Treatment of Estrogen Deficiency Symptoms in Women Surviving Breast Cancer, Part 3

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There are several million breast cancer survivors worldwide. In the United States, 180,000 women were diagnosed with breast cancer in 1997, and approximately 97,000 of these women have an extremely low chance of suffering a recurrence of their cancer. With an average age at diagnosis of 60 years and a 25-year expected duration of survival, the current number of breast cancer survivors in the United States may approach 2.5 million women. Since breast cancer is now being detected at an earlier stage than previously and since adjuvant chemotherapy may cause ovarian failure, an increasing number of women are becoming postmenopausal at a younger age after breast cancer treatment. This conference was convened in September 1997 to consider how menopausal breast cancer survivors should be treated at the present time and what future studies are needed to develop improved therapeutic strategies. A total of 47 breast cancer experts and 13 patient advocates participated. The proceedings of the conference are being published in six installments in successive issues of oncology. This third part focuses on the prevention of osteoporosis and the cardiovascular effects of estrogens and antiestrogens. [ONCOLOGY 13(3):397-432, 1999]

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Bisphosphonates for Osteoporosis Treatment and Prevention

Nelson B. Watts, MD: All of the bisphosphonates share a common chemical structure in which two phosphonic acids are bound to a carbon. These compounds avidly bind to surfaces of metabolically active bone. They are effective when given intravenously or orally but are poorly absorbed when given by mouth. For this reason, they must be taken on an empty stomach, with water only, and at least 30 minutes must be allowed for adequate absorption before any food is ingested. Bisphosphonates are not metabolized, and excretion by the kidneys is the only means of eliminating these agents from the body. For these reasons, patients who have renal insufficiency should be given these agents with caution, if at all.

Once absorbed, bisphosphonates bind to bone surfaces; later, after bone remodeling is complete, they are buried away from active bone surfaces and are no longer pharmacologically active. This results in very long retention of these drugs in the body, in some instances, for 10 years or more. The specific action of bisphosphonates is inhibition of osteoclasts that resorb bone. Bisphosphonates may also interfere with recruitment of precursor cells, the differentiation of precursor cells into mature osteoclasts, and increase osteoclast apoptosis.

Bisphosphonates can be altered chemically by modifying one or both of the two side chains, which changes not only their potency but also their side effect profiles. These targeted alterations in structure increase the antiresorptive effects on bone from 100- to 1,000-fold in vitro. Sequential changes in these side chains have resulted in the development of first-, second-, and third-generation compounds. Etidronate (Didronel), a first-generation bisphosphonate, has been used for the treatment of bone diseases for over 2 decades. Second- and third-generation bisphosphonate agents, such as risedronate and ibandronate, are already in the advanced phases of clinical trials. Most of the data on osteoporosis prevention and treatment has been obtained with alendronate (Fosamax), the first bisphosphonate approved by the FDA for both the treatment and prevention of menopausal osteoporosis.

Phase III Trial of Alendronate

The average 30-year-old woman loses bone gradually, and by age 70 has lost 20% of her spinal bone mass, and, therefore, falls two standard deviations below the mean bone density for a 30-year-old. The average age of women enrolled in the phase III trial of alendronate[1] was 67 years and the
average bone density was about 2.3 standard deviations below peak bone mass for a 30-year-old. Approximately 1,000 women participated in the trial at 18 centers in the United States and 19 centers throughout the world. Patients were randomized to receive a placebo or one of three doses of alendronate (5, 10, or 20 mg/d). Changes in spinal bone mineral density constituted the objective end point of the study.

All patients received calcium, which prevented bone loss in the control group. A dose-response effect of alendronate was evident, with the maximal effect observed with the 10-mg dose, which, in the US cohort, resulted in a 6% increase in spinal bone mass at 1 year, 8% at 2 years, and 10% at 3 years (Figure 1).[2] The 20-mg dose afforded no additional benefit. Based on these data, the recommended alendronate dose to treat osteoporosis was set at 10 mg/d.

**Fracture Intervention Trial**

Another study, the Fracture Intervention Trial, examined the rate of fractures in over 2,000 women. Entry into the study required a previous vertebral fracture and low femoral neck bone mineral density. When compared with placebo, alendronate treatment for 3 years resulted in a 55% reduction in clinically apparent vertebral fractures, a 48% reduction in wrist fractures, and a 51% reduction in hip fractures.[3]

The data from these two studies are intriguing, because the antifracture effect was site-independent, whereas the improvement in bone mass was not. Spinal bone mass increased to a greater extent than hip mass, which, in turn, was greater than wrist bone mass. When comparing studies, it is notable that fracture data are derived from studies of older women. Younger women have a lower fracture rate and do not generate a sufficient number of fractures for valid statistical analysis. For that reason, fracture rate studies involve older women.

**Other Trials of Alendronate**

The Early Postmenopausal Intervention Cohort, or EPIC,[4] included a placebo arm, 2.5- and 5.0-mg alendronate arms, and an open-label estrogen-progesterone arm (Figure 2 and Figure 3). Because the use of estrogen in this trial would prevent blinding, women were initially asked if they would be willing to take estrogen, and were then assigned to one of two strata: Women willing to take estrogen were assigned to stratum 1 and were randomized to placebo, one of two doses of alendronate (2.5 or 5.0 mg/d), or an estrogen-progestin combination. Those not willing to take estrogen were assigned to stratum 2 and were randomized only to placebo or one of the two alendronate doses.

Data from stratum 2 subjects revealed a 1% per year bone loss in the spine, total hip, and total body among the placebo recipients despite calcium supplementation. Both the 2.5- and 5.0-mg alendronate groups showed an increase in bone mass, with the 5.0-mg group showing the greatest effect. In the 5.0-mg alendronate group, 86% of patients gained bone but 14% did not. The latter finding has convinced me to monitor bone markers or repeat bone density measurements in order to identify nonresponding patients.

Longer-term follow-up data are available from a dose range-finding study.[5] In the placebo group, after 3 years there was a 4.5% loss of bone mass in the lumbar spine and a slightly lesser loss of total body bone mass. In women who received 5 mg of alendronate daily for a total 5 years, there was an early increase in spinal bone mass of 2% to 3% and then stabilization after approximately 1 to 2 years until year 5.

**Alendronate vs Estrogen**

Data from stratum 1 patients in the EPIC study provide a comparison between alendronate and estrogen.[4] Patients receiving calcium plus placebo lost bone, while patients receiving calcium plus alendronate, either 2.5 or 5.0 mg/d, increased bone mass but not to the same extent as the estrogen-progestin group (Figure 2 and Figure 3). Similar findings were noted with respect to total body and forearm bone density measurements. Alendronate and estrogen-progestin produced similar improvements in total body bone density, but estrogen-progestin was slightly superior in increasing forearm bone density. Because these patients do not yet have established osteoporosis, prevention of bone loss is the overriding consideration; therefore the “better” effect of estrogen-progestin may not be clinically important.

With respect to the dose range-finding study, data extend to 5 years in the alendronate groups and to 3 years in the placebo group. After 2 years, the 20-mg arm was terminated, which permitted evaluation of what happens after the agent is stopped. The deoxypyridinoline collagen cross-link marker fell by 40% upon initiation of alendronate and remained suppressed as long as treatment was continued but quickly returned to baseline levels upon cessation of therapy. This suggests that bone remodeling is controlled for as long as treatment is given but reverts to baseline soon after it is stopped.
Bone mass increased with the 20-mg dose over the 2 years of treatment. Then, when the drug was stopped, bone mass remained higher than in patients who continued taking the 5-mg daily dose over the next 3 years. It is of interest that the decline in bone mass observed after stopping alendronate was lower than that seen in the placebo group. This suggests some long-term residual effect of drug remaining in bone. The residual effect was observed at all bone sites. These studies also provide information about drug tolerability. In the prevention trials, there were no differences in side effects between patients taking placebo and alendronate. This is interesting, since some patients who took alendronate after the drug was approved experienced gastrointestinal side effects, particularly esophagitis.

