



Online article and related content
current as of November 10, 2009.

Raloxifene and Cardiovascular Events in Osteoporotic Postmenopausal Women: Four-Year Results From the MORE (Multiple Outcomes of Raloxifene Evaluation) Randomized Trial

Elizabeth Barrett-Connor; Deborah Grady; Andreas Sashegyi; et al.

JAMA. 2002;287(7):847-857 (doi:10.1001/jama.287.7.847)

<http://jama.ama-assn.org/cgi/content/full/287/7/847>

Correction	Contact me if this article is corrected.
Citations	This article has been cited 307 times. Contact me when this article is cited.
Topic collections	Women's Health; Menopause; Randomized Controlled Trial Contact me when new articles are published in these topic areas.
Related Articles published in the same issue	February 20, 2002 JAMA. 2002;287(7):921.
Related Letters	Raloxifene and Risk of Cardiovascular Events Dean F. Mayer et al. JAMA. 2002;288(1):42.

Subscribe
<http://jama.com/subscribe>

Permissions
permissions@ama-assn.org
<http://pubs.ama-assn.org/misc/permissions.dtl>

Email Alerts
<http://jamaarchives.com/alerts>

Reprints/E-prints
reprints@ama-assn.org

Raloxifene and Cardiovascular Events in Osteoporotic Postmenopausal Women

Four-Year Results From the MORE (Multiple Outcomes of Raloxifene Evaluation) Randomized Trial

Elizabeth Barrett-Connor, MD

Deborah Grady, MD

Andreas Sashegyi, PhD

Pamela W. Anderson, MD

David A. Cox, PhD

Krzysztof Hozowski, MD

Pentti Rautaharju, MD

Kristine D. Harper, MD

for the MORE Investigators

CORONARY HEART DISEASE (CHD) is the leading cause of death among postmenopausal women in the United States and most of the Western world.¹ In observational studies, postmenopausal women who take hormone replacement therapy (HRT), alone or with a progestin, have approximately 30% less risk of CHD compared with untreated postmenopausal women.² Randomized clinical trials have not confirmed a beneficial effect of HRT on either the progression of coronary atherosclerosis or the risk of cardiovascular (CV) events in postmenopausal women with existing CHD.^{3,4} In the Heart and Estrogen/progestin Replacement Study (HERS),³ and in preliminary information from the Women's Health Initiative (WHI),^{5,6} women assigned to receive HRT experienced an early increased risk of acute coronary events. In the Women's Estrogen for Stroke Trial (WEST),⁷ women assigned to estradiol had an increased risk of stroke compared with placebo during the first 6 months of treatment.

Context Raloxifene, a selective estrogen receptor modulator, improves cardiovascular risk factors, but its effect on cardiovascular events is unknown.

Objective To determine the effect of raloxifene on cardiovascular events in osteoporotic postmenopausal women.

Design Secondary analysis of data from the Multiple Outcomes of Raloxifene Evaluation trial, a randomized, double-blind, placebo-controlled trial conducted between November 1994 and September 1999.

Setting Outpatient and community settings at 180 sites in 25 countries.

Participants A total of 7705 osteoporotic postmenopausal women (mean age, 67 years).

Intervention Patients were randomly assigned to receive raloxifene, 60 mg/d (n=2557), or 120 mg/d (n=2572), or placebo (n=2576) for 4 years.

Main Outcome Measures Cardiovascular events, including coronary events (myocardial infarction, unstable angina, or coronary ischemia) and cerebrovascular events (stroke or transient ischemic attack), collected as safety end points and subsequently adjudicated by a cardiologist blinded to therapy. Cardiovascular risk at study entry was determined by the presence of multiple cardiovascular risk factors or prior coronary events or revascularization procedure.

Results In the overall cohort, there were no significant differences between treatment groups in the number of combined coronary and cerebrovascular events: 96 (3.7%) with placebo, 82 (3.2%) with 60 mg/d of raloxifene, and 94 (3.7%) with 120 mg/d of raloxifene. Relative risks (RRs) were 0.86 (95% confidence interval [CI], 0.64-1.15) and 0.98 (95% CI, 0.74-1.30) for 60 mg/d and 120 mg/d of raloxifene, respectively. Similar results were obtained when coronary and cerebrovascular events were analyzed separately. Among the subset of 1035 women with increased cardiovascular risk at baseline, those assigned to raloxifene had a significantly lower risk of cardiovascular events compared with placebo (RR, 0.60; 95% CI, 0.38-0.95 for both raloxifene groups). The number of cardiovascular events during the first year was not significantly different across groups in the overall cohort ($P=.94$), or among women at increased cardiovascular risk ($P=.86$) or with evidence of established coronary heart disease ($P=.60$).

Conclusions Raloxifene therapy for 4 years did not significantly affect the risk of cardiovascular events in the overall cohort but did significantly reduce the risk of cardiovascular events in the subset of women with increased cardiovascular risk. There was no evidence that raloxifene caused an early increase in risk of cardiovascular events. Before raloxifene is used for prevention of cardiovascular events, these findings require confirmation in trials with evaluation of cardiovascular outcomes as the primary objective.

JAMA. 2002;287:847-857

www.jama.com

Author Affiliations and Financial Disclosures are listed at the end of this article.

A list of the MORE Investigators has been published previously (JAMA. 1999;282:637-656).

Corresponding Author and Reprints: Elizabeth

Barrett-Connor, MD, Division of Epidemiology, Department of Family and Preventive Medicine, University of California, San Diego School of Medicine, 9500 Gilman Dr, No. 0607, La Jolla, CA 92093-0607 (e-mail: ebarrettconnor@ucsd.edu).

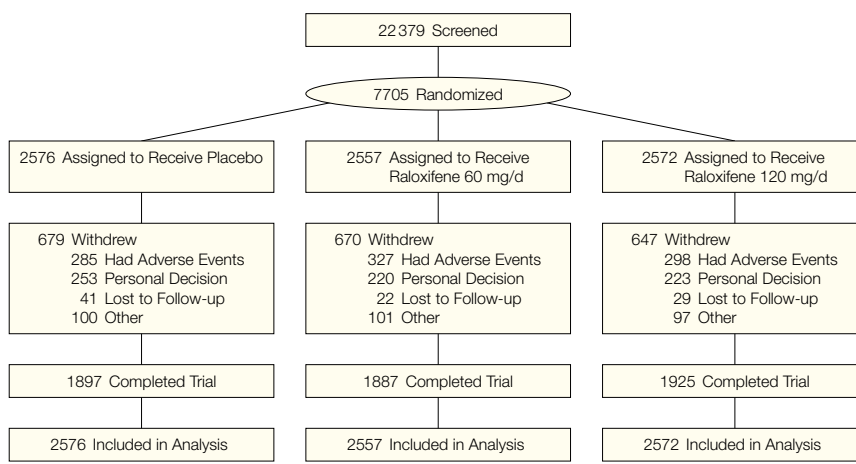
Pooled analyses of smaller, short-term trials^{8,9} and recent reports from observational studies¹⁰⁻¹² also suggest a transient increase in risk of recurrent CV events after initiation of HRT in postmenopausal women.

The Multiple Outcomes of Raloxifene Evaluation (MORE) trial was a double blind, placebo-controlled trial designed to determine the effect of raloxifene, a selective estrogen receptor modulator, on bone mineral density and vertebral fractures in 7705 postmenopausal women with osteoporosis.^{13,14} Raloxifene reduced the risk of osteoporotic vertebral fractures and newly diagnosed breast cancer without increasing the risk of endometrial cancer but increased the risk of venous thromboembolic events to an extent similar to that of HRT and tamoxifen.¹³⁻¹⁷

Although raloxifene has favorable effects on low-density lipoprotein cholesterol (LDL-C) and other risk factors for CHD^{18,19} and improves vascular endothelial function in postmenopausal women,²⁰ the effect of raloxifene on the risk of arterial CV events is unknown. Whether raloxifene affects the risk of CV events in postmenopausal women is currently being tested prospectively in the Raloxifene Use for The Heart (RUTH) trial, which enrolled 10 101 postmenopausal women with established CHD or with multiple risk factors for acute CHD events; however, results will not be available for several years.²¹

In the MORE trial, CV events and mortality were reported as adverse events and serum lipid concentrations were measured. We used these data to determine the early and overall effects of 4 years of raloxifene therapy on the occurrence of major arterial CV events, including coronary and cerebrovascular events. Since the MORE cohort was at relatively low risk for CV events overall, we also determined the effect of raloxifene on coronary and cerebrovascular events among women at increased risk for these events as defined by the presence of multiple CV risk factors or evidence of established CHD at baseline.

