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# Is Progestin an Independent Risk Factor for Incident Venous Thromboembolism? A Population-Based Case-Control Study

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## Abstract

**Introduction—**Because the risk of venous thromboembolism (**VTE**) associated with progestin is uncertain, we tested oral contraceptives, estrogen and progestin as independent VTE risk factors.

**Materials and Methods—**Using longitudinal, population-based Rochester Epidemiology Project resources, we identified all Olmsted County, MN women with objectively-diagnosed incident VTE over the 13-year period, 1988–2000 (n=726) and one to two Olmsted County women per case matched on age, event year and duration of prior medical history (n=830), and reviewed their complete medical history in the community for previously-identified VTE risk factors (i.e., hospitalization with or without surgery, nursing home confinement, trauma/fracture, leg paresis, active cancer, varicose veins and pregnancy/postpartum), and oral contraceptive, oral estrogen, and oral or injectable progestin exposure. Using conditional logistic regression we tested these hormone exposures as VTE risk factors, both unadjusted and after adjusting for previously-identified VTE risk factors.

**Results—**In unadjusted models, oral contraceptives, progestin alone, and estrogen plus progestin were significantly associated with VTE. Individually adjusting for body mass index (**BMI**) and previously-identified VTE risk factors, these effects remained essentially unchanged except that progestin alone was not associated with VTE after adjusting for active cancer. Considering only case-control pairs without active cancer, progestin alone was positively but non-significantly associated with VTE (OR=2.49; p=0.16). Adjusting for BMI and previously-identified VTE risk factors including active cancer, oral contraceptives, estrogen alone, and progestin with or without estrogen were significantly associated with VTE.

**Conclusions—**Oral contraceptives, estrogen alone, estrogen plus progestin, and progestin with or without estrogen are independent VTE risk factors.

### Keywords

venous thromboembolism; deep vein thrombosis; pulmonary embolism; progestin; epidemiology

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## Introduction

Oral contraceptives containing estrogen and progestin,[1,2] oral or injectable progestins for non-contraceptive therapy (e.g., dysfunctional uterine bleeding),[3] and postmenopausal hormone therapy with estrogen plus progestin[4–11] or estrogen alone[9,12–14] are reported risk factors for deep vein thrombosis (**DVT**) and pulmonary embolism (**PE**). VTE risk associated with oral contraceptives appears to vary by estrogen dose and type of progestin.[1,15,16] Oral contraceptives containing lower dose estrogen (< 50 microgram ethinyl estradiol) combined with "newer generation" progestins (e.g., desogestrel or gestodene) may have higher VTE risk than lower dose estrogen combined with older generation progestin (e.g., levonorgestrel).[1,4,16–18] Among postmenopausal women, VTE risk also varies by estrogen type[9] and mode of delivery.[6,19] However, the risk of VTE with progestin alone or in combination with estrogen is uncertain, with studies to date showing a non-significant 1.7- to 2.4-fold increased risk.[3,20,21]

To further address the role of progestin as a risk factor for VTE, we performed a population-based case-control study nested within the inception cohort of Olmsted County women with objectively-diagnosed VTE to test oral contraceptives, estrogen alone, progestin alone, and the combination of non-contraceptive progestin and estrogen as risk factors for incident VTE among women.

## Materials and Methods

### Study Setting and Design

Using the longitudinal and population-based resources of the Rochester Epidemiology Project[22] we identified all Olmsted County, MN residents with incident deep vein thrombosis (**DVT**) and/or pulmonary embolism (**PE**) over the 35-year period, 1966–2000, as previously described.[23,24] We then performed a case-control study nested within the Olmsted County population. The Rochester Epidemiology Project provides an enumeration of the entire Olmsted County population from which controls can be sampled as described elsewhere,[22] Using this system, one to two age- (± one year) and sex-matched Olmsted County residents who had an episode of medical care within ± one year of the case event date and whose medical record number was closest to the case's medical record number were selected as controls as previously described.[25,26] The date of the episode of care was assigned as the index date for controls, and the date of the incident VTE event was assigned as the index date for cases. Since a patient's medical record number is assigned sequentially and in perpetuity, matching on medical record number assures a similar length of medical history among cases and matched controls.

