

Causal Inference Framework for Considering the Cardiovascular Risks Associated with Ortho Evra

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This brief document addresses the question “Does Ortho Evra cause more cardiovascular side effects than combination oral contraceptives with 30 to 40 µg of ethinyl estradiol, all other things being equal.” Ten elements of causal inference are considered. The first nine elements are based on Bradford Hill’s landmark paper from 1965¹ (enclosed). A tenth element (“consensus”) is not a causal consideration, *per se*. However, it does play an important role in applied scientific practices² and is therefore included for discussion.

Notes:

- Causal inference cannot be based on a mechanical “formula” or set of criteria. However, a framework for discussion can be helpful in defining and clarifying specific issues.
- There is more than one framework for causal inference. This document is *not* intended as a metaphysical or academic consideration of the topic. Rather, it is intended as a pragmatic outline that can be used to address the question at hand.
- None of these elements in the framework are essential, except perhaps for element #4 (temporality).
- Much of what we know about the safety and efficacy of the Ortho Evra patch out of necessity comes from our understanding of and experience with combination oral contraceptives. Although the method of delivery and pharmacokinetics of Ortho Evra differs from that of oral contraceptives, its biological activity is identical and its pharmacokinetics is well understood.
- Large scale randomized trials to evaluate adverse effects may never be performed. It is therefore essential to draw conclusions from ongoing epidemiological observations and other sources of information.

¹ Hill, A. B. (1965). The environment and disease: association or causation? *Proceedings of the Royal Society of Medicine*, 58, 295-300.

² See Kuhn, T. S. (1970). *The Structure of Scientific Revolutions*. Chicago: University of Chicago Press.

Framework for Causal Inference

Considerations ³	Notes
1. Strength	<p>Stronger associations are more like to indicate causality. Risk ratio estimates (such as rate ratios and odds ratios) are used to measure the strength of an association; large risk ratios are less easily explained away by confounding.⁴</p> <p>Two independent studies on this specific issue have been completed.⁵ Results from Boston Collaborative Drug Surveillance Program studies (Jick et al.; results spread across several papers) have made two comparisons: Ortho Evra to a combination oral contraceptive with 35 µg EE and the progestin norgestimate, and Ortho Evra to combination oral contraceptives with 30 µg EE and the progestin levonorgestrel. These studies are addressed carefully in my other consult. Very briefly, the first comparison derived a summary odds ratios of 1.23 and the second comparison derived an odds ratio of 2.0. Studies are done in the same population (are not independent). If we average these results, the Jick group estimates an <i>OR</i> of about 1.6, representing a 60% increase in risk with Ortho Evra.</p> <p>The i3 group compared Ortho Evra to currently marketed norgestimate containing oral contraceptives. This group found a relative risk of 2.2 or 2.4, depending on whether one uses the results from cohort analysis or case-control analysis; this represents about a 130% increase in risk.</p> <p>In interpreting these results, we must consider their precision and validity. These estimates are imprecise because they are based on a limited number of cases. However, in my view, it is more important to consider potential systematic errors in these estimates. My opinion is that these estimates are reasonable and, if anything, are more likely to be biased toward the null than away from the null. I therefore believe that given current knowledge, a conservative estimate of risk is “about a doubling compared to currently-marketed low-dose formulations.”</p>
2. Consistency	<p>Findings from diverse studies in different populations completed under a variety of circumstance demonstrate similar conclusions.</p> <p>The following results suggest that results have been consistent: (a) a greater than expected number of thromboembolism cases observed in the</p>

³ Hill never referred to these elements as “criteria.”

⁴ “We must not be too ready to dismiss a cause-and-effect hypothesis merely on the grounds that the observed association appears to be slight. There are many occasions in medicine when this is in truth so (Hill, 1965, p. 296, c. 2, ¶4).”

⁵ Additional information comes from four decades on the study of combination oral contraceptives, which have identical biological activity