Figure 1. Flow of Patients



METHODS

Study Design and Participants

Study participants were enrolled in the MORE study at 180 sites in 25 countries. Details of the study design, eligibility criteria, and flow of participants through the trial have been published.¹³⁻¹⁵ Patients were at least 2 years postmenopausal and had osteoporosis documented either by prior vertebral fracture or bone mineral density T score of less than -2.5 . Women were excluded if they had a history of stroke or venous thromboembolic disease during the past 10 years. Women with coronary artery disease, hypertension, hypercholesterolemia, type 2 diabetes mellitus, or other risk factors for CV disease were not excluded. The primary outcomes of MORE were bone mineral density and vertebral fractures. Measurement of serum lipid concentrations was a secondary objective of the trial, and assessment of major CV events (including CV death) was a safety objective of the trial. The protocol was approved by the ethical review board at each site. All women gave written informed consent to participate in the study in accordance with the ethical principles stated in the Declaration of Helsinki.

Randomization and Blinding

Details of the randomization and blinding procedures have been published.¹³⁻¹⁵ Briefly, women were strati-

fied by site and randomly assigned to receive raloxifene 60 mg/d or 120 mg/d or placebo (FIGURE 1). The sponsor supplied randomly numbered kits containing identically appearing raloxifene and placebo tablets. The women received 2 tablets daily: 2 placebo, 1 placebo and 1 tablet of 60-mg raloxifene, or 2 tablets of 60-mg raloxifene. In addition, all women were provided with 500 mg of calcium and 400 to 600 IU of cholecalciferol per day, beginning at study entry. Participants, investigators, laboratory staff, and those who adjudicated the CV outcomes were blinded to treatment assignment.

Baseline Assessments and Follow-up

At baseline, information on age, ethnicity, years of education, reproductive history, prior postmenopausal hormone use, cigarette smoking, alcohol consumption, and health conditions was reported (TABLE 1). In addition, women were asked whether they had previously experienced any of the following CV events or procedures: myocardial infarction (MI), coronary artery bypass graft (CABG) surgery, percutaneous coronary intervention, or stroke. Other baseline clinical assessments included height, weight, blood pressure, pulse, a standard 12-lead electrocardiogram (ECG), and measurement of serum lipid concentrations (total cholesterol, high-

density lipoprotein cholesterol [HDL-C], and triglycerides) and fasting blood glucose. Use of all prescription and over-the-counter medications was recorded at baseline. Follow-up visits were scheduled at 3 and 6 months after enrollment and every 6 months thereafter.

CV Risk Assessment

We assessed CV risk for each woman by assigning a risk score based on evidence of established CHD or the presence of CV risk factors, adapted from criteria established previously for enrollment of women in the RUTH trial.²¹

Women with a prior MI, percutaneous coronary intervention, or CABG surgery received a score of 4 points, regardless of the timing of the event or procedure relative to enrollment. Women with diabetes mellitus (fasting blood glucose >140 mg/dL [>7.8 mmol/L]) or taking hypoglycemic medication) received 3 points. Women 70 years or older received 2 points; those between age 65 and 70 years received 1 point. Women who were current smokers (10 or more cigarettes per day for 6 months before enrollment), had hypertension (systolic blood pressure >160 mm Hg,

diastolic blood pressure >95 mm Hg, or taking antihypertensive medication), or had hyperlipidemia (LDL-C >160 mg/dL [4.14 mmol/L] or HDL-C <45 mg/dL [1.17 mmol/L] with triglycerides >250 mg/dL [2.82 mmol/L], or receiving hypolipidemic therapy) received 1 point for each condition. The combination of current smoking, hypertension, and hyperlipidemia was scored 4 points. Women with 4 or more risk points were considered to be at increased risk for CV events.²¹ Based on these criteria, 1035 (13.4%) were defined as being at high risk for CV events,

Table 1. Baseline Characteristics of Participants in Multiple Outcomes of Raloxifene Evaluation (MORE) and Randomization Trial*

Characteristics	All Enrolled Women (N = 7705)				Women at Increased Cardiovascular Risk (n = 1035)			
	Placebo (n = 2576)	Raloxifene		P Value	Placebo (n = 317)	Raloxifene		P Value
		60 mg/d (n = 2557)	120 mg/d (n = 2572)			60 mg/d (n = 359)	120 mg/d (n = 359)	
Body mass index, kg/m ²	25 (4)	25 (4)	25 (4)	.99	26 (4)	26 (4)	26 (4)	.45
Current smoker	16.3	16.8	16.5	.92	25.8	23.4	24.0	.75
>3 Alcoholic drinks per week	17.1	18.2	17.0	.42	16.7	14.5	15.9	.71
Diabetes mellitus†	1.9	3.2	2.3	.02	13.6	19.8	16.4	.10
Prior CHD or stroke								
MI	2.4	1.8	2.5	.25	19.2	13.1	17.8	.08
CABG	0.4	0.3	0.7	.06	3.2	1.9	5.0	.07
PCI	0.5	0.5	0.3	.41	4.1	3.9	2.2	.32
Stroke	0.7	0.4	0.3	.12	1.9	1.1	0.6	.27
Concomitant medications								
Lipid-lowering agents	6.7	8.7	7.1	.02	19.2	20.6	18.4	.75
ACE inhibitors	5.4	5.3	5.8	.77	13.6	13.9	16.2	.58
Diuretics	9.7	9.2	8.5	.30	29.3	25.6	26.5	.53
Aspirin	17.7	16.6	17.0	.56	25.2	24.2	28.7	.36
β-Blockers	9.6	10.1	10.5	.58	26.8	27.6	30.4	.55
Calcium channel blockers	8.8	8.4	8.3	.78	25.2	18.9	26.5	.04
Demographics								
Age, mean (SD), y	67 (7)	66 (7)	66 (7)	.34	72 (5)	72 (5)	72 (5)	.38
Postmenopause, mean (SD), y	19 (8)	19 (9)	19 (8)	.26	24 (7)	24 (7)	24 (7)	.70
White	95.7	96.0	95.3	.49	94.3	96.1	95.5	.54
Prior estrogen therapy	28.6	29.8	28.6	.53	24.9	27.6	24.2	.56
Hysterectomy	22.4	23.7	21.9	.25	28.1	26.4	21.2	.09
CHD risk factors								
Cholesterol, mean (SD), mmol/L‡								
Total	6.14 (1.07)	6.18 (1.04)	6.12 (1.07)	.11	6.52 (1.1)	6.51 (1.06)	6.42 (1.09)	.41
LDL	4.00 (0.98)	4.04 (0.95)	3.99 (0.96)	.10	4.35 (1.05)	4.38 (0.94)	4.3 (0.98)	.58
HDL	1.56 (0.39)	1.55 (0.38)	1.55 (0.40)	.83	1.48 (0.37)	1.43 (0.36)	1.45 (0.38)	.32
Triglycerides, mean (SD), mmol/L§	1.26 (0.68)	1.28 (0.81)	1.26 (0.75)	.59	1.55 (0.84)	1.52 (0.78)	1.47 (0.76)	.38
Blood pressure, mean (SD), mm Hg								
Systolic	135 (20)	136 (20)	136 (20)	.55	148 (22)	150 (22)	149 (22)	.51
Diastolic	79 (11)	79 (10)	79 (11)	.83	83 (12)	83 (11)	82 (12)	.86

*P values are for overall treatment group differences (analysis of variance for continuous variables or Pearson χ^2 test for categorical variables). Data are presented as percentages unless otherwise indicated. CHD indicates coronary heart disease; MI, myocardial infarction; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; and ACE, angiotensin-converting enzyme.