For this study, we limited VTE cases to women with objectively-diagnosed VTE over the 13-year period, 1988–2000, because progestin use prior to 1988 was very uncommon. For example, of the 253 women residents with incident VTE over the time frame, 1980–1987, and their 255 matched controls, only 8 (1.6%) of the total 508 women received progestin. The study was approved by the Mayo Clinic and Olmsted Medical Center Institutional Review Boards.

### Measurements

Using explicit criteria, trained and experienced nurse abstractors reviewed all medical records (inpatient, outpatient, emergency department, nursing home, autopsy, death certificate, etc.) in the community[27] for cases and controls who provided consent to review of their medical records for research purposes. All records were reviewed from date first seen by a REP healthcare provider until the earliest of death, date of last medical record follow-up or 2000, as previously performed.[23,25] For cases, data were recorded on the method of diagnosis and

type of incident VTE event (DVT, PE or both; chronic thromboembolic pulmonary hypertension). A DVT was categorized as objectively-diagnosed when symptoms or signs of acute DVT were present and the diagnosis was confirmed by contrast, computed tomographic or magnetic resonance imaging venography, compression venous duplex ultrasonography, impedance plethysmography or pathology examination of thrombus removed at surgery or autopsy. A PE was categorized as objectively-diagnosed when symptoms and/or signs of acute PE were present and the diagnosis was confirmed by pulmonary angiography, a ventilation/perfusion lung scan interpreted as high probability for PE, computed tomographic pulmonary angiography, magnetic resonance imaging or pathology examination of thrombus removed at surgery or autopsy. Mayo Clinic pathologists performed all autopsy examinations and completed the death certificates of persons dying within Olmsted County during the study period.

For Olmsted County residents meeting our criteria for objectively-diagnosed DVT or PE and matched controls, the study nurses also collected data from the medical record on date of incident event (cases) or index episode of care (controls); patient age at index; gender; patient location at index (four categories, defined as community-dwelling, confined to a hospital, community-dwelling but hospitalized in the previous 90 days, or confined to a nursing home [including chronic rehabilitation facility]); body mass index (**BMI**; $kg/m^2$); active cancer (recent tumor burden without curative surgery, chemotherapy, or radiotherapy, excluding non-melanoma skin cancer); serious neurologic disease with leg paresis (stroke or other disease affecting the nervous system with associated leg paresis, or acute stroke with leg paresis requiring hospitalization within the previous three months); any surgery requiring general, spinal, or epidural anesthesia; trauma/fracture resulting in hospital admission (major fracture or severe soft tissue injury); varicose veins (varicose veins, or treated varicose veins [injection sclerotherapy or stripping]); type, dose and dose schedule of oral, intramuscular or subcutaneous hormone therapy (estrogen; progestin); and for women, pregnancy or postpartum at the time of the incident event and oral contraceptive use. Hospitalization with or without surgery, nursing home confinement, trauma/fracture, leg paresis, pregnancy or postpartum, oral contraceptive use and hormone therapy had to have been documented in the three months before the incident VTE event for cases or the index episode of medical care for controls. Active cancer had to have been documented in the three months before or three months after the incident VTE event. Varicose veins could be documented any time before the incident event. Body mass index was based on the most recent height and weight measurements before the index date. If either height or weight was missing, the value was imputed based on case status and 10-year age group (mean value was used). Hormone therapy was categorized as use of estrogen only, progestin only, or non-contraceptive estrogen plus progestin in the three months before index date.

## Analysis

Estrogen use and progestin use overlapped to a significant degree in this population (43% of those on estrogen were also on progestin; 78% of those on progestin were on estrogen). To separate out the effects of these two hormone therapies, we tested estrogen alone, progestin alone and the combination of non-contraceptive estrogen plus progestin (dosed concurrently or sequentially per month) as well as oral contraceptives as potential VTE risk factors using conditional logistic regression. We first performed three unadjusted models: (1) one with the variables estrogen alone, progestin alone, and non-contraceptive estrogen plus progestin (subsequently referred to as “the estrogen/progestin variables”) vs. no hormone therapy); (2) one with oral contraceptives vs. none, and (3) one both oral contraceptives and the estrogen/progestin variables vs. none. We next performed models with both oral contraceptives and the estrogen/progestin variables in which we individually adjusted for each baseline characteristic previously identified as an independent risk factor for VTE.[25] Specifically, we estimated the

