ORTHO EVRA™ Report

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Acronyms and terms:

- Ortho EVRA™ = "the patch" = norelgestromin / EE transdermal system (Ortho-McNeil Pharmaceutical, Inc. and Johnson & Johnson Pharmaceutical Research and Development)
- COC = combination oral contraceptive
- EE = ethinyl estradiol
- VTE = venous thromboembolism (pulmonary embolism, deep venous thrombosis; for the purposes here, this excludes superficial venous event)
- AMI = acute myocardial infarction
- IS = ischemic stroke
- AER = adverse event reports (spontaneous reports of a suspected adverse drug reaction)
- BCDSP = Boston Collaborative Drug Surveillance Program, Boston University School of Medicine. This is the group that published studies with Jick as the lead author.
- i3 = i3 Drug Safety of Auburndale, MA. This is the group that published the study with Cole as lead author.
- OR = odds ratio
- RR = risk ratio or rate ratio

The Ortho EVRA transdermal contraceptive patch was approved by the U.S. Food and Drug Administration in November of 2001 and first marketed in April of 2002. It is a combination hormonal contraceptive consisting of 6 mg of norelgestromin and 0.75 mg of ethinyl estradiol delivered via a three layer 20 cm^2 patch applied to the skin. Three consecutive 7-day patches are followed by one patch-free week every 28-day cycle. Although its delivery and pharmacokinetics differ from combination oral contraceptives, its biological activity is comparable to that of norgestimate containing combination pills. This report documents my professional opinion to a reasonable degree of scientific certainty about the pharmacological, clinical trial, and post-marketing data concerning the safety and efficacy of this product.

1 INTERPRETATION OF EPIDEMIOLOGIC EVIDENCE

1.1 Framework for judging causality. Epidemiologists have established criteria for the interpretation of epidemiologic evidence when inferring causality. Some of these criteria derive from the Report of the Advisory Committee to the Surgeon General of the Public Health Service of 1964.[1] Criteria were later expanded in Bradford Hill's landmark paper on causal inference.[2] The debate of causal inference in epidemiology is endless and frequently updated.[3] Through this debate, key constructs have been established and are now widely accepted. This includes the fact that statistical methods alone cannot establish proof of causality. However, when coupled with clinical, physiological, experimental, and other forms of data, results from epidemiologic studies can provide a framework upon which judgments about causality can be made. In applying these judgments, the following criteria have been established: (a) consistency of association, (b) strength of association, (c) specificity of association, (d) temporality, (e) biological gradient ("dose-response"), (f) biological plausibility, (g) coherence, (h) experimentation, (i) analogy, and (j) statistical significance. None of these criteria are *sine quo non*, but each has a role in weighing epidemiologic evidence.

1.2 Judging the precision and validity of specific studies. Many factors must be taken into account when addressing results from specific studies. Observed associations must be weighed in terms of their precision and validity. Standard statistical techniques, such as confidence intervals, are useful in quantifying the precision of estimates (assuming certain conditions have been met). However, confidence intervals are *not* useful in helping us evaluate the validity of results. It is, therefore, contingent upon us to judge the extent to which non-random errors such as those due to information bias, selection bias, and confounding explain apparent associations.

1.3 A note on statistical significance. Special note is made to "statistical significance." Statistical significance is also referred to as statistical hypothesis testing. Statistical

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[1] U.S. Department of Health, Education, and Welfare. (1964). *Smoking and Health. Report of the Advisory Committee to the Surgeon General of the Public Health Service.* Retrieved April 21, 2003, from http://sgreports.nlm.nih.gov/NN/B/B/M/Q/segments.html

[2] Hill, A. B. (1965). The environment and disease: association or causation? *Proceedings of the Royal Society of Medicine, 58*, 295-300.

[3] See, for example, Rothman, K. J. (Ed.). (1988). *Causal Inference*. Chestnut Hill, MA: Epidemiology Resources, Inc.

hypothesis testing is often misinterpreted by both the layman and professional. "A great deal of mischief has been associated with the test of significance".[4] Such mischief frequently interferes with common sense interpretation of data.

The main result of significance testing is the *P*-value. *P*-values provide hypothetical probabilities of observed differences in data or differences that are more extreme assuming the null hypothesis is true *and* certain conditions have been met. Many fallacies exist when interpreting such results. For example, many people believe that *P*-values represent the probability that the null hypothesis is correct: this is not true. Neither do *P*-values quantify the size or importance of an effect. Moreover, the practice of using fixed-levels of *P*-values to categorically declare the significance of a finding is ill-advised. Although a thorough discussion of origins of such misunderstandings are beyond the scope of this report, [5] let us state that use of $P < .05$ as a threshold of "significance" is especially inadvisable.[6] In fact, significance questing at any level should be avoided.[7]

Significance testing can also be carried out with confidence intervals and critical values. However, these do not diminish the aforementioned limitations.

2 SUMMARY OF FINDINGS FROM THE CLINICAL TRIALS

2.1 Systematic review of trial data. I am relying on a Cochrane Collaboration report to help summarize results from the clinical trials about the contraceptive patch. The Cochrane Collaboration is an independent international not-for-profit organization that prepares, maintains and promotes systematic reviews of all relevant randomized controlled clinical trials of health care in an attempt to improve health care by using objective evidence.[8] Cochrane Collaboration reports are deemed highly credible by the clinical and research communities.

The pertinent Cochrane Collaboration review on this subject was written by Gallo and coworkers in 2003.[9] This review identified relevant trials by searching MEDLINE, Popline, the Cochrane Controlled Trials Register, EMBASE, and LILACS. In addition, the manufacturer of the patch was contacted to identify published and unpublished trials that might have been missed. All randomized controlled trials in any language that compared the patch with COCs were analyzed. The Cochrane review was based on these published sources:

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[4] Bakan, D. (1966). The test of significance in psychological research. *Psychological Bulletin, 66*, 1-29.
[5] Lehmann, E. L. (1993). The Fisher, Neyman-Pearson Theories of Testing Hypotheses: One Theory or Two? *Journal of the American Statistical Association, 88*(424), 1242-1248.
[6] A favorite quote of mine that makes this clear is "certainly god loves $P = .06$ nearly as much as $P = .05$" (source of quote uncertain).
[7] Cohen, J. (1994). The earth is round ($p < .05$). *American Psychologist, 49*, 997-1002. Rothman, K. J. (1986). Significance questing. *Ann Intern Med, 105*(3), 445-447.
[8] See http://www.cochrane.org/.
[9] Gallo, M. F., Grimes, D. A., & Schulz, K. F. (2003). Skin patch and vaginal ring versus combined oral contraceptives for contraception. *Cochrane Database Systematic Review, DOI: 10.1002/14651858.CD.003552*(1), Art. No. CD003552.