†Women with a preexisting condition of diabetes, baseline fasting blood glucose of at least 140 mg/dL (7.8 mmol/L), or baseline use of hypoglycemic agent.

‡To convert total cholesterol and low-density lipoprotein (LDL) and high-density lipoprotein (HDL) from mmol/L to mg/dL divide by 0.02589.

§To convert triglycerides from mmol/L to mg/dL divide by 0.0113.

202 with a prior acute coronary event or procedure and the remainder with no prior history of acute coronary events but with multiple CV risk factors.

Ascertainment and Adjudication of CV Events

Cardiovascular events were collected by asking women at each visit if they had an MI, CABG surgery, percutaneous coronary intervention, or a stroke since the previous visit and by recording unsolicited reports of adverse CV events. For each reported event, the investigator reviewed available documentation, including ECG reports, cardiac enzyme results, procedure reports, hospitalization records, discharge summaries, or letters from physicians and provided a written summary of these findings to the sponsor. All summaries of reported CV events through 4 years of follow-up were reviewed and adjudicated by a board-certified cardiologist, who was contracted by the sponsor, was not associated with the trial, and was blinded to treatment assignment. No original source documents were available to the adjudicator.

All reported deaths were adjudicated to be due to either CV or non-CV causes. Cardiovascular deaths included coronary death (fatal MI, sudden death, unwitnessed death in the absence of other likely noncoronary causes, and death related to a coronary artery procedure) and cerebrovascular death (fatal stroke). Nonfatal CV outcomes included coronary events (MI, unstable angina, or coronary ischemia) and cerebrovascular events (stroke or transient ischemic attack). Based on review of the case summaries, the adjudicator determined that MI was present in women with symptoms compatible with MI (ie, chest pain or anginal equivalent) who had documentation of either elevated cardiac enzyme levels (ie, cardiac enzymes >2-fold above the upper limit of normal or deemed consistent with MI by the local laboratory) or positive ECG findings compatible with MI (ie, pathological Q waves, ST depression or elevation or T-wave inversion); in hospitalized patients with a discharge diagnosis of MI;

or in patients who had an MI according to a physician's statement in the medical record. Unstable angina was deemed to be present in hospitalized patients with anginal symptoms (ie, chest pain or anginal equivalent) with a primary diagnosis of this condition. A diagnosis of coronary ischemia was made for women hospitalized with chest symptoms consistent with angina but without additional supporting evidence of unstable angina or other acute coronary syndromes.

Cerebrovascular events included stroke and transient ischemic attack. Stroke was deemed to be present in patients with symptoms compatible with stroke who had documentation of either positive computed tomographic scan result (read by a physician as consistent with recent stroke) or with persistent neurological deficit (>24 hours); in hospitalized patients with a discharge diagnosis of stroke; or in patients who had a stroke according to a physician's statement. Transient ischemic attack was deemed to have occurred in hospitalized patients with symptoms compatible with stroke but for whom a diagnosis of stroke was not established or for patients with a primary diagnosis of transient ischemic attack.

Serial ECGs

A standard 12-lead ECG was obtained at baseline and at 24 and 48 months or at early discontinuation. The ECG results were coded by the Epidemiological Cardiology Research Center (EPICARE) at Wake Forest University, using the NOVACODE serial classification system.²² Persons interpreting the ECGs had no knowledge of treatment assignment, clinical symptoms, or cardiac enzymes. Incident MI and myocardial ischemia based on ECG changes were defined by changes in Q wave and ST-T wave scores. Incident MI required an increase in Q wave score of at least 25 points (grade 2), or at least 15 points (grade 1) with clinically significant ST-T wave evolution from the baseline ECG (change in ST-T score of at least 10). Myocardial ischemia was defined as borderline isolated Q-wave evolution with-

out evolving ST-T waves or ischemic evolution of ST-T waves without a significant Q wave.²³ Serial ECGs were obtained independent of the reporting of clinical CV events and were not used in the adjudication of the clinical CV events because of the lack of temporal association between them. Cardiovascular events identified from serial ECGs were not included in the analysis of clinically reported events.

Measurement of Serum Lipids

Total cholesterol, HDL-C, and triglyceride concentrations were measured in all women at baseline. Follow-up measurements were performed in serum obtained at 6, 12, 24, 36, and 48 months using previously described methods.¹⁸ Total cholesterol was measured at follow-up visits in all women, whereas only samples from the 2738 women enrolled at the 14 study sites that had at least 100 enrolled patients were assayed for HDL-C and triglyceride concentrations. Low-density lipoprotein cholesterol levels were calculated using the Friedewald equation.²⁴

Statistical Analyses

Procedures in SAS Version 6.09 were used to perform all statistical analyses (SAS Institute Inc, Cary, NC). Analyses were performed using the intention-to-treat principle with patients allocated to assigned treatment regardless of compliance or other postbaseline factors. Unless otherwise stated, all hypotheses were tested at the .05 (2-sided) level of significance. No adjustments were made for multiple comparisons.

Baseline patient characteristics were compared using analysis of variance for continuous data and Pearson χ^2 test for categorical data. Kaplan-Meier curves were generated to assess the cumulative incidence of all CV events (coronary and cerebrovascular events combined), and coronary and cerebrovascular events separately. To examine early and longer-term effects of raloxifene on CV risk, we compared across treatment groups the number of women with a CV event (coronary and cerebrovascular events combined and ana-

lyzed individually) after 1 and 4 years of treatment using Pearson χ^2 test, and calculated relative risks (RRs) and 95% confidence intervals (CIs) for each raloxifene treatment group compared with placebo. Post hoc power calculations, performed using a 1-sided, continuity-corrected Pearson χ^2 test, suggested that the data provided 80% power to detect a 1.9-fold increase in risk of CV events in the first year with raloxifene 60 mg/d (1.8-fold when raloxifene dose groups were pooled) over placebo in the total cohort and a 2.5-fold increase in risk in the first year with raloxifene 60 mg/d (2.3-fold when the raloxifene dose groups were pooled) over placebo in the high-risk subset. Through 4 years, the data provided 80% power to observe a 29% and 41% RR reduction in the total cohort and high-risk subset, respectively.

We assessed whether treatment group imbalances in baseline characteristics confounded the observed results by performing multivariate regression analysis, including factors for treatment, baseline characteristics, and the interaction between treatment and baseline characteristics in the model.

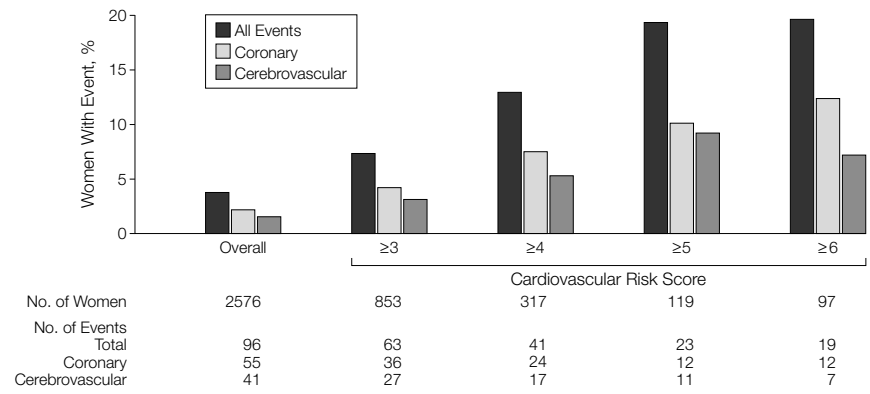
For analysis of serum lipid concentrations, percentage changes in these markers were compared between treatment groups using an analysis of variance on rank transformed data from all women with a baseline and at least 1 postbaseline measurement. Missing end point observations were imputed by carrying forward the last available post-baseline observation.

