# Venous Thromboembolism, Myocardial Infarction, and Stroke Among Transdermal Contraceptive System Users

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**OBJECTIVE:** To estimate the incidence of venous thromboembolism, acute myocardial infarction, and ischemic stroke among transdermal contraceptive system users compared with users of norgestimate-containing oral contraceptives with 35 mcg ethinyl estradiol.

**METHODS:** We began with insurance claims data from UnitedHealthcare. We identified women exposed to the transdermal contraceptive system or norgestimate-containing oral contraceptives from April 2002 through December 2004. Outcomes were confirmed from medical records. We calculated incidence rates and age-adjusted incidence rate ratios. In a nested case-control analysis, we investigated and controlled for confounding.

**RESULTS:** There were 49,048 woman-years of transdermal contraceptive system exposure and 202,344 woman-years of norgestimate-containing oral contraceptives exposure. There was a more than two-fold increase in the venous thromboembolism rate (incidence rate ratio 2.2, 95% confidence interval [CI] 1.3–3.8) among transdermal contraceptive system users (20 cases, 40.8 per 100,000 woman-years) compared with norgestimate-containing oral contraceptives users (37 cases, 18.3 per 100,000 woman-years). Acute myocardial infarction occurred in three transdermal contraceptive system users compared with seven among norgestimate-containing oral contraceptives users (incidence rate ratio 1.8, 95% CI 0.5–6.8). No strokes occurred among transdermal contraceptive system users, whereas 10 occurred among norgestimate-containing oral contraceptives users. In the nested case-control analysis, after exclusions for high-risk factors, the odds ratio for venous thromboembolism was 2.4 (95% CI 1.1–5.5).

**CONCLUSION:** There was a more than two-fold increase in the risk of venous thromboembolism associated with use of the transdermal contraceptive system. Acute myocardial infarction and stroke occurred too rarely to ascertain precise risk estimates.

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**LEVEL OF EVIDENCE: II**

The norelgestromin/ethinyl estradiol transdermal contraceptive system (Ortho Evra, Ortho-McNeil Pharmaceuticals Inc, Raritan, NJ) was approved by the U.S. Food and Drug Administration (FDA) on November 20, 2001, and launched in the United States at the end of April 2002. It is administered by application of three consecutive 7-day patches followed by one patch-free week, for a 28-day cycle. It contains 6.00 mg norelgestromin and 0.75 ethinyl estradiol. The active progestin is comparable to that in oral contraceptive products that contain norgestimate. Open label trials have demonstrated efficacy comparable to that of oral contraceptives and superior compliance, 88% for the transdermal contraceptive system, compared with 78% for oral contraceptives.[1–3] Adverse effects, such as breast discomfort, application site reactions, and dysmenorrhea were more common in transdermal contraceptive system users than in oral contraceptive users.[1–3]

At the time of this study's inception, it was not known whether users of the transdermal contraceptive system face the same risk of acute myocardial infarction (AMI), ischemic stroke, and venous throm-

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boembolism as do users of oral contraceptives. Women using the transdermal patch have average levels of circulating estrogen 60% higher than women using oral contraceptive pills, although the peak levels are lower.[4] These data led the FDA to change the labeling for the transdermal contraceptive system in November 2005 to include a warning regarding possible increased risk of thrombotic events.[5]

There has been only one published study to date comparing the risk of venous thromboembolism in women who used the transdermal contraceptive system with women who used oral contraceptive pills and no published studies comparing the risk of other thrombotic events, such as AMI or ischemic stroke, in users of the transdermal contraceptive system with users of other hormonal contraception. Jick et al[6] reported a relative risk of 0.9 (95% CI 0.5–1.6) for venous thromboembolism in users of the transdermal contraceptive system compared with users of norgestimate-containing oral contraceptives with 35 mcg ethinyl estradiol in February 2006.

