Cardiovascular Side-Effects of Hormonal Contraceptives

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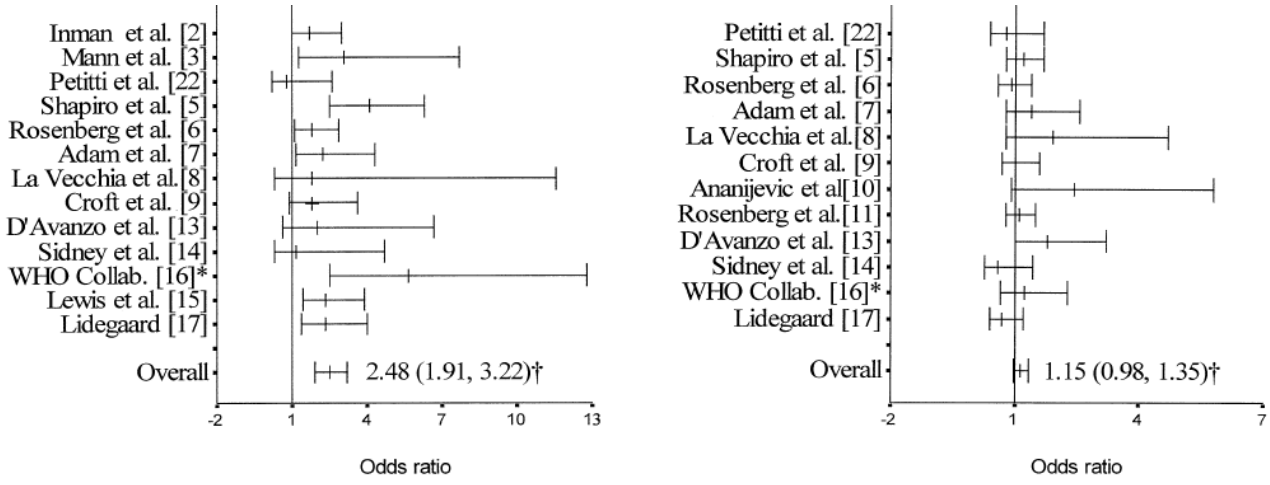
This is a summary of the epidemiologic information that has established facts about the cardiovascular side-effects of hormonal contraceptives. The focus of this overview is the dose-response between estrogen and risk with the objective of shedding light on the cardiovascular side-effects of the Ortho Evra patch (Ortho-McNeil Pharmaceuticals Inc., Raritan, NJ). Although the method of drug delivery and pharmacokinetics of the patch differs from that of the pill, its hormonal content and biological activity is identical. Thus, much of what we know about the patch has been derived from more than four decades of experience with combination oral contraceptives.

Hormonal Contraceptives and Myocardial Infarction

Epidemiologic studies of hormonal contraceptives and myocardial infarction risk were reviewed recently in a 2002 meta-analysis by Khader et al.[1] A rigorous protocol was used to identify articles for review. Ultimately, 23 independent studies were synthesized into this meta-analysis. Nineteen of the studies were case-control studies; four were cohort studies. Evidence of publication bias was lacking (funnel plot analysis, Kendall's test).

Results from individual studies are summarized in these two figures from the original article. *OR*s for current users are plotted in the left figure; *OR*s for former user are seen in right figure.



The summary odds ratio for myocardial infarction for current user (versus nonuse) is 2.48 (95% CI: 1.91–3.22). The point estimate of 2.48 indicates a 148% increase in the risk of acute myocardial infarction. The summary odds ratio for former users is 1.15 (95% CI: 0.98–

[1] Khader, Y. S., Rice, J., John, L., & Abueita, O. (2003). Oral contraceptives use and the risk of myocardial infarction: a meta-analysis. *Contraception, 68*(1), 11-17.

1.35), indicating little if any increase in risk associated with former use.[2] *RR*s were similar in younger and older users, and in smokers and non-smokers.