Other Bisphosphonates
Other bisphosphonates are also currently under study. At the American Society for Bone and Mineral Research (ASBMR) meeting in September 1997, data on the third-generation bisphosphonate risedronate were presented.[6] The results show similar increases in bone mass compared with alendronate.

Published data are also available from two recent studies from England[7] and France,[8] showing the effectiveness of intermittent cyclical etidronate for the prevention of bone loss in recently menopausal women.

Summary
Bisphosphonates are about as effective as estrogen for both the prevention of bone loss in the early postmenopausal period and for the treatment of established postmenopausal osteoporosis. At least in younger women, it appears that therapy must be continued indefinitely for ongoing efficacy. The bisphosphonate regimen is somewhat restrictive, in that patients must take the medication first thing in the morning after an overnight fast and ingest nothing but water for 30 minutes while remaining upright. A small percentage of patients have problems complying with this regimen. Otherwise, these agents are well tolerated and very safe. These results make bisphosphonates an excellent choice for most women who are at risk for osteoporosis and cannot or will not take estrogen.

Additional information on metastatic disease makes the bisphosphonates particularly attractive for breast cancer survivors. Several of these agents have been shown to reduce the risk of fractures from skeletal metastases and slow the progression of metastases.[9] By slowing remodeling, bone becomes a less hospitable environment for foreign invaders. For all of these reasons, bisphosphonates provide an attractive option for women surviving breast cancer.

Discussion
Dr. Melody Cobleigh asked about methods for reducing the cost of these agents. In response, Dr. Watts commented on the use ofibandronate every 3 months by intravenous injection. This method could be more cost-effective while still practical.

Dr. JoAnn Pinkerton asked for clarification about the incidence of gastric and esophageal ulcers and pancreatitis and the potential for delayed side effects with a drug that remains in the bone over the long term. Dr. Watts replied that the rapid return of bone remodeling upon cessation of the drug is reassuring. The release of drug from cryptic sites in bone over time might provide continued supply of pharmacologically active drug, but this is calculated to provide the equivalent of only 2 weeks of drug in a patient stopping medication after 10 years. Dr. Watts commented that in his clinical practice, 10% to 15% of patients experience gastrointestinal side effects from alendronate due to local irritation of the esophagus. He believes that most patients who have symptoms stop the drug and, thus, do not develop esophageal ulcers. He was unaware of pancreatitis or gastric ulceration in association with ingestion of bisphosphonates.

Another question focused on the potential for differential effects of bisphosphonates on bony metastases. Dr. Watts concurred that this might be a possibility, but that no data yet support this concept.

Dr. Rena Vassilopoulou-Sellin asked whether or not data exist to determine the long-term effects of a drug that can reside in bone for as long as 20 to 40 years. Dr. Watts cited 8-year follow-up data in patients treated with etidronate that demonstrated no detrimental effect.[10] The main concern would be complete inhibition of remodeling, which does not appear to happen.

Dr. Watts was asked about his approach to the patient who finds alendronate intolerable due to gastrointestinal side effects. He advised switching such patients to cyclic etidronate, even though this drug does not have FDA approval for osteoporosis prevention. He advised the use of intravenous pamidronate (Aredia) every 3 months for those who cannot tolerate oral bisphosphonate. He indicated, however, that there are no direct comparative data on the relative efficacy of these alternative approaches.
Dr. Watts was then asked about the combined use of bisphosphonates and calcitonin or estrogen for severe osteoporosis. He was aware of no data on the combination of bisphosphonates and calcitonin. He commented on two small open-label studies in both older and younger women demonstrating similar effects from estrogens and bisphosphonates separately and slightly greater effects when a bisphosphonate and estrogen were used in combination.[11,12]

Nasal Calcitonin and Fluorides for Osteoporosis Treatment and Prevention

Michael Kleerekoper, MD: The properties of calcitonin as an inhibitor of bone resorption can be contrasted with those of fluoride, a potent stimulator of bone formation. Calcitonin was approved for use in the early 1980s, has been extensively studied with respect to pharmacology and pharmacokinetics, and has undergone phase I-III clinical trials. It costs approximately $2 per day for the nasal spray. Calcitonin is very safe, with only minimal, short-term side effects, and exerts no continuing effects on bone after it has been discontinued.

In contrast, fluoride has not yet been approved for use by the FDA and has not been extensively studied in large trials. It causes a substantial number of short- and long-term side effects, and exerts long-lasting effects on the skeleton after it has been discontinued.

Calcitonin and Fracture Prevention

Although studies of calcitonin on bone density are extensive, minimal data on fracture prevention are available. Data presented at the 1998 ASBMR meeting[13] were provided by Novartis. The study involved a placebo arm and three doses of calcitonin (100, 200, and 400 IU) given daily by nasal spray. Approximately 230 postmenopausal women were entered into each arm.

At the end of 1 year, a significant effect on bone density (1.0% to 1.5% increase) was observed at each dose of calcitonin, but no dose-response effect was apparent. The significant improvement of calcitonin over placebo lost its statistical significance in the second and third year. The increase in bone mass occurred only in the lumbar spine and not in other skeletal sites.

With respect to fracture prevention, the 200-IU dose, but not the other doses, caused a statistically significant reduction in fractures; 33 fractures occurred in the 270 subjects receiving 200 IU of calcitonin vs 50 fractures in the 253 women receiving placebo. Most of the fracture reduction occurred during the first year. Since the 200-IU dose exerted only minimal effects on bone density, the mechanism for fracture prevention is uncertain.

Patients receiving calcitonin reported a myriad of side effects, but none occurred statistically significantly more often than in women given placebo. Surprisingly, and for unclear reasons, a large number of women dropped out of the trial, even though side effects were mild.

Fluoride and Fracture Prevention

With respect to fluoride, recent studies of 2 years’ duration[14,15] suggested that use of lower doses (ie, 25 mg/d) in a sustained-release formulation (Neosten) are preferable to use of high doses (75 mg/d), which may produce deleterious effects on fracture rate. The higher dose, used in independent studies conducted by Riggs and Melton[16] and Kleerekoper et al[17] caused a continuing increase in bone mass for up to 10 years. This dose produced increases in bone mass of up to 40% and exerted more potent effects on the skeleton than did estrogen, bisphosphonates, or calcitonin.

Fracture risk data, however, demonstrated no benefit of fluoride and perhaps a detrimental effect in some patients.

Many experts concluded from these data that fluoride produces abnormal bone with increased susceptibility to fracture. Patients in these early trials had very severe osteoporosis and perhaps did not respond because of the minimal amount of cancellous bone present at the start of therapy.

More recent data are available on lower-dose fluoride given in a sustained-release preparation.[15] In this study, the sustained-release preparation was given in combination with calcium citrate on a 12 months on–2 months off basis for a number of years. Bone mass increased by approximately 5% during the 2-year period of therapy—an effect substantially less than the 40% increment previously observed with the higher doses.

With respect to fracture prevention, results differed depending on the amount of bone mass at the start of the trial. Women were divided into two groups: those with a bone mineral density > 65% of peak adult bone mass at entry into the study and those with a bone mineral density < 65%. Fluoride therapy prevented fractures in patients with higher bone mass but had no effect in those with lower mass. It may be that the earlier trial with higher dose fluoride did not demonstrate efficacy because of the severity of osteoporosis in the women studied.