RESULTS

Baseline Characteristics

In the overall study cohort, women in the placebo and raloxifene groups were generally similar at baseline with regard to demographics, CHD risk factors, and prior evidence of CHD (Table 1). The only exception was a greater proportion of women in the raloxifene groups compared with placebo with evidence of diabetes at baseline ($P=.02$). Use of CV medications also was balanced across treatment groups except for lipid-lowering therapy, which was greater at baseline among women as-

Figure 2. Cardiovascular Event Rate vs Cardiovascular Risk Score in the Placebo Group



Data represent percentage of women in the placebo group with any cardiovascular event, coronary event, or cerebrovascular event. Numbers under the graph summarize sample sizes and the numbers of women who experienced at least 1 event.

signed to receive raloxifene compared with placebo (Table 1). On average, women were 67 years old, 19 years postmenopausal, primarily white (96%), and had a mean body mass index of 25 kg/m². Women had a borderline-high mean serum concentration of total cholesterol (238 mg/dL [6.15 mmol/L] and LDL-C (155 mg/dL [4.01 mmol/L]). Most women were normotensive and without established coronary artery disease, with less than 3% reporting a prior coronary event or procedure (Table 1). There was no significant difference across treatment groups among women in the high-CV risk subset in age, other demographics, or in most CHD risk factors (Table 1). As in the overall cohort, there were more women in the high-risk group with evidence of diabetes in the raloxifene 60 mg/d compared with the other groups, although the difference was not statistically significant ($P=.10$) in this subset. There also tended to be fewer women with a prior history of MI ($P=.08$) or CABG ($P=.07$) in the raloxifene 60 mg/d group compared with the other groups. Use of lipid-lowering therapy and most other CV medications was balanced across treatment groups at baseline except for calcium channel blockers, which was less ($P=.04$) in the raloxifene 60 mg/d group.

Data were analyzed through 48 months of follow-up, during which time

1996 participants (25.9%) discontinued from the study before its completion: 679 in the placebo group, 670 in the raloxifene 60 mg/d group, and 647 in the raloxifene 120 mg/d group. At 4 years, vital status was known for 5709 (74%) of the 7705 women originally enrolled in the trial. Women for whom vital status could not be confirmed included those who discontinued the trial early, primarily due to an adverse event ($n=910$, 46% of discontinuations) or personal decision ($n=696$, 35% of discontinuations). Compared with women who remained in the trial at 4 years, those who discontinued early were slightly older (67.2 vs 66.2 years; $P<.001$), were more years past menopause (19.9 vs 18.3 years; $P<.001$), and had slightly higher serum triglyceride levels (115.9 mg/dL [1.31 mmol/L] and 111.5 mg/dL [1.26 mmol/L]; $P=.004$). Among the women who discontinued early, there were no significant differences across the treatment groups in baseline characteristics or most risk factors for CV disease ($P\geq.30$), with the exceptions of total cholesterol (placebo, 238.2 [6.17]; 60-mg/d raloxifene, 240.5 [6.23]; 120-mg/d raloxifene, 234.7 mg/dL [6.08 mmol/L]; $P=.03$) and LDL-C (placebo, 154.8 [4.01]; 60-mg/d raloxifene, 157.5 [4.08]; 120 mg/d raloxifene, 151.7 mg/dL [3.93 mmol/L]; $P=.01$).

Ninety-two percent of participants took at least 80% of the study medication, and 83% took at least 90% of the study medication. Compliance did not differ significantly across treatment groups ($P = .99$ for 80%; $P = .55$ for 90% compliance).

CV Events

Placebo Event Rates. FIGURE 2 summarizes the incidence of CV events among women assigned to receive placebo in the overall cohort and among subsets of women with increasing CV risk scores. Among all participants, the placebo rate of CV events was 3.7% for all CV events, 2.1% for coronary events,

and 1.6% for cerebrovascular events. The rate of coronary and cerebrovascular events increased progressively as the CV risk score increased from 3 to 6 (Figure 2). The placebo event rate for women with a CV risk score of 4 or more was approximately 3.5-fold higher than in the overall cohort: 12.9% for all CV events, 7.6% for coronary events, and 5.4% for cerebrovascular events.

Treatment Comparisons Overall and in Subsets at Higher CV Risk. A total of 272 women experienced at least 1 major CV event during the trial: 156 experienced at least 1 coronary event (31 fatal; 125 nonfatal) and 117 experienced at least 1 cerebrovascular event (14 fa-

tal, 102 nonfatal, and 1 nonfatal event that was subsequently fatal) (TABLE 2). Overall, coronary events included MI or coronary death (44%), unstable angina (39%), and coronary ischemia (17%); cerebrovascular events included nonfatal or fatal strokes (68%) and transient ischemic attacks (32%). The distribution of events was similar among women in the high-risk subset (data not shown).

Kaplan-Meier survival curves show the cumulative incidence of coronary and cerebrovascular events together and coronary and cerebrovascular events alone over time (FIGURE 3). For the total study population, there was no evidence for a time trend of an early in-

Table 2. Summary of Cardiovascular Events at 4-Year Follow-up in Participants in the Multiple Outcomes of Raloxifene Evaluation (MORE) and Randomization Trial

Variables	No. (%)			Overall P Value†	Relative Risk (95% Confidence Interval)*	
	Placebo	Raloxifene			Raloxifene 60 mg/d	Raloxifene 120 mg/d
		60 mg/d	120 mg/d			
All Enrolled Women (N = 7705)						
Total No.	2576	2557	2572
Any cardiovascular event	96 (3.7)‡	82 (3.2)	94 (3.7)	.55	0.86 (0.64-1.15)	0.98 (0.74-1.30)
Nonfatal	82	70	75	.64	0.86 (0.63-1.18)	0.92 (0.67-1.25)
Fatal	15	12	19	.45	0.81 (0.38-1.72)	1.27 (0.65-2.49)
Any coronary event	55 (2.1)	45 (1.8)	56 (2.2)	.51	0.82 (0.56-1.22)	1.02 (0.71-1.47)
Nonfatal§	46	36	43	.55	0.79 (0.51-1.21)	0.94 (0.62-1.41)
Fatal	9	9	13	.60	1.01 (0.40-2.53)	1.45 (0.62-3.36)
Coronary death, MI, UA	45	39	44	.80	0.87 (0.57-1.34)	0.98 (0.65-1.48)
Any cerebrovascular event	41 (1.6)‡	37 (1.4)	39 (1.5)	.91	0.91 (0.58-1.41)	0.95 (0.62-1.47)
Nonfatal	36	34	33	.94	0.95 (0.60-1.52)	0.92 (0.57-1.47)
Fatal	6	3	6	.56	0.50 (0.13-1.96)	1.00 (0.32-3.10)
Any stroke	32	22	26	.40	0.69 (0.40-1.18)	0.81 (0.49-1.36)
Women at Increased Cardiovascular Risk (n = 1035)¶						
Total No.	317	359	359
Any cardiovascular event	41 (12.9)‡	28 (7.8)	28 (7.8)	.03	0.60 (0.38-0.95)	0.60 (0.38-0.95)
Nonfatal	35	24	20	.02	0.61 (0.37-0.99)	0.50 (0.30-0.85)
Fatal	7	4	8	.45	0.50 (0.15-1.67)	1.01 (0.37-2.75)
Any coronary event	24 (7.6)	18 (5.0)	18 (5.0)	.27	0.66 (0.37-1.19)	0.66 (0.37-1.19)
Nonfatal§	20	16	12	.18	0.71 (0.37-1.34)	0.53 (0.27-1.05)
Fatal	4	2	6	.37	0.44 (0.09-2.29)	1.32 (0.38-4.63)
Coronary death, MI, UA	20	18	16	.55	0.79 (0.43-1.47)	0.71 (0.37-1.34)
Any cerebrovascular event	17 (5.4)‡	10 (2.8)	10 (2.8)	.12	0.52 (0.24-1.10)	0.52 (0.24-1.10)
Nonfatal	15	8	8	.09	0.47 (0.21-1.07)	0.47 (0.21-1.07)
Fatal	3	2	2	.78	0.59 (0.10-3.43)	0.59 (0.10-3.43)
All strokes	14	6	6	.03	0.38 (0.15-0.94)	0.38 (0.15-0.94)

*Raloxifene compared with placebo.

