

Yaz® and Yasmin®: Risk of VTE

Take Away Points:

- *The recent media on drospirenone-containing combined oral contraceptives is **not based on any new evidence***
- ***Higher quality epidemiological studies have not found an increase in venous thromboembolism risk with drospirenone-containing combined oral contraceptives compared to other combined oral contraceptives; however, several studies of lower quality have found an increased risk.***
- *If an increased risk truly exists with drospirenone-containing combined oral contraceptives, it is estimated to be about 1.5 to 3 times that of other combined oral contraceptives, which is still considerably **lower than the risk of venous thromboembolism associated with pregnancy and the postpartum period.***
- ***Drospirenone-containing combined oral contraceptives offer no established advantage to other combined oral contraceptives for conditions such as acne and premenstrual syndrome.***

Recent media reports are citing, once again, increased risks of venous thromboembolism (VTE) with drospirenone-containing combined oral contraceptives (COCs) compared to COCs containing other progestins. However, this media attention is not based on new evidence. Instead, the reports were triggered by Tony Merchant, a class-action lawyer in Regina, who recently supplied the media with a published report from Canada Vigilance. This report collated the adverse reactions reported to Canada Vigilance in which drospirenone was the suspected cause. Of these reports, 23 resulted in death.¹

Adverse reaction reports linking drospirenone use to death must be taken very seriously. However, while the Canada Vigilance program is an important tool for identifying signals about adverse drug reactions in the post-marketing period, its findings cannot be evaluated in isolation. Canada Vigilance reports are generated when an adverse drug reaction is suspected, but they do not have to be confirmed. Also, these reports do not consider the denominator – that is, the total number of people who have taken the drug across the country. As a result, the actual level of risk relating to drospirenone (if any) cannot be determined from these reports alone.

Ideally, the risks associated with drospirenone would be answered with a randomized-controlled trial (RCT). This study design minimizes the influence of confounding variables in order to determine the real effect of the drug in question. However, these designs are not feasible to identify rare adverse effects because researchers would need to recruit an enormous number of subjects. Therefore, prospective epidemiological studies provide the strongest evidence for rare adverse effects of commonly used medications.²

Two prospective epidemiological studies (including 5-year follow up)³⁻⁵ did not find an increased risk of adverse events with drospirenone-containing COCs compared to either levonorgestrel-containing^{3,5} or any other COC.⁴ In

contrast, increased risks of drospirenone containing COCs have been reported in all but two of the published studies using retrospective designs.⁶⁻¹⁵ The increased risk estimated by the other studies ranged from 1.45- to 3.3-fold.^{6,7,9-11}

On the basis of these data, Health Canada issued the following Advisory in 2011: “Overall, the body of current evidence suggests that the risk of blood clots is 1.5 to 3 times higher with oral contraceptives that contain drospirenone relative to those that contain levonorgestrel, a different hormone.¹⁶ No new information has emerged to modify this advisory.

The next step is to put this into perspective. When baseline risks are very small, even three-fold increases do not amount to a large proportion of added events. For instance per 10 000 women years of exposure to drospirenone, the following number of VTEs have been estimated:¹⁷

Estimated Rates of VTE in Women According to Risk	
Risk Factor	# per 10 000 women years
Non-pregnant, non COC user	1 to 5 ¹⁷
Non-drospirenone containing COC user	3 to 9 ¹⁷
Drospirenone containing COC user	3 to 14 ¹⁸
Pregnancy	5 to 20 ¹⁷
Postpartum (12 weeks only)	40 to 65 ¹⁷

These estimates suggest VTE risk is highest in pregnancy and preventing unwanted pregnancies through the use of COCs does help reduce overall VTE risk. It is also worth noting that the chance of VTE is highest within the first month of starting a COC, so those who discontinue a COC and then restart more than a month after discontinuation, will again face the elevated risk of the first month.¹⁹ Therefore, ‘pill scare’ may result in higher VTE risk through unwanted pregnancies and/or interruption of use.

Finally, while drospirenone-containing COCs are indicated for acne as well as contraception, there is no evidence that these oral contraceptives are any more effective than COCs containing other progestins.²⁰ There is also no evidence drospirenone-containing COCs are superior to other COCs for premenstrual syndrome.²¹ Therefore, if a patient wishes to switch to another form of contraception, encourage she start the new contraceptive without interruption.

When asked to switch/discontinue:

- The usual risk versus benefit considerations should be applied on an individual basis.
- Explain the risk of all COCs in the context of VTE and that we still don't know if drospirenone does impart a greater risk than other COCs. Explain risk of VTE is higher during pregnancy/postpartum than from any type of COC; discontinuing the COC risks unwanted pregnancy.
- If patient wants to switch, ensure a smooth transition to avoid an interruption of hormonal contraception > 1 month.

