Selective Estrogen-Receptor Modulators —
Mechanisms of Action and Application to Clinical Practice
B. Lawrence Riggs, M.D., and Lynn C. Hartmann, M.D.

The selective estrogen-receptor modulators (SERMs) represent a major therapeutic advance for clinical practice. Unlike estrogens, which are uniformly agonists, and antiestrogens, which are uniformly antagonists, the SERMs exert selective agonist or antagonist effects on various estrogen target tissues. The SERMs are chemically diverse compounds that lack the steroid structure of estrogens (Fig. 1) but possess a tertiary structure that allows them to bind to the estrogen receptor. Although some members of this class of drugs have been available for decades, their tissue-specificity in humans has only recently been recognized. Certain phytoestrogens, such as genistein, also appear to have SERM-like properties.

In this article we review the emerging understanding of the molecular basis of action of SERMs, summarize their tissue-selective agonist–antagonist effects, and place in perspective their therapeutic uses as compared with estrogen or nonestrogen alternatives.

MECHANISMS OF ACTION

In the classic model of estrogen action, the unoccupied nuclear estrogen receptor resides in the nuclei of target cells in an inactive form. Binding to an agonist, such as estradiol, alters the physicochemical properties of the estrogen receptor, allowing the receptor dimer to interact with specific DNA sequences (estrogen response elements) within the promoters of responsive genes. The DNA-bound estrogen receptor then regulates target-gene transcription, either positively or negatively (Fig. 2). However, the recognition that tamoxifen and other SERMs have tissue-specific agonist–antagonist activity led to the realization that the classic model was incomplete and that estrogen action was more complex than had been thought. The mechanisms of the tissue-selective, mixed agonist–antagonist action of SERMs, although still only partly understood, are gradually becoming clearer.

Most of the unique pharmacology of SERMs can be explained by three interactive mechanisms: differential estrogen-receptor expression in a given target tissue, differential estrogen-receptor conformation on ligand binding, and differential expression and binding to the estrogen receptor of coregulator proteins (Fig. 2).

First, target cells for estrogen action contain varying concentrations of homodimers of one or both of two species of estrogen receptors — estrogen receptor α and estrogen receptor β — as well as estrogen receptor α–estrogen receptor β heterodimers. Mice with genetic disruptions of estrogen receptor α and estrogen receptor β display different phenotypes, demonstrating that each receptor has a distinct action. Estrogen receptor α is almost always an activator, whereas estrogen receptor β can inhibit the action of estrogen receptor α by forming a heterodimer with it. Moreover, microarray analysis in mice with deletions of estrogen receptor α or estrogen receptor β showed...
that estrogen receptor β inhibited the transcription of 240 estrogen-responsive genes by 46 percent. Thus, the relative levels of expression of these two receptor isoforms will affect the cellular responsiveness to estrogens. Since two SERMs, raloxifene and tamoxifen, also bind to both isoforms, these drugs will affect the cellular responsiveness as well. Indeed, these SERMs function as pure antagonists when acting through estrogen receptor β on genes containing estrogen response elements but can function as partial agonists when acting on them through estrogen receptor α.

Second, protein crystallography and techniques that evaluate surface changes have shown that binding by estradiol, tamoxifen, raloxifene, or the pure estrogen antagonist ICI 164,384 results in a unique estrogen-receptor conformation for each ligand. Thus, the ligand binding results in various estrogen-receptor conformations that range from that assumed when the receptor is bound to estrogens at one extreme to that assumed when the receptor is bound to antiestrogens at the other extreme. SERM-bound estrogen receptors assume a continuum of intermediate shapes.

Third, more than 20 coregulator proteins have been discovered that bind to estrogen receptors and modulate their function, each acting as either a positive or a negative transcriptional regulator (a coactivator or a corepressor, respectively). Depending on the unique receptor conformation induced by ligand binding, varying combinations of coregulator proteins interact with the estrogen receptor and modulate its function in a variety of ways. The relative and absolute levels of expression of coreg-
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ulator proteins vary among estrogen target cells. In an important recent study, Shang and Brown found that tamoxifen and raloxifene, which are antiestrogens for the breast, act on mammary cells by recruiting corepressors to estrogen-receptor target promoters. In contrast, tamoxifen, which is an estrogen agonist for the endometrium, acts in endometrial cells by recruiting coactivators to the estrogen-receptor target promoters, whereas this recruitment does not occur with raloxifene, which has a neutral effect on the endometrium. The investigators also found that the tamoxifen–estrogen receptor α complex activates transcription by tethering to promoters that do not contain estrogen response elements through protein-to-protein contacts with other DNA-bound transcription factors. Moreover, the agonist effect of tamoxifen was dependent on a higher concentration of a key coactivator, steroid receptor coactivator-1 (SRC-1), in the endometrial cells. Thus, variable local concentrations of different coregulator proteins may contribute to the tissue-selective pharmacology of SERMs. Some SERMs may also facilitate the interaction of the estrogen receptor with yet-to-be-identified coactivators with which it would not normally couple. The implication of this model is that SERM activity will be influenced by the relative levels of expression of the cofactors (corepressors and coactivators) in target cells.

