

# Raloxifene produced both harms and benefits in postmenopausal women, with no reduction in cardiovascular disease risk

Barrett-Connor E, Mosca L, Collins P, et al. Effects of raloxifene on cardiovascular events and breast cancer in postmenopausal women. *N Engl J Med*. 2006;355:125-37.

**Clinical impact ratings:** GIM/FP/GP ★★★★★☆ Cardiology ★★★★★☆ Endocrinology ★★★★★☆ Geriatrics ★★★★★☆

Hematol/Thrombo ★★★★★☆ Neurology ★☆☆☆☆☆ Oncology ★★★★★☆ Rheumatology ★★★★★☆

## QUESTION

In postmenopausal women, does raloxifene reduce risk for coronary events and invasive breast cancer?

## METHODS

**Design:** Randomized placebo-controlled trial (Raloxifene Use for The Heart [RUTH] trial).

**Allocation:** Concealed.\*

**Blinding:** Blinded (clinicians, participants, outcome assessors, laboratory staff, and sponsor).\*

**Follow-up period:** Median 5.6 years.

**Setting:** 177 centers in 26 countries worldwide.

**Participants:** 10 101 postmenopausal women  $\geq 55$  years of age (mean 68 y) with or at increased risk for coronary heart disease. Exclusion criteria included recent myocardial infarction (MI) or revascularization procedure; history of cancer, venous thromboembolism (VTE), heart failure, or chronic liver or renal disease; life expectancy  $< 5$  years; and recent use of estrogen.

**Intervention:** Oral raloxifene, 60 mg/d ( $n = 5044$ ), or placebo ( $n = 5057$ ).

**Outcomes:** Coronary events (death from coronary causes, MI, or hospitalization for an acute coronary syndrome), breast cancer, death from cardiovascular causes, death from any cause, stroke, VTE, clinical fractures, and adverse events.

**Participant follow-up:** 80% completed the trial (100% included in intention-to-treat analysis).

## MAIN RESULTS

The raloxifene and placebo groups did not differ for the composite endpoint of coronary events (Table) or for any of the component outcomes individually. Raloxifene reduced risk for invasive breast cancer (Table)—in particular, estrogen-receptor-positive breast cancer; it did not prevent estrogen-receptor-negative or noninvasive breast cancer. Groups did not differ for stroke, but risks for fatal stroke and VTE were increased in the raloxifene group (Table). Raloxifene reduced clinical vertebral fractures (Table) but not nonvertebral fractures. Groups did not differ for death from cardiovascular causes or death from all causes. Hot flashes, leg cramps, peripheral edema, and gallbladder disease

were reported by more women in the raloxifene group. Groups did not differ for endometrial cancer.

## CONCLUSION

In postmenopausal women with or at increased risk for coronary heart disease, raloxifene reduced risk for invasive breast cancer, did not affect risk for coronary events, and increased risk for venous thromboembolism and fatal stroke.

*Source of funding:* Eli Lilly.

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\*See Glossary.

## Raloxifene vs placebo to prevent coronary events and breast cancer in postmenopausal women at median 5.6 yearst

Outcomes	Annualized event rates		RRR (95% CI)	NNT (CI)
	Raloxifene	Placebo		
Coronary events‡	2.06%	2.16%	4.9% (–7 to 16)	Not significant
Invasive breast cancer	0.15%	0.27%	44% (17 to 62)	843 (598 to 2182)
Vertebral fractures	0.24%	0.37%	35% (11 to 53)	774 (511 to 2462)
			RRR (CI)	NNH (CI)
Stroke	0.95%	0.86%	10% (–8 to 32)	Not significant
Fatal stroke	0.22%	0.15%	49% (0 to 124)	1363 (539 to ∞)
Venous thromboembolism	0.39%	0.27%	44% (6 to 95)	844 (391 to 6182)

†Abbreviations defined in Glossary; RRR, RRI, NNT, NNH, and CI calculated from hazard ratios in article.

‡Death from coronary causes, myocardial infarction, or hospitalization for acute coronary syndromes.

## COMMENTARY

The study by Barrett-Connor and colleagues is yet another large disease prevention trial in postmenopausal women yielding disappointing results. Like the Women's Health Initiative (WHI) estrogen trial (1), the RUTH trial showed no cardiovascular risk reduction, but did show increased risks for VTE and gallbladder disease. Unlike the WHI trial (2), RUTH did not show increased risk for all stroke but, disturbingly, risk for stroke death was increased. Unlike estrogen, raloxifene had no benefit in reducing hot flashes or nonvertebral fractures. While breast cancer risk was not increased in the WHI estrogen trial, raloxifene reduced risk for invasive estrogen-receptor-positive breast cancer by 55% in RUTH. This benefit of raloxifene, first observed in women with osteoporosis, has also been recently confirmed in women at high risk for breast cancer (3).

The clinical application of the results of this trial is complex. Older women at high risk for cardiovascular events should not rely on ralox-

ifene for chronic disease prevention. However, postmenopausal women who want to reduce risks for vertebral fracture and breast cancer; are not at high risk for stroke; and can accept the increased risks for VTE, gallbladder disease, and nuisance hot flashes and leg symptoms, raloxifene for perhaps 5 years remains a viable option. Women should be individually assessed for menopausal symptoms and risks for disease, then counseled regarding the known risks, benefits, and side effects of existing pharmacologic agents.

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## References

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