effect of oral contraceptives, estrogen alone, progestin alone, and non-contraceptive estrogen plus progestin on the odds of VTE after separately adjusting for each previously-identified independent VTE risk factor (i.e., BMI, current or recent hospitalization within the past 90 days with or without surgery, nursing home confinement, trauma or fracture, active cancer, neurologic disease with leg paresis and varicose veins).[25,26] Lastly, we estimated the effect of oral contraceptives and the estrogen/progestin variables on the odds of VTE in a multivariable model, adjusting for patient age, BMI and all of the above VTE risk factors.

In separate models, we also tested variables defined as progestin use with or without estrogen (subsequently referred to as "progestin ± estrogen") and estrogen alone versus no hormone therapy. Similar to the analyses described above, we estimated the effect of oral contraceptives, estrogen alone, and progestin ± estrogen on the odds of VTE after separately adjusting for each previously-identified independent VTE risk factor, and in a multivariable model adjusted for patient age, BMI and all previously-identified independent VTE risk factors.

## Results

Over the 13-year time frame, 1988–2000, 1400 residents of Olmsted County developed a first lifetime VTE. Of these, 1306 (93.3%) incident VTE events were objectively-diagnosed. Of the objectively-diagnosed VTE events, 726 (55.6%) occurred in women and made up the incident VTE cases for this study. The distribution of VTE events by event type was 410 (56.5%) DVT alone, 314 (43.3%) PE with or without DVT, and 2 (0.3%) chronic thromboembolic pulmonary hypertension; 81 of 726 (11.2%) VTE events were diagnosed at autopsy (78 of which were PE). The mean ± standard deviation (**SD**) patient age and duration of prior medical record documentation for the cases and matched controls (n=830) were 66.5 ± 20.2 and 66.2 ± 20.1 years of age, and 37.1 ± 21.4 and 37.4 ± 21.5 years, respectively, and did not differ significantly.

The prevalence of VTE risk factors and oral contraceptive, estrogen alone, progestin alone, and non-contraceptive estrogen plus progestin exposures among VTE cases and controls are shown in Table 1. Four cases and 14 controls had BMI imputed because of missing height (three cases and 11 controls) or weight (one case and three controls). Two of the women on non-contraceptive estrogen in the three months prior to their index date (one case and one control) were also on oral contraceptives during that same three month period. The distribution of all hormone exposures by patient age, and case-control and active cancer status is shown in Table 2. Among all 1556 cases and controls, oral contraceptive use was confined primarily to women ≤ 45 years of age; 89 (33%) of the 268 women ≤ 45 were using oral contraceptives compared to only seven (0.5%) of the 1288 women > 45 years. Non-contraceptive estrogen and/or progestin use was more evenly distributed by age; 23 (26%) women ≤ 45 used non-contraceptive estrogen and/or progestin (seven [7.9%] used progestin alone) compared to 252 (20%) women >45 years (23 [1.7%] used progestin alone). Among the 245 women using non-contraceptive estrogen, 206 (84%) received conjugated equine estrogen (**CEE**) with over 90% taking a daily oral dose of 0.625 mg or less, while 38 received a variety of estrogens, mainly esterified estrogen. Of the 137 women using non-contraceptive progestin, 110 (80%) received medroxyprogesterone acetate (**MPA**), 20 received megestrol acetate and six received a variety of progestins.

In an unadjusted conditional logistic model comparing estrogen alone, progestin alone, and non-contraceptive progestin plus estrogen (i.e., the "estrogen/progestin variables") versus no exogenous hormone exposure, progestin alone and progestin plus estrogen were significantly associated with an increased odds of incident VTE, while estrogen alone was not associated (Table 3, **Model 1**). In a model comparing oral contraceptives to no oral contraceptive, oral contraceptives also were significantly associated with VTE (Table 3, **Model 2**). Finally, in a model comparing oral contraceptives and the estrogen/progestin variables to no exogenous

hormone exposure, oral contraceptives, progestin alone and non-contraceptive estrogen plus progestin were significantly associated with VTE while again, estrogen alone was not associated (Table 3, **Model 3**).