†P value for overall treatment group differences (χ^2 test).

‡One woman in the placebo group experienced a nonfatal cerebrovascular event followed by a fatal cerebrovascular event but was not double counted in the analysis of total cardiovascular and total cerebrovascular events.

§Includes nonfatal myocardial infarction (MI), unstable angina (UA), and coronary ischemia.

||Includes nonfatal stroke and transient ischemic attacks.

¶Defined as having 4 or more risk points as described in the "Methods" section.

crease or a later decrease in risk of CV events with raloxifene (Figure 3). During the first year of the trial, there were no significant differences across treat-

ment groups in the number of women with CV events (placebo, 23 [0.8%]; raloxifene 60 mg/d, 25 [0.9%]; raloxifene 120 mg/d, 23 [0.8%]; $P = .94$); coronary

events (placebo, 15 [0.5%]; raloxifene 60 mg/d, 18 [0.7%]; raloxifene 120 mg/d, 13 [0.5%]; $P = .65$), or cerebrovascular events (placebo, 8 [0.3%]; raloxifene 60

Figure 3. Cumulative Incidence of Cardiovascular Events

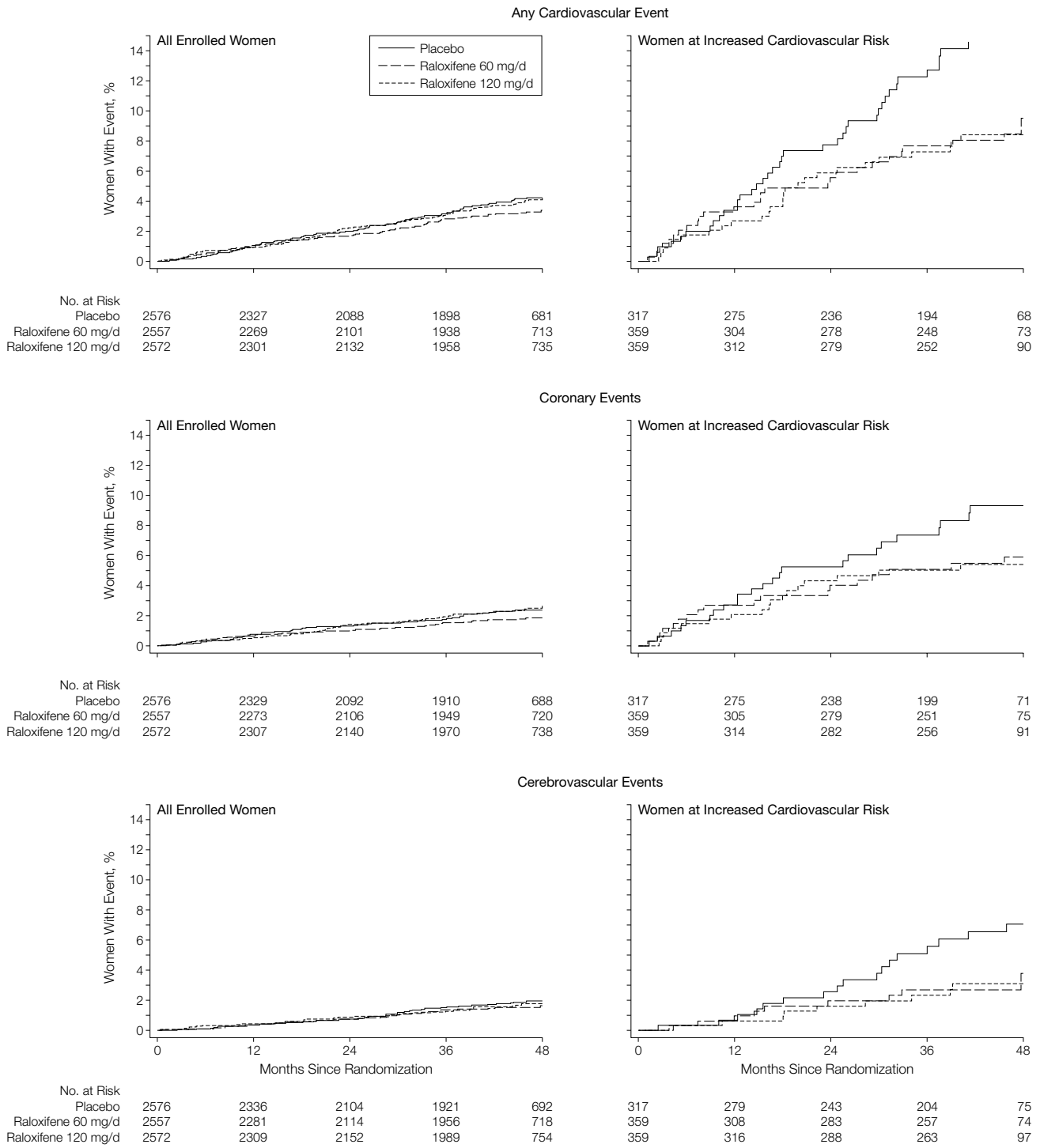
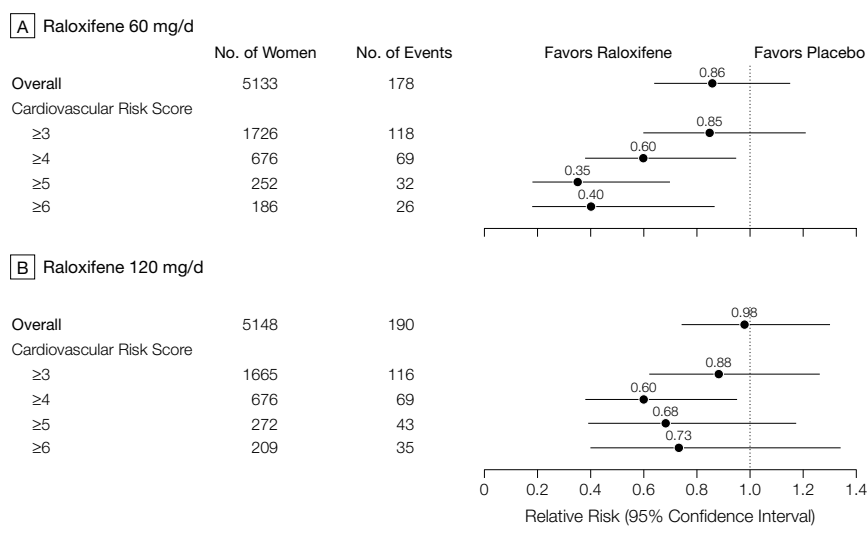


Figure 4. Relative Risk of Any Cardiovascular Events Compared by Raloxifene and Placebo

mg/d, 7 [0.2%]; raloxifene 120 mg/d, 10 [0.3%]; $P = .76$). Similar results were obtained when nonfatal and fatal events were analyzed separately ($P \geq .17$). Pooling raloxifene dose groups, the RR of experiencing any CV event during the first year in the overall study population was 1.05 (95% CI, 0.64-1.72).

In the subset of 1035 women with increased CV risk, there also was no evidence for an early increase in risk of CV events with raloxifene (Figure 3). The number of CV events during the first year among women in the high-risk subset was not significantly different across the treatment groups: 10 (3.1%), placebo; 11 (3.0%), raloxifene 60 mg/d; and 9 (2.5%), raloxifene 120 mg/d ($P = .86$). Pooling the raloxifene dose groups, the RR of experiencing any CV event during the first year among women in the high-risk subset was 0.88 (95% CI, 0.42-1.87). The Kaplan-Meier curves in the high-risk subset diverged beginning after approximately the first year, which continued through 4 years with fewer events in the raloxifene groups compared with placebo (Figure 3).