Figure 2. Estrogen-Receptor Action.

On binding an agonist or an antagonist, the estrogen receptor (the α or β isoform) undergoes a conformational change that permits its spontaneous dimerization and facilitates the subsequent interaction of the dimer with estrogen response elements (EREs) located within target genes. It has been determined that estrogen facilitates the interaction of the estrogen receptor with coactivators. An antagonist-activated estrogen receptor, on the other hand, interacts preferentially with a corepressor protein. The binding of different SERMs to the receptor permits it to adopt conformational states distinct from that induced by classic agonists or antagonists. The weight of available evidence suggests that the structure of some SERM–estrogen-receptor complexes favors corepressor recruitment and that of others favors some affinity for known coactivators. A model of the molecular action of estrogens and SERMs is shown in Figure 2.

ACTION ON TARGET TISSUES

In recent years estrogen has been the most frequently prescribed drug in the world. It was reported in 1999 to be used by 38 percent of postmenopausal American women. However, estrogen use has declined sharply in the wake of the early termination
last summer of the Women’s Health Initiative after the data and safety monitoring board decided that risks exceeded benefits.\(^9\) The Women’s Health Initiative was a prospective trial, sponsored by the National Institutes of Health, involving 16,608 postmenopausal women randomly assigned to treatment daily with 0.625 mg of conjugated estrogen and 2.5 mg of medroxyprogesterone acetate, a commonly used regimen of hormone-replacement therapy, or with placebo. The trial was originally scheduled to last 8.5 years but was stopped after 5.2 years, although the subgroup of women who had undergone hysterectomy and were taking estrogen without medroxyprogesterone was allowed to continue. Although other estrogen regimens or dosages would not necessarily have provided similar results, the trial results bring into sharper focus the risks of hormone-replacement therapy in its association with an increase in cardiovascular disease, stroke, pulmonary embolism, and breast cancer.\(^9\)

But the Women’s Health Initiative also provides the first controlled data demonstrating that hormone-replacement therapy protects against osteoporotic fractures and may decrease the occurrence of colorectal cancer.\(^9\)

One consequence of the Women’s Health Initiative findings has been an increased interest in therapy with SERMs, because of their potential to retain most of the beneficial effects of estrogen while avoiding most of its adverse effects. In the sections that follow, we review the corresponding and contrasting actions of estrogen and SERMs on various target tissues (Table 1).

**BONE**

Estrogen acts on bone cells, which contain both isoforms of estrogen receptors.\(^21,22\) However, concentrations of estrogen receptor \(\beta\) are higher in developing cancellous bone, whereas concentrations of estrogen receptor \(\alpha\) are higher in developing cortical bone.\(^23\) Estrogen deficiency is the main cause of postmenopausal osteoporosis.\(^21\) When estrogen is deficient, bone turnover increases, and bone resorption increases more than bone formation, leading to bone loss. Hormone-replacement therapy reverses these changes in women in both the early and the late phases of the postmenopausal period.\(^21\) Although it had been demonstrated by many observational studies, the Women’s Health Initiative was the first large, randomized clinical trial to show that hormone-replacement therapy reduces osteoporotic fractures, including a 34 percent reduction in both vertebral and hip fractures.\(^9\) This reduction occurred even though the study subjects were at low risk for fractures.

Although early work established that tamoxifen was an estrogen antagonist for the breast, subsequent studies in animals\(^24,25\) and clinical studies\(^26,27\) showed that it was a weak agonist for bone. In postmenopausal women, however, the gain in bone density after two years of tamoxifen therapy was small (Table 2), and half of this short-term increase was lost after five years of continued treatment.\(^34\) Tamoxifen has been reported both to increase\(^35\) and to decrease\(^36\) the risk of hip fracture. From the limited available data, toremifene appears to be a weaker bone agonist than tamoxifen.\(^37\)

