

# Clinical trials of estrogen

TrialResults-center [www.trialresultscenter.org](http://www.trialresultscenter.org)

## 1 cardiovascular prevention

Trial	Treatments	Patients	Trials design and methods
<b>combined estrogen and progestogen vs placebo</b>			
Schulman (NHLBI) (estrogen-progestogen) , 2002 [NCT00000601] n=94/99 follow-up: 6 months	intravenous estrogen followed by oral conjugated estrogen plus medroxyprogesterone for 21 days versus placebo	Postmenopausal women with unstable angina	Parallel groups double blind USA, Brazil
EAGAR , 2006 [NCT00000605] n=44/51 follow-up: 33 months	estradiol +/-medroxyprogesterone versus placebo	Postmenopausal women who had undergone coronary artery bypass graft	Parallel groups double blind USA, Canada
ERA (estrogen plus medroxyprogesterone) , 2000 [NCT00000549] n=104/105 follow-up: 3.6y	estrogen plus medroxyprogesterone acetate ( 0.625 mg of conjugated estrogen plus 2.5 mg of medroxyprogesterone acetate per day) versus placebo	Postmenopausal women with established coronary atherosclerosis	Parallel groups double-blind USA
EVTET , 2000 n=71/69 follow-up: 24 months	2 mg estradiol plus 1 mg norethisterone acetate, 1 tablet daily versus placebo	postmenopausal women younger than 70 years who had suffered previous DVT or PE	Parallel groups double-blind Norway
Hall , 1998 n=40/20 follow-up: 1 y	transdermal 17 beta-estradiol at a dose of 50 micrograms per 24 h alone for 18 days followed by 10 days of combined treatment with medroxyprogesterone acetate (MPA) 5 mg orally versus placebo	postmenopausal women with coronary artery disease aged 4475 years	Parallel groups double-blind Sweden
HERS , 1998 [NCT00319566] n=1380/1383 follow-up: 4.1 y	Premarin .625 mg daily plus medroxyprogesterone 2.5 mg daily versus placebo	women with coronary disease, younger than 80 years, and postmenopausal with an intact uterus	Cross over double-blind US

continued...

<b>Trial</b>	<b>Treatments</b>	<b>Patients</b>	<b>Trials design and methods</b>
<b>WAVE , 2002</b> [NCT00000555] n=210/213 follow-up: 2.8 y	0.625 mg/d of conjugated equine estrogen (plus 2.5 mg/d of medroxyprogesterone acetate for women who had not had a hysterectomy) versus placebo	Postmenopausal women, up to age 86, with angiographically documented coronary artery disease of at least 15 percent, but no more than 75 percent occlusion	Factorial plan double blind United States, Canada
<b>WELL-HART (estrogen-progestin) , 2003</b> [NCT00000559] n=74/76 follow-up: 3.3 y	17 beta-estradiol plus sequentially administered medroxyprogesterone acetate versus placebo	Postmenopausal women with angiographically-documented coronary disease	double blind USA
<b>WHI , 2002</b> n=8506/8102 follow-up: 5.2 y	conjugated equine estrogens, 0.625 mg/d, plus medroxyprogesterone acetate, 2.5 mg/d, in 1 tablet versus placebo	postmenopausal women aged 50-79 years with an intact uterus at baseline	Factorial plan double-blind USA
<b>WHISP , 2006</b> n=49/51 follow-up: 1 y	oral oestradiol-17beta 1 mg plus norethisterone acetate 0.5 mg daily versus placebo	post-menopausal women >55 years were enrolled between 2 and 28 days after an acute coronary syndrome	Parallel groups double-blind UK
<b>WISDOM , 2007</b> [ISRCTN63718836] n=2196/2189 follow-up: 11.9 months	combined estrogen and progestogen versus placebo	postmenopausal women aged 50-69	Parallel groups double-blind UK, Australia, New Zealand
<b>estrogen vs placebo</b>			
<b>EPAT , 2001</b> n=111/111 follow-up: 2 y	micronized 17beta-estradiol (1 mg/d) versus placebo	postmenopausal women 45 years of age or older without preexisting cardiovascular disease and with low-density lipoprotein cholesterol levels of 3.37 mmol/L or greater ( $\geq 130$ mg/dL)	Parallel groups double-blind USA
<b>ERA (estrogen alone) , 2000</b> [NCT00000549] n=100/105 follow-up: 3.6y	estrogen alone (0.625 mg of conjugated estrogen per day) versus placebo	Postmenopausal women with established coronary atherosclerosis	Parallel groups double-blind USA
<b>ESPRIT , 2002</b> n=513/504 follow-up: 24 months	oestradiol valerate 2 mg daily versus placebo	postmenopausal women, age 50-69 years who had survived a first myocardial infarction	Parallel groups double-blind England and Wales

continued...

