

Estrogen did not prevent death or nonfatal stroke in postmenopausal women with ischemic stroke or TIA

Viscoli CM, Brass LM, Kernan WN, et al. A clinical trial of estrogen-replacement therapy after ischemic stroke. *N Engl J Med*. 2001 Oct 25;345:1243-9.

QUESTION

In postmenopausal women with ischemic stroke or transient ischemic attack (TIA), is estrogen more effective than placebo for preventing cerebrovascular events?

DESIGN

Randomized {allocation concealed*}†, blinded (patients and clinicians),* placebo-controlled trial with a mean follow-up of 2.8 years (Women's Estrogen for Stroke Trial [WEST]).

SETTING

21 hospitals in the United States.

PATIENTS

664 postmenopausal women who were > 44 years of age (mean age 71 y, 84% non-Hispanic white) and had had a qualifying ischemic stroke or TIA within the previous 90 days. Exclusion criteria included ischemic stroke or TIA that was disabling or had occurred while the patient was taking estrogen, and a history of breast or endometrial cancer. All patients were included in the analysis.

INTERVENTION

Women were allocated to estradiol-17 β , 1 mg daily ($n = 337$), or placebo ($n = 327$). Every 3 months, a nurse contacted each woman to screen for outcomes using a stan-

dardized questionnaire. Medical records were reviewed for all reported events.

MAIN OUTCOME MEASURES

Death or nonfatal stroke. Secondary outcomes included TIA, nonfatal myocardial infarction (MI), and adverse events.

MAIN RESULTS

Analysis was by intention to treat (included 9 women who were censored at their last known date alive without stroke). Groups did not differ for death or nonfatal stroke, TIA, nonfatal MI, venous thromboembolic events, or breast cancer (Table). Of those who did not have a hysterectomy before the study, 2 of 189 women (1.1%) in the estradiol group were diagnosed with endometrial

cancer during the study period compared with 0 of 180 women in the placebo group.

CONCLUSION

In postmenopausal women with ischemic stroke or transient ischemic attack (TIA), estrogen was no more effective than placebo for preventing death or nonfatal stroke, TIA, or nonfatal myocardial infarction.

*See Glossary.

†Information provided by author.

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Estradiol-17 β vs placebo for postmenopausal women with ischemic stroke or transient ischemic attack‡

Outcomes at mean 2.8 y	Estradiol-17 β	Placebo	RRR (95% CI)	NNH
Death or nonfatal stroke	29%	28%	8.3% (-17 to 32)	Not significant
Fatal stroke	3.6%	1.2%	187% (-9.9 to 758)	Not significant
Transient ischemic attack	8.9%	7.6%	19% (-29 to 92)	Not significant
Nonfatal myocardial infarction	4.2%	3.7%	20% (-50 to 143)	Not significant
			RRR (CI)	NNT
Venous thromboembolic event	0.89%	1.2%	20% (-235 to 80)	Not significant
Breast cancer	1.5%	1.5%	0% (-243 to 70)	Not significant

‡Abbreviations defined in Glossary; RRI, RRR, NNH, NNT, and CI calculated from Cox proportional hazards data in article.

COMMENTARY

The study by Viscoli and colleagues is the first randomized clinical trial to evaluate estradiol for the secondary prevention of stroke in postmenopausal women. The trial was well designed and leaves no ambiguity: Estradiol does not prevent death or stroke recurrence and might increase fatal stroke risk, although this increase did not differ statistically from placebo.

Interim results from the Women's Health Initiative Hormone Trial ($n > 27\,000$), a primary prevention trial, were that after 3 years of follow-up, conjugated equine estrogen (CEE) alone or with medroxyprogesterone acetate (MPA) was associated with a greater risk for stroke, heart attack, and blood clots than was placebo (1). An earlier trial for secondary prevention of coronary heart disease (CHD) reported a 52% increased risk for CHD events after 1 year of daily CEE plus MPA, with no benefit after 4 years (2). Therefore, neither estradiol nor CEE alone or with MPA is indicated for the sole purpose of primary or secondary prevention of stroke or CHD.

Hormone replacement therapy (HRT) is indicated for short-term (≤ 5 y) treatment of hot flashes and often requires a 6-month taper to avoid rebound symptoms. HRT is no longer approved by the Food and Drug Administration for osteoporosis treatment because other medica-

tions have been shown to be effective and estrogen has never been evaluated for fracture risk reduction in large randomized trials (3). Although HRT is still used for the prevention of osteoporosis, clinicians should use caution and educate patients about the risk for blood clots, gallbladder disease, urinary incontinence, and cardiovascular disease in older women receiving HRT (1, 2, 4).

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References

- Women's Health Initiative Hormone Replacement Therapy Update, June 2001. <http://www.nhlbi.nih.gov/whi/hrt.htm>.
- Hulley SB, Grady D, Bush T, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. *JAMA*. 1998;280:605-13.
- Physicians' Desk Reference. 55th ed. Montvale, NJ: Medical Economics Company; 2001.
- Grady D, Brown JS, Vittinghoff E, et al. Postmenopausal hormones and incontinence: the Heart and Estrogen/Progestin Replacement Study. *Obstet Gynecol*. 2001;97:116-20.