The effects of raloxifene on bone are well established. In postmenopausal women with osteoporosis, treatment with raloxifene decreased markers of bone turnover by 30 to 40 percent after one year and increased bone density at several scanning sites by 2 to 3 percent after three years\(^30-33\) (Table 2). Raloxifene also decreased the incidence of vertebral fractures by 30 to 50 percent, depending on dosage, but did not decrease the incidence of hip fracture or other nonvertebral fractures.\(^32\) Although bisphosphonate (alendronate or risedronate) therapy does decrease nonvertebral fractures, the decrease in vertebral fractures of approximately 50 percent is only slightly greater than with raloxifene therapy.\(^38,39\)

### Table 1. Comparison of Selected Actions and Side Effects of Estrogen and Clinically Available SERMs.*

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Estrogen</th>
<th>Tamoxifen</th>
<th>Toremifene</th>
<th>Raloxifene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uterine bleeding</td>
<td>↑↑↑↑</td>
<td>↑↑↑↑</td>
<td>↑↑↑↑</td>
<td>↑↑↑↑</td>
</tr>
<tr>
<td>Hot flashes</td>
<td>↓↓↓↓</td>
<td>↑↑↑↑</td>
<td>↑↑↑↑</td>
<td>↑↑↑↑</td>
</tr>
<tr>
<td>Favorable pattern of serum lipids</td>
<td>↑↑↑↑↑↑</td>
<td>↑↑↑↑</td>
<td>↑↑↑↑</td>
<td>↑↑↑↑</td>
</tr>
<tr>
<td>Venous thrombosis</td>
<td>↑↑↑↑</td>
<td>↑↑↑↑</td>
<td>↑↑↑↑</td>
<td>↑↑↑↑</td>
</tr>
<tr>
<td>Prevention of postmenopausal bone loss</td>
<td>↑↑↑↑↑↑</td>
<td>↑↑↑↑</td>
<td>↑↑↑↑</td>
<td>↑↑↑↑</td>
</tr>
<tr>
<td>Risk of breast cancer</td>
<td>↑↑</td>
<td>↓↓↓↓</td>
<td>↓↓↓↓ §</td>
<td>↑↑</td>
</tr>
<tr>
<td>Risk of endometrial cancer</td>
<td>↑↑↑↑</td>
<td>↑↑↑↑</td>
<td>↑↑↑↑</td>
<td>↑↑↑↑</td>
</tr>
</tbody>
</table>

* Ascending arrows indicate that the drug increases the effect, and descending arrows that it decreases the effect. Horizontal arrows indicate no change. The number of arrows indicates the size of the change. 
† In perimenopausal women the action would be ↑↑. 
‡ This effect can be prevented by concurrent treatment with a progestin. 
§ The only available data are for inhibition of breast-cancer growth. 
¶ This effect may be attenuated by concurrent treatment with androgen-derived progestins.\(^20\)
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Despite the fact that bone density increases to a much greater extent (4 to 9 percent more at the same bone-density scanning sites), although the explanation for this paradox is unclear, Riggs and Melton have suggested that much of the antifracture effect of antiresorptive drugs such as raloxifene at cancellous bone sites results from normalization of the high level of bone turnover and thus the prevention of further microarchitectural disruption. They have also suggested that it is necessary to reach only a low therapeutic threshold to prevent osteoclasts from perforating the trabecular plates and thus to reduce fractures at sites of cancellous bone, such as the vertebrae. This low threshold can be achieved with less potent antiresorptive drugs, such as raloxifene. However, to reduce fractures at sites of cortical bone, such as the hip, it is necessary to increase bone density more substantially by using potent antiresorptive or formation-stimulating agents. Table 2 summarizes the effect of two SERMs on bone mineral density according to the results of major randomized, controlled trials.

**Table 2. Results of Major Randomized Clinical Trials of SERMs with Regard to Bone Mineral Density.**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Study Subjects</th>
<th>Duration</th>
<th>Change in Bone Mineral Density as Compared with Placebo Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>months</td>
<td>Total-Body Bone Mineral</td>
</tr>
<tr>
<td>Tamoxifen (20–30 mg/day)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Love et al.</td>
<td>140 postmenopausal women with breast cancer</td>
<td>24</td>
<td>—</td>
</tr>
<tr>
<td>Grey et al.</td>
<td>57 normal late-postmenopausal women</td>
<td>24</td>
<td>0.5†</td>
</tr>
<tr>
<td>Powles et al.</td>
<td>179 healthy women in chemoprevention trial for breast cancer</td>
<td>36</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>54 postmenopausal women</td>
<td>36</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>125 premenopausal women</td>
<td>36</td>
<td>—</td>
</tr>
<tr>
<td>Raloxifene (60 mg/day)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delmas et al.</td>
<td>302 normal postmenopausal women</td>
<td>24</td>
<td>2.0*</td>
</tr>
<tr>
<td>Lufkin et al.</td>
<td>143 postmenopausal women with osteoporosis and vertebral fractures</td>
<td>12</td>
<td>—0.1</td>
</tr>
<tr>
<td>Ettinger et al.</td>
<td>5140 postmenopausal women with osteoporosis</td>
<td>36</td>
<td>—</td>
</tr>
<tr>
<td>Johnston et al.</td>
<td>576 healthy early-postmenopausal women</td>
<td>36</td>
<td>1.7*</td>
</tr>
</tbody>
</table>