In bivariate analyses comparing oral contraceptives and the estrogen/progestin variables to no exogenous hormone exposure, and individually controlling for BMI and each previously-identified VTE risk factor, oral contraceptives, progestin alone, and non-contraceptive estrogen plus progestin, but not estrogen alone, were significantly associated with VTE except for active cancer (Table 3). After controlling for active cancer, progestin alone was no longer associated with VTE (OR=1.83; p=0.24) while conversely, estrogen alone was associated with VTE (OR=1.52; p=0.04). Only 30 women received progestin alone in the three months prior to the index date, and of these, 17 (15 cases; two controls) had active cancer (Table 2). Of the women with active cancer, 14 (13 cases; one control) had active breast, ovarian or endometrial cancer for which hormonal therapy was given as cancer therapy.

In the multivariate analysis including oral contraceptives and the estrogen/progestin variables, and adjusting for BMI and all previously-identified VTE risk factors simultaneously, oral contraceptive use, estrogen alone, and non-contraceptive estrogen plus progestin were significantly associated with VTE, while progestin alone was not (Table 4).

Since the analyses for progestin alone were so strongly confounded by active cancer, we repeated our analyses using the subset of women without active cancer. After excluding VTE cases with cancer (n=166) and their matched controls, and controls with cancer (n=19) and their matched VTE cases, we tested oral contraceptive use and the estrogen/progestin variables as VTE risk factors in the remaining 546 cases and 621 controls (546 matched sets). The risk of VTE remained significantly increased for women on oral contraceptives (OR=2.92; 95% CI: 1.60–5.33, p=<0.001), estrogen alone (OR=1.57, 95% CI: 1.02–2.41, p=0.04), and non-contraceptive estrogen plus progestin (OR=1.80, 95% CI: 1.11–2.92, p=0.02). The risk of VTE for progestin alone was increased (OR=2.49, 95% CI: 0.71–8.77, p=0.16) but non-significant, possibly due to small sample size; only eight VTE cases and five controls used progestin alone. Among the five women receiving progestin alone who were ≤ 45 years of age and without active cancer, all were receiving medroxyprogesterone acetate (**MPA**) at the following doses and indications: one control took 5 mg/day orally for 14 days for chronic anovulation, one control took one 400 mg intramuscular (**IM**) injection for amenorrhea, one VTE case took 10 mg/day orally for postmenopausal symptoms after a total abdominal hysterectomy and bilateral salpingoopherectomy, one VTE case took 150 mg IM every three months for endometriosis, and one VTE case took 400 mg IM every three months for contraception. Among the eight women who were > 45 years old and without cancer, four were taking MPA at the following doses and indications: one control took 150 mg IM every three months for menorrhagia related to von Willebrand disease, one control 400 mg IM every three months for a distant history of endometrial cancer without evidence of active cancer, and two VTE cases each were taking 10 mg oral daily for postmenopausal symptoms. The remaining “four” women were taking megestrol acetate at the following doses and indications: one women was both a control and subsequently became a VTE case and was taking 80 mg orally twice daily poor appetite, one VTE cases was taking 40 mg orally twice daily for the same indication, and one VTE case was taking 40 mg orally three times daily for a distant history of breast cancer without active disease.

Because such a small number of the women used progestin alone, we also performed bivariate analyses testing oral contraceptives, estrogen alone, and progestin with or without estrogen compared to no exogenous hormone exposure while individually controlling for BMI and each previously-identified VTE risk factor (Table 5). Unlike the bivariate models with progestin alone, the odds of VTE with progestin with or without estrogen ranged from 1.7 to 2.3 and remained significant even after controlling for active cancer (p≤ 0.01). The risk of VTE was

also increased for oral contraceptives and for estrogen alone. In a multivariate model adjusting for patient age, BMI and all previously-identified VTE risk factors simultaneously, oral contraceptives, estrogen alone, and progestin with or without estrogen were all significantly associated with VTE (Table 6).

## Discussion

Our study shows that oral contraceptives, estrogen alone, and non-contraceptive estrogen plus progestin are independent risk factors for VTE. Our results also suggest that, in the absence of active cancer, progestin alone also is a VTE risk factor although this finding did not reach statistical significance most likely due to inadequate sample size. However, we did find that progestin with or without estrogen is an independent VTE risk factor.

