The Risk of Venous Thromboembolism, Myocardial Infarction, and Ischemic Stroke Among Women Using the Transdermal Contraceptive System Compared to Women Using Norgestimate-Containing Oral Contraceptives With 35 µg Ethinyl Estradiol

Nested Case-Control Study

Revised Final Report

22 January 2009

(Originally Issued on 03 August 2006)

Prepared for Johnson & Johnson Pharmaceutical Research and Development

EXECUTIVE SUMMARY

Ortho Evra is the first transdermal contraceptive system approved by the U.S. Food and Drug Administration. Open label trials have demonstrated efficacy comparable to that of oral contraceptives and superior compliance.

At the time of this study's inception, it was not known whether users of the transdermal contraceptive system and users of oral contraceptives faced the same risks of acute myocardial infarction (AMI), ischemic stroke, and venous thromboembolism (VTE, consisting of deep vein thrombosis and pulmonary embolism). Pharmacokinetic data published in June 2005 indicated that women using the transdermal patch have average levels of circulating estrogen 60% higher than women using oral contraceptive pills, though they have lower peak levels. This information led to a label change of Ortho Evra in November 2005 to include a warning regarding possible increased risk of thrombotic events.

This case-control study, nested within a cohort of hormonal contraceptive users, was conducted using data from the Ingenix Research Data Mart (RDM), containing insurance claims information from a large U.S. health plan affiliated with Ingenix. The RDM contains medical and pharmacy claims data from health plans and large employer groups located in the Northeast, South/Southeast, Midwest, and Western United States.

This nested case-control study had the following objectives:

1. To estimate the relative risks of AMI and ischemic stroke, considered together, in current users of Ortho Evra compared to current users of norgestimate-containing oral contraceptives (NGM-OC) with 35μg ethinyl estradiol (EE), and to evaluate the relative risk in current users according to duration of use of the last course of treatment before event onset.

2. To estimate the relative risks for VTE, ischemic stroke, and AMI separately in current users of Ortho Evra compared to current users of NGM-OCs with 35μg EE, and to evaluate the relative risk in current users according to duration of use of the last course of treatment before event onset.

The cohort identified for the nested case-control study consisted of all women in the Ingenix Research Data Mart who received at least one dispensing of Ortho Evra or a NGM-OC between the ages of 15 and 44 years between April 1, 2002 and December 31, 2004. Women remained in the cohort from their first eligible dispensing through 183 days following the last day of use of hormonal contraception, as estimated from the days of contraception supplied. It was possible to exit the cohort with a discontinuation of use, and re-enter with a new eligible dispensing. All case events in this cohort were identified

by review of insurance claims and abstracted medical records. In addition, we sought a 4-fold larger random sample of women (controls) from the cohort. Controls were matched according to year of birth, date of event, and initiator status, which categorized women as either new initiators of their most recent course of hormonal contraception or other users (switchers, or those with interrupted or unknown prior use). For cases and controls, hormonal contraceptive usage status as of the event date was ascertained from pharmacy billing records, and relevant medical conditions were identified from diagnoses associated with medical insurance claims records.

The original study report of 03 August 2006 cited an exclusion criterion of all women with claims evidence of a malignancy other than non-melanoma skin cancer. However, during the conduct of the ongoing extension study, we confirmed that coding for this exclusion in the original study was slightly different than this wording suggested. Rather than excluding women from the source population with claims evidence of malignancy other than non-melanoma skin cancer (ICD-9 140.xx-208.xx, except 173.xx), the study excluded women with claims evidence of a neoplasm other than benign skin disorders (ICD-9 140.xx-239.xx, except 232.xx). The slightly broader criterion used in the prior study led to the exclusion of additional women from the source population, and a small number of corresponding cases and controls, but did not affect the internal validity of the comparisons. This has been corrected in this report and in the extension study. In addition, i3 Drug Safety contacted the editors of Obstetrics & Gynecology noting this discrepancy in the manuscript produced from this study: Cole JA, Norman H, Doherty M, Walker AM. Venous thromboembolism, myocardial infarction, and stroke among transdermal contraceptive system users. Obstetrics & Gynecology. 2007;(2, Part 1)109:339-346. The corresponding author, who is no longer affiliated with i3 Drug Safety, approved a correction to the methods section of the manuscript. The journal printed an erratum in June of 2008 (Obstetrics & Gynecology. 2008 Jun;111(6):1449).

In the original version of this Final Report, additional covariate information on risk factors was collected on cases and controls from a separate medical chart abstraction to complement covariates derived from medical and pharmacy claims data. These data are not included in this revised report, as they had no impact on our prior findings. However, all outcomes in this report were verified through medical record abstraction or through searching the National Death Index.