* P<0.05 for the comparison with placebo.
† P<0.005 for the comparison with placebo.

**BREAST**

Estrogen stimulates the proliferation of breast epithelial cells, and both endogenous and exogenous estrogens have been implicated in the pathogenesis of breast cancer. The Women’s Health Initiative showed that hormone-replacement therapy was associated with a 27 percent relative increase in invasive breast cancer (38 vs. 30 cases per 10,000 patient years), a statistic similar to the 35 percent increase found in a meta-analysis of 51 observational studies. Tamoxifen has demonstrated efficacy for the treatment and prevention of estrogen-receptor–positive breast cancer. Adjuvant tamoxifen therapy (administered after the initial surgery) significantly reduced the risk of recurrence and death from breast cancer in all age groups studied. In an overview of 37,000 women with breast cancer from 55 trials of adjuvant therapy, the proportional reduction in recurrence was 47 percent after 5 years of treatment with tamoxifen and the proportional reduction in mortality was 26 percent after 10 years. The absolute improvements in 10-year survival were 10.9 percent in node-positive and 5.6 percent in node-negative breast cancer. Women with estrogen-receptor–negative disease had little, if any, benefit.

Best results appear to be achieved after five years of treatment; thereafter, beneficial effects decrease and toxicity increases, although the optimal duration of administration is still under investigation. Tamoxifen is mainly cytostatic and slows the proliferation of breast-cancer cells by inhibiting their progression from the G1 phase of the cell cycle, but it...
also induces apoptosis in vitro and thus may possess cytotoxic properties in vivo.\textsuperscript{50} About half of women with advanced estrogen-receptor–positive breast cancer will have a response to tamoxifen therapy, whereas only 5 percent of those whose cancer is estrogen-receptor–negative will have a response.\textsuperscript{48,51}

The reduction in the risk of contralateral breast cancer in adjuvant trials of tamoxifen led to its inclusion in randomized primary-prevention trials. Among the 13,388 participants in the Breast Cancer Prevention Trial, there was a 49 percent reduction in the risk of invasive breast cancer, but benefit was limited to estrogen-receptor–positive tumors.\textsuperscript{36}

Two smaller primary-prevention trials from the Royal Marsden Hospital in London\textsuperscript{52} and from Italy\textsuperscript{53} failed to demonstrate that tamoxifen reduced the risk of breast cancer (Table 3). The recently reported International Breast Cancer Intervention Study I (IBIS-I) trial showed a 25 percent reduction in invasive breast cancer with tamoxifen.\textsuperscript{54} However, no trial has shown improvement in survival with tamoxifen; in fact, there were slightly more deaths in the tamoxifen group in the IBIS-I trial owing to an excess of thromboembolic events.\textsuperscript{54}

Toremifene is approved by the Food and Drug Administration for the treatment of advanced breast cancer.