Our findings of an increased risk of VTE with oral contraceptives are supported by multiple previous studies[1,16,28,29] but to our knowledge, ours is the first to indentify oral contraceptives as an independent VTE risk factor after controlling for other major VTE risk factors. One small study failed to find an association between oral contraceptives and fatal VTE among young women after controlling for other VTE risk factors, possibly due to small sample size.[30]

Our findings of an increased VTE risk with non-contraceptive estrogen plus progestin and with estrogen alone also are supported by several previous studies. In the Heart and Estrogen/progestin Replacement Study (**HERS**) double-blind controlled trial, postmenopausal women younger than 80 years of age who had coronary artery disease but no hysterectomy, prior VTE, breast or endometrial cancer or life threatening disease were randomized to CEE plus MPA or placebo. In a multivariate model that controlled for patient age, BMI, inpatient surgery, nonsurgical hospitalization, active cancer, leg fracture, aspirin use and statin therapy within three months prior to the VTE event, women randomized to CEE+MPA had nearly a three-fold increased risk for VTE (HR=2.7; 95% CI: 1.4, 5.1).[7] In the Women's Health Initiative (**WHI**) double-blind controlled trial, post menopausal women (age 50–79 years) randomized to CEE+MPA had a significantly increased risk for VTE (hazard ratio [**HR**]=2.11, 95% CI: 1.26, 3.55) compared to placebo.[8] Also in the WHI study, women with prior hysterectomy who were randomized to CEE alone had a significantly increased risk for DVT compared to placebo (HR=1.47, 95% CI: 1.04, 2.08), and a marginally increased risk for overall VTE (HR=1.33, 95% CI: 0.99, 1.79).[8] In a prospective cohort study (the Nurses Health Study), postmenopausal women mainly receiving estrogen alone had a two-fold increased risk for idiopathic PE (HR=2.1; 95% CI: 1.2, 3.8 [adjusted for age and BMI]). In a case-control study of members within a Washington State health maintenance organization, peri- or postmenopausal women (age 30–89 years) exposed to CEE+progestin had over a two-fold increased risk for VTE (OR=2.17; 95% CI: 1.49, 3.14) after controlling for race and cancer, while women exposed to CEE alone had a 30% higher VTE risk (OR=1.31; 95% CI: 0.91, 1.88).[9] In a prospective case-control study, postmenopausal women exposed to non-contraceptive estrogen plus progestin had a 2.7-fold increased risk of idiopathic DVT (95% CI: 1.44, 5.07), while similar women exposed to estrogen alone had a 20% higher risk (OR=1.22; 95% CI: 0.57, 2.61).[11] Finally, in analyses of the WHI study that included a longer duration of follow-up, the hazard of VTE was significantly greater for women randomized to CEE+MPA compared to women (without a uterus) randomized to CEE alone.[14] The reported incidence rates of VTE ranged from 35–62 per 10,000 person-years for women exposed to CEE+MPA,[7,10,31] and from 30–35 per 10,000 person-years for women exposed to CEE alone.[14,31]

Ours is the first study to identify progestin with or without estrogen as a risk factor for VTE in a model that controlled for age and other previously-identified VTE risk factors while also controlling for both the independent risk of estrogen alone and oral contraceptives. While the VTE risk associated with progestin alone was increased, this finding did not reach statistical

significance due to confounding by active cancer. Moreover, our sample size likely was too small to identify progestin alone as a significant VTE risk factor among women without active cancer. However, the magnitude of risk in this latter group (OR=2.49) was quite similar to the nonsignificantly increased VTE risk for injectable progestin alone as contraception (OR=2.19; 95%CI: 0.66, 7.26) found by the WHO.[20] While the progestin drug, dose, dose schedule and indication varied considerably among women in our study who were without cancer and receiving progestin alone, three VTE cases were receiving MPA at a dose of only 10 mg/day for postmenopausal symptoms, one VTE case was taking MPA 150 mg IM every three months (the typical dose for contraception), and three VTE cases were taking megestrol acetate 80–120 mg/day orally mainly as an appetite stimulant. Neither MPA or megestrol acetate are considered high VTE-risk progestins[16], and the total daily dose for the six VTE cases receiving these progestins was not especially high. Consequently, we believe progestin alone, including MPA and megestrol acetate, likely is a VTE risk factor and urge caution when considering these progestins for women with prior VTE or high VTE-risk while awaiting additional studies on VTE risk with progestin alone.