- Audet, M. C., Moreau, M., Koltun, W. D., Waldbaum, A. S., Shangold, G., Fisher, A. C., et al. (2001). Evaluation of contraceptive efficacy and cycle control of a transdermal contraceptive patch vs an oral contraceptive: a randomized controlled trial. *JAMA, 285*(18), 2347-2354.
- Dittrich, R., Parker, L., Rosen, J. B., Shangold, G., Creasy, G. W., & Fisher, A. C. (2002). Transdermal contraception: evaluation of three transdermal norelgestromin/ethinyl estradiol doses in a randomized, multicenter, dose-response study. *Am J Obstet Gynecol, 186*(1), 15-20.
- Heddon, B., Helmerhorst, F., Cronje, H., Shangold, G., Fisher, A., & Creasy, G. (2000). Comparison of efficacy, cycle control, compliance, and safety in users of a contraceptive patch vs an oral contraceptive. *International Journal of Gynaecology and Obstetrics, 78*(Supplement 2), 78.

Briefly, the clinical trials that compared the efficacy and safety of the contraceptive patch and COCs found:

- Similar efficacy with the patch and pill when used as directed (Analyses 01.01 and 01.02, p. 12)
- Higher discontinuation rates with the patch (Analyses 01.03 and 01.04, p. 13)
- Higher discontinuation rates due to adverse reactions with the patch (Analyses 01.05 and 01.06, p. 14)
- Lower compliance with the patch (Analysis 01.07, p. 15)
- Higher rates of breast discomfort with the patch (Analysis 01.10, p. 16)
- Higher rates of dysmenorrhea with the patch (Analysis 01.12, p. 17)

2.2 A note on effectiveness. Data from the trials indicate similar efficacy with the patch and pill when used as directed. However, because of higher discontinuation rates and lower compliance, we expect lower effectiveness in practice.

A distinction is drawn between *effectiveness* (the extent to which the treatment produces its intended effect in a real-world setting) and *efficacy* (the extent to which the treatment produces its effect under ideal conditions). Actual effectiveness combines information on compliance and proper use under actual conditions. For example, although failure rates for COCs within 12 months after initiation are less than 0.5% when used as directed, failure rates under actual use conditions are closer to 9%.[10] Lack of compliance and other factors contribute to this difference.

Two field surveys (observational studies) have compared the performance of the patch and pill in practice. One such study was based in Planned Parenthood clinics in the

[10] Kost, K., Singh, S., Vaughan, B., Trussell, J., & Bankole, A. (2008). Estimates of contraceptive failure from the 2002 National Survey of Family Growth. *Contraception, 77*(1), 10-21.
Fu, H., Darroch, J. E., Haas, T., & Ranjit, N. (1999). Contraceptive failure rates: new estimates from the 1995 National Survey of Family Growth. *Fam Plann Perspect, 31*(2), 56-63.

Rochester and Syracuse regions of New York State.[11] Verified continued use beyond the first three cycles of initiation was 67% for the patch and 89% for the pill. After 70 days of use, unintended pregnancy occurred at about 3 times the rate in patch users (RR = 3.2, 95% confidence interval 1.4–7.3). It should be noted, however, that the patch and pill groups in this survey differed at baseline with respect to reproductive, personal, and social characteristics.[12] Although a Cox proportional hazards model was used to adjust measured extraneous factors, the potential for residual confounding exists.

The second observational study, completed at the Medical University of South Carolina, compared Depot Medroxyprogesterone Acetate (Depo Provera), COCs, and the patch in preventing repeat pregnancies in teenagers.[13] One-year repeat pregnancy rates were 14%, 30%, and 32%, respectively. Thus, Depo Provera was superior to COCs and the patch; COCs and the patch demonstrated similar effectiveness in this high risk population, with a slight edge going to COCs.

Mention is made of an additional study: a cross-sectional Internet survey.[14] This survey did not address effectiveness. However, it found virtually no difference in satisfaction between COC- and patch-users: 87% of COC-users and 88% of patch-users reported satisfaction scores of either "4" or "5" (out of 5, where 5 represented "extremely satisfied"); only 3% and 2%, respectively, reported scores of "1" or "2", while 10% reported scores of "3".[15] The source of these data is a private firm Called Consumer Health Sciences.[16] The survey is self administered and is said to be representative of noninstitutionalized adults. However, no information about the sampling method is provided and Internet surveys of this type often suffer from "volunteer bias."[17] More importantly, this study was cross-sectional with no follow-up. Therefore, participants are hormonal contraceptive "survivors" who are likely to be satisfied with the product they have settled on. Finally, the authors report one baffling results: although Table 1 of the paper demonstrates virtually no difference in the distribution of satisfaction scores, the result from a logistic regression model (p. 283, column 2, paragraph 2) reports a prevalence OR of 2.05 for high satisfaction (scores of 4 or 5) associated with patch.[18] This is counter-intuitive and is not explained as such in the article.[19] Therefore, the only

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[11] Bakhru, A., & Stanwood, N. (2006). Performance of contraceptive patch compared with oral contraceptive pill in a high-risk population. *Obstet Gynecol, 108*(2), 378-386.

[12] For example, 4% of the COC users had been pregnant prior to starting contraception, compared to 25% of patch users.

[13] Thurman, A. R., Hammond, N., Brown, H. E., & Roddy, M. E. (2007). Preventing repeat teen pregnancy: postpartum depot medroxyprogesterone acetate, oral contraceptive pills, or the patch? *J Pediatr Adolesc Gynecol, 20*(2), 61-65.

[14] Wan, G. J., Barnowski, C. E., Ambegaonkar, B. M., Bolge, S. C., & McDonnell, D. D. (2007). Treatment satisfaction with a transdermal contraceptive patch or oral contraceptives. *Contraception, 75*(4), 281-284. This article was written by Ortho-McNeil employees.

[15] Table 1, p. 283 in Wan, 2007.

[16] http://www.chsinternational.com/survey/

[17] Internet survey participants represent a highly self-selected group.

[18] Note that the prevalence OR can not be interpreted as an RR because the outcome was not rare, affecting almost 90% of respondents.

[19] When modeled results contradict descriptive statistics, it is contingent on the authors to make clear the source of the contradiction and, if possible, to show subgroup analyses that explain the difference.

conclusion that I can derive from this article is that respondents were satisfied with either hormonal contraceptive.

Taken as a whole, data from these observational studies suggest that the Ortho EVRA transdermal contraceptive patch is either less effective or no more effective than COCs in producing their its intended effect in the actual clinical settings surveyed.

