Does the type of menopausal HT used increase the risk of venous thromboembolism?

Yes, according to a case-control study that analyzed data from 2 large UK databases in which 80,396 women aged 40 to 79 with a primary diagnosis of venous thromboembolism (VTE) between 1998 and 2017 were matched to 391,494 controls. Use of **oral conjugated equine estrogen (CEE) or estradiol was associated with an elevated risk of VTE** (odds ratio [OR], 1.49 and 1.27, respectively), while **transdermal preparations were safest (OR, 0.96) when risk of VTE was assessed**.

FAST TRACK

UK researchers identified 80,396 women with VTE matched to 391,494 controls to assess the association between VTE and different types of HT

EXPERT COMMENTARY
Andrew M. Kaunitz, MD, is University of Florida Term Professor and Associate Chairman, Department of Obstetrics and Gynecology, University of Florida College of Medicine–Jacksonville; Medical Director and Director of Menopause and Gynecologic Ultrasound Services, UF Women's Health Specialists at Emerson, Jacksonville. Dr. Kaunitz serves on the OBG MANAGEMENT Board of Editors.

Vinogradova Y, Coupland C, Hippisley-Cox J. Use of hormone replacement therapy and risk of venous thromboembolism: nested case-control studies using the QResearch and CPRD databases. BMJ. 2019;364:k4810.

The Women's Health Initiative trials, in which menopausal women were randomly assigned to treatment with oral CEE or placebo, found that statistically the largest risk associated with menopausal hormone therapy (HT) was increased VTE.[1] Recently, investigators in the United Kingdom (UK) published results of their research aimed at determining the association between the risk of VTE and the use of different types of HT.[2]

The author reports receiving grant or research support from Allergan, Bayer, and Mithra and that he is a consultant to AMAG, Merck, and Pfizer.

Details of the study

Vinogradova and colleagues used 2 UK primary care research databases, QResearch and Clinical Practice Research Datalink, to identify cases of incident VTE in general practice records, hospital admissions, and mortality records. They identified 80,396 women (aged 40 to 79 years) diagnosed with VTE between 1998 and 2017 and 391,494 control women matched by age and general practice. The mean age of the case and control women was approximately 64 years; the great majority of women were white. Analyses were adjusted for smoking, body mass index (BMI), family history of VTE, and comorbidities associated with VTE.

Types of HT used. The investigators found that 5,795 (7.2%) women with VTE and 21,670 (5.5%) controls were exposed to HT in the 90 days before the index date (the first date of VTE diagnosis for cases became the

CONTINUED ON PAGE 16

CONTINUED FROM PAGE 14

index date for matched controls). In those exposed to HT:

- 4,915 (85%) cases and 16,938 (78%) controls used oral preparations (including 102 [1.8%] cases and 312 [1.4%] controls who also had transdermal preparations)
- 880 (14%) cases and 4,731 (19%) controls used transdermal HT only.

Association of VTE with HT. Risk of VTE was increased with all oral HT formulations, including combined (estrogen plus progestogen) and estrogen-only preparations. Use of oral CEE (odds ratio [OR], 1.49) and estradiol (OR, 1.27) were both associated with an elevated risk of VTE ($P<.05$ for both comparisons). In contrast, use of transdermal estradiol (the great majority of which was administered by patch) was not associated with an elevated risk of VTE (OR, 0.96).

Direct comparison of oral estradiol and CEE found that the lower VTE risk with oral estradiol achieved statistical significance ($P = .005$). Direct comparison of oral and transdermal estrogen revealed an OR of 1.7 for the oral route of administration ($P<.001$)

FAST TRACK

Elevated risk of VTE was associated with use of oral CEE (OR, 1.49) and oral estradiol (OR, 1.27) but not with transdermal estradiol (OR, 0.96)

Study strengths and weaknesses

This study used data from the 2 largest primary care databases in the United Kingdom. Analyses were adjusted for numerous confounding factors, including acute and chronic conditions, lifestyle factors, and social deprivation. Additional sensitivity analyses were conducted and yielded results similar to those of the main analysis.

Several limitations could have resulted in some residual confounding bias. For example, drug exposure information was based on HT prescriptions and not actual use; data on some factors were not available, such as indications for HT, age at menopause, and education level; and for a small proportion of women, some data (smoking status, alcohol consumption, BMI) were missing and had to be imputed for analysis. ●

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Although randomized trials have not compared VTE risk with oral versus transdermal estrogen, prior observational studies have consistently suggested that transdermal estrogen does not elevate VTE risk; this is consistent with the results from this large UK study. In my practice, congruent with the authors' suggestions, I recommend transdermal rather than oral estrogen for patients (notably, those who are obese) who at baseline have risk factors for VTE. For menopausal women for whom use of oral estrogen is indicated, I recommend estradiol rather than CEE, since estradiol is less expensive and, based on this study's results, may be safer than CEE.

ANDREW M. KAUNITZ, MD

References

1. Manson JE, Chlebowski RT, Stefanick ML, et al. Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the Women's Health Initiative randomized trials. *JAMA*. 2013;310:1353-1368.
2. Vinogradova Y, Coupland C, Hippisley-Cox J. Use of hormone replacement therapy and risk of venous thromboembolism: nested case-control studies using the QResearch and CPRD databases. *BMJ*. 2019;364:k4810.