In 1995, an FDA advisory panel unanimously recommended the approval of this sustained-release fluoride formulation, but that approval is still pending.
Discussion

Dr. Felicia Cosman asked whether there are any data on the effects of calcitonin on nonvertebral fracture prevention. Dr. Kleerekoper replied that he was unaware of any such data. He was also asked to comment on a post hoc analysis by Riggs et al.[18] showing a reduction in fracture rate in patients with severe osteoporosis who did not gain bone mass quickly during fluoride therapy. Dr. Kleerekoper responded that most open-label trials have shown fluoride to be efficacious, whereas very few controlled trials have confirmed this.

He further noted conflicting data from a group in France headed by Meunier et al.[19] that initially reported negative data in abstract form. Later studies, presented by Dr. Jean Yves Reginster[20] at the 1997 ASBMR meeting, reported positive effects of fluoride. The two studies differed with respect to the severity of osteoporosis in the enrolled patients, Dr. Kleerekoper noted.

Dr. Jerilynn Prior commented on the efficacy of the injectable form of calcitonin when used as an analgesic in patients with acute compression fracture pain. Dr. Kleerekoper responded that this concept is generally accepted but difficult to prove and that calcitonin is an incredibly expensive analgesic.

Dr. Prior then asked about the relative efficacy of fluoride for vertebral fractures as opposed to hip fractures. Dr. Kleerekoper commented that he and Dr. Riggs disagree on the findings of an increase in hip fracture from fluorides. According to Dr. Kleerekoper, the incidence of true hip fractures requiring surgical fixation does not increase in patients receiving fluorides.

Responding to a question about long-term safety, Dr. Kleerekoper reviewed the concept that fluoride accumulates in the skeleton and replaces hydroxyapatite with a fluoroapatite crystal. This component is more resistant to remodeling and may impair the mechanical strength of bone. However, use of the drug early and in relatively small doses may diminish this effect and shift the balance toward efficacy.

Another participant requested data on the effects of fluoride on sites other than the spine. Dr. Kleerekoper cited data from Dr. Hodsman’s group in Canada,[21] indicating minimal effects on forearm bone density and from Dr. Pak’s group,[15] showing that low dose-fluoride has neither deleterious nor beneficial effects on hip bone density.

When asked whether calcitonin might be used in women with breast cancer undergoing menopause as a result of chemotherapy, Dr. Kleerekoper responded affirmatively.

A participant commented that considerable difference exists between the efficacy of parenteral and nasal calcitonin. Dr. Kleerekoper concurred, pointing out the greater efficacy of the parenteral form in terms of percentage increase in bone mass and probably in percentage of responders.

When asked to explain the lack of a dose-response relationship between fracture prevention and nasal calcitonin dose, Dr. Kleerekoper noted that the 200-IU daily dose is the one that shows statistically significant efficacy, but he offered no explanation for the lack of dose-response effects.

**Tamoxifen and Bone: Data From Breast Cancer Prevention Studies**

**Trevor Powles, MD, PhD:** Use of tamoxifen for the prevention of breast cancer allows collection of data on bone density in women who do not have the confounding effects of osteolytic bone metastases. Starting in 1990, bone density measurements were obtained using the Hologic 1000 densitometer.

Confirming the findings of Dr. Richard Love, the prospective data of Powles et al showed that tamoxifen acts as an estrogen on bone in postmenopausal women and reverses the 2% bone loss that occurs over a 2-year period in women receiving placebo. On average, bone mass increased 1% to 2% per year with tamoxifen (Figure 4).[22] The addition of exogenous estrogen as hormone replacement therapy in women receiving tamoxifen caused a small further increment in bone density in both the spine and femur. No data are available as yet on the reduction of fracture risk with tamoxifen alone or combined with estrogen.

The administration of tamoxifen to premenopausal women caused a greater reduction in bone density than was observed in women receiving a placebo. However, Powles believes that premenopausal women rendered postmenopausal by the effects of chemotherapy on ovarian function would be expected to respond to tamoxifen as an estrogen on bone, just as postmenopausal women do. This hypothesis will be examined further in long-term prospective studies.

**Discussion**

Dr. Kleerekoper stated that bone density measurements should theoretically serve as a good surrogate for data demonstrating a reduction in fracture rate. Bone density predicts fractures three times better than cholesterol predicts heart attacks, and this holds true for all measured sites.
Dr. Prior asked about the current status of data regarding fracture rate. Dr. Powles responded that approximately 2,000 women are being observed in the tamoxifen prevention trial and one adjuvant trial. Another group is receiving clodronate in addition to tamoxifen. Dr. Powles anticipates a 50-50 split in patients receiving placebo and tamoxifen. However, women who are off the study but choose to take tamoxifen and those receiving clodronate will confound interpretation of the results. At this time, the available data indicate that tamoxifen and clodronate have additive effects on bone mineral density. Regarding fracture rates, Dr. Powles said that there may not be sufficient data on women who are receiving either tamoxifen alone or placebo alone to yield meaningful data. One participant asked whether adequate safety data are available regarding combined tamoxifen and estrogen therapy. Particular concerns relate to the incidence of venous thromboembolic events and overall efficacy. Dr. Powles responded that his group is following approximately 2,500 women, the first of whom entered the trial 10 years ago. They have not detected an increased rate of thromboembolism or thrombophlebitis in the groups treated with tamoxifen alone or tamoxifen plus estrogen.

With respect to efficacy, Dr. Powles pointed out that plasma estradiol increases to levels of approximately 1,000 pmol/L in premenopausal women receiving tamoxifen, and yet the antiestrogenic effect on breast cancer tissue remains. Under these circumstances, the risk of developing breast cancer and of relapse and mortality from it are reduced. In postmenopausal women, administration of an estradiol patch increases plasma estradiol to approximately 200 pmol/L. As in premenopausal women, the effects of this increment in plasma estradiol on breast cancer in postmenopausal women should be blocked by tamoxifen as well.

To put all of this into perspective, Dr. Powles recalled that tamoxifen has been in clinical trials or clinical usage for more than 25 years, and that a great deal is known about it. This should be contrasted with raloxifene (Evista), which has been under intense study for only 5 years. Long-term safety issues are well studied for tamoxifen but require additional examination for raloxifene.

Dr. V. Craig Jordan commented that tamoxifen clearly works as adjuvant therapy for breast cancer in premenopausal women even though marked overproduction of estradiol occurs as a result of interruption of negative feedback. Consequently, the addition of a small amount of estrogen in postmenopausal women receiving tamoxifen should not pose a major safety threat, but these patients should still be monitored closely nonetheless.

Dr. Watts acknowledged that a fracture prevention study would be useful, but added that this would take tens of thousands of women and perhaps 10 to 20 years of follow-up. He pointed out that the only discrepancy between bone density measurements and fracture risk has been observed with fluoride therapy. With all of the antiresorptive agents (estrogen, calcitonin, bisphosphonates), there may be a greater antifracture effect than is predicted by the bone density studies. The increase in bone density seen with tamoxifen, as well as the other antiresorptive agents is reassuring, he said, and, in fact, these data may underestimate the antifracture effect.

**Tamoxifen and Long-Term Fracture Rate**

**Mark Olsen, MD, PhD:** The Wisconsin Tamoxifen Trial, designed as a biological and symptom toxicity study, also provides information on long-term effects of the drug on several parameters. In this trial, 140 postmenopausal women with a diagnosis of breast cancer and histologically tumor-free axillary lymph nodes were randomized to receive tamoxifen (10 mg twice daily) or placebo. The diagnosis of breast cancer could have been up to 10 years prior to enrollment. Subjects had to be clinically free of breast cancer on the basis of history, physical examination, and laboratory and radiologic studies and could not be taking any hormonal or bone-preserving drugs. Baseline bone mineral densities of the radius and lumbar spine were required to be > 80% of the values of age-matched controls. Bone mineral density, lipid levels, and symptom measurements were obtained at 3, 6, 12, 18, and 24 months.

