OBJECTIVES

We sought to assess the effects of raloxifene, a selective estrogen receptor modulator, on arterial physiology and biology in postmenopausal women with coronary artery disease (CAD).

BACKGROUND

Raloxifene improves endothelial function and markers of vascular health in vitro in experimental animals and in healthy postmenopausal women. In women whose arteries are affected by advanced atherosclerosis, however, the vascular effects of estrogen receptor modulation are unknown.

METHODS

We conducted a prospective, randomized, double-blinded, placebo-controlled, crossover trial of raloxifene, 60 mg/day for 8 weeks, in 33 consecutively eligible and consenting postmenopausal women age 50 to 75 years with known CAD. Parameters measured at the beginning and end of each treatment period included brachial artery flow-mediated dilation (FMD), the primary end point, as well as nitroglycerin-induced dilation, peripheral artery tonometry, serum lipoprotein levels, and markers of vascular function, including urinary prostaglandin, serum endothelin-1, and fibrinogen levels.

RESULTS

Baseline FMD was impaired in these women, as expected (2.84 ± 0.60%), but there was no significant difference between the effect of raloxifene (0.26 ± 0.66% increase) and placebo (0.01 ± 0.63% decrease) on this marker of endothelial function (p = 0.82). No significant raloxifene-related effects were observed on derived aortic pressure, pulse pressure, augmentation index, total cholesterol or low- and high-density lipoprotein subfractions, markers of thrombosis, or vasoconstrictor or vasodilator substances.

CONCLUSIONS

In postmenopausal women with treated CAD, selective estrogen receptor modulation with raloxifene does not improve a comprehensive set of parameters examining vascular function and serum lipoprotein levels. (J Am Coll Cardiol 2003;42:698–704) © 2003 by the American College of Cardiology Foundation
secondary prevention. This question has not previously been addressed. The situation might be expected to be different in subjects with diseased versus healthy arteries, where the effects of concomitant medications as well as advanced atherosclerosis, per se, might alter the vascular responses to selective estrogen receptor modulation. Data from the Multiple Outcomes of Raloxifene Evaluation (MORE) study (12) have suggested a cardiovascular benefit from raloxifene treatment in older women at increased risk of cardiovascular disease, whereas in the overall population, the study suggested a neutral effect. Therefore, we undertook a prospective, double-blinded, placebo-controlled study to assess the effects of raloxifene treatment on vascular physiology and biology in women with known CAD.

METHODS

Subjects. We recruited 33 consecutively eligible and consenting women age 50 to 75 years who were clinically stable and asymptomatic but had documented evidence of CAD (i.e., previously documented myocardial infarction, coronary artery bypass graft surgery, and/or angiography showing at least one coronary lesion with >70% stenosis). Eligible subjects had had no menses for >18 months, had never taken hormone replacement therapy (HRT), and had stable use or non-use of lipid-lowering medications or antihypertensive and/or antiplatelet therapy for at least six months before the study. There had also been no change in their smoking pattern for >6 months before the study. Subjects were excluded if they had a history of regular therapy with nitrates or clinical evidence of heart failure, intercurrent Raynaud’s phenomenon, and/or a history of venous thromboembolism. Subjects were only included if their postmenopausal status was confirmed by a serum follicle-stimulating hormone level >40 IU/l at the screening visit. The subjects were asked not to alter their medication for the duration of the study, other than at the direction of their managing physician. The institutional ethics committee approved the study, and each woman gave written, informed consent.

Study design. Subjects were randomized to raloxifene or matching placebo (Eli Lilly, Indianapolis, Indiana) in a double-blinded, cross-over study. Each subject was seen on five occasions. At the first visit (study screen), each participant underwent a general physical examination and medical history assessment, as well as follicle-stimulating hormone measurement. Subjects returned for four further visits: at baseline and after eight weeks of either raloxifene or placebo, with a minimum four-week washout period between treatment regimes (Fig. 1). At each visit, subjects presented at the same time of morning and had fasted since 10 PM on the previous night. Subjects also refrained from taking any medications on the morning of the test, until completion of the examination. Endothelium-dependent and independent dilation, peripheral artery tonometry, heart rate, and blood pressure were measured as described subsequently. Blood was collected and placed on ice for biochemical studies (total cholesterol, low-density lipoprotein [LDL], and high-density lipoprotein [HDL] cholesterol, triglycerides, lipoprotein[a], endothelin-1, antithrombin III [AT III], fibrinogen), and urine was sampled for prostacyclin metabolites and creatinine levels.