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	<p>clinical trials for Ortho Evra (b) a greater than expected number of spontaneously reported adverse cardiovascular events (c) positive associations seen by studies completed in two populations by the BCDSF group and i3 group (d) consistency with expectation for high-dose combination oral contraceptives, based on pharmacokinetic and observational studies of moderate and high-dose formulations.</p>
3. Specificity	<p>The association is limited to specific people and types of disease, and there is no association between the exposure and other outcomes.</p> <p>A modern interpretation of this criterion is linked to a specific pathophysiological causal mechanism. In this instance, the known prothrombogenic effects (on balance) of estrogen can specifically account for adverse cardiovascular outcomes.</p>
4. Temporality	<p>Exposure precedes onset by a reasonable amount of time.</p> <p>Studies have been careful to ascertain the time relationship between the exposure and the outcome. Risk is associated with current use, and not past use. Risks return to baseline within a month or so of stopping exposure. Duration of use with current episode of use is not associated with risk. There is likely to be a cohort effect associated with a decreased number of susceptibles with exposure to hormonal contraceptives over time.</p>
5. Biological gradient	<p>Dose-response between exposure level and risk elevation.</p> <p>Four decades of research have demonstrated progressive increases in risk for myocardial infarction, ischemic stroke, and venous thromboembolism with higher levels of estrogen (in 100 µg EE formulations down to progestin only pills). Pharmacokinetic studies show that, on average, Ortho Evra delivers the equivalent of a 50–60 µg combination oral contraceptive. Studies by the BCDSF and i3 Group demonstrate risks comparable to this level of estrogen.</p>
6. Plausibility	<p>The observed association is biologically plausible.</p> <p>Clinical and hematological studies suggest that exogenous estrogen is prothrombic on balance. The route of delivery is inconsequential to biological effect. The hypothesis about potential benefits of transdermal delivery offering safety benefits because it bypasses first-pass hepatic metabolism seems implausible given the proposed causal mechanism and time-response relationship.</p>
7. Coherence	<p>Available evidence sticks together to form a coherent argument.</p> <p>Known facts about the natural history of disease, biology of the disease,</p>

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	and clinical and epidemiologic information stick together to form a cohesive whole.
8. Experimentation	<p><i>In vivo</i> and <i>in vitro</i> experimental evidence supports observational results.</p> <p>During clinical trials of Ortho Evra, two cases of VTE were observed. One case was idiopathic, and one was associated with surgery. Whether one counts the second case (intention to treat / effectiveness analysis) or not (efficacy analysis), these represents a higher than expected occurrence. In addition, studies of vascular risk markers have found that patch users have higher levels of coagulation markers than pill users.⁶ Clinical trials of exogenous estrogen have demonstrated thrombogenic potential, even in moderate doses.⁷</p>
9. Analogy	<p>Similarities between things that are otherwise different.</p> <p>The similarity between the behavior of the Ortho Evra transdermal system and first generation combination oral contraceptives with <i>about</i> 50 µg of estrogen is striking. Both approximately double the risk of cardiovascular disease compared to 30–40 µg combination oral contraceptives.</p>
10. Consensus	<p>Collective judgment of the community of scientists and clinicians at a particular time.</p> <p>I believe the large majority of scientists and physicians familiar with this issue will agree that the cardiovascular risks of Ortho Evra are comparable to an approximately 50 µg estrogen combination oral contraceptive. Nearly all will agree that 50 µg estrogen formulations have a higher risk of thromboembolism than lower dose formulations.</p> <p>Oral contraceptive formulations have changed greatly over the years. In 1968, less than 1 percent of retail prescriptions for oral contraceptives contained less than 50 µg of estrogen. By 1988, 82 percent of combination oral contraceptive prescriptions in the U.S. had less than 50 µg estrogen. By 1994, the average estrogen dose in combination oral contraceptives was 33.6 µg⁸. In 1994, less than 4 percent of the combination oral</p>

⁶ An independent study by Johnson et al. (2008) found higher levels of free protein S, nAPCsr, alpha2M-IIa, and nAPCsr in patch users.

⁷ High rates of thromboembolism we been demonstrated in human trials of estrogen in the treatment and prevention of heart disease, prostatic cancer, and lactation suppression, and in the use of estrogen to prevent heart disease (e.g., Daniel et al., 1967; Joeffocoate et al, 1968; Millar 1968; Oliver 1961; Schrogie 1967; Bailar, 1967; Writing Group for the Women's Health Initiative Investigators, 2002).

⁸ 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.

Considerations³**Notes**

contraceptives in Denmark had 50 µg of estrogen.⁹ The percentage of oral contraceptives with 50 µg estrogen at this time is not known, but is likely to be very small, on the order of one or two percent. These marketing data and prescribing trends show that 50 µg pills no longer enjoy widespread use. There is the suggestion that high-dose formulations should be reserved for special instances, e.g., women resistant to estrogen, adiposity, and so on.

⁹ Lidegaard, O., Edstrom, B., & Kreiner, S. (2002). Oral contraceptives and venous thromboembolism: a five-year national case-control study. *Contraception*, 65(3), 187-196.