<b>Trial</b>	<b>Treatments</b>	<b>Patients</b>	<b>Trials design and methods</b>
Schulman (NHLBI) (estrogen alone) , 2002 [NCT00000601] n=100/99 follow-up: 6 months	intravenous followed by oral conjugated estrogen for 21 days, intravenous estrogen followed by oral conjugated estrogen plus medroxyprogesterone for 21 days versus placebo	Postmenopausal women with unstable angina	Parallel groups double blind USA, Brazil
WELL-HART (estrogen alone) , 2003 [NCT00000559] n=76/76 follow-up: 3.3 y	micronized 17beta-estradiol alone versus placebo	Postmenopausal women with angiographically-documented coronary disease	Parallel groups double blind USA
WEST , 2001 n=337/327 follow-up: 2.8 y	estrogen therapy (1 mg of estradiol-17beta per day) versus placebo	postmenopausal women who had recently had an ischemic stroke or transient ischemic attack	Parallel groups double-blind USA
CDP estrogen 2.5 , 1975 n=1101/2789 follow-up: 4.7 years	estrogen 2.5 mg daily versus placebo	-	Parallel groups
CDP estrogen 5 , 1975 n=1119/2788 follow-up: 1.5 years	estrogen 5.0 mg daily versus placebo	-	Parallel groups
Marmorstein , 1962 n=285/147 follow-up: 5.0 y	estrogen versus placebo	-	Parallel groups
Stamler , 1963 n=156/119 follow-up: 5.0 years	estrogen versus placebo	-	Parallel groups
VA Neurology Section (estrogen) , 1966 n=295/287 follow-up: 1.4 years	estrogen versus placebo	-	Parallel groups
<b>estrogen or thyroxine vs placebo</b>			
VA drugs (Estrogen or thyroxine) , 1968 n=427/143 follow-up: 65279;3.2 years	estrogen or thyroxine versus placebo	-	Parallel groups

More details and results :

- cholesterol lowering intervention for cardiovascular prevention in patients with prior MI or with CHD at <http://www.trialresultscenter.org/go-Q12>

- cholesterol lowering intervention for cardiovascular prevention in patients with other atherosclerotic localisation at <http://www.trialresultscenter.org/go-Q126>
- cholesterol lowering intervention for cardiovascular prevention in all chronic situations at <http://www.trialresultscenter.org/go-Q154>
- hormonal replacement therapy for cardiovascular prevention in all type of patients at <http://www.trialresultscenter.org/go-Q452>
- hormonal replacement therapy for cardiovascular prevention in primary prevention at <http://www.trialresultscenter.org/go-Q453>
- hormonal replacement therapy for cardiovascular prevention in secondary prevention at <http://www.trialresultscenter.org/go-Q454>

## References

### Schulman (NHLBI) (estrogen-progestogen), 2002:

Schulman SP, Thiemann DR, Ouyang P, Chandra NC, Schulman DS, Reis SE, Terrin M, Forman S, de Albuquerque CP, Bahr RD, Townsend SN, Cosgriff R, Gerstenblith G Effects of acute hormone therapy on recurrent ischemia in postmenopausal women with unstable angina. *J Am Coll Cardiol* 2002;39:231-7 [[11788212](#)]

### EAGAR, 2006:

Ouyang P, Tardif JC, Herrington DM, Stewart KJ, Thompson PD, Walsh MN, Bennett SK, Heldman AW, Tayback MA, Wang NY Randomized trial of hormone therapy in women after coronary bypass surgery. Evidence of differential effect of hormone therapy on angiographic progression of disease in saphenous vein grafts and native coronary arteries. *Atherosclerosis* 2006;189:375-86 [[16442114](#)] [10.1016/j.atherosclerosis.2005.12.015](https://doi.org/10.1016/j.atherosclerosis.2005.12.015)