If eligible, subjects were randomized to receive either raloxifene 60 mg/day or image-matched placebo for eight weeks. Subjects were instructed to take one tablet each morning, but to exclude the raloxifene or placebo tablet on the day of their next visit to the study center (after eight weeks). Compliance was estimated by return tablet counts.

Peripheral artery tonometry. Central arterial pressure, waveform, and the degree of pulse pressure augmentation by pulse wave reflection were studied noninvasively by sphygmocardiography (PWV Medical Blood Pressure Analysis System, Sydney, Australia) using applanation tonometry, as described by Karamanoglu et al. (13). The aortic augmentation index, aortic systolic pressure, and pulse pressure were derived from the mean value of each of the three optimized

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**Figure 1.** Study design: raloxifene and vascular reactivity.
Biochemical studies. Serum lipoproteins. The reproducibility under these test conditions (14) have previously demonstrated a high level of accuracy and by the average baseline diameter. We and other investigators index was calculated as nanograms of PGF 1

Ultrasound studies. Following tonometry studies, brachial artery reactivity was assessed by ultrasound using an ATL HDI 5000 machine (Phillips, Bothell, Washington) with a wide-band 12- to 5-MHz linear-array transducer. All studies were carried out at one site by one of two experienced sonographers. We measured changes in brachial artery diameter in response to reactive hyperemia-induced flow-mediated dilation (FMD), the primary end point, and also in response to glyceryl trinitrate (GTN), by scanning the right brachial artery longitudinally 6 to 15 cm above the elbow, as described in detail previously (14). A reliable anatomic “marker” (vein, arterial branch, or muscle sheath) was identified to allow reproducible location of the same section of artery for each of the four visits for each subject.

All ultrasound were recorded on super-VHS tape and later analyzed by two independent observers who were blinded to the identity of the subject, the stage of the experiment, and the scan sequence. For calculation of FMD, the vessel diameter at 45 to 60 s after cuff deflation was divided by the average baseline diameter. We and other investigators have previously demonstrated a high level of accuracy and reproducibility under these test conditions (14).

Biochemical studies. Serum lipoproteins. Total cholesterol and triglycerides were measured by standard enzymatic methods, using a Hitachi 917 automatic analyzer. Levels of HDL cholesterol were measured after precipitation with dextran sulfate magnesium, and LDL cholesterol was calculated using the Friedewald equation. Lipoprotein(a) was measured using a Mercodia apolipoprotein A solid-phase, two-site immunoradiometric assay (Mercodia AB, Uppsala, Sweden).

Urinary prostacyclin metabolites and creatinine. Urinary 2,3-dinor-6-keto-prostaglandin F1α (PGF1α) was assayed by radioimmunoassay after extraction and thin-layer chromatography, using a previously described method (15). Urinary creatinine was measured using the kinetic Jaffe reaction. Alkaline picate was measured at 505 nm on the Hitachi 917 analyzer. The PGF1α/creatinine index was calculated as nanograms of PGF1α/(mmol/l creatinine × 0.000113) and assigned arbitrary units, to normalize this measure of systemic prostacyclin production for renal function.

Endothelin-1. A commercially available sandwich enzyme-linked immunosorbent assay (Biomedica, Vienna, Austria) was used to measure endothelin-1 levels in ethylene diamine-tetra acetic acid-plasma samples from blood collected after each visit. Plasma stored at −70°C was thawed and added to wells containing solid-phase mouse anti-human endothelin-1 polyclonal antibody. Absorbance was measured at 450 nm against 690 nm as a reference, using a Sunrise Remote plate reader (Tecan, Grödig, Austria). The endothelin-1 standard curve was linear from 0 to 12.4 fmol/ml.

AT III and fibrinogen. Plasma AT III was measured using a STA-Stachrom AT III chromogenic assay kit (Diagnostica Stago, Asnières, France). Fibrinogen levels were determined using the Clauss method (16).

