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## Systematic review and meta-analysis of the association of combined oral contraceptives on the risk of venous thromboembolism: The role of the progestogen type and estrogen dose

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### Abstract

**Introduction:** Currently available combined oral contraceptives (COC) reportedly increase the risk of venous thromboembolism (VTE). We aimed to quantify this risk considering both progestogen type and estrogen dose.

**Materials and Methods:** PubMed, Embase and LIVIVO were searched for relevant publications until April 2017. Case-control and cohort studies including healthy women taking COC and assessing incident VTE as outcome were selected. Adjusted relative risks (RR) with 95% confidence intervals (CI) derived from random effects model using a generic inverse-variance approach are reported.

**Results:** Overall, 1,359 references were identified and 17 studies were included in the meta-analysis. The pooled RR of VTE was associated with various COC, with the association depending on their respective estrogen dose and progestogen type. Compared to the reference, levonorgestrel with 30-40 µg ethinylestradiol, the overall risk of VTE was higher for all other COC. Preparations with desogestrel with 30-40 µg estrogen showed the highest relative risk (RR: 1.46; 95% CI: 1.33-1.59), while RRs for drospirenone (30-40 µg ethinylestradiol) and desogestrel (30-40/20 µg ethinylestradiol) were lower. COC containing gestodene and cyproterone with 30-40 µg estrogen showed the lowest risk (RR: 1.27; 95% CI: 1.15-1.41 and RR: 1.29; 95% CI: 1.12-1.49, respectively).

**Conclusions:** Compared to levonorgestrel with 30-40 µg ethinylestradiol, all COC showed a significantly increased VTE risk. The association varied depending on the progestogen type and the dose of estrogen. Our results suggest that the prescription of COC with the lowest possible dose of ethinylestradiol may help to avoid VTE cases among young, healthy women.

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