/EE20 µg (ref)                            | 30/45,225                             | 28,782           | 10.4         | ---              |
| <b>New Combined Oral Contraceptive Users</b> |                                       |                  |              |                  |
|  | # VTE / # Women                       | Women-Years (WY) | IR/10,000 WY | HR (95% CI)**    |
| <b>All EE doses</b>                          |                                       |                  |              |                  |
| Drospirenone                                 | 123/106,371                           | 50,284           | 24.5         | 1.63 (1.18-2.26) |
| Levonorgestrel (ref)                         | 57/74,856                             | 40,478           | 14.1         | ---              |
| <b>EE30 Stratification</b>                   |                                       |                  |              |                  |
| DRSP/EE30µg                                  | 62/65,661                             | 32,907           | 18.8         | 1.24 (0.79-1.94) |
| LNG/EE30µg (ref)                             | 29/30,359                             | 16,735           | 17.3         | ---              |
| <b>EE20 Stratification*</b>                  |                                       |                  |              |                  |
| DRSP/EE20µg                                  | 61/40,710                             | 17,377           | 35.1         | 2.50 (1.39-4.49) |
| LNG/EE20 µg (ref)                            | 14/19,467                             | 9,524            | 14.7         | ---              |

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

\*Restricted Post 3/16/2006, the initial approval date of the DRSP/EE20µg formulation (i.e LNG dispensed prior to this date not included in reference)

\*\* Adjusted by a propensity score to predict exposure to drospirenone

Table 3: Venous Thromboembolism Risk with DRSP/EE30 compared to LNG/EE30, stratified by the year of COC initiation (2001-2006 and 2007-2009)

| Drug Name                                    | All Combined Oral Contraceptive Users |                  |              |                  |
|--|---------------------------------------|------------------|--------------|------------------|
|  | # VTE / # Women                       | Women-Years (WY) | IR/10,000 WY | HR (95% CI)**    |
| <b>2001-2006</b>                             |                                       |                  |              |                  |
| DRSP/EE30 $\mu$ g                            | 82/98,484                             | 55,785           | 14.7         | 2.70 (1.60-4.56) |
| LNG/EE30 $\mu$ g (ref)                       | 18/41,648                             | 31,022           | 5.8          | ---              |
| <b>2007-2009</b>                             |                                       |                  |              |                  |
| DRSP/EE30 $\mu$ g                            | 69/64,675                             | 40,432           | 17.1         | 1.35 (0.90-2.01) |
| LNG/EE30 $\mu$ g (ref)                       | 38/40,696                             | 27,334           | 13.9         | ---              |
| <b>New Combined Oral Contraceptive Users</b> |                                       |                  |              |                  |
|  | # VTE / # Women                       | Women-Years (WY) | IR/10,000 WY | HR (95% CI)**    |
| <b>2001-2006</b>                             |                                       |                  |              |                  |
| DRSP/EE30 $\mu$ g                            | 41/43,867                             | 22,386           | 18.3         | 2.51 (1.12-5.64) |
| LNG/EE30 $\mu$ g (ref)                       | 7/15,392                              | 9,055            | 7.7          | ---              |
| <b>2007-2009</b>                             |                                       |                  |              |                  |
| DRSP/EE30 $\mu$ g                            | 21/21,794                             | 10,521           | 20.0         | 0.76 (0.42-1.39) |
| LNG/EE30 $\mu$ g (ref)                       | 22/14,967                             | 7,680            | 28.6         | ---              |

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

\*\* Adjusted by a propensity score to predict exposure to drospirenone

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

| <b>Drug Name</b>         | <b>All Combined Oral Contraceptive Users</b> |                         |                     |                             |
|--------------------------|--|-------------------------|---------------------|-----------------------------|
| <b>Direct Comparison</b> | <i># VTE / # Women</i>                       | <i>Women-Years (WY)</i> | <i>IR/10,000 WY</i> | <b><i>HR (95% CI)**</i></b> |
| DRSP/EE20                | 85/75,524                                    | 35,004                  | 24.3                | <b>1.21 (0.88-1.68)</b>     |
| DRSP/EE30 (ref)          | 86/81464                                     | 50,411                  | 17.1                | ---                         |
|                          | <b>New Combined Oral Contraceptive Users</b> |                         |                     |                             |
| <b>Direct Comparison</b> | <i># VTE / # Women</i>                       | <i>Women-Years (WY)</i> | <i>IR/10,000 WY</i> | <b><i>HR (95% CI)**</i></b> |
| DRSP/EE20                | 61/40,710                                    | 17,377                  | 35.1                | <b>1.55 (0.99-2.41)</b>     |
| DRSP/EE30 (ref)          | 32/30,370                                    | 15,155                  | 21.1                | ---                         |