Statistical analysis. Descriptive data are expressed as the mean value ± SEM. The prospectively defined primary end point of this study was the change in FMD (post-treatment minus pre-treatment values) on raloxifene versus placebo. The changes on active and placebo treatments were compared by the paired Student t test and corrected for multiple comparisons (17,18). Baseline values before each treatment were also compared by the paired t test corrected. The treatment “order effect” was explored using standard regression techniques in terms of changes from baseline values for all outcome variables. Statistical significance was inferred at two-sided p < 0.05, and comparisons used intention-to-treat analyses.

The study power was calculated on an expected baseline FMD of 4 ± 0.5% (mean ± SEM), based on our previous studies in women with known CAD (19), as well as other studies showing raloxifene to have no less than half of the effect of conventional estrogen replacement on FMD (20,21). Using these conservative estimates, this study of 33 women had over 90% power to detect a 3% improvement in FMD at the two-sided p ≤ 0.05 significance level, using data from our previous studies of measurement reproducibility (14). The study also had sufficient power (>80%) to detect changes in tonometric indexes and endothelin-1 levels, of the magnitude previously observed with raloxifene and estrogen in healthy postmenopausal women (11,22).

Results

Subjects. All 33 postmenopausal women enrolled in the study (66 ± 6 years old) completed both treatments arms, with 96% compliance for raloxifene and 97% for placebo. Baseline characteristics are listed in Table 1. There were no major or minor adverse events reported throughout the treatments, and all women were clinically stable and well. All subjects had CAD documented by angiography, with ≥70% stenosis in at least one major epicardial artery. Twenty-six subjects previously had coronary artery bypass grafting, and 13 had percutaneous transluminal coronary angioplasty before enrollment (3.1 ± 0.4 years). Eighteen subjects previously had a myocardial infarction. Seventeen subjects had a history of hypertension, and five had non-insulin-dependent diabetes mellitus. Thirteen subjects had a family history of CAD in a first-degree relative <55 years of age. Of the 33 subjects included, 6 currently smoked and 7 were ex-smokers. The mean cigarette exposure in the smokers was 13 ± 4 pack-years. All 33 women in the trial were taking cardioactive medications at the time of enrollment (Table 2), but none changed drugs or dosages during the treatment phases or washout period.
Table 1. Effects of Raloxifene and Placebo in Postmenopausal Women With Coronary Artery Disease

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Raloxifene</th>
<th>Placebo</th>
<th>ΔChange</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline vessel diameter (mm)</td>
<td>3.56 ± 0.09</td>
<td>3.38 ± 0.09</td>
<td></td>
</tr>
<tr>
<td>Baseline blood flow (l/min)</td>
<td>66 ± 9</td>
<td>60 ± 8</td>
<td></td>
</tr>
<tr>
<td>Reactive hyperemia (%)</td>
<td>985 ± 178</td>
<td>914 ± 86</td>
<td></td>
</tr>
<tr>
<td>Flow-mediated dilation (%)</td>
<td>2.84 ± 0.60</td>
<td>3.10 ± 0.66</td>
<td></td>
</tr>
<tr>
<td>GTN-mediated dilation (%)</td>
<td>11.70 ± 1.15</td>
<td>14.13 ± 1.03</td>
<td></td>
</tr>
<tr>
<td>Aortic SBP (mm Hg)</td>
<td>138 ± 3</td>
<td>136 ± 4</td>
<td></td>
</tr>
<tr>
<td>Pulse pressure (mm Hg)</td>
<td>56 ± 3</td>
<td>56 ± 3</td>
<td></td>
</tr>
<tr>
<td>Augmentation index (%)</td>
<td>33 ± 1</td>
<td>32 ± 1</td>
<td></td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>66 ± 2</td>
<td>66 ± 2</td>
<td></td>
</tr>
<tr>
<td>Brachial blood pressure (mm Hg)</td>
<td>146/79 ± 4/2</td>
<td>144/76 ± 4/2</td>
<td></td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>4.9 ± 0.2</td>
<td>4.7 ± 0.1</td>
<td></td>
</tr>
<tr>
<td>LDL cholesterol (mmol/l)</td>
<td>2.7 ± 0.1</td>
<td>2.5 ± 0.1</td>
<td></td>
</tr>
<tr>
<td>HDL cholesterol (mmol/l)</td>
<td>1.37 ± 0.06</td>
<td>1.29 ± 0.06</td>
<td></td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>1.9 ± 0.1</td>
<td>2.0 ± 0.1</td>
<td></td>
</tr>
<tr>
<td>Lipoprotein(a) (mg/l)</td>
<td>540 ± 79</td>
<td>526 ± 77</td>
<td></td>
</tr>
<tr>
<td>Fibrinogen (g/l)</td>
<td>3.7 ± 0.1</td>
<td>3.3 ± 0.1</td>
<td></td>
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<tr>
<td>Antithrombin III (IU/ml)</td>
<td>1.10 ± 0.02</td>
<td>1.05 ± 0.03</td>
<td></td>
</tr>
<tr>
<td>Endothelin-1 (fmol/ml)</td>
<td>1.02 ± 0.24</td>
<td>1.10 ± 0.27</td>
<td></td>
</tr>
<tr>
<td>PGFl2/creatinine index (u)</td>
<td>514 ± 107</td>
<td>460 ± 78</td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as the mean value ± SEM. When comparing the change with raloxifene to that with placebo, there were no significant differences in any of the measured parameters.