2.3 Serious thromboembolic events that were observed during the trials. A review article on the safety and tolerability of the patch derived from randomized controlled trials of the subject reported the occurrence of one case of idiopathic pulmonary embolism and one case of pulmonary embolism following surgery.[20] Neither case was fatal. The FDA medical reviewer deemed that both events should be counted because many women "may not always use the drug approved for chronic use according to the proper or labeled directions. So we cannot ignore this case just because of a protocol violation."[21] These trials considered a total of 1706 person-years of experience. Thus, the observed PE rate was 12 per 10,000 person-years (90% confidence interval by exact Mid-P procedure: 3 to 33).[22] The FDA reviewer states, "Although this rate is not statistically significant compared to the sponsor's estimated rate of VTE, it is still clinically important and is of potential concern." I concur.

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[20] Sibai, B. M., Odlind, V., Meador, M. L., Shangold, G. A., Fisher, A. C., & Creasy, G. W. (2002). A comparative and pooled analysis of the safety and tolerability of the contraceptive patch (Ortho Evra/Evra). *Fertil Steril, 77*(2 Suppl 2), S19-26; See p. S23.

[21] FDA. (2001). *Medical Officer's Review; NDA 21-180 Ortho EVRA contraception patch*, p. 43. Additional careful consideration of the potential for increased risk of VTE are found on the Reviewer's Summary of Safety on pp. 49 – 51.

[22] Calculated with WinPepi, Compare.exe version 1.55. Abramson, J. H. (2004). *WINPEPI* (PEPI-for-Windows): computer programs for epidemiologists. *Epidemiologic Perspectives & Innovations, 1*(1), 6.

3 EE EXPOSURE DOSE AND THE RISK OF THROMBOEMBOLISM

3.1 Pathophysiology. It is well known that COCs have a net prothrombotic effect on procoagulant, anticoagulant, and fibrinolytic hemostatic pathways. It is well accepted that such disturbances are mediated primarily through the EE component of COCs. Effects are dose-related: the greater the estrogen dose, the higher the prothrombotic effect, and the higher the risk of thromboembolism.[23] This dose-response relationship has been demonstrated in both laboratory and epidemiologic studies.

Until the mid-1990s, the progestin component of COCs was thought to contribute relatively little to the risk of thrombosis. However, it is now known that some progestins are more thrombogenic than others. Third generation COCs, in particular, have been associated with a higher VTE risks than second generation formulations. This fact might be related to the estrogenic profile of third generation progestins.[24]

3.2 Risks of VTE. Baseline risks of serious thromboembolic events (pulmonary embolisms and deep vein thromboses, excluding superficial venous thromboses) in populations vary considerably because of differing prevalences of complementary cause and differences in methods of case ascertainment.[25] With this said, a typical baseline risk of VTE is slightly less than 1 per 10.000 person-years in women of childbearing age is often cited.[26] This risk increases to approximately 2 or 3 per 10,000 person-years in users of low-dose second generation COCs.[27]

The typical 50 µg EE COCs (that were popular a generation ago) have *about* twice the risk of current low-dose formulations. The still older formulations of the 1970s, which contained more than 50 µg EE, had about twice the risk of the 50 µg EE formulations.[28]

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[23] See review articles by Stadel and Vandenbroucke:
Stadel, B. V. (1981). Oral contraceptives and cardiovascular disease (first of two parts). *N Engl J Med, 305*(11), 612-618. Stadel, B. V. (1981). Oral contraceptives and cardiovascular disease (second of two parts). *N Engl J Med, 305*(12), 672-677.

[24] Vandenbroucke, J. P., Rosing, J., Bloemenkamp, K. W., Middeldorp, S., Helmerhorst, F. M., Bouma, B. N., et al. (2001). Oral contraceptives and the risk of venous thrombosis. *N Engl J Med, 344*(20), 1527-1535. See especially p. 1531.

[25] As an example, the baseline risk of VTE in, say, a population of average age 35 will differ significantly from that of a population of women of average age 25.

[26] Farley, T. M., Meirik, O., & Collins, J. (1999). Cardiovascular disease and combined oral contraceptives: reviewing the evidence and balancing the risks. *Hum Reprod Update, 5*(6), 721-735.
Hannaford, P. C., & Owen-Smith, V. (1998). Using epidemiological data to guide clinical practice: review of studies on cardiovascular disease and use of combined oral contraceptives. *Bmj, 316*(7136), 984-987.
Vandenbroucke, J. P., Koster, T., Briet, E., Reitsma, P. H., Bertina, R. M., & Rosendaal, F. R. (1994). Increased risk of venous thrombosis in oral-contraceptive users who are carriers of factor V Leiden mutation. *Lancet, 344*(8935), 1453-1457.

[27] Vandenbroucke, J. P., Rosing, J., Bloemenkamp, K. W., Middeldorp, S., Helmerhorst, F. M., Bouma, B. N., et al. (2001). Oral contraceptives and the risk of venous thrombosis. *N Engl J Med, 344*(20), 1527-1535. See especially p. 1531. See Table 1 for current best evidence of the risk of VTE among apparent health users of available low-dose COCs.

[28] Meade, T. W., Greenberg, G., & Thompson, S. G. (1980). Progestogens and cardiovascular reactions associated with oral contraceptives and a comparison of the safety of 50- and 30-microgram oestrogen preparations. *Br Med J, 280*(6224), 1157-1161.

Recent evidence suggests that this dose-response extends downward from 35 μg to 20 μg formulations.[29] Thus, expected rates of VTE per 10,000 person-years in industrially developed populations of women of childbearing age without other known risk factors are approximately:

- Non-users: <1 (about 0.8)
- 20 μg EE: 2
- 35 μg EE: 3
- 50 μg EE 5
- 80 μg EE 8
- 100 μg EE 10

For the aforementioned reasons, these expected rates cannot be taken too literally. In fact, there is reason to believe these cited rates are underestimates of true rates.[30] Nevertheless, these expected rates provide a rough guide for putting risks associated with various hormonal contraceptives into perspective.

3.3 Utilization data. Because of the known dose-response relationship between EE dose and thromboembolism, oral contraceptives sold in the United States and overseas have decreased in estrogen content over time. When first widely used in the 1960s, it was not uncommon for formulations to contain at least 100 μg of estrogen. These high-dose formulations yielded to 50 μg formulations in the 1970s and 1980s. By the mid 1980s, most formulations contained 50 μg of EE or less. In the late 1980s and 1990s, formulations containing 30 – 40 μg were the rule.[31] This downward trend in estrogen content reflects the accepted fact that it is in the public interest to use the lowest effective EE dose in COC formulations.