### ERA (estrogen plus medroxyprogesterone), 2000:

Herrington DM, Reboussin DM, Brosnihan KB, Sharp PC, Shumaker SA, Snyder TE, Furberg CD, Kowalchuk GJ, Stuckey TD, Rogers WJ, Givens DH, Waters D Effects of estrogen replacement on the progression of coronary-artery atherosclerosis. *N Engl J Med* 2000;343:522-9 [[10954759](#)] [10.1056/NEJM200008243430801](https://doi.org/10.1056/NEJM200008243430801)

### EVTET, 2000:

Hibraaten E, Qvigstad E, Arnesen H, Larsen S, Wickstrm E, Sandset PM Increased risk of recurrent venous thromboembolism during hormone replacement therapy—results of the randomized, double-blind, placebo-controlled estrogen in venous thromboembolism trial (EVTET). *Thromb Haemost* 2000;84:961-7 [[11154141](#)]

### Hall, 1998:

Hall G, Pripp U, Schenck-Gustafsson K, Landgren BM Long-term effects of hormone replacement therapy on symptoms of angina pectoris, quality of life and compliance in women with coronary artery disease. *Maturitas* 1998;28:235-42 [[9571599](#)]

### HERS, 1998:

Hulley S, Grady D, Bush T, Furberg C, Herrington D, Riggs B, Vittinghoff E Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. *JAMA* 1998;280:605-13 [[9718051](#)]

Grady D, Applegate W, Bush T, Furberg C, Riggs B, Hulley SB Heart and Estrogen/progestin Replacement Study (HERS): design, methods, and baseline characteristics. *Control Clin Trials* 1998;19:314-35 [[9683309](#)]

Simon JA, Hsia J, Cauley JA, Richards C, Harris F, Fong J, Barrett-Connor E, Hulley SB Postmenopausal hormone therapy and risk of stroke: The Heart and Estrogen-progestin Replacement Study (HERS). *Circulation* 2001;103:638-42 [[11156873](#)]

### WAVE, 2002:

Waters DD, Alderman EL, Hsia J, Howard BV, Cobb FR, Rogers WJ, Ouyang P, Thompson P, Tardif JC, Higginson L, Bittner V, Steffes M, Gordon DJ, Proschan M, Younes N, Verter JI Effects of hormone replacement therapy and antioxidant vitamin supplements on coronary atherosclerosis in postmenopausal women: a randomized controlled trial. *JAMA* 2002;288:2432-40 [[12435256](#)]

**WELL-HART (estrogen-progestin), 2003:**

Hodis HN, Mack WJ, Azen SP, Lobo RA, Shoupe D, Mahrer PR, Faxon DP, Cashin-Hemphill L, Sanmarco ME, French WJ, Shook TL, Gaarder TD, Mehra AO, Rabbani R, Sevanian A, Shil AB, Torres M, Vogelbach KH, Selzer RH Hormone therapy and the progression of coronary-artery atherosclerosis in postmenopausal women. *N Engl J Med* 2003;349:535-45 [[12904518](#)] [10.1056/NEJMoa030830](#)

**WHI, 2002:**

Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, Jackson RD, Beresford SA, Howard BV, Johnson KC, Kotchen JM, Ockene J Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. *JAMA* 2002;288:321-33 [[12117397](#)]

Design of the Women's Health Initiative clinical trial and observational study. The Women's Health Initiative Study Group. *Control Clin Trials* 1998;19:61-109 [[9492970](#)]

**WHISP, 2006:**

Collins P, Flather M, Lees B, Mister R, Proudler AJ, Stevenson JC Randomized trial of effects of continuous combined HRT on markers of lipids and coagulation in women with acute coronary syndromes: WHISP Pilot Study. *Eur Heart J* 2006;27:2046-53 [[16899475](#)] [10.1093/eurheartj/ehl183](#)

**WISDOM, 2007:**

Vickers MR, Martin J, Meade TW The Women's international study of long-duration oestrogen after menopause (WISDOM): a randomised controlled trial. *BMC Womens Health* 2007;7:2 [[17324282](#)] [10.1186/1472-6874-7-2](#)

Vickers MR, MacLennan AH, Lawton B, Ford D, Martin J, Meredith SK, DeStavola BL, Rose S, Dowell A, Wilkes HC, Darbyshire JH, Meade TW Main morbidities recorded in the women's international study of long duration oestrogen after menopause (WISDOM): a randomised controlled trial of hormone replacement therapy in postmenopausal women. *BMJ* 2007 Aug 4;335:239 [[17626056](#)]