Cl = confidence intervals; GTN = glyceryl trinitrate; HDL and LDL = high- and low-density lipoprotein; PGFl2 = 2,3-dinor-6-keto-prostaglandin F1α; SBP = systolic blood pressure.

Vascular reactivity studies. Baseline vessel diameter, blood flow, and degree of reactive hyperemia after cuff release did not alter significantly over the course of the study (Table 1). Similarly, raloxifene treatment did not have a significant effect on these parameters, as compared with placebo. Multiple linear regression analysis did not reveal any “order effect” in subjects randomly assigned to raloxifene treatment before placebo. There was a small but not statistically significant difference in FMD after treatment with raloxifene (0.26 ± 0.66% increase) compared with placebo (0.01 ± 0.63% decrease; p = 0.82) (Fig. 2).

Furthermore, we did not find a significant difference in GTN-mediated dilation after active treatment with raloxifene (2.43 ± 1.15% increase) compared with placebo (0.58 ± 1.00% increase). Similarly, raloxifene had no significant effect on FMD or GTN responses when only the nonsmokers (n = 20) or current/former smokers (n = 13) were analyzed separately. In the entire subject group, neither FMD nor GTN at baseline correlated significantly with the baseline lipoprotein or blood pressure levels.

Table 2. Concomitant Medication Usage by the 33 Postmenopausal Women With Coronary Artery Disease

<table>
<thead>
<tr>
<th>Medications</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>28</td>
</tr>
<tr>
<td>Statins</td>
<td>27</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>9</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>9</td>
</tr>
<tr>
<td>AT II receptor antagonists</td>
<td>4</td>
</tr>
<tr>
<td>Fish oil</td>
<td>2</td>
</tr>
<tr>
<td>Fibrates</td>
<td>1</td>
</tr>
</tbody>
</table>

ACE = angiotensin-converting enzyme; AT II = angiotensin II.

Tonometry. Aortic systolic blood pressure did not alter throughout the course of the study (following raloxifene: 136 ± 4 mm Hg; following placebo: 134 ± 2 mm Hg). Similarly, for raloxifene versus placebo, there were no significant differences in pulse pressure (56 ± 3 mm Hg vs. 55 ± 2 mm Hg) or the augmentation index (32 ± 1% vs. 33 ± 1%). There was no difference in the resting heart rate of subjects due to treatment with raloxifene versus placebo (66 ± 2 beats/min vs. 65 ± 2 beats/min). Brachial artery blood pressure did not significantly alter throughout the study (raloxifene: 144/76 ± 4/2 mm Hg; placebo: 140/75 ± 3/1 mm Hg).

Lipoproteins. Total cholesterol measured after raloxifene was 4.7 ± 0.1 mmol/l, as compared with 5.1 ± 0.2 mmol/l...
for placebo (p = NS) (Table 1). Levels of LDL cholesterol after raloxifene (2.5 ± 0.1 mmol/l) were similar to those with placebo (2.8 ± 0.2 mmol/l). Likewise, there was no significant change in HDL cholesterol levels after raloxifene (1.29 ± 0.06 mmol/l), as compared with placebo (1.36 ± 0.07 mmol/l). Levels of triglycerides and lipoprotein(a) remained unchanged throughout the study.