Our results are likely to be valid. Due to the unique features of the REP, our study avoids referral bias and other potential distortions of including a too healthy population. All VTE cases met strict criteria for objectively-confirmed acute DVT and/or PE based direct review of their source documents (i.e., imaging, surgical and autopsy reports) rather than depending on administrative codes. We were able to accurately separate incident from recurrent VTE events and confirm controls to not have VTE because of the long duration of medical records for both cases and controls (mean of 37 years for both). We included the entire spectrum of VTE disease occurring in the community, including persons with rapidly fatal and chronic care facility (e.g., nursing home) events who did not reach the hospital. We insured a comparable control group by performing a population-based study where both cases and controls were residents from the same community with similar lifetime access to medical care.

It is also important to address the limitations of our study. Since the racial and ethnic demography of Olmsted County is predominantly white of non-Hispanic ancestry, our findings may not be generalizeable to populations of other races or ethnicities. We required that all risk factors be documented in the medical record prior to the onset of the VTE event. Data on actual use of oral contraceptives, estrogen, and progestin, rather than what was prescribed, could not be reliably ascertained from the medical records. Our sample size was too small to test the effect of different estrogen and progestin types and combinations, doses, dose schedules and modes of delivery on VTE risk. Newer synthetic progestins with altered estrogenic, androgenic and/or glucocorticoid effects may have different risks for VTE.[32]

In conclusion, oral contraceptives, estrogen alone, non-contraceptive estrogen plus progestin, and progestin with or without estrogen are independent risk factors for incident VTE. While the independent VTE risk of progestin alone remains uncertain, our findings along with those of previous studies suggest the risk may be important. Consequently, we urge caution when considering progestin alone for women with prior VTE or other VTE risk factors.

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**Table 1**

Prevalence of Venous Thromboembolism Risk Factors and Hormone Exposure among Cases and Controls

| Exposure | Case N=726 | Control N=830 |
|---|---|---|
| | — n (%) — | |
| Body mass index (kg/m$^2$) | 27.92 ± 8.00 | 25.97 ± 5.77 |
| Hospitalization, with or without surgery | 302 (41.60) | 71 (8.55) |
| Nursing home confinement | 126 (17.36) | 78 (9.40) |
| Trauma/fracture | 111 (15.29) | 26 (3.13) |
| Active cancer | 166 (22.87) | 19 (2.29) |
| Neurologic disease with leg paresis | 50 (6.89) | 5 (0.60) |
| Varicose veins | 247 (34.02) | 254 (30.60) |
| Pregnancy or postpartum | 24 (3.31) | 10 (1.20) |
| Oral contraceptives | 59 (8.13) | 37 (4.46) |
| Estrogen alone | 65 (8.95) | 73 (8.80) |
| Progestin alone | 23 (3.17) | 7 (0.84) |
| Non-contraceptive estrogen plus progestin | 59 (8.13) | 48(5.78) |

**Table 2**

Prevalence of Hormone Exposure by Patient Age and Active Cancer Status

| Characteristic | Patient Age ≤ 45 Years | | Patient Age > 45 Years | |
|---|---|---|---|---|
| | Cases (n=125) | Controls (n=143) | Cases (n=601) | Controls (n=687) |
| | — *n (%)* — | | | |
| Oral contraceptives | 53 (42) | 36 (25) | 6 (1) | 1 (0) |
| No Active Cancer | | | | |
| Estrogen alone | 5 (4) | 4 (3) | 50 (8) | 69 (10) |
| Progestin alone | 3 (2) | 2 (1) | 5 (1) | 3 (0) |
| Estrogen plus progestin | 3 (2) | 3 (3) | 47 (8) | 44 (6) |
| No estrogen or progestin | 98(78) | 133 (93) | 349 (58) | 553 (80) |
| Active Cancer | | | | |
| Estrogen alone | 0 | 0 | 10 (2) | 0 |
| Progestin alone | 2(2) | 0 | 13 (2) | 2 (2) |
| Estrogen plus progestin | 1(1) | 0 | 8 (1) | 1 (0) |
| No estrogen or progestin | 13(10) | 1 (1) | 119 (20) | 15 (2) |