3.4 Myocardial infarction and stroke. In addition to increasing the risk of venous thromboembolic diseases, hormonal COCs increase the risk of acute myocardial infarction (AMI) and ischemic stroke (IS). Risks of AMI and IS are approximately three to four times greater in COC users than in comparable nonusers with no known risk factors. Moreover, COC-associated risks multiply the risks of other known cardiovascular

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Gerstman, B. B., Piper, J. M., Tomita, D. K., Ferguson, W. J., Stadel, B. V., & Lundin, F. E. (1991). Oral contraceptive estrogen dose and the risk of deep venous thromboembolic disease. *American Journal of Epidemiology, 133*(1), 32-37.

Stadel, B. V. (1981). Oral contraceptives and cardiovascular disease (first of two parts). *N Engl J Med, 305*(11), 612-618.

Stadel, B. V. (1981). Oral contraceptives and cardiovascular disease (second of two parts). *N Engl J Med, 305*(12), 672-677.

[29] Lidegaard, O., Edstrom, B., & Kreiner, S. (2002). Oral contraceptives and venous thromboembolism: a five-year national case-control study. *Contraception, 65*(3), 187-196.

[30] Heinemann, L. A., & Dinger, J. C. (2007). Range of published estimates of venous thromboembolism incidence in young women. *Contraception, 75*(5), 328-336.

[31] Gerstman, B. B., Gross, T. P., Kennedy, D. L., Bennett, R. C., Tomita, D. K., & Stadel, B. V. (1991). Trends in the content and use of oral contraceptives in the United States, 1964-88. *American Journal of Public Health, 81*(1), 90-96.

Gerstman, B. B., Burke, L., Delaney, J., & McLellan, B. (1996). Steroidal contraceptive use update, United States, 1989-1994. *Pharmacoepidemiology and Drug Safety, 5*(3), 141-147.

risk factors such as smoking, a history of preeclampsia, hypertension, hyperlipidemia, and diabetes. Because risks are age-related and multiplicative, and because these outcomes are relative rare at younger ages, risks are concentrated in older users with concurrent risk factors. AMI- and IS-associated hormonal contraceptive risks are related to both the estrogen content and progestin content of formulations, with dose-response relationships established for both hormonal components. Note that in contrast to AMI and IS, VTE-associated risks are relatively unconfounded by cardiovascular risk factors such as smoking and hypertension.

4 EE EXPOSURE DOSE AND THE PATCH

Pharmacokinetics studies demonstrate that exposure to EE when using the Ortho EVRA transdermal patch is about 60% greater with about twice the variability of low dose second generation COCs. One study, for example, found mean ± standard deviation serum concentrations of EE of 70.9 ± 11.0 pg/mL in patch users compared to 43.5 ± 5.66 pg/mL in COC users.[32] Another study found 80.0 ± 26.8 pg/mL in patch users compared to 49.3 ± 13.3 pg/mL in COC users.[33] This mean level of exposure is comparable to the 50–60 µg EE COC formulations. In addition, the high variability of EE exposure suggests that some patients are exposed to significantly higher than average doses, while others are exposed to significantly lower doses. Those receiving significant higher EE exposures are expected to demonstrate thromboembolism risks comparable to high dose formulations with 80 - 100 µg EE. Those receiving lower doses are at an increased risk of therapeutic failure (pregnancy).

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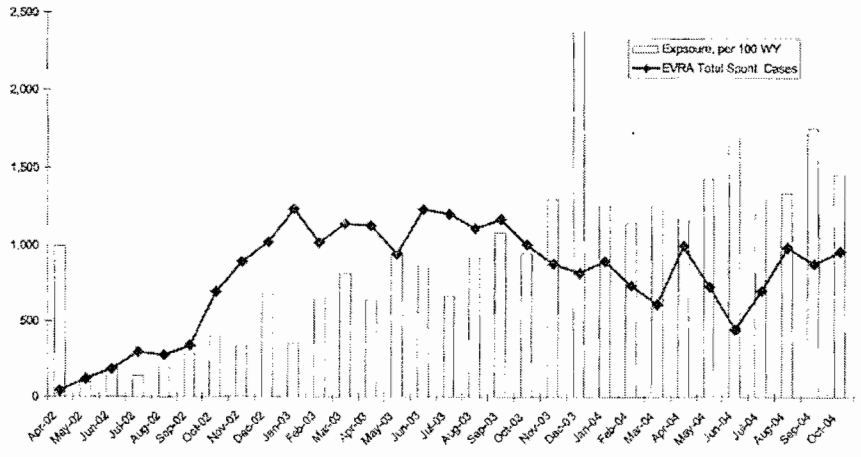
[32] van den Heuvel, M. W., van Bragt, A. J.. Alnabawy, A. K., & Kaptein, M. C. (2005). Comparison of ethinylestradiol pharmacokinetics in three hormonal contraceptive formulations: the vaginal ring, the transdermal patch and an oral contraceptive. *Contraception, 72*(3), 168-174.

[33] Devineni, D., Skee, D., Vaccaro, N., Massarella, J., Janssens, L., LaGuardia, K. D., et al. (2007). Pharmacokinetics and pharmacodynamics of a transdermal contraceptive patch and an oral contraceptive. *J Clin Pharmacol, 47*(4), 497-509. This reference reports coefficients of variation (*CV*) for exposure dose. The *CV* statistic measures variability relative to the size of the mean (i.e., *CV* = standard deviation / mean). This is not appropriate for measuring physiological effects, so I have converted the reported *CV*s to standard deviations according to the relationship $s = \frac{\bar{x} \cdot CV}{100}$.

5 SPONTANEOUS REPORTS OF ADVERSE EVENTS

Soon after the patch was introduced to the market, a signal of possible increased risk of adverse reactions was generated through receipt of spontaneous reports received by regulatory agencies. The following chart illustrates the total number of spontaneous reports received worldwide from April 2002 to October 2004:[34]

ORTHO EVRA®Exposure and Total Spontaneous Reports Received
(April 2000 to October 2004)



*Bars represent worldwide exposure while line represents received global spontaneous reports
**Patient exposure is estimated from sales and sample data.h

This graph shows that the number of reports increased rapidly after introduction of the product. The number of reports leveled off and declined just slightly thereafter. This pattern is typical of spontaneous event monitoring systems and is sometimes referred to as "the Weber effect." However, the large number of adverse event reports, rapid rise in the number of reports, and the sustained high frequency suggested that the product needed further scrutiny.

