Estrogen Plus Progestin and Risk of Venous Thrombosis

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Context Postmenopausal hormone therapy increases the risk of venous thrombosis. It is not known whether other factors influencing thrombosis add to this risk.

Objective To report final data on incidence of venous thrombosis in the Women’s Health Initiative Estrogen Plus Progestin clinical trial and the association of hormone therapy with venous thrombosis in the setting of other thrombosis risk factors.

Design, Setting, and Participants Double-blind randomized controlled trial of 16,608 postmenopausal women between the ages of 50 and 79 years, who were enrolled in 1993 through 1998 at 40 US clinical centers with 5.6 years of follow up; and a nested case-control study. Baseline gene variants related to thrombosis risk were measured in the first 147 women who developed thrombosis and in 513 controls.

Intervention Random assignment to 0.625 mg/d of conjugated equine estrogen plus 2.5 mg/d of medroxyprogesterone acetate, or placebo.

Main Outcome Measures Centrally validated deep vein thrombosis and pulmonary embolus.

Results Venous thrombosis occurred in 167 women taking estrogen plus progestin (3.5 per 1000 person-years) and in 76 taking placebo (1.7 per 1000 person-years); hazard ratio (HR), 2.06 (95% confidence interval [CI], 1.57-2.70). Compared with women between the ages of 50 and 59 years who were taking placebo, the risk associated with hormone therapy was higher with age: HR of 4.28 (95% CI, 2.38-7.72) for women aged 60 to 69 years and 7.46 (95% CI, 4.32-14.38) for women aged 70 to 79 years. Compared with women who were of normal weight and taking placebo, the risk associated with taking estrogen plus progestin was increased among overweight and obese women: HR of 3.80 (95% CI, 2.08-6.94) and 5.61 (95% CI, 3.12-10.11), respectively. Factor V Leiden enhanced the hormone-associated risk of thrombosis with a 6.69-fold increased risk compared with women in the placebo group without the mutation (95% CI, 3.09-14.49). Other genetic variants (prothrombin 20210A, methylenetetrahydrofolate reductase C677T, factor XIII Val34Leu, PAI-1 4G/5G, and factor V HR2) did not modify the association of hormone therapy with venous thrombosis.

Conclusions Estrogen plus progestin was associated with doubling the risk of venous thrombosis. Estrogen plus progestin therapy increased the risks associated with age, overweight or obesity, and factor V Leiden.