Most pertinent for this report is the analysis of estrogen dose, summarized here:

- Formulations with ≥ 50 μg estrogen have an odds ratio of 3.62 (95% CI 2.22–5.90)
- Formulations with 30–49 μg estrogen have an odds ratio of 1.97 (95% CI: 1.43–2.71)
- Formulations with 20 μg estrogen have an odds ratio of 0.92 (95% CI: 0.21–4.08)

Note that the dose-response extends through low-dose formulations. Also note that the data for 20 μg formulations is consistent with no increase in risk.[3]

Smoking, hypertension, hypercholesterolemia, factor V Leiden, and G20210A mutation were confirmed as independent risk factors. The table from the article addressing these study factors is reproduced here. Readers are encouraged to refer to the original article (enclosed) for specifics:

Table 3
Combined odds ratio (OR) of myocardial infarction (MI) associated with oral contraceptives (OCs) use in subgroups by study characteristics

Subgroups	No. of studies	OR	95% CI	p-value*
OCs Exposure				
Past vs. never use [5–11,13,14,16,17,22]	12	1.15	0.98, 1.35	0.0965
Current vs. never use [2,3,5–9,13–17,22]	13	2.48	1.91, 3.22	<0.0005
Current vs. noncurrent use [4,6,11,14,16,24]	6	3.00	1.70, 5.28	<0.0005
Study location				
Past use (US) [5,6,11,14,22]	5	1.02	0.84, 1.24	0.8268
Past use (Europe) [7–10,13,16,17,24]	8	1.20	0.98, 1.46	0.0801
Current use (US) [5,6,14,22]	4	2.46	1.79, 3.37	<0.0005
Current use (Europe) [2,3,7–9,13,15–17]	9	2.62	2.10, 3.26	<0.0005
Type of OC				
First generation [14,15,17,18,20,21]	6	2.21	1.30, 3.76	0.0036
Second generation [15–21]	7	2.17	1.76, 2.69	<0.0005
Third generation [15–21]	7	1.27	0.96, 1.67	0.0940
Estrogen dose				
20 μg [17,18]	2	0.92	0.21, 4.08	0.9179
30–49 μg [17,18,20,21]	4	1.97	1.43, 2.71	<0.0005
≥50 μg [7,16,17,20,21]	5	3.62	2.22, 5.90	<0.0005
Cigarette smoking				
No [3,5,9,10,12,14,18,20,21,24]	10	1.84	1.32, 2.57	<0.0005
Yes [3,5,6,10–12,14,16,18,20,22–24]	13	1.90	1.38, 2.62	<0.0005
Combined effect of OCs and one of another risk factors compared with absence of both				
Smoking [5,6,9,12,13,15,16,20,21,23]	10	9.52	5.41, 16.72	<0.0005
Hypertension [9,13,16,21]	4	9.30	3.89, 22.23	<0.0005
Hypercholesterolemia [13,21]	2	9.90	1.83, 53.53	0.0078
Prothrombin mutation [20,21]	2	2.08	1.50, 2.90	<0.0005

CI = confidence interval.
* Two-tailed.

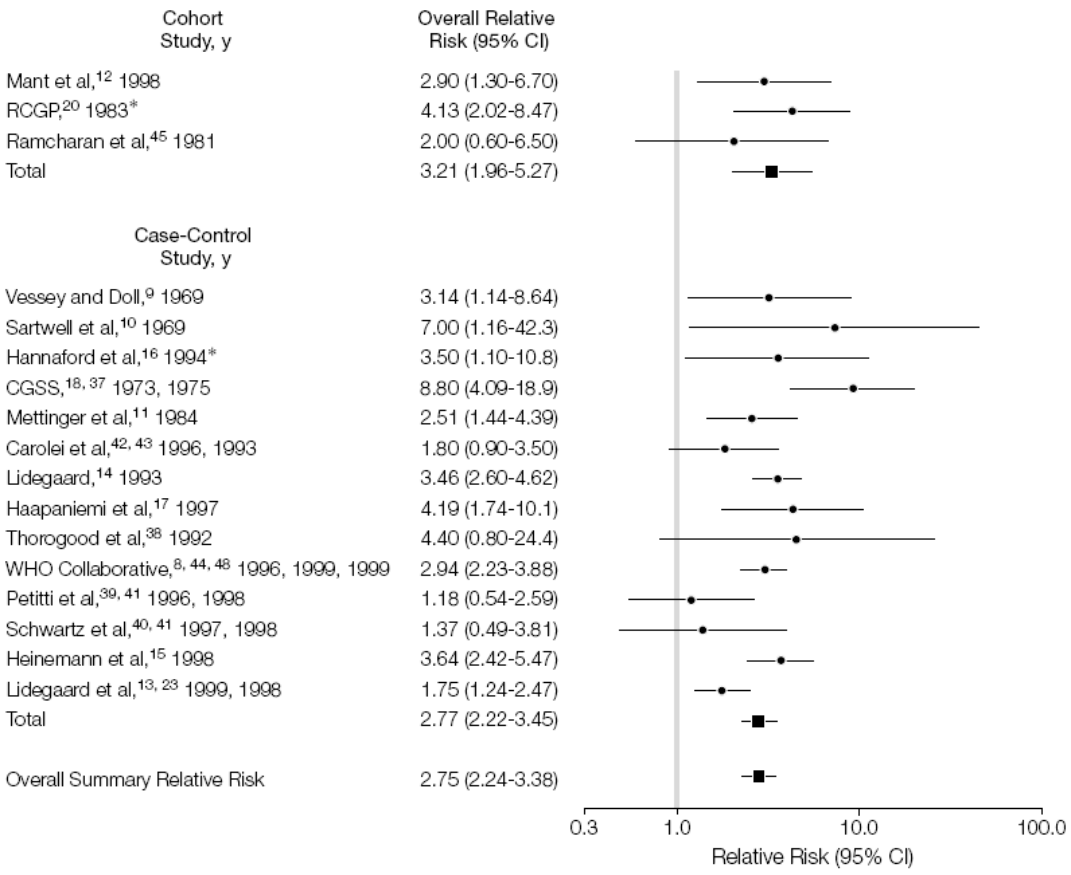
Third generation formulations were found to have lower risks than first and second generation formulations. However, it is unclear whether these benefits are associated primarily with favorable effects of third generation progestins, with the lower estrogen content typically found in third generation formulations, or with selective prescribing practices.