After 2 years, the study was unblinded and the patients were allowed to determine whether to begin, continue, or discontinue tamoxifen in consultation with their personal oncologist. Three years later, subjects were contacted, and those who were recurrence-free and had continued on the same treatment as their original randomization were asked to make one visit to the clinic to answer a questionnaire, have fasting blood samples obtained, and lumbar bone mineral density determined. The 10-year follow-up consisted of a single information-seeking telephone call to the patient, or if the patient had died, to a family member or personal physician.

Over the first 2 years, the placebo group had a decrease in bone mineral density at both sites while the tamoxifen group maintained or gained bone mineral density (P = .001). At 1 year, the tamoxifen
group showed a significant decrease in alkaline phosphatase compared with those taking placebo, suggesting a decrease in bone turnover. At 2 years, the group taking tamoxifen had decreased osteocalcin. At the 5-year time point, bone mineral density was preserved in the subgroup of patients who were taking tamoxifen but showed further declines in those who were receiving placebo.

At 10 years, patients were asked specifically about fractures of the hip, wrist, or other sites. Fracture rates were similar in the two initially randomized groups, but event rates were not high enough to draw meaningful conclusions.

The major set of end points in this study involved lipids and cardiovascular (CV) events. At entry and during the study, patients were not allowed to take lipid-lowering agents. Fasting cholesterol level was required to be < 310 mg/dL and triglycerides, < 190 mg/dL. No additional hormonal agents were allowed, and normal liver function tests were required.

Tamoxifen use over 2 years resulted in favorable changes in levels of total cholesterol, low-density lipoprotein (LDL) cholesterol, lipoprotein(a), homocysteine, and fibrinogen. There was a tendency for high-density lipoprotein (HDL) cholesterol to fall slightly in the tamoxifen recipients, although this did not reach statistical significance. Platelet levels also decreased. The incidence of thrombophlebitis, stroke, and myocardial infarction did not differ between the tamoxifen and placebo arms.

At the 10-year evaluation, there had been 14 deaths (11 in the placebo group vs 3 in the tamoxifen group). A modest, nonsignificant improvement in disease-free survival was observed in the tamoxifen group at 4 to 5 years. Overall survival curves, however, began to diverge at approximately 5 years, and at the 10-year time point statistically significant improvement was observed in patients originally randomized to tamoxifen.

Discussion

Dr. Kleerekoper noted that the fracture rates in the first 10 years after menopause are so low that the size of the study required to demonstrate significant differences in fracture rates with any of these drugs would be substantial. Dr. William Hazzard pointed out that breast cancers and bone fractures occur primarily after menopause and that their incidence is increasing. He posed the following question: What is the most efficacious approach to the prevention of fractures in the 80-year-old woman with breast cancer?

Dr. Kleerekoper recommended treatment of the bones during the perimenopausal or early menopausal period to prevent the bone loss that will inevitably occur later without therapy. Another participant pointed out that there are limitations of the Wisconsin Tamoxifen Study in terms of fracture rates. Since the number of actual events was very, very small, it is impossible to make any judgment from these data about the efficacy of tamoxifen, or lack thereof, in preventing fractures. The fact that the bone densities were measured only at the spine is another limitation, and it appeared as if bone density might have actually increased in the placebo group at the last follow-up. This could well be osteophytosis or accumulated crush fractures. Since various factors could have confounded these results, one should not make any firm conclusions about the ability of tamoxifen to prevent fractures from these data.

Three-Pronged Approach to Osteoporosis

Michael Wills, MD: A three-pronged approach to retarding the progression of osteoporosis would involve the following: (1) diet, (2) exercise, (3) drug therapy.

Diet and Vitamin Supplementation

Nearly 30 years ago, Nordin’s group[23] demonstrated that women over age 55 to 60 years experience a decrease in intestinal absorption of calcium. Evidence suggests that, by the ninth decade of life, women actually malabsorb calcium. The mechanism for this calcium malabsorption is unknown, but it could result from a reduction in 1-alpha-hydroxylase activity and a consequent reduction in conversion of 25-hydroxyvitamin D to 1,25-hydroxyvitamin D.

In view of this, Dr. Wills personally recommends 800 IU of vitamin D supplement together with 1,500 mg of elemental calcium for patients over 65 years of age. Calcium carbonate tablets (40% calcium) are appropriate but may cause constipation, whereas calcium citrate (20% calcium) requires a larger number of tablets. Use of vitamin D and calcium has been controversial in the past, but this is probably due to the lack of attention to the age-related declines noted above.

The recent study of Dawson-Hughes et al[24] showed that supplementation with calcium and vitamin D results in a moderate reduction in the rate of bone loss while significantly reducing the number of nonvertebral fractures; 26 fractures in the 202-patient placebo group vs 11 fractures in the 187 patients given supplements. This study supports the use of vitamin D and calcium in older patients.
postmenopausal women.

**Exercise**
The National Aeronautics and Space Administration (NASA) zero-gravity studies in space demonstrated that bone formation is stimulated by a combination of gravitational and weight-bearing forces. Weight-bearing combined with muscular activity, but not muscle activity independently, increases bone mineral density. Low-repetition muscular activity combined with a weight load is ideal.

Use of a gym may not be practical for some patients, and walking, jogging and low-impact aerobics are good alternatives for these individuals. Cycling and swimming are good for the heart but not for strengthening bone. Thirty minutes of walking three times per week is the minimum recommendation; the pace of walking must be sufficiently brisk to elevate the pulse.

**Drug Therapy**
An overview of comparisons of the three classes of agents (hormone replacement therapy [estrogens with progestins], calcitonin, and bisphosphonates) compared increments in bone mineral density of the spine. After 2 years, estrogens increased this parameter by 2% to 5%, nasal calcitonin by 2% to 3%, and alendronate by 5% to 7%. Comparing femoral neck bone mineral densities, estrogens increased this measurement by 1% to 6% and alendronate by 4% to 6%. (No data on nasal calcitonin are available.)

With respect to fracture rates, the relative risk for hormone replacement therapy is 0.39 for vertebral fractures and 0.3 to 0.6 for hip fractures. Early studies of calcitonin reported a relative risk for vertebral fractures of 0.52.[25] Based on data presented at the September 1997 ASBMR meeting, the reduction in relative risk of new vertebral fractures is probably slightly less.[26] For alendronate vs placebo, the relative risks are 0.53 and 0.49 for new vertebral fractures and new hip fractures, respectively.[27]

It should be emphasized that patients need to follow a very careful regimen when taking alendronate. It should be taken on an empty stomach while sitting or standing and washed down with at least one full glass of water; also, the patient needs to remain upright for at least 30 minutes after taking the drug. Without strict adherence to these instructions, the rate of esophageal irritative symptoms is substantial. Various non-FDA approved agents, such as the thiazides and potassium bicarbonate, have favorable effects on bone density but are not as potent as other agents.

**Perspective of a Patient Advocate**
Phyllis Tyzenhouse, DrPh: I would like to emphasize that only 47% of postmenopausal female physicians in the United States—not quite a majority—take hormone replacement themselves. Do these physicians have information that is not available to patients considering hormone replacement therapy? Dr. Susan Love questions whether menopause is really a disease that requires treatment, or whether it is just another of life's transitions that can be traversed without drug therapy. Are women being pressured by drug companies or other groups to take drugs?

**Cost and Other Patient Concerns**
Conjugated estrogen (Premarin), the most widely sold prescription drug in the country, is also quite expensive. Cost is an important concern for patients and should be considered when an inexpensive drug, such as sodium fluoride, is now in the process being approved by the FDA for the treatment of osteoporosis.

Patients are frightened by the word “hormone”; this term raises a red flag. The battle with the beef industry over the use of growth hormone in beef cattle is an example of that perspective. Other examples include the facts that 20% of women stop taking hormone replacement therapy within 9 months, and that 20% to 30% of women never fill their prescriptions.