\begin{table}[h]
\centering
\begin{tabular}{|c|ccccc|}
\hline
\textbf{Variable} & \textbf{NSABP P-1 Study\textsuperscript{36}} & \textbf{Royal Marsden Hospital Trial\textsuperscript{52}} & \textbf{Italian Trial\textsuperscript{53}} & \textbf{IBIS-I\textsuperscript{54}} \\
\hline
\textbf{Primary outcome} & Breast cancer & Breast cancer & Breast cancer & Breast cancer \\
\hline
\textbf{Secondary outcome} & Bone, cardiovascular & — & Cardiovascular, psychometrics & Thromboembolic, cardiovascular, endometrial cancer \\
\hline
\textbf{Eligibility} & Age $\geq$60 yr, or 35–59 yr with a 5-yr predicted risk of $\geq$1.66%, lobular carcinoma in situ & Age 30–70 yr with a family history & Age 35–70 yr after hysterectomy & Age 35–70 yr with a family history, lobular carcinoma in situ or atypia \\
\hline
\textbf{No. of women} & 13,388 & 2471 & 5408 & 7152 \\
\hline
\textbf{Study drugs} & Tamoxifen vs. placebo & Tamoxifen vs. placebo & Tamoxifen vs. placebo & Tamoxifen vs. placebo \\
\hline
\textbf{Age distribution (\%)} & & & & \\
\hline
$<$50 yr & 39 & 61 & 38 & —\textsuperscript{†} \\
50–60 yr & 31 & 39 & 50 & —\textsuperscript{§} \\
$>$60 yr & 30 & 12 & & \\
\hline
\textbf{Family history of breast cancer (\%)} & 77 & 96 & 18 & 97 \\
\hline
\textbf{Mean follow-up (mo)} & 55 & 70 & 46 & 50 \\
\hline
\textbf{Effect on invasive breast cancer} & & & & \\
No. taking placebo in whom breast cancer developed & 175 & 64 & Not reported & 85 \\
No. taking tamoxifen in whom breast cancer developed & 89 & 54 & — & 64 \\
Relative difference (\%) & $-49$\textsuperscript{‡} & $-5$\textsuperscript{¶} & $-4$\textsuperscript{§} & $-25$\textsuperscript{¶} \\
\hline
\end{tabular}
\caption{Results of Major Trials of SERMs for the Primary Prevention of Breast Cancer.\textsuperscript{20}}
\end{table}

\textsuperscript{a} IBIS-I denotes International Breast Cancer Intervention Study I, and NSABP National Surgical Adjuvant Breast and Bowel Project.

\textsuperscript{b} The median age in the trial was 51 years.

\textsuperscript{c} P<0.001.

\textsuperscript{d} The difference was not significant.

\textsuperscript{e} The confidence interval was 54 to 104.
cancer. However, in head-to-head randomized trials, tamoxifen and toremifene were found to have very similar efficacy and side-effects profiles\(^6\)
\(^3\) and exhibited cross-resistance with each other.\(^8\)

In the Multiple Outcomes of Raloxifene Evaluation (MORE) trial, which was designed to assess antifracture efficacy, raloxifene reduced the risk of breast cancer by 76 percent.\(^9\) Because the MORE trial was conducted in older women with osteoporosis who were not at increased risk for breast cancer, these favorable results cannot necessarily be extrapolated to younger women who are at high risk for breast cancer. This issue should be resolved by the ongoing Study of Tamoxifen and Raloxifene (STAR) trial, which is a head-to-head comparison of the efficacy of raloxifene and tamoxifen in women at increased risk for breast cancer.\(^{10,11} \) (Table 4). A phase 1 trial with arzoxifene (LY353381.HCl), a new third-generation SERM, demonstrated stable disease in 6 of 32 tamoxifen-resistant patients with metastatic breast cancer,\(^{12} \) and phase 2 studies are under way. Several large trials addressing unresolved questions regarding the role of SERMs in the prevention and treatment of breast cancer are ongoing (Table 4).

### Genitourinary Tract

Estrogen deficiency induces atrophic changes in the genitourinary tract and symptoms of dyspareunia. In postmenopausal women with an intact uterus, administration of unopposed estrogen increases the incidence of endometrial carcinoma.\(^{13,14} \) Combination treatment with progestin prevents this increase,\(^{15,16} \) but the progestin component of hormone-replacement therapy is the main cause of the common treatment-related problems of edema and premenstrual syndrome–like symptoms. Yet another major problem with hormone-replacement therapy is breakthrough and withdrawal vaginal bleeding. The use of raloxifene obviates both problems, because it does not stimulate the endometrium and does not require progestin treatment. Over a period of three years, endometrial thickness as assessed by ultrasonography and vaginal bleeding were similar in raloxifene-treated subjects and those given placebo.\(^{17} \) Moreover, hormone-replacement therapy, but not raloxifene or tamoxifen therapy, significantly increases urinary incontinence.\(^{18} \) However, like estrogen, but unlike raloxifene, tamoxifen is associated with a 2.5-fold increase in endometrial carcinoma.\(^{19} \) So vaginal bleeding in women receiving tamoxifen should be promptly investigated.