[2] Odds ratio from observational studies that are this close to 1 are interpreted as either no increase in risk or as minimal increase in risk.
[3] It is also consistent with selective prescribing to women at lower baseline risk than average.

Hormonal Contraceptives and Ischemic Stroke

Epidemiologic studies of combination hormonal contraceptives and ischemic stroke risk are reviewed by Gillum et al. (2000).[4] Like the previous review, this article used a rigorous method to identify studies. Sixteen studies (14 case-control and 2 cohort) were ultimately considered. Evidence of publication bias was lacking (funnel plot analysis and Kendall's τ). This figure from the publication summarizes results from the individual studies that constitute this meta-analytic review:

Figure 1. Overall Relative Risk for Ischemic Stroke and 95% Confidence Intervals (CIs) for Included Studies



RCGP indicates Royal College of General Practitioners; CGSS, Collaborative Group for the Study of Stroke in Young Women; and WHO, World Health Organization. The asterisk indicates that the earlier RCGP cohort study data are used for subgroup analysis of cohort studies, but do not contribute to the overall summary relative risk calculation.

[4] Gillum, L. A., Mamidipudi, S. K., & Johnston, S. C. (2000). Ischemic stroke risk with oral contraceptives: A meta-analysis. *JAMA, 284*(1), 72-78..

The summary odds ratio for current hormonal contraceptive use was 2.75 (95% CI: 2.24–3.38). The following dose-response between estrogen content and risk was found:

- Formulations with >50 μg of estrogen had a relative risk of 4.53 (95% CI: 2.17–9.50)
- Formulations with 50 μg estrogen had a relative risk of 2.78 (95% CI: 2.00–3.85)
- Formulations with < 50 μg of estrogen had a relative risk of 2.08 (95% CI: 1.55–2.80).

Test for trend *P*-value = 0.01.

When restricting analyses to studies that were able to statistically adjust for smoking and hypertension , the odds ratio of associated with current use of 50 μg estrogen formulations was 1.93 (95% CI: 1.35–2.74). However, two of these studies showed *OR*s just slightly above 1; these are the study by Petitti et al. and the study by Schwartz et al—visible in the figure on the prior page. Reasonable explanations for these lower risk estimates include lower estrogen levels in current formulations, selective prescribing, random variation, and more complete control for confounding.

