

Hormone replacement therapy was associated with increased venous thromboembolism and deep venous thrombosis

Grady D, Wenger NK, Herrington D, et al., for the Heart and Estrogen/progestin Replacement Study Research Group. Postmenopausal hormone therapy increases risk for venous thromboembolic disease. The Heart and Estrogen/progestin Replacement Study. *Ann Intern Med.* 2000 May 2;132:689-96.

QUESTION

In women with coronary artery disease, does hormone replacement therapy (HRT) (estrogen plus progestin) increase the risk for venous thromboembolism (VTE)?

DESIGN

Randomized (unclear allocation concealment*), blinded (patients, investigators, and outcome assessors),* placebo-controlled trial with a mean follow-up of 4.1 years (Heart and Estrogen/progestin Replacement Study [HERS]).

SETTING

20 U.S. outpatient and community settings.

PATIENTS

2763 postmenopausal women between 44 and 79 years of age (mean age 67 y, 89% white) who had established coronary artery disease and who had not had a hysterectomy. Exclusion criteria were recent coronary events; recent use of hormone therapy; history of VTE, breast cancer, or endometrial cancer; uncontrolled hypertension; diabetes; or other life-threatening disease. Follow-up was 100% for mortality and 98% for other outcomes.

INTERVENTION

1380 women were allocated to HRT (conjugated equine estrogen, 0.625 mg/d plus medroxyprogesterone acetate, 2.5 mg/d) and 1383 to placebo. Data on risk factors were collected (fractures, nonfatal myocardial infarction, stroke, congestive heart failure, and transient ischemic attack).

MAIN OUTCOME MEASURES

Documented and suspected VTE events.

MAIN RESULTS

During follow-up, more women in the HRT group had VTE and deep venous thrombosis than did women in the placebo group (Table) ($P = 0.003$ and 0.008 , respectively). The groups did not differ for pulmonary embolism ($P = 0.08$) (Table),

although few pulmonary emboli occurred (11 in the HRT group vs 4 in the placebo group). Subgroup analyses showed a trend toward increased risk for idiopathic VTE (relative hazard 3.1, 95% CI 0.8 to 11.3) and increased nonidiopathic VTE (relative hazard 2.5, CI 1.2 to 5.3).

CONCLUSION

In older women with coronary artery disease, HRT increased the risk for VTE and deep venous thrombosis.

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*See Glossary.

Hormone replacement therapy (HRT) vs placebo in women with coronary artery disease†

Outcomes at mean 4.1 y	HRT	Placebo	Relative hazard (95% CI)‡	NNH (CI)
Venous thromboembolism	2.5%	0.9%	2.7 (1.4 to 5.0)	256 (157 to 692)
Deep venous thrombosis	1.8%	0.7%	2.8 (1.3 to 6.0)	339 (198 to 1150)§
Pulmonary embolism	0.8%	0.3%	2.8 (0.9 to 8.7)	Not significant

†Abbreviations defined in Glossary.

‡Relative hazard ratio calculated by using Cox-proportional hazards model with intention-to-treat analyses.

§ NNH for deep venous thrombosis provided by author.

COMMENTARY

Decisions about HRT seem to get harder every day. First, HERS (1) raised doubts about benefits for heart disease, and now the report by Grady and colleagues indicates that HRT increases the risk for VTE. Although this finding was not seen in an earlier randomized controlled trial (RCT) in healthy women (2) (only 4 cases of VTE occurred), comparable risks have been reported in observational studies (3) as well as in RCTs of selective estrogen-receptor modifiers like raloxifene (4). Thus, the finding is probably real, but is it important? For the average menopausal woman, the risk for VTE is small (smaller than in the HERS participants) and probably less important than other benefits (relief of symptoms and prevention of osteoporosis) or risks (possible increase in breast cancer) of HRT. However, women who have a lower-extremity fracture, recent surgery or other hospitalization, cancer, congestive heart failure, myocardial infarction, or stroke should probably avoid HRT. These factors increase the risk for VTE 2- to 30-fold, and they accounted for 75% of all cases of VTE in HERS. In these patients, clinicians should consider bone-specific agents for osteoporosis and alternatives to HRT for menopausal symptoms.

An important question is whether topical HRT, which avoids the first-pass effects on the liver, carries the same risk. An Italian study, where 80% of HRT use was with transdermal estrogen, reported a 2-fold increased risk for VTE but had only 6 exposed cases (5).

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