The objective of this study was to estimate the risks of venous thromboembolism, acute myocardial infarction, and ischemic stroke among users of the norelgestromin/ethinyl estradiol transdermal contraceptive system compared with that among users of norgestimate-containing hormonal contraceptives with 35 mcg ethinyl estradiol. We conducted a cohort study to estimate incidence rates of the study outcomes, with a nested case-control study to examine the influence of possible confounding factors.

## MATERIALS AND METHODS

The primary source of data was a database of eligibility, pharmacy claims, and medical claims from UnitedHealthcare, a major national health insurer. We supplemented the claims data with review of abstracted medical records, as described below. The individuals covered by UnitedHealthcare are geographically diverse across the United States. UnitedHealthcare provides fully insured coverage for physician, hospital, and prescription drug services. The providers of these services submit their claims for payment directly to the health plan. Data are maintained for research purposes in a de-identified format and are only re-identified (for the purposes of medical record abstraction) following approval by an appropriate institutional review board.

Using the pharmacy dispensing records, we identified all women between the ages of 15 and 44 years with commercial insurance coverage, complete medical and pharmacy benefits, and at least one dispensing of the norelgestromin/ethinyl estradiol transdermal contraceptive system or a norgestimate-containing oral contraceptive (OC) with 35 mcg ethinyl estradiol during the study period of April 1, 2002, through December 31, 2004. We then excluded women with insurance claims mentioning malignancy other than nonmelanoma skin cancer, coagulation defects, long-term anticoagulant use, prior venous thromboembolism, chronic inflammatory diseases, or chronic renal failure. The final study cohort consisted of women who had at least 183 days of continuous enrollment in the health plan.

We used the outpatient pharmacy records to identify all dispensings of the transdermal contraceptive system or a norgestimate-containing OC during the study period. We included, for follow-up, periods of "current" and "recent" exposure to the transdermal contraceptive system and norgestimate-containing OCs. Current exposure periods encompassed days from the dispensing date through the number of days of contraception supplied, plus an additional 28 days to allow for gaps in prescription refills. Recent exposure time began after the end date of current exposure and continued through the following 183 days. Each dispensing of the transdermal contraceptive system or a norgestimate-containing OC reset the exposure window to current. Dispensing of any hormonal contraception other than the transdermal contraceptive system or a norgestimate-containing OC ended the current or recent exposure period. Norgestimate-containing OC dispensings that occurred before April 2002, with the days supplied extending into April 2002, were also considered in the analysis.

We calculated person-time of follow-up for all women beginning on the later of their initial date of the transdermal contraceptive system or other norgestimate-containing OC dispensing, or April 1, 2002. Follow-up continued through the earliest of their date of health plan disenrollment, index date of the outcome, death, or December 31, 2004.

The study endpoints were venous thromboembolism, AMI, and ischemic stroke, individually, and the following combined endpoints:

1) AMI and ischemic stroke,
2) AMI, ischemic stroke, and pulmonary embolism, and
3) AMI, ischemic stroke, and venous thromboembolism.

We confirmed all cases through medical record abstraction. To identify potential cases, we initially identified all women in the final study cohort with a medical claim (inpatient or outpatient) associated with

a diagnosis or procedure code for these outcomes during periods of current or recent exposure to the transdermal contraceptive system or a norgestimate-containing OC. For these potential cases, we printed and reviewed the chronological medical and pharmacy claims listings (profiles). Trained nurses, blinded to the study hypothesis, abstracted the medical records of potential cases whose sequence of events recorded in the profiles was possibly consistent with venous thromboembolism, AMI, or stroke, using a standard form. Medical record abstractions could be completed for 83% of the potential cases. Reasons for not completing abstractions included provider refusal to participate or the patient's records having been transferred to another facility. A physician who was otherwise unaffiliated with the study reviewed the completed abstraction forms to adjudicate case status. Criteria for verifying outcomes using the abstracted data were developed before the review, based on commonly used clinical guidelines. Specifically, the criteria for verifying occurrence of venous thromboembolism included documentation of the following elements:

- A likely clinical scenario (leg pain, swelling for venous thromboembolism, shortness of breath, dyspnea for pulmonary embolism) or chart record of diagnosis of thrombosis from a physician.
- Positive results from appropriate diagnostic procedures (computed tomography scan, ventilation/perfusion scan, pulmonary angiogram, ultrasonography, magnetic resonance imaging, or venogram).
- Appropriate therapy (antithrombotic therapy, thrombolytic therapy, antiplatelet therapy), or appropriate monitoring of antithrombotic therapy (prothrombin time/partial thromboplastin time/International Normalization Ratio), or extended treatment.

The reviewing physician was not aware of the exposure status of any potential case, and the form he reviewed contained no information on contraceptive exposure.

We conducted a search of the National Death Index, for women who disenrolled from the health plan before 2003 and did not have subsequent reenrollment. At the time of the study, 2003 was the most recently available data from the National Death Index. Disenrollees with a high probability match, based on National Death Index algorithms, were retained. The National Death Index Plus service provided causes of death along with the fact and date of death.

We calculated incidence rates for each of the study outcomes during current periods of transdermal contraceptive system and norgestimate-containing OC exposure. We examined the occurrence of study outcomes during recent exposure periods (the 183 days after the end of current exposure) and observed few events, indicating no evidence of a prothrombotic effect in the recent period. Therefore, we restricted attention of the cohort analysis to report events during periods of current use as defined in this section, and we will refer to these simply as "use" or "exposure" below, to avoid confusion with recent exposure. We constructed Poisson regression models to calculate incidence rate ratios[7] for transdermal contraceptive system exposure compared with norgestimate-containing OC exposure with adjustment for age group (15–29, 30–39, 40–44). All analyses were conducted with SAS 8.2 (SAS Institute, Cary, NC).

To investigate the possibility of residual confounding, we conducted a case-control analysis nested within the study cohort. All of the cases were incorporated in this analysis, and the date of the outcome (AMI, stroke, or venous thromboembolism) was designated as the index date. Four control women were randomly selected from the study population and matched to each case. A candidate control was assigned the index date of the case and matched if she had the same birth year as the case, at least 6 months of health plan enrollment as of the case's index date, current or recent exposure to the transdermal contraceptive system or a norgestimate-containing OC as of the case's index date, and the same pattern of the transdermal contraceptive system or norgestimate-containing OC usage as the case (new initiators, switchers, or those with interrupted or unknown prior use). Controls were not eligible to be matched to a given case if they had a history of the same event before the case's index date. As with the cohort analysis, we initially examined the occurrence of study outcomes during recent exposure periods for the case-control analysis. We observed few events, suggesting no evidence of a prothrombotic effect in the recent period. We restricted attention to report events during periods of current use.

We classified cases and controls according to covariates based on medical and pharmacy claims. In addition, we obtained covariate information from abstracted medical records for the physician visit associated with the start of the most recent course of the transdermal contraceptive system or norgestimate-containing OC therapy. The covariate data included information on demographics (age, race, geography), hormonal contraceptive use history (use of professional

samples, age at first use), medical history (history of cardiovascular disease, diabetes, hyperlipidemia, blood pressure), high-risk factors for thrombotic events (pregnancy, trauma, major surgery, prolonged immobilization, anticoagulant or antithrombolytic therapy, personal or family history of thrombotic events), lifestyle characteristics (cigarette smoking, physical exercise, body mass index), and measures of health care use (frequency of physician visits, hospitalizations, and emergency room visits).

We calculated odds ratios comparing transdermal contraceptive system exposure with norgestimate-containing OC exposure in association with the study outcomes using conditional logistic regression to account for the matching of cases and controls. Although the focus was on current exposure, the regression model included all cases and controls with current exposure status, along with cases and controls with recent exposure status, to account for any residual bias. Terms in the model indicated current or recent transdermal contraceptive system or norgestimate-containing OC exposure. For calculation of adjusted odds ratios, we initially considered all covariates for inclusion in multivariate models on the combined end point of AMI, stroke, and venous thromboembolism. Any variables responsible for a greater than 10% change in the odds ratio were included in all adjusted analyses.