Patients become concerned when they learn that so-called public information services, such as the National Osteoporosis Foundation, which has an 800 number hot-line, are supported by Merck, the manufacturer of alendronate. In response to a telephone call, the information received from this foundation is a pamphlet listing sites for obtaining a free bone-density measurement but no information on how to interpret the results.

Patients also suspect that the cut-off values for bone density are set too high, and suspect that this is a ploy to convince them to start taking medication. Since only 3% of women die from osteoporosis, do the other 97% really need treatment?

Advertisements provide another inducement: An ad featuring a young, nicely dressed woman says, “Menopause—a time to look ahead.” This is perceived as a subtle “plug” for taking Premarin. Another ad talks about “bone appetite” and advises one to take a supplement to reduce signs of
osteoporosis. All of these elements raise concerns among patients about the real need for these medications.

Other Issues
Other factors should be considered when evaluating the reasons why less than one-fifth of women take hormone replacement over the long term. It may be due to lack of convenient treatment facilities and transportation to get to those facilities. Difficulty in getting time off from work may prevent access. Lack of money for drugs and lack of supervision in taking them compromise the patient’s ability to follow a regimen. For most women, therefore, the choice is not just to take hormone replacement or something else. Rather, the issues of cost and access are equally important and should be addressed.

Estrogen Deficiency, Lipids, and Risk of CV Disease

William Hazzard, MD: Curvilinear relationships exist between aging and CV disease. The exponential increase in all-cause mortality with age applies equally well to death from CV disease but is gender-dependent (Figure 5). There is approximately a one-decade lag in comparable risks between men and women, such that, for example, 65- to 74-year-old women have a rate of ischemic heart disease comparable to that of 55- to 64-year-old men. Analysis of age-adjusted causes of death reveals twice the rate of heart disease in men than women. For cancer, the rate is 50% higher for men; for stroke, 20% higher; and for atherosclerosis, 30% higher.

Do these conditions explain, in part, the fact that women live longer than men—7 years longer if considered from birth, 5 years longer if considered from age 60, and 1 year longer if considered at age 85? Cardiovascular disease accounts for approximately half this differential, while cancer contributes another 20% and stroke another 0.5%.

Gender Differential in Heart Disease Incidence
The gender differential with respect to heart disease incidence is not uniform across the life span, but rather, peaks before 50 years of age and declines gradually to approach that of men at approximately 70 to 75 years of age. However, the ratio of CV deaths remains higher in men even into their 90s. The major question is, what accounts for this marked differential prior to age 50 (five- to sixfold higher rate of CV disease in men than women) and its continuation, albeit at a diminishing rate, into the 90s?

Another way to look at the data is to ask, what proportion of individuals die from a particular disease? Fewer than 10% of men in their 20s die of ischemic heart disease, whereas 50% do so at age 50. The proportion does not change much after that.

Similar phenomena occur in women but with a lag of one decade. The number of women dying from ischemic heart disease is actually higher in women at age 75 than in men of a comparable age simply because more woman live to this age of vulnerability. Thus, women are now living to the age of risk of CV death and that risk is concentrated in the postmenopausal years. The major clinical dilemma facing women and their physicians is the trade-off between prevention of heart disease with estrogens and the increased risk of breast cancer.

Estrogen and Lipid Levels
An interesting means of examining the effects of estrogen on heart disease is to compare heart disease rates in premenopausal and postmenopausal women of the same age. Data going back 30 to 40 years and subsequently replicated many times demonstrate a substantially increased risk for postmenopausal women.

What proportion of this increased risk is related to lipid levels, and if lipid-related, what proportion is sex hormone-dependent? Data from the Lipid Research Clinic studies[28] of the 1970s illustrate this point. Data regarding LDL-cholesterol levels demonstrate increases in women between puberty and the era of the menopause but a greater increase in men (Figure 6).[28] However, the slope of increase in men flattens out and plateaus at age 50 and beyond, whereas the slope abruptly rises in women during menopause, such that mean LDL levels are higher in postmenopausal women than in men of comparable age. From these data, one can conclude that these changes are related to hormonal events, particularly the decline in estrogen levels that occurs during menopause.

Patterns of HDL cholesterol also reflect hormonal changes. Levels of HDL drop rather abruptly in boys as they pass through puberty, presumably in response to the rise in testosterone secretion. High-density lipoprotein levels remain lower in men throughout adult life but may increase during the years that testosterone gradually falls, the years of the so-called male menopause. This later change is subtle and has not been widely reproduced. In contrast, HDL levels in postmenopausal women do not clearly decline, as might be predicted from the fall in estrogen.
Integration of this information by calculating LDL/HDL ratios reveals higher LDL/HDL ratios in men than in women during and after puberty. However, there is a narrowing of the gender differential at menopause, although men still have higher LDL/HDL ratios and, therefore, higher CV risk. Based on these data, the sex differential in lipoproteins accounts for approximately 25% to 50% of the sex differential in coronary heart disease. Thus, both sex steroid levels and lipoprotein changes independently contribute to the lower risk in women.

Hormone replacement therapy changes lipid levels in a predictable fashion. In women taking combination oral contraceptives with both estrogen and progestin components, LDL levels are slightly higher than in those who do not take these contraceptives. Estrogens alone reduce LDL and raise HDL levels. The difference is the progestational component, which, in most instances, is androgenic and has HDL-suppressive and LDL-augmenting effects that offset the effects of estrogen. These interacting effects are predictable but complex.

Carefully designed interventional studies with fat intake maintained at stable levels demonstrate that estrogen alone produces a profound decrease in LDL and a dramatic increase in HDL, thus markedly improving the LDL/HDL ratio.[29] These data support the hypothesis that estrogen should have a major beneficial effect in countering those components of heart disease that are mediated by the adverse effects of lipids.

**Discussion**

Dr. Prior commented that the effects of oral estrogen on lipids are substantially greater than those of the transdermal preparations. Dr. Hazzard agreed and attributed these to the first-pass effects of estrogen on the liver. Dr. Jeffrey Perlman pointed out that the androgenic properties and lipid effects of the 19-nor-progestins differ from those of the less (or non-) androgenic 17-alpha-hydroxyprogestins, such as medroxyprogesterone acetate (MPA).

Dr. Henry Burger raised the question of whether menopause itself has significant effects on lipids, or whether these lipid changes are an effect of aging. Dr. Hazzard held that the changes are probably hormonal to a large extent but agreed that it has been difficult to precisely correlate sex steroid levels with lipid levels in postmenopausal women.

**Nonlipid Effects of Estrogens on CV Disease**

**Thomas Clarkson, DVM:** A controversy has existed with respect to whether the CV benefit of ovarian hormone replacement in women is real, or whether it is an artifact of patient selection bias. The cynomolgus monkey provides a useful model for investigating this question. Patient selection bias is not a problem, nor is compliance, and one can quantify pathologic changes using histomorphometry to determine the extent and severity of coronary artery atherosclerosis.

The reproductive biology of these monkeys is almost identical to that of human beings; they reach natural menopause at about 25 years of age and they have all of the same problems following menopause that human patients have. They have a 97% homology with human beings in their DNA, so that one would expect most of their organ systems and their cell biology to be very much like those of people. The animals are matched for age, and then the presence or absence of ovarian hormones is a principal variant.

**Results of Studies in the Monkey Model**

Surgically menopausal monkeys were given either no hormonal treatment or estradiol in Silastic implants to mimic the follicular phase of each of their monthly menstrual cycles. They were given estradiol alone or together with progesterone in the same way (Figure 7).[30] They were all fed a moderately atherogenic diet.

The effect of hormonal therapy on plasma lipid concentrations was not very striking, but the severity of coronary artery atherosclerosis was reduced to about half—an interesting number given that most people believe that hormone replacement therapy reduces coronary events by about half. There was absolutely no difference in outcome between estradiol alone and estradiol plus progesterone. These data are often cited as evidence that progestin replacement does not attenuate the benefits of estradiol replacement. The effect of the progesterone observed in this study, however, does not extend to some of the artificial progestins, as mentioned below.