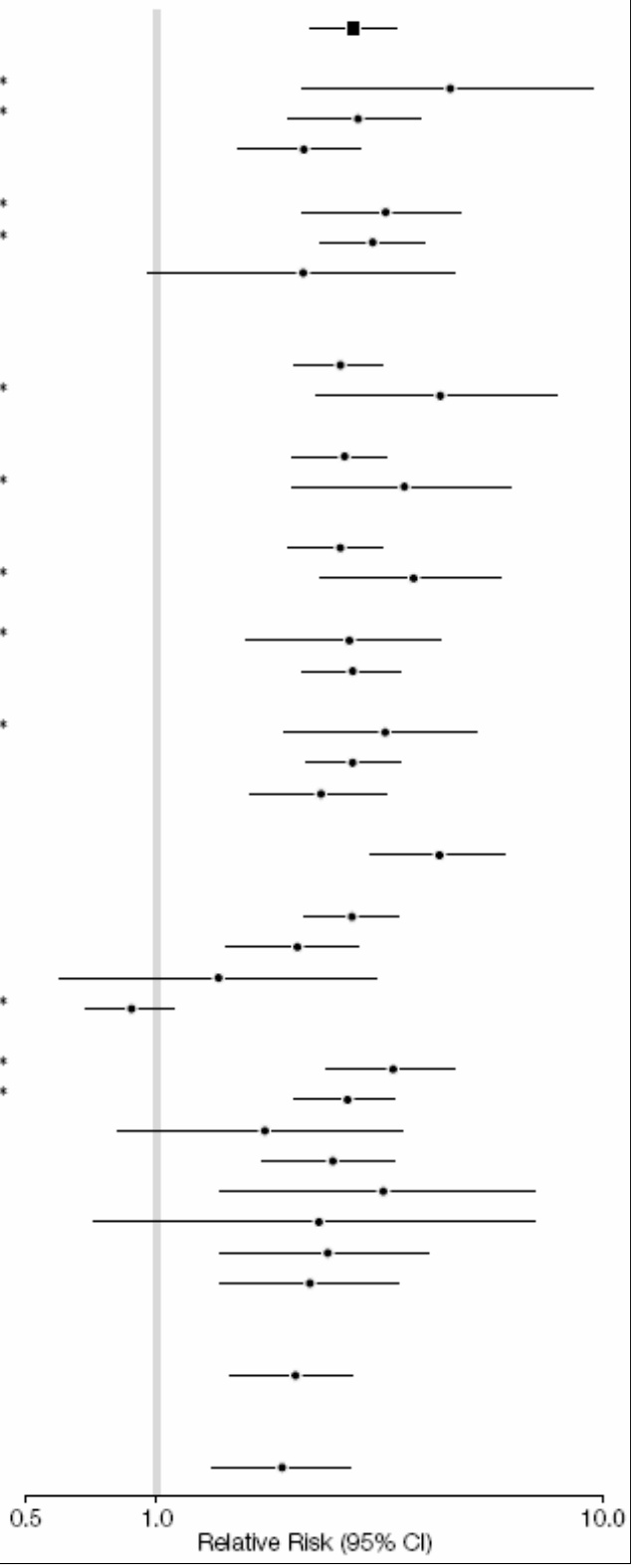
Studies of formulations containing third generation progestins demonstrated lower elevations in risk compared to first and second generation formulations. The authors note "lower estrogen dosages in later-generation estrogen[5] [sic] preparations may account for the difference" (p. 76, c. 3, ¶1). Also note that selective prescribing and more complete control for confounding may explain these results.

Figure 4 from the original publication is reproduced on the next page. This figure summarizes results associated with various cofactors. The authors noted no statistical interaction in the relative risk by any of these cofactors, i.e., "the relative stroke risk with OC use was minimally affected by the presence of other risk factors" (p. 74, c. 3, ¶3).

[5] "Estrogen" should read "progestin".

Figure 4. Influence of Study Characteristics on Estimation of Relative Risk (and 95% Confidence Intervals [CIs]) of Oral Contraceptives (OCs) for Ischemic Stroke