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**Table 3**

Univariate and Bivariate Odds Ratios (P-values) for An Association of Oral contraceptives, Estrogen Alone, Progestin Alone, and Non-Contraceptive Estrogen plus Progestin With Incident Venous Thromboembolism After Adjusting Individually for Body Mass Index and Previously-Identified Venous Thromboembolism Risk Factors[25]

| Venous Thromboembolism Risk Factor | Oral Contraceptives | Estrogen Alone | Progestin Alone | Non-contraceptive Estrogen plus Progestin |
|---|---|---|---|---|
| | — OR (CI, P-value) — | | | |
| Model 1 | | 1.27 (0.88–1.85, 0.21) | 4.02 (1.70–9.47, 0.002) | 1.66 (1.07–2.58, 0.02) |
| Model 2 | 2.66 (1.53–4.62, <0.001) | | | |
| Model 3 | 2.66 (1.52–4.64, <0.001) | 1.27 (0.88–1.85, 0.88) | 4.01 (1.69–9.53, 0.003) | 1.66 (1.07–2.58, 0.02) |
| Body mass index (kg/m$^2$) | 2.60 (1.47–4.61, 0.001) | 1.35 (0.92–1.97, 0.13) | 4.17 (1.74–9.98, 0.001) | 1.93 (1.22–3.04, 0.005) |
| Hospitalization, with or without surgery | 3.29 (1.72–6.27, <0.001) | 1.32 (0.84–2.06, 0.23) | 3.92 (1.50–10.23, 0.01) | 1.73 (1.04–2.87, 0.03) |
| Nursing home confinement | 2.66 (1.52–4.64, <0.001) | 1.30 (0.89–1.89, 0.18) | 3.88 (1.63–9.25, 0.002) | 1.73 (1.11–2.69, 0.02) |
| Trauma/fracture | 2.57 (1.46–4.51, 0.001) | 1.32 (0.90–1.94, 0.15) | 3.67 (1.53–8.81, 0.004) | 1.85 (1.17–2.93, 0.009) |
| Active cancer | 2.97 (1.66–5.32, <0.001) | 1.52 (1.01–2.28, 0.04) | 1.83 (0.67–5.02, 0.24) | 1.70 (1.07–2.72, 0.03) |
| Neurologic disease with leg paresis | 3.03 (1.70–5.41, <0.001) | 1.26 (0.86–1.83, 0.23) | 4.02 (1.69–9.57, 0.002) | 1.61 (1.03–2.52, 0.04) |
| Varicose veins | 2.64 (1.51–4.62, <0.001) | 1.26 (0.86–1.83, 0.23) | 4.05 (1.71–9.60, 0.002) | 1.65 (1.06–2.56, 0.03) |
| Pregnancy or postpartum | 3.47 (1.88–6.41, <0.001) | 1.26 (0.86–1.83, 0.23) | 3.93 (1.64–9.42, 0.002) | 1.66 (1.07–2.57, 0.03) |

**Table 4**

Multivariate Odds Ratios and 95% Confidence Intervals (CI) for An Association of Previously-Identified Venous Thromboembolism Risk Factors[25], Oral Contraceptives, Estrogen Alone, Progestin Alone and Non-Contraceptive Estrogen Plus Progestin With Incident Venous Thromboembolism

| Characteristic | Odds Ratio | 95% CI | P-value |
|---|---|---|---|
| Patient age | 1.24 | 0.88, 1.73 | 0.2157 |
| Body mass index (kg/m$^2$) | 1.08 | 1.05, 1.11 | <0.0001 |
| Major surgery | 18.95 | 9.22, 38.97 | <0.0001 |
| Hospitalization for acute medical illness | 5.07 | 3.12, 8.23 | <0.0001 |
| Nursing home confinement | 4.63 | 2.77, 7.74 | <0.0001 |
| Trauma/fracture | 4.56 | 2.46, 8.46 | <0.0001 |
| Active cancer | 14.64 | 7.73, 27.73 | <0.0001 |
| Neurologic Disease with leg paresis | 6.10 | 1.97, 18.89 | 0.0017 |
| Varicose veins | 1.22 | 0.89, 1.68 | 0.2239 |
| Pregnancy or postpartum | 4.24 | 1.30, 13.84 | 0.0166 |
| Oral contraceptives | 4.03 | 1.83, 8.89 | 0.0005 |
| Estrogen alone | 1.81 | 1.06, 3.09 | 0.0304 |
| Progestin alone | 1.20 | 0.40, 3.63 | 0.7430 |
| Non-contraceptive estrogen plus progestin | 2.53 | 1.38, 4.63 | 0.0027 |