In addition, we identified variables associated with the combined study end point of AMI, stroke, and venous thromboembolism in a multivariate regression including terms for other risk factors present with $P \leq .20$. Variables identified at this step were number of physician visits, number of hospital stays, and use of CYP3A4 inhibitor medications. We then obtained odds ratio estimates, both with and without control of each of the identified risk factors added singly to a model with only the exposure terms present. None of the identified risk factors caused the odds ratio to change by 10% or more.

In a further analysis, we examined the odds ratio for venous thromboembolism after exclusion of cases and controls with indicators of high-risk factors of trauma, pregnancy, major surgery, postoperative complications, or anticoagulant or antithrombolytic therapy.

We analyzed the association with venous thromboembolism according to new initiator status and duration of exposure to the transdermal contraceptive system and norgestimate-containing OCs. A goal of this analysis was to determine whether events occurred differentially among transdermal contraceptive system users with a shorter duration of use (because the transdermal contraceptive system was launched at the start of the study period), compared with norgestimate-containing OC users who possibly had a longer duration of use.

This study followed the Health Insurance Privacy and Portability Act (HIPAA) guidelines for protection of patient confidentiality. Because this study used protected health information to link insurance claims to patient medical records, we operated with the oversight of the New England Institutional Review Board, which approved the protocol and privacy practices. We also obtained a waiver of authorization from their privacy board to allow the use of protected health information without obtaining patient authorization. The protected health information of women used for this study was in accordance with the approved study protocol and privacy practices.

The current study had its genesis in discussions between the FDA and Johnson and Johnson, the manufacturer of the transdermal contraceptive system, concerning case reports that each had received of venous thromboembolism in users of the transdermal contraceptive system. The study design began with a proposal from us and underwent revisions after review from both Johnson and Johnson and the FDA. Johnson and Johnson commissioned the study under a research contract that guaranteed the authors full control over final publication. As the study progressed, the FDA received interim reports, as did Johnson and Johnson. (See the FDA's "Questions and Answers" at http://www.fda.gov/cder/drug/infopage/orthoevra/qa20060920.htm for more details.) The current report reflects comments and requests for clarification and analysis from the FDA. On September 20, 2006, with the final study results in hand, the FDA announced further labeling changes for the transdermal contraceptive system and specifically cited this study as a basis for its further action. Johnson and Johnson did not participate in the preparation of this report, nor did it review the report before submission for publication.

i3 Drug Safety is a unit of Ingenix, a medical information company that belongs to United Health Group. UnitedHealthcare also belongs to United Health Group. UnitedHealthcare is a major purchaser of essentially all pharmaceutical products licensed in the United States. Other than facilitating communications with physicians for chart abstractions, UnitedHealthcare had no role in the conception, conduct, interpretation, or reporting of this study.

## RESULTS

The study population consisted of 340,377 women who received at least one dispensing of the

norelgestromin/ethinyl estradiol transdermal contraceptive system (98,790 women) or a norgestimate-containing OC (256,981 women) between April 1, 2002, and December 31, 2004. These women contributed 49,048 woman-years of transdermal contraceptive system exposure and 202,344 woman-years of norgestimate-containing OC exposure during the observation period. The median age of the women was 25 years.

Table 1 provides incidence rates and adjusted incidence rate ratios of the study outcomes. There was a more than two-fold risk of venous thromboembolism in association with transdermal contraceptive system exposure compared with norgestimate-containing OC exposure (adjusted incidence rate ratio 2.2, 95% confidence interval [CI] 1.3–3.8). For AMI, transdermal contraceptive system exposure was associated with an incidence rate ratio of 1.8 (95% CI 0.5–6.8) based on only three events in transdermal contraceptive system users and seven in norgestimate-containing OC users. No ischemic stroke events occurred among transdermal contraceptive system users.

