

Prescribe This Combined OC With CV Safety in Mind

With a variety of formulations available, which combined oral contraceptive should you recommend to minimize risk for not only pulmonary embolism, but also stroke and myocardial infarction?

Yee Lam, MD, PhD, Catherine Coe, MD, Anne Mounsey, MD

Yee Lam,
Catherine Coe,
and **Anne Mounsey**
are in the Department
of Family Medicine at
the University of North
Carolina School of
Medicine, Chapel Hill.

PRACTICE CHANGER

When prescribing combined oral contraceptives, choose one containing levonorgestrel and low-dose estrogen (20 µg) to minimize risk for pulmonary embolism, ischemic stroke, and myocardial infarction.

STRENGTH OF RECOMMENDATION

B: Based on a good-quality, patient-oriented cohort study.¹

A 28-year-old woman presents to your office for a routine health maintenance exam. She is currently using an oral contraceptive containing desogestrel and ethinyl estradiol for contraception and is inquiring about a refill for the coming year. What would you recommend?

When choosing a combined oral contraceptive (COC) for a patient, clinicians often have tried-and-true favorites. However, some of them may be placing patients at increased risk for venous thromboembolic events.

In general, when compared with nonusers, women who use COCs have a two- to four-fold increase in risk for venous thromboembolism (VTE) and an increased risk for myocardial infarction (MI) and stroke.^{2,3} More specifically, higher doses of estrogen combined with the progesterones gestodene, desogestrel, and levonorgestrel, are associated with a higher risk for VTE.²⁻⁶

In 2012, the European Medicines Agen-

cy warned that COCs containing drospirenone were associated with a higher risk for VTE than other preparations, despite similar estrogen content.⁷ The FDA produced a similar statement that same year, recommending that providers carefully consider the risks and benefits before prescribing contraceptives containing drospirenone.⁸


The risks for ischemic stroke and MI have not been clearly established for varying doses of estrogen and different progestones. This large observational study fills that informational gap by providing risk estimates for the various COC options.

STUDY SUMMARY

One COC comes out ahead

The authors used an observational cohort model to determine the effects of different doses of estrogen combined with different progestones in COCs on the risks for pulmonary embolism (PE), ischemic stroke, and MI.¹ Data were collected from the French national health insurance database and the French national hospital discharge database.^{9,10} The study included nearly 5 million women ages 15 to 49, living in France, who had at least one prescription filled for COCs between July 2010 and September 2012.

The investigators calculated the absolute and relative risks for first PE, ischemic stroke, and MI in women using COC formulations containing either low-dose estrogen (20 µg) or high-dose estrogen (30-40 µg) combined with one of five progestones (norethisterone, norgestrel,

 **Is your “go to” choice for oral contraception putting your patient at risk for thromboembolism?**



levonorgestrel, desogestrel, gestodene). The relative risk (RR) was adjusted for confounding factors, including age, complimentary universal health insurance, socioeconomic status, hypertension, diabetes, and consultation with a gynecologist in the previous year.

The absolute risk per 100,000 woman-years for all COC use was 33 for PE, 19 for ischemic stroke, and 7 for MI, with a composite risk of 60. The RRs for low-dose estrogen vs high-dose estrogen were 0.75 for PE, 0.82 for ischemic stroke, and 0.56 for MI. The absolute risk reduction (ARR) with low-dose estrogen vs high-dose estrogen was 14/100,000 person-years of use; the number needed to harm (NNH) was 7,143.

Compared with levonorgestrel, desogestrel and gestodene were associated with higher RRs for PE but not arterial events (2.16 for desogestrel and 1.63 for gestodene). For PE, the ARR with levonorgestrel compared to desogestrel and gestodene, respectively, was 19/100,000 and 12/100,000 person-years of use (NNH, 5,263 and 8,333, respectively). The authors concluded that for the same progesterone, using a lower dose of estrogen decreases risk for PE, ischemic stroke, and MI, and that oral contraceptives containing levonorgestrel and low-dose estrogen resulted in the lowest overall risks for PE and arterial thromboembolism.

WHAT'S NEW?

Low-dose estrogen + levonorgestrel confer lowest risk

Prior studies have shown that COCs increase the risk for PE and may also increase the risks for ischemic stroke and MI.^{3,11} Studies have also suggested that a higher dose of estrogen in COCs is associated with an increased risk for VTE.^{11,12} This study shows that 20 µg of estrogen combined with levonorgestrel is associated with the lowest risks for PE, MI, and ischemic stroke.