Analysis of AERs received between April 2002 and April 15, 2006 revealed 548 venous thrombotic events associated with Ortho EVRA. Ninety-two (92%) percent of these cases were reported in the United States. Two-hundred ninety two (292) were medically confirmed. Among medically confirmed cases, 24% were ISs, 3% were MIs and other arterial embolisms, 36% were pulmonary emboli, and 37% were venous thromboses.[35]

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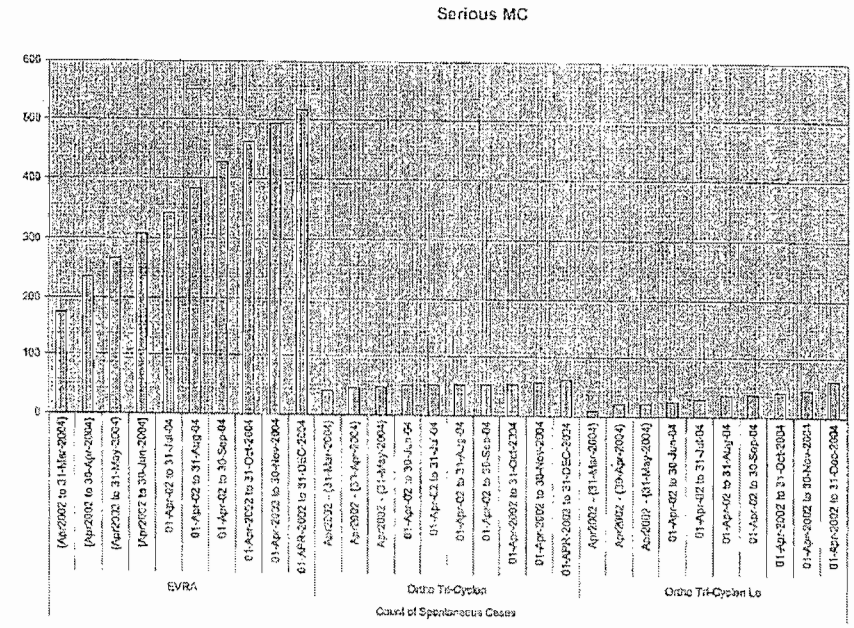
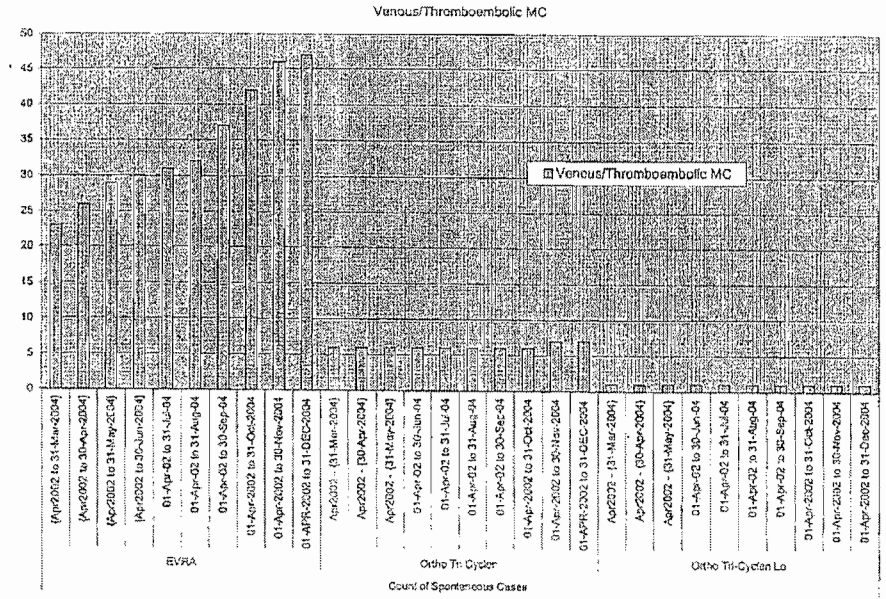
[34] Johnson & Johnson Pharmaceutical Research & Development, L. L. C. (2004). *EVRA / Ortho EVRA Update December 15, 2004 (Exhibit 416 Kennedy 12/14/06)* (Protected Document).
[35] Johnson & Johnson Pharmaceutical Research & Development, L. L. C. (2006). *Ortho EVRA and Ortho Tri-Cyclen Cumulative Report of Spontaneously Reported Cases of Thromboembolic Events Through April 15, 2006 (POE 06773519 -)*. Table 1, p. 11.

The following chart illustrates the number of medically confirmed spontaneous reports of serious events received for Ortho Evra in comparison to Ortho Tri-Cyclen and Ortho Tri-Cyclen Lo for the period April 2002 to December 2004:[36]

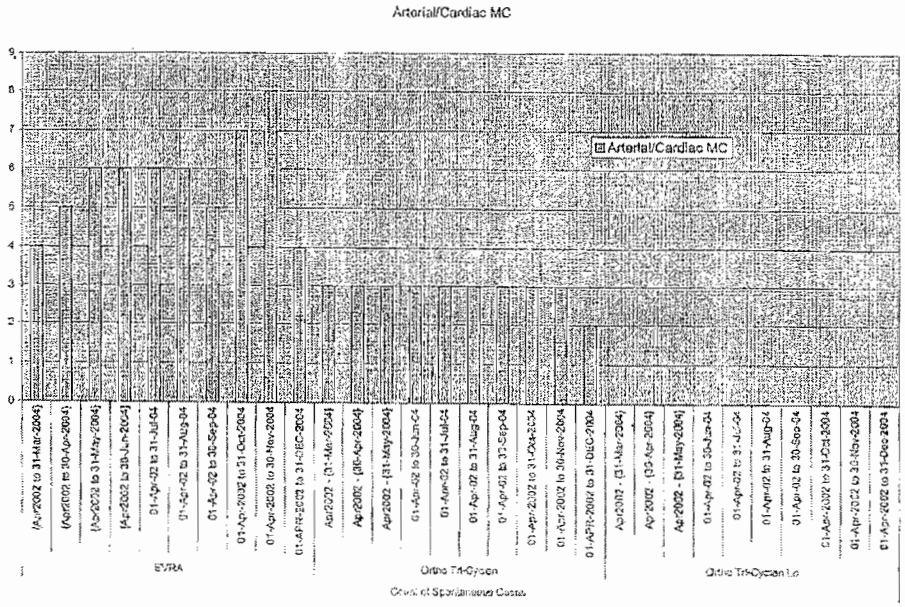


Data for medically confirmed venous thromboembolic events are:

