Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial

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CONTEXT: Despite decades of use and considerable research, the role of estrogen alone in preventing chronic diseases in postmenopausal women remains uncertain.

OBJECTIVE: To assess the effects on major disease incidence rates of the most commonly used postmenopausal hormone therapy in the United States.

DESIGN, SETTING, AND PARTICIPANTS: A randomized, double-blind, placebo-controlled disease prevention trial (the estrogen-alone component of the Women's Health Initiative [WHI]) conducted in 40 US clinical centers beginning in 1993. Enrolled were 10,739 postmenopausal women, aged 50-79 years, with prior hysterectomy, including 23% of minority race/ethnicity.

INTERVENTION: Women were randomly assigned to receive either 0.625 mg/d of conjugated equine estrogen (CEE) or placebo.

MAIN OUTCOME MEASURES: The primary outcome was coronary heart disease (CHD) incidence (nonfatal myocardial infarction or CHD death). Invasive breast cancer incidence was the primary safety outcome. A global index of risks and benefits, including these primary outcomes plus stroke, pulmonary embolism (PE), colorectal cancer, hip fracture, and deaths from other causes, was used for summarizing overall effects.
RESULTS: In February 2004, after reviewing data through November 30, 2003, the National Institutes of Health (NIH) decided to end the intervention phase of the trial early. Estimated hazard ratios (HRs) (95% confidence intervals [CIs]) for CEE vs placebo for the major clinical outcomes available through February 29, 2004 (average follow-up 6.8 years), were: CHD, 0.91 (0.75-1.12) with 376 cases; breast cancer, 0.77 (0.59-1.01) with 218 cases; stroke, 1.39 (1.10-1.77) with 276 cases; PE, 1.34 (0.87-2.06) with 85 cases; colorectal cancer, 1.08 (0.75-1.55) with 119 cases; and hip fracture, 0.61 (0.41-0.91) with 102 cases. Corresponding results for composite outcomes were: total cardiovascular disease, 1.12 (1.01-1.24); total cancer, 0.93 (0.81-1.07); total fractures, 0.70 (0.63-0.79); total mortality, 1.04 (0.88-1.22), and the global index, 1.01 (0.91-1.12). For the outcomes significantly affected by CEE, there was an absolute excess risk of 12 additional strokes per 10 000 person-years and an absolute risk reduction of 6 fewer hip fractures per 10 000 person-years. The estimated excess risk for all monitored events in the global index was a nonsignificant 2 events per 10 000 person-years.

CONCLUSIONS: The use of CEE increases the risk of stroke, decreases the risk of hip fracture, and does not affect CHD incidence in postmenopausal women with prior hysterectomy over an average of 6.8 years. A possible reduction in breast cancer risk requires further investigation. The burden of incident disease events was equivalent in the CEE and placebo groups, indicating no overall benefit. Thus, CEE should not be recommended for chronic disease prevention in postmenopausal women.

DOI of Published Version
10.1001/jama.291.14.1701

Source
JAMA. 2004 Apr 14;291(14):1701-12. Link to article on publisher's site

Journal/Book/Conference Title
JAMA : the journal of the American Medical Association

Related Resources
Link to article in PubMed

PubMed ID
15082697

Repository Citation
Anderson, Garnet L.; Limacher, Marian C.; Assaf, Annlouise R.; Bassford, Tamsen; Beresford, Shirley A. A.; Black, Henry R.; Bonds, Denise E.; Brunner, Robert L.; Brzyski, Robert G.; Caan, Bette; Chlebowski, Rowan T.; Curb, J. David; Gass, Margery; Hays, Jennifer; Heiss, Gerardo; Hendrix, Susan L.; Howard, Barbara V.; Hsia, Judith; Hubbell, F. Allan; Jackson, Rebecca D.; Johnson, Karen C.; Judd, Howard; Kotchen, Jane Morley; Ku, Lewis H.; LaCroix, Andrea Z.; Lane, Dorothy S.; Langer, Robert D.; Lasser, Norman L.; Lewis, Cora E.; Manson, JoAnn E.; Margolis, Karen L.; Ockene, Judith K.; O'Sullivan, Mary Jo; Phillips, Lawrence; Prentice, Ross L.; Rifai, Cheryl; Robbins, John; Rossouw, Jacques E.; Sarto, Gloria E.; Stefanick, Marcia L.; Van Horn, Linda; Wactawski-Wende, Jean; Wallace, Robert B.; and Wassertheil-Smoller, Sylvia, “Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women’s Health Initiative randomized controlled trial” (2004). Women’s Health Research Faculty Publications. 416. https://escholarship.umassmed.edu/wfc_pp/416