References:

1. CBC News. Yaz, Yasmin birth control pills suspected in 23 deaths. [2013 Jun 11; cited 2013 Jun 12] Available at <http://www.cbc.ca/news/canada/british-columbia/story/2013/06/11/birth-control-pills-yaz-yasmin.html>
2. Berlin JA, Glasser SC, Ellenberg SS. Adverse event detection in drug development: recommendations and obligations beyond phase 3. *Am J Public Health*. 2008; 98(8): 1366-71
3. Dinger JC, Heinemann LA, Kuhl-Habich D. The safety of a drospirenone-containing oral contraceptive: final results from the European Active Surveillance Study on oral contraceptives based on 142,475 women-years of observation. *Contraception* 2007;75:344–54.
4. Seeger JD, Loughlin J, Eng PM, Clifford CR, Cutone J, Walker AM. Risk of thromboembolism in women taking ethinylestradiol/drospirenone and other oral contraceptives. *Obstet Gynecol* 2007;110:587–93
5. FDA Advisory Committee Joint Meeting: Reproductive Health Drugs; Drug Safety and Risk Management. 2011 [www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ReproductiveHealthDrugsAdvisoryCommittee/UCM284784]
6. Parkin L, Sharples K, Hernandez RK, Jick SS. Risk of venous thromboembolism in users of oral contraceptives containing drospirenone or levonorgestrel: nested case-control study based on UK General Practice Research Database. *Br Med J* 2011;342:d1239.
7. Jick SS, Hernandez RK. Risk of non-fatal venous thromboembolism in women using oral contraceptives containing drospirenone compared with women using oral contraceptives containing levonorgestrel: case-control study using United States claims data. *Br Med J* 2011;342:d2151.
8. Dinger J, Assmann A, Mohner S, Minh TD. Risk of venous thromboembolism and the use of dienogest- and drospirenone-containing oral contraceptives: results from a German case-control study. *J Fam Plann Reprod Health Care* 2010;36:123–9.
9. FDA Drug Safety Communication: Updated information about the FDA-funded study on risk of blood clots in women taking birth control pills containing drospirenone. 2011 [www.fda.gov/Drugs/DrugSafety/ucm299305.htm].
10. Lidegaard O, Nielsen LH, Skovlund CW, Skjeldstad FE, Lokkegaard E. Risk of venous thromboembolism from use of oral contraceptives containing different progestogens and oestrogen doses: Danish cohort study, 2001–9. *Br Med J* 2011;343:d6423.
11. Gronich N, Lavi I, Rennert G. Higher risk of venous thrombosis associated with drospirenone-containing oral contraceptives: a population-based cohort study. *Can Med Assoc J* 2011;183:E1319-25
12. Lidegaard O, Lokkegaard E, Svendsen AL, Agger C. Hormonal contraception and risk of venous thromboembolism: national follow-up study. *Br Med J* 2009;339:b2890.
13. Leppe M, Culig J. Difference between drospirenone-containing oral contraceptives and other oral contraceptives related to risk of venous thromboembolism. *J Fam Plann Reprod Health Care* 2012;38:137–8.
14. Vlieg AV, Helmerhorst FM, Vandenbroucke JP, Doggen CJM, Rosendaal FR. The venous thrombotic risk of oral contraceptives, effects of oestrogen dose and progestogen type: results of the MEGA case-control study. *Br Med J* 2009;339:b2921.
15. Lidegaard O, Lokkegaard E, Jensen A, Skovlund CW, Keiding N. Thrombotic stroke and myocardial infarction with hormonal contraception. *N Engl J Med* 2012;366:2257–66.
16. Health Canada. Yasmin and Yaz (drospirenone): Updated information on increased risk of blood clots. 2011 Dec 5, cited 2013 Jun 12. Available at <http://www.healthykanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2011/13563a-eng.php>
17. U.S. Food and Drug Administration. FDA drug safety communication: updated information about the risk of blood clots in women taking birth control pills containing drospirenone. 2011 Sept 26; cited 2013 Jun 12. Available at <http://www.fda.gov/drugs/drugsafety/ucm299305.htm>
18. Wu CQ, Grandi SM, Fillion KB, et al. Drospirenone-containing oral contraceptive pills and the risk of venous and arterial thrombosis: a systematic review. *BJOG*. 2013; 120(7): 801-11.

19. The Society of Obstetricians and Gynecologists of Canada. Position statement: hormonal contraception and risk of venous thromboembolism (VTE). Updated 2013 Feb; cited 2013 Jun 12. Available at http://sogc.org/media_updates/position-statement-hormonal-contraception-and-risk-of-venous-thromboembolism-vte/
20. Arowojolu AO, Gallo MF, Lopez LM, Grimes DA. Combined oral contraceptive pills for treatment of acne. Cochrane Database of Systematic Reviews 2012, Issue 7. Art. No.: CD004425. DOI: 10.1002/14651858.CD004425.pub6
21. Arowojolu AO, Gallo MF, Lopez LM, Grimes DA. Combined oral contraceptive pills for treatment of acne. Cochrane Database of Systematic Reviews 2012, Issue 7. Art. No.: CD004425. DOI: 10.1002/14651858.CD004425.pub6