**Hemostatic parameters.** Fibrinogen was not significantly affected by either treatment (following raloxifene: 3.3 ± 0.1 g/l; placebo: 3.6 ± 0.1 g/l). No change was observed in plasma levels of AT III (raloxifene: 1.05 ± 0.03 IU/ml; placebo: 1.10 ± 0.02 IU/ml).

**Vasodilator/vasoconstrictor parameters.** There was no significant difference in levels of endothelin-1 measured after each treatment (raloxifene: 1.10 ± 0.27 fmol/l; placebo: 1.20 ± 0.25 fmol/l), as compared with the corresponding baseline values. Furthermore, the PGI1c/creatinine index was not significantly altered by either treatment arms (following raloxifene: 460 ± 78 U; placebo: 427 ± 64 U).

**DISCUSSION**

In this study, we have found that clinically relevant doses of raloxifene, shown to improve bone mineral density (8), as well as vascular function (11) in healthy postmenopausal women, had no measurable effect on markers of endothelial- or smooth muscle-dependent dilator function, arterial pressure waveform, blood pressure, serum lipoproteins, and markers of thrombosis and vascular tone control when administered for eight weeks to postmenopausal women with known CAD.

The neutral finding of this study is surprising in the context of previously published results. In vitro, raloxifene has been shown to stimulate NO release rapidly from cultured human endothelial cells, via nongenomic activation of endothelial nitric oxide synthase (eNOS) (9). In experimental animals, raloxifene dilates healthy rabbit coronary arteries via an estrogen receptor- and NO-dependent pathway (10). Similarly, raloxifene improves endothelial dysfunction in spontaneously hypertensive rats by increasing NO release (23). Rapid relaxation has also been reported in femoral veins from ovariectomized female pigs after treatment with raloxifene (24). In healthy postmenopausal women, raloxifene improves flow-mediated vasodilation of the brachial artery (11), a NO-dependent response, consistent with the in vitro findings in healthy human cells, as described earlier.

The results of our study in women with CAD suggest that the situation is different in the setting of advanced atherosclerosis. This may be due to the effects of atherosclerosis itself and/or the effects of therapies used in its treatment. Firstly, eNOS levels are markedly reduced in the presence of atherosclerosis (25), potentially limiting the beneficial effects that estrogen receptor modulation may have via increasing NO production.

Secondly, many of the women in this study were taking cardioactive medications, such as statins and/or antihypertensive agents, including angiotensin-converting enzyme inhibitors. Such treatments are well known to alter endothelial function, vascular compliance, lipoprotein levels, and vasodilator or vasoconstrictor bioavailability (26,27). We aimed to assess the effects of raloxifene in women with atherosclerosis in the presence of their normal treatment regimens, not only for ethical reasons but also to mimic the “real-life” situation in which any additional treatment for “secondary prevention” would be prescribed.

Thirdly, it may be that our sample size was too small to detect an important effect. By using a cross-over, placebo-controlled design and estimating effect sizes from previous publications reporting the effects of selective estrogen receptor modulators and HRT on the parameters measured in the current study, our study was estimated to have >90% power to demonstrate significant treatment-associated effects on the primary end point—arterial endothelial function—and similar power for many of the secondary end points measured. Regarding some measurements, a relatively small sample size may have had an impact on our results. For example, raloxifene treatment was associated with an approximate 10% fall in LDL cholesterol and fibrinogen levels in our study, which were not statistically significant results, but data consistent with the findings of other larger studies (4,8).

It may also be possible that the length of time for active treatment (eight weeks) was insufficient to confer beneficial effect in these subjects. Still, eight weeks should indeed be sufficient to measure significant changes in the major end point—FMD—considering the apparent nongenomic mechanism of action (i.e., increased eNOS activity), with no accompanying increase in eNOS messenger ribonucleic acid or protein synthesis (9). Furthermore, major studies of the estrogen effects on vascular reactivity, even if via a genomic effect on eNOS, have similarly utilized treatment durations of several weeks only (20,21).

