

## Systematic review with meta analysis

# The risk of arterial thrombosis increases with the use of combined oral contraceptives

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Commentary on: Roach RE, Helmerhorst FM, Lijfering WM, *et al.* Combined oral contraceptives: the risk of myocardial infarction and ischemic stroke. *Cochrane Database Syst Rev* 2015;8:CD011054.

## Context

While the risk of venous thrombosis with use of combined oral contraceptives (COC) is now convincingly quantified to be threefold to sixfold increased, depending mainly on the type of progestogen, there are few and less consistent studies on the risk of arterial endpoints. Therefore, a meta-analysis on available evidence might be relevant.

## Method

This Cochrane review includes data from 24 studies assessing the risk of thrombotic stroke and/or myocardial infarction in women of reproductive age using COC as compared with non-users. Criteria for including and excluding studies were specified, as was information on categorising the studies' risk of bias in ascertainment of exposure and assessment of end points.

## Findings

The analysis included 23 case-control studies together with 4631 (48%) events included, and 1 cohort study with 5036 (52%) events. The meta-analysis concludes that low dose (<50 µg oestrogen) COC do not confer an increase of thrombotic stroke and they do not raise the risk for myocardial infarction, and different progestogens do not confer a differential risk, however, the analysis does state that high oestrogen dose COC (50 µg oestrogen) may double the risk of arterial thrombosis; relative risk=2.0 (1.3 to 2.9).

## Commentary

In a field of 24 studies, with a single study accounting for more than half of the included events, it is relevant to ask what a meta-analysis adds as compared to the one big study mentioned above. First, the large cohort study assessed exposures daily through a 15-year period,<sup>1</sup> whereas 22 of the 23 others were case-control studies assessing the exposure retrospectively (one was a nested case-control study). Next, young women suspected for thrombotic stroke or myocardial infarction are generally extensively examined, with relatively clear criteria for judging whether the event is real. Therefore, the outcome diagnoses in this age group are generally fairly valid.

The results of the cohort study, nevertheless, differed from the conclusion of the meta-analysis by concluding that COC conferred a significantly increased relative risk of ischaemic stroke increasing from 1.6 (1.4 to 1.9) for COC with 20 µg oestrogen, over 1.8 (1.6 to 1.9) with 30–40 µg oestrogen, to 2.0 (1.5 to 2.7) with COC with 50 µg oestrogen, the latter estimate in accordance with the meta-analysis.

Therefore, a substantial part of the 23 case-control studies must have found a protecting influence from COC on the risk of thrombotic stroke and myocardial infarction to achieve an overall RR of about unity. The problem is that all of the studies included in the meta-analysis found OR of thrombotic stroke from COC substantially above 1, and typically between 2 and 4. Therefore, the overall estimate of the risk of thrombotic stroke with use of COC in the meta-analysis is incompatible with the results of the included studies.

There are also some inconsistencies with the bias table. According to the Method section, 'first, exposure to COC had to be confirmed through a prescription database in order for the risk of bias to be classified as low'. Nevertheless, the Danish cohort study with such an ascertainment was classified as a study with a 'high risk' of bias. The same study was classified as having a high risk of bias in the outcome assessment; despite all women in Denmark, suspected for thrombotic stroke, go through CT and/or MR examinations.

## Implications for practice

The influence of COC on the risk of thrombotic stroke is significant and in the order of 50–100% increased for low-dose COC. There are no consistent differences according to the progestogen type. Therefore, the total thrombotic risk with use of COC is mainly a result of the substantially increased risk of venous thromboembolism. Women generally are advised to use COC with first-generation or second-generation progestogens, which include norethisterone, levonorgestrel or norgestimate, with the lowest possible dose of oestrogen.

Competing interests None declared.

Provenance and peer review Commissioned; internally peer reviewed.

## Reference

1. Lidegaard Ø, Løkkegaard E, Jensen A, *et al.* Thrombotic stroke and myocardial infarction with hormonal contraception. *N Engl J Med* 2012;366:2257–66.