Data Stratifications	No. of Studies	Relative Risk (95% CI)
Overall	16	2.75 (2.24-3.38)
Estrogen dose		
High (>50 µg)	4	4.53 (2.17-9.50)*
Medium (50 µg)	5	2.78 (2.00-3.85)*
Low (<50 µg)	7	2.08 (1.55-2.80)
Progesterone type†		
First generation	3	3.21 (2.16-4.77)*
Second generation	3	3.05 (2.37-3.91)*
Third generation	3	2.11 (0.96-4.64)
Control for risk factors in study design		
Smoking		
Yes	11	2.55 (2.07-3.14)
No	5	4.27 (2.34-7.82)*
Hypertension		
Yes	11	2.58 (2.08-3.22)
No	5	3.56 (2.05-6.18)*
Smoking and hypertension		
Yes	9	2.52 (2.01-3.16)
No	7	3.75 (2.39-5.91)*
Alcohol use		
Yes	4	2.66 (1.63-4.33)*
No	12	2.77 (2.18-3.51)
Study design type		
Cohort	3	3.21 (1.96-5.27)*
Case-control	14	2.77 (2.22-3.45)
Population controls	9	2.34 (1.67-3.27)
Hospital controls (includes outpatient controls)	8	4.32 (3.11-6.02)
Exposure classification		
Current vs noncurrent use	14	2.77 (2.22-3.44)
Current vs never use	7	2.03 (1.47-2.82)
Ever vs never use	3	1.37 (0.60-3.11)
Past vs never use	9	0.86 (0.69-1.08)*
Independent effect of OC use among:		
Smokers	7	3.41 (2.51-4.63)*
Nonsmokers	7	2.68 (2.09-3.43)*
With history of hypertension	3	1.73 (0.83-3.60)
Without history of hypertension	5	2.47 (1.80-3.38)
With migraine history	4	3.22 (1.45-7.16)
Without migraine history	4	2.30 (0.74-7.18)
Age <35 y	7	2.41 (1.42-4.09)
Age ≥35 y	7	2.23 (1.42-3.50)
Low-dose OCs (<50 µg)		
Study design control for smoking and hypertension	6	2.04 (1.51-2.76)
Population-based studies controlling for smoking and hypertension	5	1.93 (1.35-2.74)



Hormonal Contraceptives and Venous Thromboembolic Events

There are no recent review articles on the topic of venous thromboembolism associated risks. Accordingly, I have compiled a comprehensive summary table of all relevant studies. Duplication is avoided in this table: in circumstances where the results of a study are published in multiple articles, the most recent or complete publication is cited.

This body of literature spanning almost four decades is consistent in demonstrating a positive association between estrogen dose and risk. The dose-response relation in the dose range above 50 µg was established in the 1970s (Inman et al., 1970; Stolley et al., 1975, Bottiger et al., 1980). The dose-response relationship into below 50 µg estrogen was established more recently (Vessey et al., 1986; Gerstman et al., 1991; WHO, 1995; Lewis et al., 1999; Lidegaard et al., 2002).

TABLE. Epidemiological studies of estrogen-related VTE risk.

Study	Type	Period and population	Relative Risk estimates	Notes
Grant, E. C. (1969). Venous effects of oral contraceptives. *Br Med J*, 4(5675), 73-77.	Clinical trial	1960s UK (the article is not clear about the time period)		Difficult to calculate risks based on reported information (Table III and Table IV) but authors note in several places the problems with "tablets containing 0.075 and 0.09 mg of ethinyl estradiol, e.g., "Vein complaints, leg cramps and thrombophlebitis were significantly more frequent with the combined preparations that contained a relative low dose of progestin and a high dose of oestrogen than the other groups tested" (p. 73, c1. ¶1).
Inman, W. H., Vessey, M. P., Westerholm, B., & Engelund, A. (1970). Thromboembolic disease and the steroidal content of oral contraceptives. A report to the Committee on Safety of Drugs. *Br Med J*, 2(5703), 203-209.	Surveillance	1965–69, UK 1968–69, Sweden & Denmark	>50µg vs. 50µg formulations: *RR* = 2.5 (chi-square 14.2 with 1 df; Table III on p. 205)	This study was competed before low dose oral contraceptives were available. The *RR* for 100 mcg EE vs. 50 mcg EE COCs was 2.5 for VTE and was 2.1 for MI (Table VII, p. 209). There were not enough cases to evaluate cerebral events. Data were analyzed separately for RR for ethinyl estradiol and mestranol formulations.
Stolley, P. D., Tonascia, J. A., Tockman, M. S., Sartwell, P. E., Rutledge, A. H., & Jacobs, M. P. (1975). Thrombosis with low-estrogen oral contraceptives. *Am J Epidemiol*, 102(3), 197-208.	Case-control	1970–73, U.S., hospital based	Use vs. non-use: *OR* = 7.2 ≥100µg vs. non-use *OR* = 10.1 (4.7–21.7) <100µg vs. non-use *OR* = 4.7 (2.7– 8.2) For idiopathic cases	Although cases included both venous and myocardial events, more than 90% of cases were VTEs. Less than 8% of events were myocardial, about 2% were other systematic embolism (Table 2, p. 199). Use of low dose formulations was rare at the time.