With careful quantitation of coronary artery atherosclerosis, it was possible to determine how much of the atherosclerosis had actually been inhibited by the hormonal intervention. Having all of the animals' lipoprotein and apolipoprotein data, it was possible to ascertain how much of this inhibition of atherosclerosis was due to favorable effects on plasma lipoproteins and how much to plasma lipid-independent phenomena. This analysis showed that approximately one-quarter to one-third of the beneficial effect was due to favorable changes in the plasma lipoproteins, but, indeed,
approximately 70% to 75% of the benefit was plasma lipid-independent.

**Effects of Estradiol on LDL Metabolism**

What explains the nonlipid effects? Two phenotypic categories represent the plasma lipid-independent effects of estradiol on coronary arteries. The first derives from the work of Dr. Janice Wagner, who put two labels on the monkeys' LDL particles in order to measure both their entry into and efflux out of the coronary arteries. The notion is that atherogenesis is, in fact, the degree of “positive balance” of LDL particles, so that the LDL that enters the arteries but fails to efflux reflects the rate of progression of the atherogenesis.

Dr. Wagner can quantitate this very precisely.[31] Major differences were found between animals that were estrogen-deprived and animals that were estrogen-replaced. Normal monkeys accumulated approximately 2 to 3 µg/g of LDL per coronary artery per hour; that represents the background rate of progression of coronary atherogenesis. Oophorectomy increased this normal level of LDL accumulation of about 2.8 µg/g/h to a little over 16 µg/g/h, and ovarian hormone replacement normalized it. This represents a phenotypic description of coronary artery LDL metabolism.

Estrogen deprivation shifts LDL metabolism into positive balance; estrogen replacement corrects that problem. What are the modulators of this? Wagner and colleagues believe that there are two principal modulators: The first, and larger, effect is the interaction of estrogen with the proteoglycans of the intima of the arteries. This interaction causes the proteoglycans to actually bind more of the LDL particles so that they cannot return to the plasma.

The second effect relates to the oxidation of LDL particles within the intima of the coronary arteries, which is prevented by estradiol. Thus, the particles are not internalized by way of the scavenger receptor of the macrophages and are retained in the arteries.

**Effect of Estrogens on Endothelial Function**

The second major phenotypic category that is plasma lipid-independent is the effect of estrogen deprivation or estrogen replacement on coronary endothelial function. My colleague Koudy Williams has done pioneering work in this area.[32] Moderately atherosclerotic postmenopausal cynomolgus monkeys were given no hormonal treatment. During quantitative angiography, they received acetylcholine, an endothelial agonist, which produced constriction of their coronary arteries. In contrast, a few minutes after the monkeys were given estradiol replacement, the process could be normalized; ie, under those conditions, when acetylcholine was perfused, the coronary arteries dilated. This is a very important clinical finding.

The primary mechanism for this observation is that estradiol controls both the production of nitric oxide, via the up-regulation of nitric oxide synthase (NOS) within the coronary arteries, and the release of nitric oxide. This effect of estradiol may be due, in part, to some inhibition of the release of the vasoconstrictor endothelin, but this theory is controversial.

Ischemic chest pain that is not associated with stenotic lesions of coronary arteries is a very common clinical entity in women. This entity now seems to be associated, in large part, with estrogen deprivation and is relieved better by estrogen replacement than by nitroglycerin treatment.[32a, 32b]

Our group has conducted a major research effort aimed at determining the critical plasma estradiol that facilitates this important functional capacity of coronary arteries.[33] We obtained quantitative angiograms in 76 monkeys, which were divided into quartiles of plasma estradiol, according to their estradiol level at the time of the angiogram. We found that an estradiol level of approximately 60 pg/mL was the threshold level below which constriction occurs and above which dilation ensues.

**Effects of Progestins**

We have been intrigued by the attenuation of the beneficial effects of estrogen by the coadministration of medroxyprogesterone (MPA). This is a very controversial subject. We found that estradiol treatment produced about a 50% reduction in coronary atherosclerosis in oophorectomized animals, with no attenuation of the effect from the addition of progesterone.

Adams and colleagues[34] reported a similar study in which surgically menopausal monkeys received no treatment, received conjugated estrogens alone (at a dose equivalent to a 0.625-mg in humans), or were given that same amount of conjugated estrogens and MPA (equivalent to a human dose of 2.5 mg continuously). Conjugated estrogens produced a very robust effect on initiating atherosclerosis. This effect was markedly attenuated by the addition of the MPA, to such an extent that it was no longer significantly different from the untreated group.

One hears frequently at meetings about five retrospective observational studies showing that progestins have no impact on the effects of estrogen. Two of those studies were with levonorgestrel and two were with norethindrone. The Nurses’ Health Study,[35] which really addressed the issue,
was based on only eight events in the combined-therapy group, and, therefore, I do not feel confident about their MPA data. Only time will tell whether the results of the studies in monkeys or the studies in nurses are correct. This potential attenuation of estrogen’s effects is not generalizable to all progestins, but rather, seems to be a unique property of MPA. Norethindrone or levonorgestrel, for example, do not share this effect, nor does the new agent nomogestrel. Similar effects can be seen with respect to vasomotion; ie, nice dilation with conjugated estrogens alone and marked attenuation with conjugated estrogens plus MPA.[36]

**Effects of Antiestrogens**

What does the future hold? Interestingly, the same issues surrounding hormone replacement therapy that are important to women in the general population are important to those surviving breast cancer. As stated earlier in this meeting, many women who do not have breast cancer will not take currently available hormone replacement therapy. If you ask why this is true, fear of breast cancer looms above all of the other reasons, and, for those with a uterus, the inconvenience of progestin therapy.

Thus, there is a need to find an intervention that neither requires a progestin nor poses a risk of breast cancer and, hopefully, protects against it. I will present some data on raloxifene from our trials in monkeys because it is a possible candidate for such an intervention. Our expectation was that the effects of raloxifene would resemble those of tamoxifen, which were published in early 1997. There was about a 50% reduction in the development of coronary artery atherosclerosis extent from control with tamoxifen, in contrast to the much more robust effect of the conjugated estrogens of about 70%. The assumption was made that a similar effect probably would be seen with raloxifene.

A very large trial was planned in which 125 monkeys were randomized into five groups: a premenopausal group and four groups that were oophorectomized.[37] The surgically postmenopausal monkeys were randomized to receive placebo, raloxifene at the intended clinical dose, raloxifene at five times that amount, or conjugated estrogens (at a dose equivalent to the 0.625-mg level for women).

The effects on plasma lipids were similar to those that have been reported for women. The premenopausal monkeys had lower LDL and higher HDL levels. Treatment with conjugated estrogens made the oophorectomized monkeys much more like the premenopausal ones, lowering their LDL levels and increasing their HDL levels. Raloxifene produced some lowering of LDL but had no real effect on HDL, as is seen in women.

The coronary arteries of these monkeys were examined using quantitative morphometry. The oophorectomized, placebo-treated monkeys (no-treatment group) had more severe atherosclerosis than the premenopausal monkeys. Treatment with conjugated estrogens protected the animals almost completely, and their coronary arteries were similar to those of the premenopausal animals. Neither the low dose nor the high dose of raloxifene had any effect on atherosclerosis extent.