**Table 5**

Univariate and Bivariate Odds Ratio (P-value) for An Association of Oral contraceptives, Estrogen Alone, and Progestin With or Without Estrogen With Incident Venous Thromboembolism After Adjusting Individually for Patient Age, Body Mass Index and Previously-Identified Venous Thromboembolism Risk Factors[25]

| Model | Oral Contraceptives | Estrogen Alone | Progestin ± Estrogen |
|---|---|---|---|
| | — OR (95% CI, P-value) — | | |
| Age-adjusted only | 2.64 (1.52–4.60, <0.001) | 1.29 (0.89–1.87, 0.18) | 2.02 (1.36–2.99, <0.001) |
| Body mass index (kg/m$^2$) | 2.59 (1.47–4.57, 0.001) | 1.36 (0.93–1.99, 0.11) | 2.30 (1.53–3.45, <0.001) |
| Hospitalization, with or without surgery | 3.22 (1.70–6.13, <0.001) | 1.33 (0.85–2.09, 0.21) | 2.08 (1.33–3.27, 0.002) |
| Nursing home confinement | 2.64 (1.52–4.60, <0.001) | 1.31 (0.90–1.91, 0.16) | 2.07 (1.39–3.07, <0.001) |
| Trauma/fracture | 2.56 (1.46–4.47, 0.001) | 1.34 (0.91–1.96, 0.14) | 2.16 (1.43–3.26, <0.001) |
| Active cancer | 2.97 (1.66–5.32, <0.001) | 1.52 (1.01–2.28, 0.04) | 1.72 (1.12–2.65, 0.013) |
| Neurologic Disease w/Leg paresis | 3.01 (1.69–5.35, <0.001) | 1.27 (0.87–1.85, 0.21) | 1.98 (1.33–2.95, <0.001) |
| Varicose veins | 2.63 (1.51–4.58, <0.001) | 1.27 (0.88–1.85, 0.20) | 2.02 (1.36–2.99, <0.001) |
| Pregnancy or postpartum | 3.45 (1.87–6.34, <0.001) | 1.27 (0.87–1.84, 0.21) | 2.00 (1.35–2.97, <0.001) |

**Table 6**

Multivariate Odds Ratios and 95% Confidence Intervals (CI) for An Association of Previously-Identified Venous Thromboembolism Risk Factors[25], Oral Contraceptives, Estrogen Alone, and Progestin With or Without Estrogen With Incident Venous Thromboembolism

| Characteristic | Odds Ratio | 95% CI | P-value |
|---|---|---|---|
| Patient age | 1.24 | 0.89, 1.74 | 0.2002 |
| Body mass index (kg/m$^2$) | 1.08 | 1.05, 1.10 | <0.0001 |
| Major surgery | 18.68 | 9.09, 38.40 | <0.0001 |
| Hospitalization for acute medical illness | 4.99 | 3.08, 8.10 | <0.0001 |
| Nursing home confinement | 4.57 | 2.74, 7.61 | <0.0001 |
| Trauma/fracture | 4.44 | 2.40, 8.23 | <0.0001 |
| Active cancer | 14.09 | 7.45, 26.65 | <0.0001 |
| Neurologic Disease w/Leg paresis | 6.12 | 1.98, 18.92 | 0.0017 |
| Varicose veins | 1.23 | 0.89, 1.70 | 0.2036 |
| Pregnancy or postpartum | 4.23 | 1.29, 13.83 | 0.0170 |
| Oral contraceptives | 4.10 | 1.86, 9.02 | 0.0005 |
| Estrogen alone | 1.78 | 1.04, 3.04 | 0.0342 |
| Progestin ± estrogen | 2.16 | 1.26, 3.70 | 0.0051 |