Study	Type	Period and population	Relative Risk estimates	Notes
Bottiger, L. E., Boman, G., Eklund, G., & Westerholm, B. (1980). Oral contraceptives and thromboembolic disease: effects of lowering oestrogen content. *Lancet*, 1(8178), 1097-1101.	Surveillance and vital statistics	1966–70, Sweden	>50 µg vs. ≤50 µg *RR* = 1.44 (*P* < .001) Information extrapolated from Figure 2 and Table 9	This early study pieced together vital statistics, morbidity data, oral contraceptive sales data, and spontaneous reports of adverse reaction. The writing is hard to follow at times. Evidence of a dose-response is based primarily on parallel (ecological) declines in estrogen content the identified outcomes identified. For example, the reported rate of thromboembolism dropped from 25.9 per 100000 users in 1966−70 (the period when 50+ mcg formulations were marketed) to 7.2 in 1974-77 (after formulations with more than 50 µg were eliminated).
Vessey, M., Mant, D., Smith, A., & Yeates, D. (1986). Oral contraceptives and venous thromboembolism: findings in a large prospective study. *British Medical Journal (Clin Res Ed)*, 292(6519), 526.	Cohort	1968–86, UK (Oxford)	*RR*s based on reported rates: 50 µg: 10.0 <50 µg: 6.5 none: 1 (referent) *Rates* per 1000 woman-years: 50 µg: 0.62 <50 µg: 0.39 none: 0.06	"Our findings are consistent with the view that the risk is lower with pills containing < 50 mcg oestrogen, but the data are too few to confirm this" (p. 526, c. 2, para. 2).
Helmrich, S. P., Rosenberg, L., Kaufman, D. W., Strom, B., & Shapiro, S. (1987). Venous thromboembolism in relation to oral contraceptive use. *Obstet Gynecol*, 69(1), 91-95.	Case-control	1976–83, N. American cities	*RR*s (95% CIs) compared to non-use. >50µg: 11 (3.9–30) 50 µg: 5.5 (2.1–15) <50µg: 11 (3.7–32)	The authors' conclude "Confidence intervals were wide, however, so that a reduction in the risk in users of lower dose formulations relative to users of higher dose formulations cannot be ruled out." (p. 91, c. 1. para 1/abstract).
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.	Cohort	1980–86, U.S. (Michigan)	>50µg: 1.7 (0.9–3.0) 50 µg: 1.5 (1.0–2.1) <50 µg: 1 (referent) When restricted to confirmed cases, >50µg: 3.2 50 µg: 2.0 <50 µg: 1 (referent) Rates (per 10,000 woman-years) >50µg: 10 50 µg: 7.0 <50 µg: 4.2	The study was designed to be conservative in its risk estimates, with biases designed toward the null. A similar study based in the same population and published in the *International Journal of Epidemiology* (1990) found a dose-response relationship between estrogen potency and VTE but found no relationship between progestin potency and VTE.