At 4 years, the incidence of CV events (coronary and cerebrovascular events combined or analyzed individually) among all 7705 participants did not differ significantly across the treatment groups (Table 2). Similar results were ob-

served when nonfatal and fatal events were analyzed separately and for the combined outcomes of coronary death/MI/unstable angina, and all (fatal plus nonfatal) strokes (Table 2). Among the 1035 women in the high-risk subset, there were significantly fewer CV events among women assigned to raloxifene (RR, 0.60; 95% CI, 0.38-0.95 for both raloxifene groups; Table 2). The number of nonfatal CV events also was significantly less in the raloxifene groups (RR, 0.61; 95% CI, 0.37-0.99 for the 60-mg/d group and RR, 0.50; 95% CI, 0.30-0.85 for the 120-mg/d group) in this subset, but the number of fatal CV events was small and not significantly different. Similar trends were observed when coronary and cerebrovascular events were analyzed individually; however, most of the differences were not statistically significant and most of the 95% CIs included 1.0 (Table 2). The exception was the combined outcome of all strokes, for which there were significantly fewer strokes among women receiving raloxifene compared with those receiving placebo (RR, 0.38; 95% CI, 0.15-0.94). The proportion of women in the high-risk subset with a prior MI or evidence of diabetes at baseline, both important risk factors for CV events, was relatively high (approximately 17% for each), and was slightly imbalanced across

treatment groups. However, adjusting the analyses for these baseline variables did not change the inference.

To determine whether the significant reduction in CV events observed with raloxifene among those with 4 or more risk points also was detectable in subsets of women at lower or higher CV risk, we analyzed the RR of CV events in the raloxifene groups compared with placebo across the range of CV risk scores from 3 or more points through 6 or more points (Figure 4). For the raloxifene 60-mg/d group, the risk of CV events among women with a risk score of at least 3 was similar to that in the overall cohort and not reduced significantly compared with placebo. However, as observed for women with at least 4 CV risk points, raloxifene 60 mg/d was associated with significantly lower risk of CV events among subsets of women with risk scores of at least 5 (RR, 0.35; 95% CI, 0.18-0.70) and at least 6 (RR, 0.40; 95% CI, 0.18-0.87). The reduction in risk of CV events with raloxifene 60 mg/d tended to be greater as the CV risk score increased from at least 3 through at least 6 points (Figure 4). Although the risk of CV events tended to be lower in the raloxifene 120-mg/d group compared with placebo among women with a risk score at least 5 or at least 6, the CIs were wide and none were significantly different from placebo (Figure 4).

Only 202 women who were enrolled in the MORE trial had established CHD (prior MI, CABG surgery, or percutaneous coronary intervention): 66, placebo; 56, raloxifene 60 mg/d; and 80, raloxifene 120 mg/d. Among these women, 4 (7.1%) in the raloxifene 60-mg/d group vs 15 (22.7%) in the placebo group experienced a coronary or cerebrovascular event during the trial (RR, 0.31; 95% CI, 0.12-0.82) compared with 12 (15%) in the raloxifene 120-mg/d group (RR, 0.66; 95% CI, 0.33-1.31). Similar results were obtained when coronary events were analyzed separately, but the differences were not statistically significant (RR, 0.39; 95% CI, 0.12-1.31 for raloxifene 60 mg/d; RR, 0.92; 95% CI, 0.39-2.13 for raloxifene 120 mg/d). There were 9 cerebrovascular events among

women with established CHD: 6 (9%) in the placebo, 1 (1.7%) in the raloxifene 60-mg/d (RR, 0.20; 95% CI, 0.03-1.25), and 2 (2.5%) in the raloxifene 120-mg/d (RR, 0.28; 95% CI, 0.06-1.18) groups. There were 11 CV events among women with established CHD during the first year of the trial: 5 (7.5%) in the placebo, 3 (5.3%) in the raloxifene 60-mg/d, and 3 (3.7%) in the raloxifene 120-mg/d groups (RR, 0.71; 95% CI, 0.18-2.82 for raloxifene 60 mg/d and RR, 0.50; 95% CI, 0.13-1.94 for raloxifene 120 mg/d; $P = .60$).

CV Events Identified From Serial ECGs. Serial ECGs obtained at baseline and at 2 and 4 years were analyzed for changes consistent with incident Q wave, MI, or myocardial ischemia. The number of women with incident MI (placebo, 9 [0.4%]; raloxifene 60 mg/d, 8 [0.4%]; raloxifene 120 mg/d, 5 [0.2%]; $P = .22$) or either incident MI or myocardial ischemia (placebo, 110 [4.8%], raloxifene 60 mg/d, 89 [3.9%]; raloxifene 120 mg/d, 89 [3.9%]; $P = .56$) identified from ECG changes from baseline to 4 years was not significantly different between treatment groups.

Serum Lipids

Compared with placebo, raloxifene treatment for 4 years resulted in significant reductions in total and LDL-C but not HDL-C levels (FIGURE 5). Reductions in total cholesterol and LDL-C levels were observed in the raloxifene 60-mg/d and 120-mg/d groups as early as 6 months (median percentage change: total cholesterol, -5% and -6%; LDL-C, -8% and -9%; both $P < .001$ vs placebo), and those levels were maintained throughout the 4 years of the study (Figure 5). The median 2.4% decrease in serum triglyceride levels in the placebo group was significantly different from the median 1.1% and 1.5% increase in serum triglyceride levels in the raloxifene 60-mg/d and 120-mg/d groups, respectively ($P = .004$ for overall treatment group difference). The absolute median increase in serum triglyceride levels in both raloxifene groups was 0.89 mg/dL (0.01 mmol/L) over 4 years. Relative to placebo, the effects of raloxifene on total, LDL-C, and HDL-C

levels among women in the high-risk subset were comparable to those observed in the whole cohort although no significant change in triglyceride levels was observed in this subset (Figure 5).

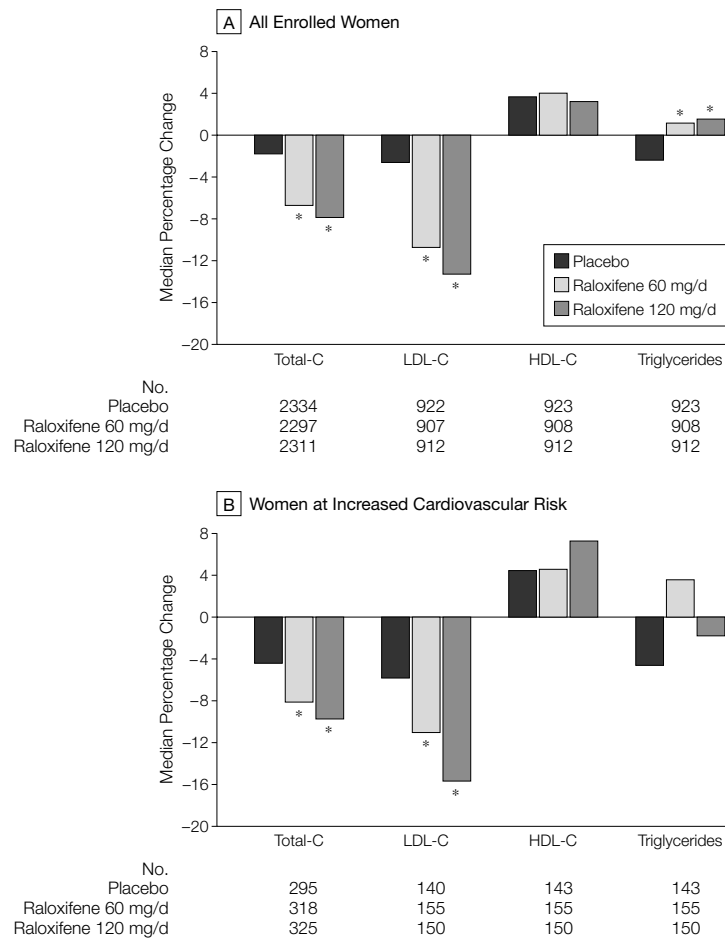
Overall, 1069 women (13.9%) reported taking lipid-lowering therapy at baseline or at any time during the trial. Excluding these women from the analyses, raloxifene decreased total cholesterol and LDL-C levels by an amount comparable to that observed in the overall cohort (data not shown). Significantly fewer women treated with raloxifene initiated new lipid-lowering therapy during the course of the study both in the entire study cohort (pla-

cebo, 232 [9.7%]; raloxifene 60 mg/d, 137 [5.9%]; raloxifene 120 mg/d, 122 [5.1%]; $P < .001$) and among women in the high-risk subset (placebo, 37 [14.5%]; raloxifene 60 mg/d, 28 [9.8%]; raloxifene 120 mg/d, 22 [7.5%]; $P = .03$).