**Natural Selective Estrogen Receptor Modulators**

The phytoestrogens derived from soy are considered to be natural selective estrogen receptor modulators (SERMS). Soy is a very rich source of two phytoestrogens, genistein and daidzein, that have molecular structures similar to that of estradiol. In the past, these phytoestrogens had been called weak estrogens because they bind weakly to the estrogen receptor (ER)-alpha. They now should be called fairly robust estrogens because they bind to ER-beta with relatively high affinity. Other reasons for focusing on soy are the outcomes among aging women in Japan who eat their native diet, which is rich in soy. Regarding the average urinary excretion of genistein and daidzein among Japanese women, it is about 3,000 nmol/d, compared with the rather trivial 35 nmol/d for US women. As Japanese women age, they have very little coronary heart disease, very low rates of breast cancer, and very low rates of endometrial cancer.

One of our first challenges was to determine whether the well-known cardioprotective effect of soy protein was due to its phytoestrogens, its protein moiety, or some interaction of the two. Our approach to the problem was to compare the plasma lipoprotein responses of monkeys that were fed diets containing intact soy protein with responses of monkeys fed soy protein from which phytoestrogens had been extracted ([Figure 8]).[38]

Administration of soy protein led to large decreases in plasma LDL concentrations, an effect that was lost with removal of the phytoestrogens. Large increases in plasma HDL concentrations occurred with unextracted phytoestrogens; these increases were lost with phytoestrogen extraction. The effects of soy phytoestrogens on cognitive function remain uncertain. In a study of Japanese-American women in Seattle, Rice and coworkers[39] reported that women who consumed
taro more frequently than three times per week lost the protection afforded by hormone replacement against cognitive dysfunction. Obviously, studies of cognitive function will be important in all future studies that are conducted with soy phytoestrogens. We have increased our efforts to study the effects of these substances on the brain. Very recent data from our laboratory have shown that the soy isoflavones and phytoestrogens are comparable to estradiol in their effects on the messages for nerve growth factor and for the neurotransmitter choline acetyltransferase.[40] The question of whether soy estrogens function as estrogen antagonists in the mammary gland and uterus is critically important. Indeed, data show that they do have estrogen antagonistic effects in these tissues.[41]

In the breast, the usual response to estradiol was seen, but there was no significant effect of soy estrogens. Importantly, soy estrogens block the mammary gland proliferation induced by estradiol. In the endometrium, soy estrogens also act as antiestrogens and can prevent the endometrial hyperplasia resulting from treatment with estradiol. Atherosclerosis protection was observed in the presence of phytoestrogens, and that protection was lost when they were removed. Soybean estrogens were equivalent to conjugated estrogens alone in their ability to dilate the coronary arteries. Finally, there was a very major effect on postangioplasty restenosis. No measurable effect of conjugated estrogens was found, but there was a 70% inhibition of restenosis with soybean estrogens. This effect is thought to be due to the binding of genistein to ER-beta and to the fact that it is a very powerful inhibitor of tyrosine kinase.

**Discussion**

Responding to several questions, Dr. Clarkson discussed why prepubertal girls or girls with delayed puberty do not experience CV events in the presence of low estradiol levels. In their animal studies, the length of time that the animal is estrogen-deprived is overpoweringly the determinant of CV events, rather than the age superimposed on that. Atherogenicity of the diet is also important. In order to telescope the event with respect to time, monkeys are fed about twice as much dietary cholesterol as people consume. Their plasma cholesterol concentrations are around 400 mg/dL; thus, atherosclerosis occurs within that unusual background.

In fact, Dr. Clarkson noted, prepubertal monkeys are not protected. They studied female monkeys from weaning age until puberty, during which time they showed progression of their coronary artery atherosclerosis. Notably, this stopped immediately with the onset of puberty.

A participant noted that when the first synthetic estrogen, diethylstilbestrol, was given to men for prostate cancer, they died of heart disease. Also, when estrogen was originally given to men in the Coronary Drug Project, it was discontinued because they died of heart disease. The participant asked, what does estrogen do to male endothelium? What’s the effect of having a Y chromosome?

Dr. Clarkson indicated that excess mortality in the Coronary Prevention Trial was probably due to the rather high dose of conjugated estrogens used. A substantial number of thromboembolic events occurred. People have been generally unwilling to study lower doses to determine whether there is a CV-safe dose of conjugated estrogens because of preliminary studies showing that one cannot find a CV-protective dose of conjugated estrogens that does not adversely affect libido.

The soy phytoestrogens have huge potential in this regard, Dr. Clarkson said. They are nonfeminizing in males; they are equally cardioprotective in males as in females; and they appear to strongly protect against prostate cancer—a big plus. As a result, Clarkson’s institution is launching studies of phytoestrogens in male monkeys and male patients.

An audience member cited a study by Peter Collins from England, in which he put estrogen directly into the coronary arteries of men and women who had atherosclerosis. It caused vasodilatation and desirable effects in women but had no effects whatsoever in men. Therefore, it is possible that estrogen has gender-specific effects on the vasculature.

In response to a question regarding the appropriate dietary content of phytoestrogen, Dr. Clarkson indicated that the minimally effective dose is about 50 mg/d of total soy isoflavones; effectiveness increases up to doses of about 70 or 75 mg/d. It is doubtful that higher doses have any additional benefits. Thus, 75 mg/d seems to be appropriate. Most good soy isolates contain about 2 mg/g, and, consequently, 30 g/d of soy protein isolate is appropriate. There is substantial interest among the industry as to how this should be delivered. The community is divided between those believing that a pill is best and behavioral scientists who say women are more likely to take a nutritional supplement.

In reply to a question asking why the effects of MPA and testosterone are different in the dilution model, Dr. Clarkson described his working hypothesis. His group, along with Fred Naftolin's group at Yale, reported on the sites of active aromatase in coronary arteries at the 1997 Menopause Society
Meeting.[42] Coronary arteries have a substantial amount of aromatase. Where macrophages begin to form in response to intimal lesions, they become very rich in aromatase.

At present, Dr. Clarkson’s group believes that atherogenesis in males may, in fact, be modulated by estradiol—somewhat akin to what occurs in the brain. This depends on the conversion of testosterone to estradiol. This group now thinks that aromatization of testosterone to estrogen can result in vasodilatation in the same way that estrogen treatment induces vasodilatation in females.

**Role of Estrogens and SERMs in Preventing Heart Disease**

**Elizabeth Barrett-Connor, MD:** The greatest benefit from estrogen is the short-term control of menopausal symptoms. This is true for women with or without breast cancer. I have not been persuaded that any of the other treatments are any safer for relief of symptoms; they are untested and certainly not as effective.

**Estrogen and Heart Disease**

The goal in the asymptomatic menopausal patient is to prevent something that she may not get—heart disease. The effects of estrogen in preventing heart disease have not been proven in randomized trials, except in the monkey model.

Many observational studies have examined the effect of estrogen replacement therapy on CV disease in women. A meta-analysis by Grady et al[43] shows about a 35% reduction in heart disease among women taking estrogen replacement. All or almost all of these studies include women taking unopposed estrogen without any progestin.

To date, about seven studies have compared estrogen and progestin users to nonusers. These studies demonstrate the same level of protection as is seen with unopposed estrogen. In the majority of studies, women were not using MPA, but rather, more androgenic progestins. Nevertheless, these data might be interpreted as showing that the addition of a progestin does not abrogate the putative benefit of estrogen alone.

The mechanisms whereby estrogen might prevent heart disease are numerous. Lipid effects have been clearly demonstrated; there is evidence that estrogens are calcium antagonists; they have antioxidant effects and influence the nitric oxide system; they act as angiotensin converting enzyme (ACE) inhibitors and cause both endothelial- and non–endothelial-dependent vasodilatation.

Consistent with conclusions drawn from meta-analyses of observational studies, the putative effects of estrogen in preventing CV disease are biologically plausible.