### Cardiovascular System

Coronary artery disease accounts for one third of all deaths in postmenopausal women.\(^{20} \) Both estrogen and SERM therapy induce a beneficial serum lipid profile, although the patterns of these changes differ (Table 5). The main serum lipid changes with oral estrogen are increases in high-density lipoprotein (HDL) cholesterol and triglycerides and decreases in low-density lipoprotein (LDL) cholesterol. Tamoxifen, toremifene, and raloxifene also decrease LDL cholesterol but, unlike estrogen, do not increase triglycerides. Toremifene, unlike other SERMs, increases HDL cholesterol.\(^{21} \) Treatment with estrogen or SERMs changes the blood-coagulation indexes in the direction of enhanced clotting, and estrogen, but not raloxifene, increases indexes of inflammation (Table 5). Also, estrogen, but not raloxifene, retarded experimentally induced atherosclerosis in a monkey model,\(^{22} \) whereas raloxifene was 75 percent as effective as estrogen in a rabbit

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**Table 4. Major Large-Scale Trials Involving SERMs.**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATLAS (Adjuvant Tamoxifen Longer against Shorter) trial(^1)(^{11} )</td>
<td>Assessment of optimal duration of tamoxifen adjuvant therapy</td>
</tr>
<tr>
<td></td>
<td>Accrual goal is 20,000 pre- and postmenopausal patients with breast cancer</td>
</tr>
<tr>
<td></td>
<td>Therapy: tamoxifen for 5 yr vs. 10 yr (or longer)</td>
</tr>
<tr>
<td>ATTM (Adjuvant Tamoxifen Treatment Offers More) trial(^1)(^{12} )</td>
<td>Assessment of optimal duration of tamoxifen adjuvant therapy</td>
</tr>
<tr>
<td></td>
<td>Accrual goal is 8000–20,000 pre- and postmenopausal patients with breast cancer</td>
</tr>
<tr>
<td></td>
<td>Therapy: tamoxifen for 2 yr (group 1) vs. 7 yr (group 2)</td>
</tr>
<tr>
<td>IBIS2 (International Breast Cancer Intervention Study)(^1)(^{13} )</td>
<td>Primary prevention of breast cancer</td>
</tr>
<tr>
<td></td>
<td>Accrual goal is 16,000 women at high risk for breast cancer (age, 35–70 yr)</td>
</tr>
<tr>
<td></td>
<td>Therapy: anastrozole vs. placebo</td>
</tr>
<tr>
<td>STAR (Study of Tamoxifen and Raloxifene)(^1)(^{14} )</td>
<td>Primary prevention of breast cancer</td>
</tr>
<tr>
<td></td>
<td>Accrual goal is 22,000 postmenopausal women at high risk for breast cancer</td>
</tr>
<tr>
<td></td>
<td>Therapy: 20 mg tamoxifen per day vs. 60 mg of raloxifene per day for 5 yr</td>
</tr>
<tr>
<td>CORE (Continuing Outcomes Relevant to Evista)(^1)(^{15} )</td>
<td>4000 postmenopausal women who were previous participants in the MORE</td>
</tr>
<tr>
<td></td>
<td>(Multiple Outcomes of Raloxifene Evaluation) trial</td>
</tr>
<tr>
<td></td>
<td>Receiving raloxifene or placebo for an additional 4 yr, completion by 2003</td>
</tr>
<tr>
<td></td>
<td>Primary end point is breast-cancer prevention; secondary end points are</td>
</tr>
<tr>
<td></td>
<td>non-vertebral fractures and uterine safety</td>
</tr>
<tr>
<td>RUTH (Raloxifene Use in the Heart)(^1)(^{16} )</td>
<td>Effect of raloxifene vs. that of placebo in prevention of coronary events</td>
</tr>
<tr>
<td></td>
<td>and death from coronary causes</td>
</tr>
<tr>
<td></td>
<td>10,000 postmenopausal women at risk for coronary disease</td>
</tr>
<tr>
<td></td>
<td>Duration of 7.5 yr, completion by 2005</td>
</tr>
</tbody>
</table>

* The trial is not open in the United States.
† The trial has been completed, and the data are under analysis.
model. Moreover, in ovariectomized rats, raloxifene was as effective as estrogen in enhancing nitric oxide–induced coronary-artery dilatation and in retarding injury-induced intimal thickening of the carotid artery.

Observational studies have found that women receiving hormone-replacement therapy have a 30 to 35 percent lower risk of coronary disease. Thus, the reports of two randomized clinical trials of hormone-replacement therapy that failed to show benefit in postmenopausal women with established coronary artery disease were unexpected, although another trial demonstrated that estrogen therapy retarded the development of subclinical atherosclerosis. However, the results of the Women’s Health Initiative in postmenopausal women, the large majority of whom were not at high risk for coronary heart disease, are of particular concern: participants had a 23 percent increase in cardiovascular disease (37 vs. 30 cases per 10,000 person-years) and a 38 percent increase in strokes (29 vs. 21 cases per 10,000 person-years). Thus, there is no current justification for the use of hormone-replacement therapy to prevent or treat cardiovascular disease.