COMMENT

In this secondary analysis of data from this large study of osteoporotic postmenopausal women, raloxifene did not significantly reduce the risk of CV events in the overall study population, which was at relatively low risk for CV events, but it did significantly lower the risk of CV events in a subset of women at high risk for acute coro-

Figure 5. Effect of Raloxifene on Serum Lipid Concentrations



Data represent median percentage changes from baseline to 4 years. Numbers of women represented in each treatment group are shown below each risk factor. Total-C indicates total cholesterol; LDL-C, low-density lipoprotein cholesterol; and HDL-C, high-density lipoprotein cholesterol. The asterisk indicates $P < .05$ compared with placebo (analysis of variance on ranked data).

nary events and in those with established CHD. The number of CV events was small, but there was no evidence that raloxifene treatment was associated with an early increase in CV morbidity or mortality in the overall cohort, among women at high risk for or among women with established CHD.

Women enrolled in the MORE trial were selected for increased risk for osteoporotic fracture rather than for an increased risk of CV disease¹³; thus, the overall study cohort was predominantly women without established CHD and was at relatively low risk for CV events. Overall, CV mortality in MORE (1.5 per 1000 women-years) was less than that reported for women in the general US population (2.95 per 1000 women-years).²⁵ That MORE enrolled women worldwide rather than only in the United States may have contributed to this difference. However, the rate of acute coronary events and mortality in MORE was in the range of those reported previously for postmenopausal women in primary CV prevention studies such as the Women's Health Study²⁶ and the Air Force/Texas Coronary Atherosclerosis Prevention Study²⁷ and is comparable to that observed in the Nurses Health Study.²⁸ We adapted criteria established previously for identification of postmenopausal women at high risk for acute coronary events for enrollment in the RUTH trial²¹ in order to identify 1035 women at increased CV risk in the MORE trial, 202 having experienced a prior coronary event or undergone a procedure and 833 with no prior coronary events but with multiple risk factors. The annual coronary event rate in this subset was about 3.5-fold higher than in the overall cohort, and the progressive increase in coronary and cerebrovascular event rates as the CV risk score increased further supports the validity of the method used to identify women at increased risk. As expected, the incidence of CV events was highest (23%) among the 202 women who entered the MORE trial with established CHD and is comparable with the combined incidence of 28% for coronary and cerebrovascular events observed in HERS.³

During the first year of the trial, the number of fatal or nonfatal events due to coronary artery or cerebrovascular disease did not differ significantly across treatment groups in the overall study population, among the 1035 women at high risk or among the 202 women who entered the study with established CHD. This provides no evidence of an early increase in risk for CV events although there were too few events during the first year to draw more definitive conclusions. Hypotheses suggested to explain the early increase in risk of CV events with HRT observed in HERS,³ WEST,⁷ and other studies^{5,6,9} include a prothrombotic effect on the arterial system similar to the effect of HRT to increase the risk of venous thrombotic events or a proinflammatory effect at the vessel wall that could promote plaque destabilization in women with susceptible lesions.²⁹ The former seems unlikely given the preliminary evidence that neither raloxifene nor tamoxifen³⁰ cause an early increase in CV risk, and yet both increase the risk of venous thromboembolism by a magnitude comparable to that of HRT.^{13,16,17} The finding that, in contrast to HRT,³¹ neither raloxifene¹⁹ nor tamoxifen³² increase C-reactive protein levels in postmenopausal women together with studies showing that HRT increases circulating levels of matrix metalloproteinase-9 (MMP-9)³³ lend support to a proinflammatory hypothesis related to plaque destabilization. However, direct evidence to support a role for C-reactive protein, MMP-9, or other markers of inflammation in early CV risk associated with HRT is lacking.

Although raloxifene did not significantly affect the overall risk of CV events in the total study population, it was associated with a significant 40% reduction in risk of coronary and cerebrovascular events in the 13% of women at high risk. Because of the post hoc nature of these analyses and the relatively small number of events involved, the possibility that the significant risk reduction with raloxifene observed in the high-risk subset was a chance finding cannot be discounted. However, the reduction in risk for CV events was statistically signifi-

cant for raloxifene 60 mg/d across several subsets of women with increasing risk for CV, was consistent over time, and was significant in the small subset of women with established CHD. The separate incidences of coronary and cerebrovascular events were fewer in the raloxifene 60 mg/d group compared with placebo in the high-risk subset although these differences did not reach statistical significance. The effects observed with raloxifene 120 mg/d were less consistent, but whether this represents a true difference in effect between the doses is unknown.

Overall, raloxifene improved total cholesterol and LDL-C levels with no effect on HDL-C levels, effects comparable to those previously reported in a 6-month trial of 390 healthy postmenopausal women.¹⁸ The effects of raloxifene on serum lipid concentrations in the high-risk subset were comparable to those observed for the total cohort. Thus, the effect of raloxifene to lower the risk of CV events in this subset, if real, is not likely explained by a greater improvement in serum lipid concentrations among these women.

There are several limitations to our study. The MORE trial was not designed to test the effect of raloxifene on CV outcomes, and larger trials with greater numbers of events are needed to confirm these findings. Cardiovascular events were assessed by self-report and complete supporting evidence for adjudication of events was not available in many cases. The study was not designed to confirm vital status or to obtain information on CV events occurring in women who discontinued the trial early. The overall incidence and total number of CV events in this trial were small, providing limited power to detect treatment group differences, especially in the number of events through the first year of the trial. Finally, all of the women in MORE had osteoporosis defined by bone mineral density or previous vertebral fracture, so whether these findings can be generalized to non-osteoporotic women is uncertain.

In summary, there was no evidence that raloxifene caused an early increase

in risk of CV events, either overall or among postmenopausal women at high risk for or with CHD. Raloxifene therapy for 4 years did not significantly affect the overall risk of CV events in the total MORE cohort but did significantly reduce the risk of CV events among women at high risk for and among those with established CHD. Before raloxifene is used for prevention of CV events, these findings must be confirmed by an adequately powered, randomized trial with CV events as predefined outcomes.

Author Affiliations: Division of Epidemiology, Department of Family and Preventive Medicine, University of California, San Diego, La Jolla (Dr Barrett-Connor); Department of Epidemiology and Biostatistics, University of California, San Francisco (Dr Grady); Lilly Research Laboratories, Indianapolis, Ind (Drs Sashegyi, Anderson, Cox, and Harper); Medical Center, Railway Hospital, Warsaw, Poland (Dr Hozowski); and Department of Public Health Services, Wake Forest University, Winston-Salem, NC (Dr Rautaharju).

Financial Disclosures: Dr Barrett-Connor has served as a consultant for and has received research support from Eli Lilly & Co. Dr Grady receives or has received salary support via contracts with the University of California, San Francisco, from Berlex Laboratories, Eli Lilly, Pfizer, and Wyeth-Ayerst Research. Drs Sashegyi, Anderson, Cox, and Harper are full-time employees of and own stock in Eli Lilly & Co.

Author Contributions: Dr Barrett-Connor had full access to all the data in this study and takes responsibility for the integrity of the data and accuracy of the data analysis.

Study concept and design: Grady, Anderson, Cox, Harper.

Acquisition of data: Barrett-Connor, Sashegyi, Hozowski, Rautaharju.

Analysis and interpretation of data: Barrett-Connor, Grady, Anderson, Cox, Rautaharju, Harper.

Drafting of the manuscript: Barrett-Connor, Anderson, Cox.

Critical revision of the manuscript for important intellectual content: Barrett-Connor, Grady, Sashegyi, Anderson, Cox, Hozowski, Rautaharju, Harper.

Statistical expertise: Grady, Sashegyi.

Obtained funding: Hozowski.

Administrative, technical, or material support: Anderson, Cox, Rautaharju, Harper.

Study supervision: Barrett-Connor, Harper.