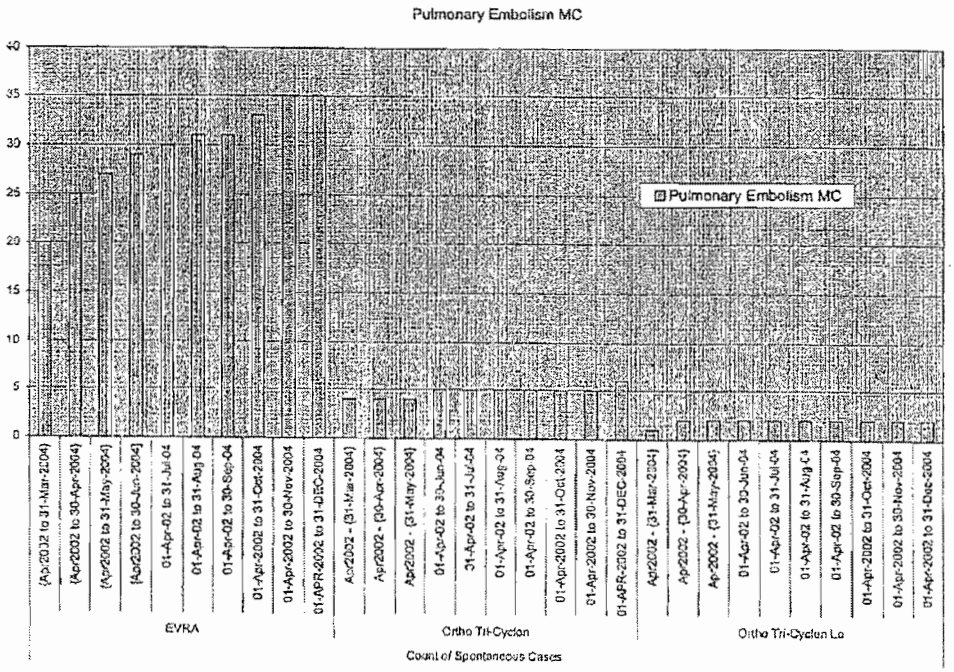


[36] Johnson & Johnson Pharmaceutical Research & Development, L. L. C. (2005). *Exhibit P-31 Kennedy 9/25/06 (POE 00127881 - POE 00127915).*

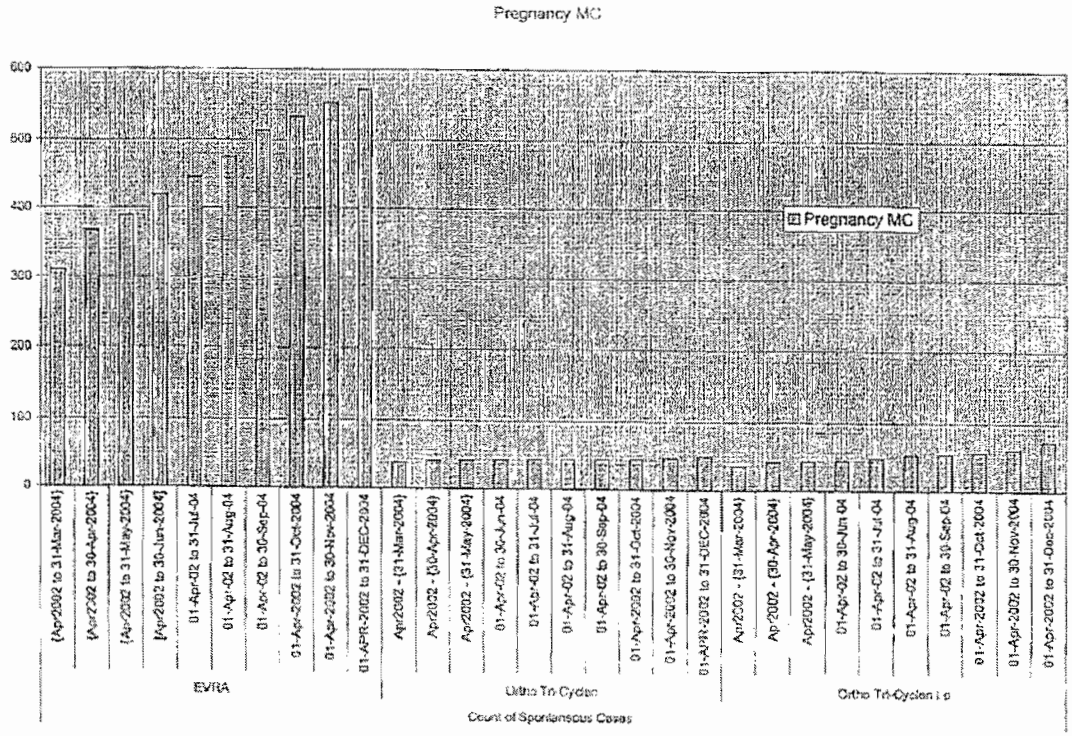
Data for medically confirmed arterial cardiac events are:



Data for medically confirmed pulmonary emboli are:



Data for medically confirmed pregnancies are:



These and similar analyses of AERs over time suggested that further study was necessary.

6 ANALYTIC EPIDEMIOLOGIC STUDIES

In response to these concerns, Johnson & Johnson Pharmaceutical Research and Development funded two epidemiologic research groups to study thromboembolic risks associated with the patch. One of the groups is the Boston Collaborative Drug Surveillance Program (BCDSP) of the Boston University School of Medicine. The lead author of these studies is Dr. Susan Jick. The other group is i3 Drug Safety of Auburndale, MA. The lead author of the published results from this study is Dr. J. Alexander Cole.[37]

6.1 BOSTON COLLABORATIVE DRUG SURVEILLANCE PROGRAM STUDIES

6.1.1 BCDSP STUDY COMPARING PATCH USERS TO NORGESTIMATE/35 MG EE COC USERS

This nested case-control study was published in two parts: as an initial article[38] and as a follow-up article with additional data.[39] Briefly, this study found no differences in risk between patch users and pill users. VTE rates reported in the initial study were 5.3 per 10,000 in patch users and 4.2 per 10,000 in pill users. The *OR* from the case-control analysis from the second publication for nonfatal idiopathic VTE was 1.1 (95% confidence interval: 0.6–2.1). When combined with data from the first publication, the *OR* was 1.0 (95% confidence interval: 0.7–1.5). As with any epidemiologic study, we must consider the precision and validity of these estimates.

Precision concerns are addressed by the reported confidence intervals. The intervals from this study are consistent with modest harm and some modest benefit.

Validity concerns are not addressed by the confidence intervals, but can be addressed in terms of the potential for information bias, selection bias, and confounding. Of these potential biases, the most serious are information biases due to misclassification.

This study relied on computerized claims data to identify exposures and outcomes. Medical records were *not* available to validate case status. Instead, subsequent anticoagulant use was used to increase the predictive value of such ascertainment. This is a technique I innovated in the late 1980s.[40] Although this technique increases the

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[37] The i3 study may be in other sources referred to as the "Walker study," because Alexander Walker is the senior researcher from this group and is the corresponding author.

[38] Jick, S. S., Kaye, J. A., Russmann, S., & Jick, H. (2006). Risk of nonfatal venous thromboembolism with oral contraceptives containing norgestimate or desogestrel compared with oral contraceptives containing levonorgestrel. *Contraception, 73*(6), 566-570.