How to reconcile these findings with previous data showing benefit is unclear. One possible interpretation is that cardiovascular outcomes associated with hormone-replacement therapy represent the algebraic summation of its prothrombotic or proinflammatory effects and its antiatherosclerotic effects and that the balance between them will be determined by such variables as oral as compared with transdermal administration, the types and dosages of estrogens and progestins, the age at onset of therapy, and other factors. Consistent with this speculation is the recent report that raloxifene decreased cardiovascular events by 40 percent in the 10,000 person-years and a 38 percent increase in strokes (29 vs. 21 cases per 10,000 person-years). Thus, there is no current justification for the use of hormone-replacement therapy to prevent or treat cardiovascular disease.

Table 5. Comparative Effects of Oral Hormone-Replacement Therapy and SERMs on Serum Lipids, Indexes of Inflammation, and Blood Coagulation.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hormone-Replacement Therapy</th>
<th>Tamoxifene</th>
<th>Toremifene</th>
<th>Raloxifene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-density lipoprotein cholesterol</td>
<td>–12†</td>
<td>–19†</td>
<td>–21†</td>
<td>–12†</td>
</tr>
<tr>
<td>High-density lipoprotein cholesterol</td>
<td>7†</td>
<td>–2</td>
<td>14†</td>
<td>0</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>18†</td>
<td>31†</td>
<td>–14†</td>
<td>–3†</td>
</tr>
<tr>
<td>Apolipoprotein A-I</td>
<td>13†</td>
<td>5</td>
<td>13†</td>
<td>3</td>
</tr>
<tr>
<td>Apolipoprotein B</td>
<td>–4</td>
<td>–9†</td>
<td>–10†</td>
<td>–9†</td>
</tr>
<tr>
<td>Lp(a) lipoprotein</td>
<td>–19†</td>
<td>–14†</td>
<td>–53†</td>
<td>–7†</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>–1</td>
<td>—</td>
<td>—</td>
<td>–10†</td>
</tr>
<tr>
<td>Plasminogen activator inhibitor type 1</td>
<td>–19†</td>
<td>—</td>
<td>—</td>
<td>8</td>
</tr>
<tr>
<td>Homocysteine</td>
<td>–7†</td>
<td>—</td>
<td>—</td>
<td>–8†</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>84†</td>
<td>—</td>
<td>—</td>
<td>–7</td>
</tr>
<tr>
<td>Tumor necrosis factor α</td>
<td>–11†</td>
<td>—</td>
<td>—</td>
<td>–5†</td>
</tr>
<tr>
<td>Interleukin-6</td>
<td>11</td>
<td>—</td>
<td>—</td>
<td>1</td>
</tr>
</tbody>
</table>

* Data are from the Postmenopausal Estrogen/Progestin Interventions Trial Writing Group, Love et al., Walsh et al., Saarto et al., Walsh et al., and Cox et al.
† P<0.05 for the comparison with placebo.

**CENTRAL NERVOUS SYSTEM**

Estrogen has diverse effects on brain function. Estrogen receptor α is found mainly in the hypothalamus. Estrogen receptor β is more widely distributed throughout the brain and is concentrated at loci involved in cognition and memory. Many studies have shown that estrogen treatment enhances both of these functions. However, data from objective testing carried out during the Heart and Estrogen/Progestin Replacement Study (HERS) failed to show that hormone-replacement therapy increased energy levels or improved mental health and depressive symptoms any more than placebo. A recent 3-year prospective observational study in elderly women in Cache County, Utah, found that estrogen use for 10 or more years reduced the risk of Alzheimer’s disease by 67 percent. However, this protection has not as yet been demonstrated in randomized clinical trials. No studies of the effect of
SERMs in reducing the risk of Alzheimer’s disease have been undertaken.

Although estrogen is highly effective in reducing hot flashes, all SERMs studied thus far act as anti-estrogens for the hypothalamic centers regulating gonadotrophin secretion. During the early postmenopausal period, tamoxifen increased the incidence of hot flashes by 17 percent as compared with placebo, and raloxifene increased them by 7 percent. This is less of a problem in women who are in the late postmenopausal period; hot flashes caused only 0.7 percent of the patients to discontinue therapy. In studies in ovariectomized rats, raloxifene was able to reproduce the ability of estrogen to restore the reduction in choline acetyltransferase activity in the hippocampus but not in the hypothalamus. It is important to note, however, that raloxifene treatment does not impair cognition in postmenopausal women.