**EPAT, 2001:**

Hodis HN, Mack WJ, Lobo RA, Shoupe D, Sevanian A, Mahrer PR, Selzer RH, Liu Cr CR, Liu Ch CH, Azen SP Estrogen in the prevention of atherosclerosis. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 2001;135:939-53 [[11730394](#)]

**ERA (estrogen alone ), 2000:**

Herrington DM, Reboussin DM, Brosnihan KB, Sharp PC, Shumaker SA, Snyder TE, Furberg CD, Kowalchuk GJ, Stuckey TD, Rogers WJ, Givens DH, Waters D Effects of estrogen replacement on the progression of coronary-artery atherosclerosis. *N Engl J Med* 2000;343:522-9 [[10954759](#)] [10.1056/NEJM200008243430801](#)

Herrington DM, Reboussin DM, Klein KP, Sharp PC, Shumaker SA, Snyder TE, Geisinger KR The estrogen replacement and atherosclerosis (ERA) study: study design and baseline characteristics of the cohort. *Control Clin Trials* 2000;21:257-85 [[10822123](#)]

**ESPRIT, 2002:**

Cherry N, Gilmour K, Hannaford P, Heagerty A, Khan MA, Kitchener H, McNamee R, Elstein M, Kay C, Seif M, Buckley H Oestrogen therapy for prevention of reinfarction in postmenopausal women: a randomised placebo controlled trial. *Lancet* 2002;360:2001-8 [[12504395](#)]

**Schulman (NHLBI) (estrogen alone), 2002:**

Schulman SP, Thiemann DR, Ouyang P, Chandra NC, Schulman DS, Reis SE, Terrin M, Forman S, de Albuquerque CP, Bahr RD, Townsend SN, Cosgriff R, Gerstenblith G Effects of acute hormone therapy on recurrent ischemia in postmenopausal women with unstable angina. *J Am Coll Cardiol* 2002;39:231-7 [[11788212](#)]

**WELL-HART (estrogen alone), 2003:**

Hodis HN, Mack WJ, Azen SP, Lobo RA, Shoupe D, Mahrer PR, Faxon DP, Cashin-Hemphill L, Sanmarco ME, French WJ, Shook TL, Gaarder TD, Mehra AO, Rabbani R, Sevanian A, Shil AB, Torres M, Vogelbach KH, Selzer RH Hormone therapy and the progression of coronary-artery atherosclerosis in postmenopausal women. N Engl J Med 2003;349:535-45 [12904518] [10.1056/NEJMoa030830](https://doi.org/10.1056/NEJMoa030830)

**WEST, 2001:**

Viscoli CM, Brass LM, Kernan WN, Sarrel PM, Suissa S, Horwitz RI A clinical trial of estrogen-replacement therapy after ischemic stroke. N Engl J Med 2001;345:1243-9 [11680444] [10.1056/NEJMoa010534](https://doi.org/10.1056/NEJMoa010534)

**CDP estrogen 2.5, 1975:**

The Coronary Drug Project. Findings leading to discontinuation of the 2.5-mg day estrogen group. The coronary Drug Project Research Group. JAMA 1973;226:652-7 [4356847]

**CDP estrogen 5, 1975:**

The Coronary Drug Project. Initial findings leading to modifications of its research protocol. JAMA 1970;214:1303-13 [4320008]

**Marmorstein, 1962:**

MARMORSTON J, MOORE FJ, HOPKINS CE, KUZMA OT, WEINER J Clinical studies of long-term estrogen therapy in men with myocardial infarction. Proc Soc Exp Biol Med 1962;110:400-8 [14470097]

**Stamler, 1963:**

SCHWARTZ SO, GREENSPAN I, BROWN ER LEUKEMIA CLUSTER IN NILES, ILL. IMMUNOLOGIC DATA ON FAMILIES OF LEUKEMIC PATIENTS AND OTHERS. JAMA 1963;186:106-8 [14056521]

STAMLER J, PICK R, KATZ LN, PICK A, KAPLAN BM, BERKSON DM, CENTURY D Effectiveness of estrogens for therapy of myocardial infarction in middle-age men. JAMA 1963;183:632-8 [13983325]

**VA Neurology Section (estrogen), 1966:**

An evaluation of estrogenic substances in the treatment of cerebral vascular disease. Report of the Veterans Administration Cooperative Study of Atherosclerosis, Neurology Section. Circulation 1966;33:II3-9 [4378175]

**VA drugs (Estrogen or thyroxine), 1968:**