Table 2 shows cases and controls in the nested case-control analysis. Due to the matching on age, cases and controls had similar age group distributions. For venous thromboembolism, 33% of cases and controls were between the ages of 15 and 29 years, 57% of cases (55% of controls) were between the ages of 30 and 39 years, and 10% of cases (12% of controls) were between the ages of 40 and 44 years.

The odds ratios incorporate adjustment for the matching factors (birth year and new initiator status), along with recent exposure status. The odds ratios were similar to the results of the cohort analysis. None of the covariates derived from medical and pharmacy claims data resulted in a greater than 10% change in the exposure effect. Adjustment for smoking, as recorded in the medical record, increased the apparent relative risk for venous thromboembolism in relation to the transdermal contraceptive system but seemed highly implausible in that the change resulted from an apparent protective effect of smoking on outcome and a strong association between recorded smoking and use of the transdermal contraceptive system.

When we performed stratification according to women who were new initiators compared with those who were not new users, the odds ratios were equivalent, but the confidence intervals were wider due to the lower numbers of cases and controls in each stratum. Among women who were new initiators, the odds ratio for venous thromboembolism associated with use of the transdermal contraceptive system was 2.2 (95% CI 0.8–6.1). For women who were not new users, the odds ratio for venous thromboembolism associated with use of the transdermal contraceptive system was 2.1 (95% CI 0.8–5.7).

Among new initiators, we investigated the risk according to duration of use. Although the data became too spare to calculate odds ratios, there was no discernible pattern with respect to duration of use of the transdermal contraceptive system. Among transdermal contraceptive system–exposed cases, 50% had 90 days or less of exposure, compared with 48% of transdermal contraceptive system–exposed controls. For norgestimate-containing OC–exposed cases, 66% had 90 days or less of exposure, compared with 41% of norgestimate-containing OC–exposed controls.

We then excluded cases and controls with high-risk factors of recent trauma, pregnancy, major surgery, postoperative complications, or anticoagulant or antithrombolytic therapy. The exclusions had the effect of further increasing the relative risk of venous thromboembolism among transdermal contraceptive system users (Table 3, odds ratio [OR] 2.4, 95% CI 1.1–5.5).

**Table 1. Incidence Rates and Rate Ratios**

| | Transdermal Contraceptive System Use | | NGM-OC Use | | | |
|---|---|---|---|---|---|---|
| | Cases | Incidence Rate (Per 100,000 WY) | Cases | Incidence Rate (Per 100,000 WY) | Incidence Rate Ratio* | 95% CI |
| VTE | 20 | 40.8 | 37 | 18.3 | 2.2 | 1.3–3.8 |
| AMI | 3 | 6.1 | 7 | 3.5 | 1.8 | 0.5–6.8 |
| Stroke | 0 | 0.0 | 10 | 4.9 | – | – |
| AMI, Stroke | 3 | 6.1 | 17 | 8.4 | 0.7 | 0.2–2.5 |
| AMI, Stroke, PE | 12 | 24.5 | 33 | 16.3 | 1.5 | 0.8–2.9 |
| AMI, Stroke, VTE | 23 | 46.9 | 54 | 26.7 | 1.8 | 1.1–2.9 |

NGM-OC, norgestimate-containing oral contraceptive; WY, woman-years; CI, confidence interval; VTE, venous thromboembolism; AMI, acute myocardial infarction; PE, pulmonary embolism.
* Incidence rate ratio adjusted for age group.