[39] Jick, S., Kaye, J. A., Li, L., & Jick, H. (2007). Further results on the risk of nonfatal venous thromboembolism in users of the contraceptive transdermal patch compared to users of oral contraceptives containing norgestimate and 35 microg of ethinyl estradiol. *Contraception, 76*(1), 4-7.

[40] Gerstman, B. B., Freiman, J. P., & Hine, L. K. (1990). Use of subsequent anticoagulants to increase the predictive value of Medicaid deep venous thromboembolism diagnoses. *Epidemiology, 1*(2), 122-127.

predictive value of case ascertainment, correct ascertainment compared to record review remains limited, with predictive value positives of approximately 65% for probable cases.

In addition, there is an unknown false negative rate. The study by Cole et al.[41] raised this issue by pointing out that the high proportion of VTE cases that were pulmonary emboli is consistent with the fact that cases of deep venous thrombosis may have been missed.

Although of lesser concern, there is also the potential for misclassification of patch and pill use in this study. Drug exposure as ascertained with automated, insurance claims databases is never entirely certain. There will be an unknown number of false positive exposures. For example, a claim might be paid, but the prescription may stay in the package or be given away to a friend. In addition, a certain proportion of exposures will be missed (false negative exposures). For example, a professional sample may be distributed, but this would not appear in the claims data. Adding to this uncertainty are quality control concerns about the [relatively new and untested] PharMetrics database.

Misclassification of exposures and outcomes in epidemiologic studies, if random, will tend to bias estimates of risk toward the null.[42] This means that exposure-associated risks will tend to be underestimated. I corroborated this effect in a study I published in 1991.[43] Comparing 50 μg formulations to low dose formulations, the *RR* increased from 1.5 to 2.0 when case ascertainments were restricted to medical record-confirmed cases. A similar effect was found when comparing formulations with more than 50 μg EE to low-dose formulations, where the *RR* increased from 1.7 to 3.2 when using medical record-confirmed cases. Random misclassification will decrease the statistical power of the study.

It may also be noted that this study compared patch-associated risks to norgestimate COCs. In 1997, a World Health Organization meeting of scientific experts concluded that there was insufficient data to draw conclusions with regard to COCs containing norgestimate and that it is unclear whether norgestimate is better characterized as a second generation or third generation COC.[44] The use of norgestimate containing COCs thus provides a weak baseline for comparison.

Gerstman, B., Lundin, F., Bosco, L., & Tomita, D. (1986). Exploration of drug-associated risk using health care coverage data bases. In *Proceedings of the 5th International Conference on Pharmacoepidemiology*. Detroit: Lewis Publishers. Gerstman, B., & Lundin, F. E. (1986). Longitudinal follow-up in claims-based pharmacoepidemiologic databases. In *Proceedings of the 5th International Conference on Pharmacoepidemiology*. Detroit: Lewis.

[41] Cole, J. A., Norman, H., Doherty, M., & Walker, A. M. (2007). Venous thromboembolism, myocardial infarction, and stroke among transdermal contraceptive system users. *Obstet Gynecol, 109*(2 Pt 1), 339-346.

[42] Bross, I. D. J. (1954). Misclassification in 2x2 tables. *Biometrics, 10*, 478-486.

[43] Gerstman, B. B., Piper, J. M., Tomita, D. K., Ferguson, W. J., Stadel, B. V., & Lundin, F. E. (1991). Oral contraceptive estrogen dose and the risk of deep venous thromboembolic disease. *American Journal of Epidemiology, 133*(1), 32-37.

[44] Cardiovascular disease and steroid hormone contraception. Report of a WHO Scientific Group. (1998). *World Health Organ Tech Rep Ser, 877*, i-vii, 1-89. Also see FDA medical review of 11/21/01, pp. 11–12.

We must also consider other types of biases in this study. These include (a) comparison of non-constant hazards over time (e.g., duration of use bias), (b) subtle prescribing-pattern biases, (c) diagnostic suspicion bias, (d) incomplete control for extraneous factors ("residual confounding"), (e) funding source bias,[45] and f) exclusion of fatal cases. The authors addressed these concerns in various parts of their publication. Although these types of biases can never be ruled out with absolute certainty, it is my opinion that these biases are of less concern than aforementioned concerns about misclassifications of cases.

6.1.2 BCDSP STUDY COMPARING THE PATCH TO LEVONORGESTREL/30 MG EE COCS

This study is not yet published but is available as a Johnson & Johnson Pharmaceutical Research and Development report.[46] In contrast to the prior BCDSP study, this study found a positive association between patch use and VTE risk. The risk of idiopathic VTE comparing patch users to 30 μg EE levonorgestrel-containing COCs was 2.0 (95% confidence interval: 0.9–4.1).[47] The study base consisted of 15–44 year old women who used ORTHO EVRA or who were first-time users of 30 μg the study COC. Other than this difference, this study has similar strengths and limitations as the prior study (section 6.1.1). Risk analyses for IS and AMI are also presented. The results for these outcomes are less reliable because of (a) the small numbers of cases (and resultant imprecision of estimates), (b) case ascertainment for arterial events is particularly unreliable in this data base, (c) fatal cases are excluded, and (d) confounding factors are not adequately controlled for.

6.1.3 OTHER BCDSP ANALYSES

BCDSP published two additional studies using PharMetrics data. One study looked at cerebral venous sinus thrombosis as an outcome. The pathogenesis of this outcome is similar to that of other VTEs. It is therefore surprising to find this outcome published as a separate paper when it could have been included in one of the aforementioned analyses. Briefly, few cerebral venous sinus cases were found in levonorgestrel COC, norgestimate COC, desogestrel COC, and contraceptive patch users (2, 7, 5, and 0 cases,

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[45] Friedberg, M., Saffran, B., Stinson, T. J., Nelson, W., & Bennett, C. L. (1999). Evaluation of conflict of interest in economic analyses of new drugs used in oncology. *JAMA, 282*(15), 1453-1457.
Stelfox, H. T., Chua, G., O'Rourke, K., & Detsky, A. S. (1998). Conflict of interest in the debate over calcium-channel antagonists. *N Engl J Med. 338*(2), 101-106.
Rochon, P. A., Gurwitz, J. H., Simms, R. W., Fortin, P. R., Felson, D. T., Minaker, K. L., et al. (1994). A study of manufacturer-supported trials of nonsteroidal anti-inflammatory drugs in the treatment of arthritis. *Arch Intern Med, 154*(2), 157-163.
Barnes, D. E., & Bero, L. A. (1998). Why review articles on the health effects of passive smoking reach different conclusions. *JAMA, 279*(19), 1566-1570.