Study	Type	Period and population	Relative Risk estimates	Notes
Thorogood, M., Mann, J., Murphy, M., & Vessey, M. (1992). Risk factors for fatal venous thromboembolism in young women: a case-control study. *International Journal of Epidemiology*, 21(1), 48–52.	Case-control	1986–88, England and Wales	For idiopathic fatalities: *OR* = 2.1 (0.8–5.2)	Although this study included no direct head-to-head comparisons by estrogen dose, the authors concludes "risks are considerably smaller than those observed in previous studies. The observed risk may be low because the dosage of oestrogen in modern oral contraceptive preparations has been reduced, but it may also be because the cases of fatal venous thromboembolism included in this study represented only a small proportion of all cases of venous thromboembolism" (p. 48).
World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. (1995). Venous thromboembolic disease and combined oral contraceptives: results of international multicentre case-control study. *Lancet*, 346(8990), 1575–82.	Case-control	1989–93, European and non-European centers reported separately; 20– 40 year-olds	Relative risks by estrogen dose and progestin generation as reported in Table 7 on p. 1579: Europe, 1st gen.: ≥50µg estrogen: 4.1 <50µg estrogen: 3.4 non-use: 1 (referent) Europe, 2nd gen.: ≥50µg estrogen: 3.8 <50µg estrogen: 3.6 non-use: 1 (referent) Non-European, 1st gen.: ≥50µg estrogen: 3.6 <50µg estrogen: 0 (no exposed cases) non-use: 1 (referent) Non-European, 2nd gen.: ≥50µg estrogen: 3.8 <50µg estrogen: 2.8 non-use: 1 (referent)	This study focused on progestins type and thromboembolism and other risk factors (including estrogen dose). Given the time frame of the study, it is unclear to what extent cases were associated with formulations contain more than 50 µg of estrogen. Use of formulations with >50 µg estrogen were rare at the time. (See notes about the Transnational Study by Lewis 1999, below). The authors concluded: "…risks estimates among users of first and second generation progrestagens were slightly larger when used in combination with a higher rather than with a low oestrogen dose" (p. 1579, c. 1, ¶ 4).
Lewis, M. A., MacRae, K. D., Kuhl-Habichl, D., Bruppacher, R., Heinemann, L. A., & Spitzer, W. O. (1999). The differential risk of oral contraceptives: the impact of full exposure history. *Human Reproduction*; 14(6), 1493–9. ["Transnational Study"]	Case-control	1993–95, Germany & UK	50µg vs. 30-40 µg* *OR* = 2.89 (95% CI: 1.04 - 8.01)	* Dr. Lewis confirms a technical and typographical errors in Table 7 (p. 1497). Dr. Lewis writes "having unearthed the original DB, we find that there are no > 50 EE2 products in this population. Therefore the error is entirely in my designation of 1st gen products as > (=) 50 EE2 in this and other papers" (4/7/08 email). Therefore, references to ">50 µg EE" but should read "50 EE" throughout this article. With reference to progestin type: after controlling for the cohort effect, duration of use, and other known determinants (including estrogen dose), the apparent increase in risk associated with third generation progestins was negated.

Study	Type	Period and population	Relative Risk estimates	Notes
Lidegaard, O., Edstrom, B., & Kreiner, S. (2002). Oral contraceptives and venous thromboembolism: a five-year national case-control study. *Contraception*, 65(3), 187-196.	Case-control	1994–98, Denmark	*OR*s (95% CIs) 50µg EE: 1.6 (0.9 - 2.8) 30–40 µg EE: 1.0 (referent) 20 µg EE: 0.6 (0.4-0.9) Test for trend *P* = .02	The study had good control of potential confounders and progestin type. It addressed duration of use and potential interactions. The authors state "There was generally no interaction or effect modification between the identified risk factors and OC use. This finding principally indicates that the total risk among women with combined risk factors corresponds to a multiplication of the *OR*s for the separate risk factors" (p. 192, c. 1, ¶1). They also state "after correction for progestin types and length of use, a very clear dose-response relationship between estrogen dose and risk of VTE was demonstrated. The explanation is primarily that many users of older, high-dose pills have taken the pills for many years and , secondly, that they contain older progestin types"
Evra Trial (Sibai et al., 2002; FDA Medical Officer's Review, NDA 21-180, P. 43)	Clinical trial			Two cases observed (one idiopathic) during approximately 1706 woman-years of exposure. Expected number of cases ≈ 0.15 (roughly). No non-exposed cases.
Boston Collaborative Drug Surveillance Program studies comparing VTE risk in Ortho Evra users to COCs	Nested case-control	2002–06 U.S., (Pharmetrics)	Ortho Evra vs. COC w/35µg EE + NORG: *OR* = 1.23 (0.9–1.8) Ortho Evra vs. vs. 30µg EE + LEVO: *OR* = 2.0 (0.9–4.1)	This study is reviewed extensively in my prior opinion. PK show that the Ortho Evra delivers about 60% more estrogen than a low dose combination oral contraceptive; on average total dose is comparable to that of a 56 µg of combination oral contraceptive.
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.	Nested case-control	2002–04, U. S., (UnitedHealth Care)	Ortho Evra vs. COCs w/ "low dose" EE + NORG: *OR* = 2.4 (1.1–5.5) Rates (per 10,000): Ortho Evra: 4.1 COC: 1.8	This study is reviewed extensively in my prior opinion.
Lidegaard, O., Lokkegaard, E., Svendsen, A. L., & Agger, C. (2008, May 2, 2008). Hormonal contraception and risk of venous thromboembolism: Dose reduction matters. European Society of Contraception, Copenhagen.	Case-control	1995–2005; Denmark		Conference proceedings abstract; full article pending. "The risk also decreased significantly with decreasing dose of estrogen."