**Table 2. Odds Ratios, Nested Case-Control Analysis**

| | Transdermal Contraceptive System Use | | NGM-OC Use | | | |
|---|---|---|---|---|---|---|
| | Cases | Controls | Cases | Controls | Matched Odds Ratio* | 95% CI |
| VTE | 20 | 41 | 37 | 150 | 2.0 | 1.0–4.1 |
| AMI | 3 | 9 | 7 | 34 | 2.1 | 0.3–15.5 |
| Stroke | 0 | 6 | 10 | 30 | – | – |
| AMI, Stroke | 3 | 15 | 17 | 64 | 0.7 | 0.2–3.1 |
| AMI, Stroke, PE | 12 | 36 | 33 | 129 | 1.4 | 0.6–3.2 |
| AMI, Stroke, VTE | 23 | 56 | 54 | 214 | 1.7 | 0.9–3.2 |

NGM-OC, norgestimate-containing oral contraceptive; CI, confidence interval; VTE, venous thromboembolism; AMI, acute myocardial infarction; PE, pulmonary embolism.

* Odds ratios from conditional model including cases and controls associated with current or recent use of the transdermal contraceptive system or NGM-OCs; model accounts for matching factors (birth year and new initiator status).

**Table 3. Odds Ratio for Venous Thromboembolism After Exclusion of Cases and Controls With High-Risk Factors**

| | Transdermal Contraceptive System Use | NGM-OC Current Use |
|---|---|---|
| Cases | 16 | 26 |
| Controls | 28 | 105 |
| Matched OR (95% CI)* | 2.4 (1.1–5.5) | |

NGM-OC, norgestimate-containing oral contraceptive; OR, odds ratio; CI, confidence interval.

* Odds ratio from model including cases and controls associated with current or recent use of the transdermal contraceptive system or NGM-OCs; model accounts for matching factors (birth year and new initiator status).

## DISCUSSION

Current users of the norelgestromin/ethinyl estradiol transdermal contraceptive system experienced a more than two-fold increased risk of venous thromboembolism, compared with norgestimate-containing OC users. The risk attributable to use of the transdermal contraceptive system was 22.5 per 100,000 woman-years, whereas the number needed to harm was 4,444. The result was not ascribable to confounding by differential use of the transdermal system in women predisposed to venous thromboembolism. Among women who did not possess transient exogenous risk factors for venous thromboembolism, transdermal contraceptive system use was associated with an increased risk of venous thromboembolism, compared with norgestimate-containing OC use (OR 2.4, 95% CI 1.1–5.5).

The incidence rate of venous thromboembolism associated with norgestimate-containing OC use was 18.3 per 100,000 woman-years and is consistent with published estimates of venous thromboembolism rates among users of oral contraceptives containing second-generation progestins of levonorgestrel and norgestrel. These range from 16 to 36 per 100,000 woman-years.[8–10] The observed incidence rate of venous thromboembolism associated with transdermal contraceptive system use at 40.8 per 100,000 woman-years is similar to Jick et al's[6] reported rate of venous thromboembolism associated with transdermal contraceptive system use, at 52 per 100,000 woman years. However, our observation of a 2.4-fold increased risk of venous thromboembolism associated with transdermal contraceptive system use differs from Jick et al's reported odds ratio of 0.9. This difference could be ascribable to chance variation, because we note overlapping confidence intervals of our 2.4 odds ratio for venous thromboembolism (95% CI 1.1–5.5) compared with Jick et al's reported odds ratio (95% CI 0.5–1.6). There were also important differences between the two studies. Jick et al did not confirm outcomes by chart review, but rather relied on insurance claims for care and drug dispensing. The high proportion of venous thromboembolism cases that were pulmonary embolism in the Jick study (38 pulmonary embolism out of 68 venous thromboembolism, or 68%) suggests that many cases of deep vein thrombosis may have been missed. In addition, Jick et al accepted only new use of the study drug as a valid exposure. Although this seems reasonable at first blush, it means that prior norgestimate users were excluded from the norgestimate group but were allowed into the transdermal contraceptive system group. Because of its recent introduction, the transdermal contraceptive system could not be in the prior use category for the norgestimate users. This asymmetry meant that the transdermal contraceptive system–exposed patients could well have been more experienced users of hormonal contraception. Because

venous thromboembolism risk predominates early in use, this differential history could well have depressed the apparent risk in transdermal contraceptive system users. The phenomenon is known as a survivor cohort effect. The transdermal contraceptive system users in Jick et al's study could have preferentially "survived" prior norgestimate use, whereas there was no comparable filter on the norgestimate users.

