

# Comparison of risk of pulmonary embolism and arterial thromboembolism with oral contraceptives according to dose and type of estrogen-progestin

## Question

In women taking combined oral contraceptives, consisting of an estrogen and progestin, which type is associated with the lowest risk of pulmonary embolism, ischemic stroke, and myocardial infarction?

## The study

**Who?** The study included almost 5 million women in France, aged 15 to 49 years, who received at least one prescription for an oral contraceptive pill and had no history of pulmonary embolism (PE), ischemic stroke, myocardial infarction, or cancer.

**What?** Women were followed from the time of first prescription for an oral contraceptive pill until one of the following events occurred: discontinuation of oral contraceptive pill; hospital discharge for pulmonary embolism, ischemic stroke, myocardial infarction, or cancer; onset of pregnancy; age 50 years; hospital discharge after orthopedic leg surgery or gynecologic surgery; death; or end of study period (about 2 years).

## What the researchers found

For any given combined oral contraceptive pill, those with a lower dose of estrogen (20 µg versus 30 to 40 µg) were associated with a lower risk of venous and arterial thromboembolism, regardless of the progestin type. The combination of 20 µg estrogen with levonorgestrel had the lowest overall risk for pulmonary embolism and arterial thromboembolism.

## The bottom line

In women using a combined oral contraceptive pill, a lower dose of estrogen was associated with a lower risk of pulmonary embolism and arterial thromboembolism.

## Summary of findings

Effects of combined oral contraceptive type (estrogen–progestin dose) on pulmonary embolism, ischemic stroke, and myocardial infarction

Comparison	Relative risk reduction or increase (95% CI)*			Composite events
	Pulmonary embolism	Ischemic stroke	Myocardial infarction	
<b>Estrogen dose</b>				
20 µg vs 30 to 40 µg	25% reduced risk (15 to 33)	18% reduced risk (4 to 30)	44% reduced risk (21 to 61)	26% reduced risk (18 to 33)
<b>Progestin, estrogen dose vs levonorgestrel, 30/40 µg† (# of women)</b>				
Levonorgestrel, 20 µg (759, 868)	27% reduced risk (11 to 40)	32% reduced risk (14 to 47)	72% reduced risk (47 to 87)	35% reduced risk (24 to 45)
Desogestrel, 20 µg (688,220)	60% increased risk (41 to 82)	NS	NS	22% increased risk (10 to 35)
Desogestrel, 30 µg (651,656)	118% increased risk (93 to 147)	20% reduced risk (1 to 36)	NS	52% increased risk (36 to 69)
Gestodene, 20 µg (237,788)	34% increased risk (6 to 87)	28% reduced risk (1 to 50)	72% reduced risk (34 to 99)	NS
Gestodene, 30 µg (164,196)	43% increased risk (7 to 87)	NS	NS	NS
Norethisterone, 35 µg (81,051)	44% reduced risk (17 to 65)	NS	NS	25% reduced risk (4 to 42)

	Relative risk reduction or increase (95% CI)*			
Comparison	Pulmonary embolism	Ischemic stroke	Myocardial infarction	Composite events
Norgestrel, 50 µg (71,172)	66% increased risk (14 to 134)	113% increased risk (50 to 194)	150% increased risk (45 to 299)	100% increased risk (57 to 151)

CI = confidence interval; NS = not significant.

\*Adjusted for age, complementary universal health insurance, medical risk factors, gynecologic visits in past year, and type of progestin.

†Most commonly prescribed oral contraceptive in France ( $n = 2,882,313$ ).

*This Evidence Summary is based on a study by Weill A, Dalichampt M, Raguideau F, et al. **Low dose oestrogen combined oral contraception and risk of pulmonary embolism, stroke, and myocardial infarction in five million French women: cohort study.** BMJ. 2016 May 10;353:i2002. PubMed (<https://www.ncbi.nlm.nih.gov/pubmed/27164970?dopt=Abstract>)*

### Which combined oral contraceptive pill has the lowest risk of pulmonary embolism, ischemic stroke and myocardial infarction?

Millions of women worldwide receive oral contraceptive pills for birth control or to control excessive menstrual bleeding. Use of oral contraceptives is associated with a small but important increased risk of pulmonary embolism, as well as stroke and myocardial infarction.

This study of more than 5 million women looked at the risk of developing these thrombotic events in association with 8 different types of combined oral contraceptive pills available in France. The estrogen component was the same (ethinyl estradiol), but in doses varying from 20 to 50 µg and the progestin component was 1 of 4 different types.

The investigators made 2 important observations:

1. Oral contraceptive pills with a higher estrogen dose (30 to 40 µg) were associated with an increased risk for thrombosis compared with lower estrogen doses (20 µg).
2. The risk of pulmonary embolism was higher when low-dose estrogen was combined with desogestrel or gestodene compared with levonorgestrel.

The first observation supports what others have already observed about the dose-dependent association of risk of thrombosis with estrogen. The second observation suggests that while estrogen is key to thrombotic risk, the type of progestin may also be a

contributing factor.

There are important limitations to this population-based cohort study that must be considered. Data on why a particular oral contraceptive pill was selected and on additional risk factors such as family history of thrombosis or smoking were not available in the database. Furthermore, the study duration was likely too short to capture arterial thrombotic events such as myocardial infarction. More important, deep vein thrombosis (DVT) was not included as an outcome because the database included only hospital-based events. Failure to collect these data should not affect the comparisons between drugs, but it will have resulted in an underestimation of the overall incidence of venous thromboembolism because DVT is diagnosed more often than PE.

Despite these limitations, this large study provides useful estimates of the thrombotic risk for combined oral contraceptives and suggests that the overall thrombotic risk is small (ranging from 7 to 33 in 100,000 women taking combined oral contraceptive pills for 1 year). It also confirms the association between oral contraceptive pill-associated thrombosis and age: About 1 in 4 thrombotic events occurred in women over 35 years of age.

**Doctor, I have heard that the birth control pill (oral contraceptive pill) can cause blood clots. Is it safe for me to take one?**

The risk of forming a blood clot when taking an oral contraceptive pill is low. About 1-2 out of 10,000 women who take the pill for 1 year will be diagnosed with a blood clot in their lungs or have a heart attack or stroke. To keep this risk as low as possible, we recommend you start with the pill containing the lowest dose of hormones, particularly estrogen.

However, it is important to understand that the risk of blood clots while taking the pill maybe higher if you are over 35 years of age, smoke, or have family members who have had blood clots. Women who have these additional risk factors may wish to discuss their options with a gynecologist.

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