Medical expertise: Anderson.

Principal investigator of ECG laboratory: Rautaharju.

Funding/Support: This study was funded by Eli Lilly & Co.

Role of the Sponsor: The MORE trial protocol was designed by the sponsor in consultation with the coordinating center at the University of California, San Francisco. Study medication and randomization codes were provided by the sponsor. Data on cardiovascular events, on which the present study is based, were by investigators at their respective sites without regard to causality or treatment group assignment. The cardiologists who adjudicated the cardiovascular events were compensated for their time but were not otherwise involved in the trial or associated with the sponsor. Data analyses were performed by the statistical group of the sponsor (Dr Sashegyi) with review by and input from the corresponding author (Dr Barrett-Connor). The manuscript was written by

Drs Barrett-Connor and Cox and was reviewed by each of the coauthors. The manuscript also was reviewed before submission both by a study publications committee consisting of a majority of nonsponsor investigators and by sponsor staff.

Acknowledgment: We are indebted to Kathryn Krueger, MD, for implementation of the study and contributions to the data analysis plan, Somnath Sarkar, PhD, for contributions to the statistical analysis plans and for his guidance and consultancy during the statistical analyses, and to Yiyong Fu, MS, for extensive statistical programming support. We also thank Imre Pavo, MD, for critically reviewing the manuscript, William Groh, MD, and Chamoun Chamoun, MD (Kranert Institute of Cardiology, Indiana University School of Medicine) for adjudication of the cardiovascular events, and all of the MORE trial investigators who made this study possible.

REFERENCES

- Mosca L, Manson JE, Sutherland SE, Langer RD, Manolio T, Barrett-Connor E. Cardiovascular disease in women. *Circulation*. 1997;96:2468-2482.
- Barrett-Connor E, Grady D. Hormone replacement therapy, heart disease, and other considerations. *Annu Rev Public Health*. 1998;19:55-72.
- Hulley S, Grady D, Bush T, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. *JAMA*. 1998;280:605-613.
- Herrington DM, Reboussin DM, Brosnihan KB, et al. Effects of estrogen replacement on the progression of coronary-artery atherosclerosis. *N Engl J Med*. 2000;343:522-529.
- Lenfant C. Statement from Claude Lenfant, MD, Director, National Heart, Lung, and Blood Institute on preliminary trends in the Women's Health Initiative. WHI HRT Update. Bethesda, Md: National Heart, Lung, and Blood Institute; April 6, 2000. Available at: <http://www.nhlbi.nih.gov/whi/hrt-en.htm>. Accessed January 22, 2002.
- Rossouw JE. Early risk of cardiovascular events after commencing hormone replacement therapy. *Curr Opin Lipidol*. 2001;12:371-375.
- Viscoli CM, Brass LM, Kernan WN, Sarrel PM, Sussisa S, Horwitz RJ. A clinical trial of estrogen-replacement therapy after ischemic stroke. *N Engl J Med*. 2001;345:1243-1249.
- Hemminki E, McPherson K. Impact of postmenopausal hormone therapy on cardiovascular events and cancer: pooled data from clinical trials. *BMJ*. 1997;315:149-153.
- Hemminki R, McPherson K. Value of drug-licensing documents in studying the effect of postmenopausal hormone therapy on cardiovascular disease. *Lancet*. 2000;355:566-569.
- Grodstein F, Manson JE, Stampfer MJ. Postmenopausal hormone use and secondary prevention of coronary events in the Nurses' Health Study: a prospective, observational study. *Ann Intern Med*. 2001;135:1-8.
- Heckbert SR, Kaplan RC, Weiss NS, et al. Risk of recurrent coronary events in relation to use and recent initiation of postmenopausal hormone therapy. *Arch Intern Med*. 2001;161:1709-1713.
- Alexander KP, Newby LK, Hellkamp AS, et al. Initiation of hormone replacement therapy after acute myocardial infarction is associated with more cardiac events during follow-up. *J Am Coll Cardiol*. 2001;38:1-7.
- Cummings SR, Eckert S, Krueger KA, et al. The effect of raloxifene on risk of breast cancer in postmenopausal women. *JAMA*. 1999;281:2189-2197.
- Ettlinger B, Black DM, Mitlak BH, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. *JAMA*. 1999;282:637-645.
- Cauley JA, Norton L, Lippman ME, et al. Continued breast cancer risk reduction in postmenopausal

women treated with raloxifene. *Breast Cancer Res Treat*. 2001;65:125-134.

16. Grady D, Wenger NK, Herrington D, et al. Postmenopausal hormone therapy increases risk for venous thromboembolic disease. *Ann Intern Med*. 2000;132:689-696.

17. Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. *J Natl Cancer Inst*. 1998;90:1371-1388.

18. Walsh BW, Kuller LH, Wild RA, et al. Effects of raloxifene on serum lipids and coagulation factors in healthy postmenopausal women. *JAMA*. 1998;279:1445-1451.

19. Walsh BW, Paul S, Wild RA, et al. The effects of hormone replacement therapy and raloxifene on C-reactive protein and homocysteine in healthy postmenopausal women: a randomized, controlled trial. *J Clin Endocrinol Metab*. 2000;85:214-218.

20. Saitta A, Altavilla D, Cucinotta D, et al. Randomized, double-blind, placebo controlled study on the effects of raloxifene and hormone replacement therapy on plasma nitric oxide concentrations, endothelin-1 levels and endothelium-dependent vasodilation in postmenopausal women. *Arterioscler Thromb Vasc Biol*. 2001;21:1512-1519.

21. Mosca L, Barrett-Connor E, Wenger NK, et al. Design and methods of the Raloxifene Use for The Heart (RUTH) study. *Am J Cardiol*. 2001;88:392-395.

22. Rautaharju PM, Calhoun HP, Chaitman BR. NOVACODE serial ECG classification system for clinical trials and epidemiologic studies. *J Electrocardiol*. 1992;24(suppl):179-187.

23. Rautaharju PM, Park LP, Chaitman BR, Rautaharju F, Zhang ZM. The NOVACODE criteria for classification of ECG abnormalities and their clinically significant progression and regression. *J Electrocardiol*. 1998;31:157-187.

24. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem*. 1972;18:499-502.

25. Biostatistical Fact Sheet. Women and cardiovascular disease. Washington, DC: American Heart Association. Available at: <http://216.185.102.50/statistics/biostats/biowow.htm>. Accessed October 22, 2001.

26. Lee IM, Cook NR, Manson JE, Buring JE, Hennekens CH. Beta-carotene supplementation and incidence of cancer and cardiovascular disease: the Women's Health Study. *J Natl Cancer Inst*. 1999;91:2102-2106.

27. Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels. *JAMA*. 1998;279:1615-1622.

28. Grodstein F, Manson JE, Colditz GA, Willett WC, Speizer FE, Stampfer MJ. A prospective, observational study of postmenopausal hormone therapy and primary prevention of cardiovascular disease. *Ann Intern Med*. 2000;133:933-941.

29. Herrington DM. The HERS trial results: paradigms lost? *Ann Intern Med*. 1999;131:463-466.

30. Reis SE, Costantino JP, Wickerham DL, Tanchiu E, Wang J, Kavanah M. Cardiovascular Effects of Tamoxifen in Women With and Without Heart Disease: Breast Cancer Prevention Trial. *J Natl Cancer Inst*. 2001;93:16-21.

31. Cushman M, Legault C, Barrett-Connor E, et al. Effect of postmenopausal hormones on inflammation-sensitive proteins: the postmenopausal Estrogen/Progestin interventions (PEPI) study. *Circulation*. 1999;100:717-722.

32. Cushman M, Costantino JP, Tracy RP, et al. Tamoxifen and cardiac risk factors in healthy women: suggestion of an anti-inflammatory effect. *Arterioscler Thromb Vasc Biol*. 2001;21:255-261.

33. Zanger D, Yang BK, Ardans J, et al. Divergent effects of hormone therapy on serum markers of inflammation in postmenopausal women with coronary artery disease on appropriate medical management. *J Am Coll Cardiol*. 2000;36:1797-1802.