CAVEATS

Cohort study, no start date, incomplete tobacco use data

This is an observational cohort study, so it is subject to confounding factors and bi-

ases. It does, however, include a very large population, which improves validity. The study did not account for COC start date, which may be confounding because the risk for VTE is highest in the first three months to one year of COC use.¹² Data on tobacco use, a significant independent risk factor for arterial but not venous thromboembolism, was incomplete; however, in other studies, it has only marginally affected outcomes.^{3,13}

CHALLENGES TO IMPLEMENTATION

Increased vaginal spotting

One potential challenge to implementing this practice changer may be the increased rate of vaginal spotting associated with low-dose estrogen. COCs containing 20 µg of estrogen are associated with spotting in approximately two-thirds of menstrual cycles over the course of a year.¹⁴ That said, women may prefer to endure the spotting in light of the improved safety profile of a lower-dose estrogen pill.

REFERENCES

1. 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;353:i2002.
2. Lidegaard Ø, Løkkegaard E, Svendsen AL, et al. Hormonal contraception and risk of venous thromboembolism: national follow-up study. *BMJ*. 2009;339:b2890.
3. Lidegaard Ø, Løkkegaard E, Jensen A, et al. Thrombotic stroke and myocardial infarction with hormonal contraception. *N Engl J Med*. 2012;366:2257-2266.
4. Stegeman BH, de Bastos M, Rosendaal FR, et al. Different combined oral contraceptives and the risk of venous thrombosis: systematic review and network meta-analysis. *BMJ*. 2013;347:f5298.
5. FDA. Combined hormonal contraceptives (CHCs) and the risk of cardiovascular disease endpoints. www.fda.gov/downloads/drugs/drugsafety/ucm277384. Accessed July 5, 2017.
6. Seeger JD, Loughlin J, Eng PM, et al. Risk of thromboembolism in women taking ethinyl estradiol/drospirenone and other oral contraceptives. *Obstet Gynecol*. 2007;110:587-593.

continued on next page >>

>> continued from previous page

7. European Medicines Agency. PhVWP monthly report on safety concerns, guidelines and general matters. 2012. www.ema.europa.eu/docs/en_GB/document_library/Report/2012/01/WC500121387.pdf. Accessed July 5, 2017.
8. FDA. FDA Drug Safety Communication: Updated information about the risk of blood clots in women taking birth control pills containing drospirenone. 2012. www.fda.gov/Drugs/DrugSafety/ucm299305.htm. Accessed July 5, 2017.
9. Tuppin P, de Roquefeuil L, Weill A, et al. French national health insurance information system and the permanent beneficiaries sample. *Rev Epidemiol Sante Publique*. 2010;58:286-290.
10. Moulis G, Lapeyre-Mestre M, Palmaro A, et al. French health insurance databases: what interest for medical research? *Rev Med Interne*. 2015;36:411-417.
11. Farmer RD, Lawrenson RA, Thompson CR, et al. Population-based study of risk of venous thromboembolism associated with various oral contraceptives. *Lancet*. 1997;349:83-88.
12. Lidegaard Ø, Nielsen LH, Skovlund CW, et al. Risk of venous thromboembolism from use of oral contraceptives containing different progestogens and oestrogen doses: Danish cohort study, 2001-9. *BMJ*. 2011;343:d6423.
13. Zhang G, Xu X, Su W, et al. Smoking and risk of venous thromboembolism: a systematic review. *Southeast Asian J Trop Med Public Health*. 2014;45:736-745.
14. Akerlund M, Røde A, Westergaard J. Comparative profiles of reliability, cycle control and side effects of two oral contraceptive formulations containing 150 micrograms desogestrel and either 30 micrograms or 20 micrograms ethinyl oestradiol. *Br J Obstet Gynaecol*. 1993;100:832-838.

ACKNOWLEDGEMENT

The PURLs Surveillance System was supported in part by Grant Number UL1RR024999 from the National Center For Research Resources, a Clinical Translational Science Award to the University of Chicago. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Center For Research Resources or the National Institutes of Health.

Copyright © 2017. The Family Physicians Inquiries Network. All rights reserved.

Reprinted with permission from the Family Physicians Inquiries Network and *The Journal of Family Practice* (2017;66[7]:454-456).