No strokes occurred among transdermal contraceptive system users, and rates of acute myocardial infarction events were low, based on three events among transdermal contraceptive system users and seven among users of norgestimate-containing OCs. Although the incidence rate ratio for AMI associated with transdermal contraceptive system use compared with norgestimate-containing OC use was elevated (1.8), the estimate is consistent with a wide range of both protective and causative levels of association (the 95% CI of the relative risk ranges from 0.5 to 6.8). The result is therefore inconclusive.

The purpose of the nested case-control analysis was to investigate the possibility of residual confounding from the cohort analysis by variables identifiable in the medical and prescription claims data. In performing this investigation, our assumption was that covariates directly identifiable in the database could be confounding the observed association. Further, they could be correlated with other variables not directly identifiable in the database, such as prescriber preference for the transdermal contraceptive system to high-risk women, if it was perceived to be less risky than alternative contraceptive forms. Among all cases and controls, none of the covariates fulfilled a 10% "change-in-estimate" criterion. After case-control matching on year of birth and usage pattern, the odds ratios were similar to the incidence rate ratios, providing further reassurance that residual confounding by the matching factors did not bias the cohort analysis.

As with any epidemiologic study conducted within the context of an automated medical and pharmacy insurance claims database, drug exposure is never entirely certain. Although there is evidence in the claims of women receiving a prescription drug at an outpatient pharmacy, we are unable to verify that women actually used the medication. Our assumption in this study was that drugs were used beginning on the date they were dispensed. If a woman did not actually use her medication, however, exposure misclassification would result. Women with no exposure to the transdermal contraceptive system or norgestimate-containing OCs would have been classified as exposed, introducing a bias of the observed odds ratio toward the null if this phenomenon occurred differentially. Under these conditions, after correcting for differential exposure misclassification, we would expect the odds ratios to be further away from the null than originally observed.

Our study did not account for the possibility of exposure due to professional samples of the transdermal contraceptive system or norgestimate-containing OCs dispensed to women at a physician's office or clinic. Because professional samples are not submitted for reimbursement by UnitedHealthcare, evidence of their use is not present in the automated database. Therefore, we may have under-ascertained the true number of woman-years of exposure. The precise changes in the effect estimates would be related to differential rates of thrombotic events among users of professional samples compared with users who filled prescriptions for the transdermal contraceptive system or norgestimate-containing OCs at outpatient pharmacies.

Women included in this study had commercial insurance coverage through UnitedHealthcare either as a direct employment benefit or as a benefit through a spouse or as a dependent. UnitedHealthcare prescription coverage is an open formulary, with patient copayments corresponding to a tiered structure with generics in the lowest tier and brands in higher tiers. During the study period, the transdermal contraceptive system and norgestimate-containing OCs were in the same copayment tier. Therefore, economic factors should not have influenced a woman's or prescriber's selection of either method of contraception. However, because these data were from a commercial health insurance plan, the women included in this study could have better access to health services compared with women without insurance or to women with other forms of insurance. In this respect, the women included in this study are not representative of those eligible for government-sponsored health programs such as Medicaid. The ability to assess heterogeneity of the effect for women with such health insurance coverage may be limited.

In conclusion, we observed a more than two-fold increase in the risk of venous thromboembolism associated with exposure to the norelgestromin/ethinyl estradiol transdermal contraceptive system in comparison with users of norgestimate-containing oral contraceptives with 35 mcg ethinyl estradiol. Outcomes of acute myocardial infarction and ischemic stroke occurred too rarely to ascertain precise measures of association.

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