In this study, we measured a large number of parameters, which reflect arterial health as “surrogate” end points. The primary end point—arterial FMD—is well documented to reflect endothelial NO release (28), a key mediator in vascular health, and to be predictive of cardiovascular event rates (29). Brachial FMD correlates well with coronary endothelial function (30) and can be measured noninvasively and reproducibly (14), thereby lending itself to serial study of treatment effects on vascular reactivity. Previous studies using endothelial function as an end point, with statins and angiotensin-converting enzyme inhibitors as examples (31,32), have generally shown that treatments associated with improved arterial endothelium-dependent dilation are also associated with improved clinical outcomes in large clinical end-point trials (33,34). Our study’s secondary end points were chosen to allow a comprehensive assessment of vascular and serum parameters known to be
related to atherothrombosis, such as arterial compliance, lipoprotein levels, and markers of thrombosis.

Despite our neutral findings with raloxifene in older women with atherosclerosis, Clarke et al. (35) have recently documented that another selective estrogen receptor modulator—tamoxifen—increases FMD in men both with and without obstructive stenoses on coronary angiography, as well as decreasing lipoprotein and fibrinogen levels. We and other investigators (36,37) have previously documented important gender specificity of certain gender steroid-related influences on the vasculature (i.e., marked differences in the vascular and cellular responses of men and women to estrogens and androgens, related to differences in cellular receptor numbers and function). It may be speculated that such gender differences may also exist with regard to responses to estrogen receptor modulators, just as there may be differences in the characteristics of individual selective estrogen receptor modulators.

It has been suggested previously that raloxifene may be of some benefit for the treatment of hypertension, especially in patients with atherosclerosis, because of the other associated beneficial effects of raloxifene treatment, such as increased endothelium-dependent vasodilation (10,11). Indeed, blood pressure levels have been significantly decreased in spontaneously hypertensive rats treated with raloxifene (23). The results of our study, however, did not show any significant effect on blood pressure, in either the 17 subjects studied who had a history of hypertension, currently taking other medications for controlling this, or in the 16 normotensive subjects enrolled.

There are a number of published reports describing the beneficial effects of raloxifene treatment on lipoprotein profiles in healthy postmenopausal women. Raloxifene has been shown to decrease total cholesterol, LDL cholesterol, and lipoprotein(a) levels (8,38), factors which are well established as independent risk factors for CAD. Levels of HDL cholesterol and triglycerides, however, remain unchanged by raloxifene in healthy postmenopausal women (8,12,38). Despite these findings, which support a potential beneficial role for raloxifene in reducing cardiovascular risk, our study in women with established CAD has shown no significant effects of raloxifene treatment on lipid profiles. A significant contributing factor to the apparent lack of positive effects on lipid profiles may be related to pharmacologic control of lipids in the majority of these subjects by hydroxymethylglutaryl coenzyme A reductase inhibitors and/or the relatively short duration of the active treatment period.

Raloxifene is a member of the estrogen receptor modulator family, a class of compounds introduced to avoid the side effects of natural estrogen and progesterone treatments. Raloxifene has been shown to be clinically effective for the prevention of postmenopausal osteopenosis and to reduce the risk of invasive breast cancer, with no apparent increase in the risk of endometrial cancer, unlike with natural estrogen therapies (39). Furthermore, conventional HRT is associated with increased levels of C-reactive protein (5), indicating possible proinflammatory effects. In contrast, studies with raloxifene do not report an increase in plasma C-reactive protein (4,5), suggesting no indication of inflammation in healthy postmenopausal women as the result of treatment. It has also been reported that serum homocysteine levels are lowered by raloxifene (5).

In contrast, the results of the current study do not demonstrate important vascular effects of raloxifene treatment in postmenopausal women with treated CAD. The dosage used was similar to that in the more encouraging in vitro animal and healthy human studies cited earlier. As the subpopulation of high-risk women in the MORE study (12) did appear to have lower cardiovascular event rates while on raloxifene during follow-up, the place of this treatment in cardiovascular protection awaits publication of the large, ongoing Raloxifene Use for The Heart (RUTH) study (40), examining the effects of raloxifene on clinical outcomes in secondary as well as high-risk primary prevention.

**References**

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