TREATMENT AND PREVENTION OF BREAST CANCER
The treatment of breast cancer is complex and involves surgery, radiation, chemotherapy, and hormonal therapy, used singly or in combination, depending on the stage and estrogen-receptor status of the disease in the individual patient. Tamoxifen remains a mainstay of the hormonal treatment of all phases of estrogen-receptor–positive breast cancer. The aromatase inhibitors, which block estrogen synthesis, are an alternative to tamoxifen for hormonal therapy and, unlike tamoxifen, are not associated with an increased risk of thromboembolic complications or endometrial cancer. However, in postmenopausal women, aromatase inhibitors elevate the rate of bone turnover and increase the risk of fracture. In postmenopausal women with advanced estrogen-responsive breast cancer, tamoxifen and aromatase inhibitors have similar antitumor efficacy.

For adjuvant therapy in postmenopausal women, however, the recently published results of the Arimidex, Tamoxifen Alone or in Combination (ATAC) trial found that the aromatase inhibitor anastrozole alone was equivalent or superior to both tamoxifen and a combination of anastrozole and tamoxifen with regard to various response indexes when studied over a period of 33 months. Nonetheless, pending further studies, the American Society of Clinical Oncology Technology Assessment statement continues to recommend tamoxifen as the preferred hormonal adjuvant therapy for estrogen-receptor–positive breast cancer. Also, because there is insufficient information on safety and effi-
cacy, aromatase inhibitors are not recommended for premenopausal women with breast cancer.

Tamoxifen is the only approved hormonal agent for primary prevention of breast cancer. Debate continues about who should receive it for this indication, although reasonable candidates include women with a strong family history of breast cancer and those with atypical hyperplasia or lobular carcinoma in situ. Women with mutant BRCA1 or BRCA2 genes are also potential candidates, especially since prophylactic ovariectomy has recently been shown to reduce their risk of breast cancer by about 50 percent. 

However, because 80 percent of the breast cancers that develop in carriers of BRCA1 mutations are estrogen-receptor-negative, the efficacy of tamoxifen in this group has been questioned.

Although the substantial reduction in the risk of breast cancer in postmenopausal women reported from the MORE trial was encouraging, the use of raloxifene in primary prevention should await the results of the STAR trial. A cautionary note on the use of tamoxifen for prevention in premenopausal women is that it acts as a bone antagonist that results in bone loss in this age group.

The results of the STAR trial. An important observation that tamoxifen has tissue-specific effects will have proved to be the golden thread of Ariadne. It will have led to the development of remarkable new drugs that will selectively express the desirable actions and selectively suppress the undesirable actions of the various steroid hormones. If so, corticosteroids may soon become available that suppress immune function without causing bone loss, as may androgens that are anabolic without producing masculinizing effects or adverse lipid patterns, progestins that can induce endometrial atrophy without producing fluid retention, and vitamin D analogues that increase bone density without inducing hypercalcemia or hypercalciuria. Should these events come to pass, the initial observation that tamoxifen has tissue-specific effects will have proved to be the golden thread of Ariadne. It will have led to the development of remarkable new drugs that will selectively express the desirable actions and selectively suppress the undesirable actions of the various steroid hormones.

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We are indebted to Dr. Donald P. McDonnell for his assistance with the section on the molecular actions of SERMs and Figure 2.

FUTURE DIRECTIONS

As the molecular mechanisms of the action of SERMs become more completely understood, rational drug design will replace the current empirical method for the discovery of new SERMs. It is probable that the ultimate goal of SERM research will be achieved — the discovery of a tissue-selective drug that has all the beneficial effects of estrogen, has none of its adverse effects, and offers protection against breast cancer. Development of a SERM with superagonist protective actions on the cardiovascular and skeletal systems may also become feasible. Finally, recent studies suggest the even more exciting possibility that the plasticity of estrogen action exhibited by SERMs will be found to be a general feature of the steroid nuclear-receptor family of molecules. If so, corticosteroids may soon become available that suppress immune function without causing bone loss, as may androgens that are anabolic without producing masculinizing effects or adverse lipid patterns, progestins that can induce endometrial atrophy without producing fluid retention, and vitamin D analogues that increase bone density without inducing hypercalcemia or hypercalciuria. Should these events come to pass, the initial observation that tamoxifen has tissue-specific effects will have proved to be the golden thread of Ariadne. It will have led to the development of remarkable new drugs that will selectively express the desirable actions and selectively suppress the undesirable actions of the various steroid hormones.

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