The relative risks associated with exposure to Ortho Evra or NGM-OC have been estimated using odds ratios (OR) from a conditional logistic regression analysis. The regression incorporates case-control matching on year of birth, date of event, and initiator status (new initiator, switcher, unknown, or interrupted). The ORs of study outcomes associated with use of Ortho Evra and NGM-OCs are presented for the full study

population, and for the subgroups of new initiators of their most recent course of hormonal contraception, and other users (switchers, or those with interrupted or unknown prior use).

Of 219 medical charts sought for confirmation of study outcomes, abstractions were completed for 193 (88%). The most common reason for non-completion was provider refusal.

Following medical review of abstracted charts, 12 of 71 potential AMIs, 12 of 35 potential strokes and 66 of 108 potential VTEs identified through insurance claims were confirmed as study outcomes. The confirmation rates were as expected, reflecting the broad and sensitive, but nonspecific, list of insurance codes chosen to screen for possible outcomes. Following a search of the National Death Index, one additional AMI case and one additional VTE case were identified and included in the analysis.

Controls represented the general population experience of users of Ortho Evra and NGM-OCs. Ortho Evra-exposed controls and NGM-OC-exposed controls resembled one another with respect to demographics, recent history of relevant medical conditions, and other conditions associated with increased risk of thrombotic events. There were more (10% vs. 2%) hospital visits in the 90 days prior to start of hormonal contraception among current Ortho Evra-exposed controls compared with current NGM-OC exposed controls.

The primary endpoint analysis (AMI and stroke) yielded an OR below one with wide confidence intervals, (OR=0.69, 95% CI 0.15-3.13), based on 3 events in current Ortho Evra users and 17 in current users of NGM-OCs, as compared with 15 and 64 controls with current use of Ortho Evra and NGM-OCs, respectively. No strokes occurred among current or recent Ortho Evra users. There were 10 strokes in current users of NGM-OCs, for an OR (Ortho Evra vs. NGMOC) of zero. AMI was rare, with 3 and 7 in current users of Ortho Evra and NGM-OCs, respectively, as compared with 9 and 34 controls with current use of Ortho Evra and NGM-OCs, respectively. There was an estimated doubling of risk of AMI among current Ortho Evra users compared with current NGM-OC users (OR 2.06, 95% CI 0.28-15.47), but confidence intervals were wide and the result is therefore inconclusive.

There was a 2-fold increased risk of VTE events in current Ortho Evra users, compared with current NGM-OC users (OR 2.03, 95% CI 1.03-4.00). There were 22 and 40 current users of Ortho Evra and NGM-OC respectively, among the VTE cases, and 47 and 163 current users of Ortho Evra and NGM-OC respectively, among the VTE controls. The strength of the association was similar within strata of new initiators and women who were not new initiators. Among cases and controls remaining after the exclusion of

women with short-term risk factors (trauma, pregnancy, major surgery, post-operative complications, or anti-coagulant or antithrombolytic therapy) in the 90 days prior to the index date, current Ortho Evra use remained associated with an increased risk of VTE compared with current NGM-OC users (OR 2.46, 95% CI 1.10-5.52).

In the original study, medical record abstraction for further ascertainment of risk factors provided additional reassurance that Ortho Evra and NGM-OC users were similar with respect to blood pressure measurements, body mass index, and personal and family history of thrombosis (data not shown in this revised report). An unexpected finding (from the original analysis) was the control for the chart-derived indicator for documentation of current smoking on the ORs, which raised the association of VTE with Ortho Evra from a 2-fold to 3-fold increase in risk (OR 3.06, 95% CI 1.08-8.73). We believe this finding should be treated with caution. Smoking entered as a confounder because of a strong positive association with Ortho Evra use and a negative association with VTE. The first result is a priori implausible and the second contradicts established science, which has found either no effect of smoking on VTE risk or an aggravating effect. We suspect that there may have been preferential documentation of smoking in the records of Ortho Evra users. During the study period, Ortho Evra was a novel form of hormonal contraception delivery and the doctors who prescribed it may have been more careful in documenting risk factors for the various complications of hormonal contraception. There is also considerable statistical uncertainty in the analyses of the subset of cases and controls with abstracted risk factor data; the further increased VTE association could simply be a chance finding due to small numbers. In any case, the result does not change the qualitative findings.

REFERENCES

1. Cole JA, Norman H, Doherty M, Walker AM. Venous thromboembolism, myocardial infarction, and stroke among transdermal contraceptive system users. Obstet Gynecol.2007;109(2 Pt 1):339-346.
2. Cole JA, Norman H, Doherty M, Walker AM. Venous thromboembolism, myocardial infarction, and stroke among transdermal contraceptive system users, Erratum. Obstet Gynecol. 2008 Jun;111(6):1449.

Disclaimer

Information in this posting shall not be considered to be a claim for any marketed product. Some information in this posting may differ from, or not be included in, the approved labeling for the product. Please refer to the full prescribing information for indications and proper use of the product.