[46] BCDSP. (2007). *Postmarketing Study of ORTHO EVRA and Levonorgestrel Oral Contraceptives Containing Hormonal Contraceptives with 30 μg of EE in Relation to Non-Fatal Venous Thromboembolism, Ischemic Stroke and Myocardial Infarction (POE.SP096016-SP096081).* Lexington, MA: Boston Collaborative Drug Surveillance Program, Boston University School of Medicine.

[47] The report states that this was at the request of European regulatory authorities.

respectively).[48] It is not possible to derive statistically stable comparisons with this few number of cases. In addition, this outcome is age-related and age may be associated with contraceptive choice. The sensitivity and specificity of case ascertainment must also be considered. Other than the observation that CVS events are uncommon, few inferences can be derived from this study.

A study of IS and MI based on 19 IS cases and 8 MI cases was also published.[49] This study found no significant difference in patch users and norgestrel-containing COCs users. However, results from this study are inconclusive because age and other known risk factors are not adjusted for, cases are not medically confirmed, and confidence intervals for risk estimates are wide because of the limited number of cases.

6.2 I3 STUDY COMPARING PATCH USERS TO NORGESTIMATE/35 MG EE COC USERS

This observational epidemiological study, also funded by Johnson & Johnson Pharmaceutical Research and Development, found that patch users had more than twice the risk of VTE compared to users of norgestimate-containing COCs with 35 μg EE. AMI and IS occurred too infrequently to estimate their associated risks with precision, although estimates are suggestive of an increased risk of AMI.

This study included both cohort and case-control analyses. The cohort analysis found VTE rates of 4.2 per 10,000 in patch users compared to 1.8 in COC users. The age-adjusted rate ratio for VTE was 2.2 (95% confidence interval: 1.3 to 3.8). Other results from the cohort analysis, as reported in Table 1 of the published article (p. 343) are:

	Patch 49,048 person-years		NGM-COC 202,344 p-years			
	Cases	Rate per 10,000 person-yrs[50]	Cases	Rate per 10,000 person-yrs	RR	95% CI
VTE	20	4.1	37	1.8	2.2	1.3 - 3.8
AMI	3	0.6	7	0.3	1.8	0.5 - 6.8
IS	0	0.0	10	0.5	-	-
AMI + IS	3	0.6	17	0.8	0.7	0.2 - 2.5
AMI, IS, PE	12	2.5	33	1.6	1.5	0.8 - 2.9
AMI, IS, VTE	23	4.7	54	2.7	1.8	1.1 - 2.9

The case-control study analysis found an odds ratio of 2.4 (95% confidence interval: 1.1 to 5.5) for idiopathic VTE.[51]

[48] Jick, S. S. & Jick, H. (2006). Cerebral venous sinus thrombosis in users of four contraceptives: levonorgestrel-containing oral contraceptives, norgestimate-containing oral contraceptives, desogestrel-containing oral contraceptives and the contraceptive patch. *Contraception*, 24(4), 290-292.

[49] Jick, S. S. & Jick, H. (2007). The contraceptive patch in relation to ischemic stroke and acute myocardial infarction. *Pharmacotherapy*, 27(2):218-220.

[50] Rates in this table are reported per 10,000 to be consistent with those in the rest of this report.

[51] Cole, J. A., Norman, H., Doherty, M., & Walker, A. M. (2007). Venous thromboembolism, myocardial infarction, and stroke among transdermal contraceptive system users. *Obstet Gynecol, 109*(2 Pt 1), 339-346.

Although this study is similar in design to the BCDSP study, it used a more developed data source.[52] In addition, it had access to linked medical records, thus allowing confirmation of VTE cases through record review. As noted earlier, use of medical record-confirmation for case ascertainment is superior to reliance on claims data. In my expert opinion, I consider this the major distinction between the studies.

In addition, access to medical records also permitted a more thorough assessment of several potentially confounding factors.

There is also a subtle difference in the admissibility criteria used to establish the source population in this study and the BCDSP study. The BCDSP study admitted only new users of either exposure, with "new use" defined by available data, which by necessity is limited. However, a "survivor cohort effect" related to duration of hormonal contraceptive use would depress empirical rates of VTEs in patch users in the BCDSP study, biasing risk estimates toward the null.[53] In a letter from Dr. Susan Jick to Dr. Daniel Fife dated March 31, 2006, this effect was corroborated.[54]

The rate ratio for AMI in the i3 study was 1.8 (95% confidence interval 0.5 to 6.8). The confidence interval is wide because of the limited sample size: there were only three patch-exposed AMI cases. No IS cases were observed among contraceptive patch users. The rate ratio for venous and arterial events combined was 1.8 (95% confidence interval: 1.1 to 2.9). Odds ratio estimates from the nested case-control analyses were similar.

Despite the superiority of this study, biases are still possible in this study. Potential biases include misclassification of cases, subtle forms of diagnostic biases, misclassification of exposures, and incomplete control for confounding. It is my opinion that, on balance, these influences are more likely to bias the results toward the null than have the opposite effect.

In summary, this study demonstrated more than a two-fold increase in VTE risk associated with the contraceptive patch compared to norgestimate-containing COCs with 35 μg EE. Although this study was unable to estimate AMI and IS associated risks with precision because of its limited sample size, an association between contraceptive patch use and AMI is evident.

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[52] i3 used the UnitedHealthcare database., which is more established and tested than the relatively new PharMetrics database used for the BCDSP studies.

[53] In restricting the cohorts to only new users, an asymmetry in susceptibility may have been introduced because the contraceptive patch was introduced only recently introduced. Therefore, prior patch users could not be in the prior use category of the norgestimate COC users. However, prior norgestimate COC users were excluded from the patch user cohort.

[54] Letter from Dr. Jick to Dr. Fife, March 31, 2006 (pp. POE 06755504-06755505). Odds ratio estimate increases from 1.0 to 1.5 after the "new user admissibility restriction" for either formulation is removed. My perspective is that the user restriction differences in the studies had less of an effect than the information bias discussed earlier.

7 SUMMARY

My scientific opinion is that the combined physiological, experimental, and observational evidence data are consistent in showing that transdermal contraceptive patch users have, on the average, approximately twice the risk of thromboembolism compared to users of second generation COCs containing 30–40 μg of EE. This is related to the fact that contraceptive patch users absorb about 60% more EE on average compared to low dose COC users. In addition, since delivery of EE via the transdermal system is highly variable, with twice the standard deviation of COCs, risks vary greatly from patient to patient. In patients exposed to higher than average EE levels through the patch, risks are comparable to those of high dose formulations containing more than 50 μg EE. In those patients exposed to lower than average EE levels, risks are comparable to those of low-dose COCs. In those patients exposed to very low EE levels, the risk of pregnancy is higher than expected.

Respectfully submitted:

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1 / 4 / 2008
Date