**Effects of Estrogen ± Progestin on Lipids**

As discussed by Dr. Hazzard, estrogen dramatically lowers LDL cholesterol. In the Postmenopausal Estrogen/Progestin Intervention (PEPI) trial (Table 1), 875 women were randomly assigned to 3 years of therapy with one of various regimens.[44] Estrogen alone increased HDL cholesterol levels. The increments did appear to fall off somewhat with time, largely because the women who took estrogen alone were not able to continue this therapy due to endometrial hyperplasia. Micronized progesterone (the so-called natural progesterone) with estrogen was significantly superior to MPA with regard to HDL cholesterol, but all hormonal regimens were superior to placebo with regard to HDL-cholesterol elevation. If one believes that HDL cholesterol is part of the mechanism for estrogen’s protective effect, one might develop a hierarchy of therapies, with estrogen or estrogen plus micronized progesterone representing the best regimen, estrogen plus MPA, the second best approach, and, of course, placebo, the poorest.

Examination of the women in the PEPI study who continued estrogen is instructive. In women who did not develop endometrial hyperplasia and thus were able to continue the unopposed estrogen, HDL-cholesterol levels were significantly higher than levels in those receiving estrogen plus micronized progesterone. Unopposed estrogen is clearly the best way to take estrogen if the main goal is to raise HDL-cholesterol.

I would not advocate that anyone recommend hysterectomies so that all women can be treated with unopposed estrogen. Two-thirds of the women in the United States do have a uterus and, therefore, need a progestin if they are to take estrogen. The effects of added progestin on HDL-cholesterol levels must therefore be considered.

**Estrogen Dose and Route**

A study by Walsh et al showed no significant difference between smaller and larger doses of estrogen in terms of raising HDL-cholesterol or lowering LDL-cholesterol levels.[45] Thus, there is no need to exceed standard dose levels of conjugated estrogens (ie, 0.625 mg/d) to achieve the optimal benefit on lipids or lipoproteins.

With respect to the route of administration of estrogen, transdermal estradiol has much less of an
effect on HDL-cholesterol than does oral estrogen. It is not clear whether this is because the estrogen levels achieved are not the same or because of a first-pass liver effect. Both of those factors may be important. Based on these observations, oral estrogens could be preferable to transdermal preparations as a CV preventive.

Selection Bias

Given the biological plausibility for a preventive effect of estrogen against CV disease and the extremely consistent data, why would one argue that the association between estrogen and heart disease prevention may not be causal or may be exaggerated? Of concern are the major confounding biases inherent in the existing data. No matter how consistent the data, women who take estrogen in the United States, and every other country in which this has been studied, are healthier and wealthier than those who do not. Those two factors are very good for one’s health. Studies have shown that going to college is associated with a 50% reduction in risk of heart disease—a greater reduction than has been achieved in most of the estrogen studies. Consequently, there is tremendous self-selection, in that healthy women who are at a low risk of CV disease tend to be the ones who are prescribed estrogen and who continue to take it. Until recently, the packet insert for estrogen stated that women who had heart disease, high blood pressure, or diabetes should not be treated with estrogen. Consequently, those women were selectively not treated with estrogen. As a result, women at highest risk of heart disease were not given estrogen. This fact would also tend to make estrogen look better than it is.

“Prevention Bias”

Women who spend a substantial amount of time in the doctor’s office (eg, if they are taking estrogen and must go to the doctor twice a year to get their prescription renewed) have a greater opportunity for exposure to educational material in the doctor’s waiting room. In other words, they would have greater exposure to preventive information and to physicians, nurses, and health maintenance organizations (HMOs). It is known that women who take estrogen tend to have much healthier lifestyles, eat better diets, and are more likely to take vitamins and exercising than are women who do not take estrogen. We have termed this phenomenon “prevention bias.”

Every person in this field should read an insightful paper by Matthews and colleagues that was published in the American Journal of Epidemiology.[46] These investigators followed over 400 menopausal women, about half of whom elected to take estrogen and about half chose not to take hormone replacement. Factors preexisting before entry into menopause were compared in women taking or not taking estrogens.

Prior to menopause, the estrogen users had better blood pressure, higher HDL cholesterol, lower insulin, and lower weight; they drank a little bit more alcohol and were physically more active than those who did not take estrogen. These women were already much healthier, with respect to all of the risk factors that were measured in the study, before they became postmenopausal and before they made a decision about using estrogen. Thus, self-selection is a major confounding factor in trying to decide how much of the benefit is due to estrogen and how much is due to preexisting factors in women choosing to take estrogen.

Compliance Bias

About 85% of women who start taking estrogen are not taking it after 1 year. Thus, women in the reported studies are an unusual subset, ie, those who have remained on estrogen. These women are different in some way. It may be that there is some innate characteristic about compliant people, and that this difference is protective or at least responsible for part of the protection, rather than the estrogen itself.

With respect to the matter of compliance, data from the Coronary Drug Project showed that the subjects who took 80% of their placebo had a relative risk of CV disease of 0.53, ie, 50% protection, compared with those who did not.[47] That is as good as anyone has postulated for estrogen. This finding implies that there is something significant about being a compliant person that is beneficial. A similar finding was reported in the Beta Blocker Heart Attack Trial (BHAT): The risk ratio for CV disease was 0.43 among “good” placebo-takers—a reduction of more than 50% compared with the “poor” placebo-takers.[48]

Is it necessary, then, to consider whether compliance bias is part of the reason why women who take estrogen appear to be so healthy with regard to heart disease? You will always have women whom you are trying to convince to participate in your studies and they always say, “Oh but doctor, I don’t want to be in a placebo group.” However, you can reply with all honesty, “Take the placebo; it is very good for you. Just be sure you take it.”

Alternatives

If one doesn’t smoke or quits smoking, the average percentage reduction in myocardial infarction for
women is about 60%. If one completed college, that reduction is 50%. If one exercises daily, it is 45%. If one drinks one alcoholic beverage daily, the reduction is 35%. Low-dose aspirin reduces risk by 35%. These data come from a mixture of clinical trials or observational studies. (The estrogen data are all observational.) Maintaining ideal weight gives 30% protection and treating blood pressure and cholesterol, 15%. Therefore, taking estrogen is not the only thing that women can do to lower their risk of heart disease.

In summary, we cannot be sure that estrogen alone or together with a progestin prevents heart disease in postmenopausal women. Biases could explain the observed protection; results from clinical trials are necessary.

**Estrogen Use and Breast Cancer**

An updated meta-analysis by Grady et al[43] examined data regarding breast cancer risk among long-term users and ever-users of estrogen. This analysis showed that the longer the duration of estrogen use, the greater was the risk of developing breast cancer. Risk increased approximately 35% for \( \geq 5 \) years of estrogen use.

The data are fairly consistent that long-term estrogen use does increase the risk of breast cancer in healthy women. Data regarding survival, however, provide a different perspective. The Nurses’ Health Study showed a 0.80 relative risk of dying of any cause if one took estrogen for \( \geq 10 \) years.[35] That translates into a 20% reduction in mortality, which is statistically significant. This 20% survival benefit is less than the 50% that was reported earlier by this group, possibly because women who took estrogen for \( > 10 \) years had a 43% increase in death due to breast cancer.

Past hormone use (ie, ever-use), regardless of duration, was not related to mortality, a curious finding which we discussed earlier. According to the Nurses’ Health Study, as presented at the June 1997 Society for Epidemiologic Research, the increased risk for breast cancer is 4% for each year of estrogen use and the risk for estrogen plus progestin is 9% for each year of use. Since these are US data, they primarily involve the use of conjugated estrogens and MPA.

If biases do, in fact, exist relative to estrogen and heart disease risk, there are also likely to be biases that may influence the breast cancer risk noted in observational studies. In general, hormones have not been prescribed in women who have a strong family history of breast cancer. If you ask Don Gambrell, who reported that estrogen reduced the risk of breast cancer by 50%, he will acknowledge that he rarely prescribes estrogen for a woman who has a family history of breast cancer. That certainly could have made estrogen appear safer than it is.

Traditionally, we do not start women on estrogen replacement unless they have a negative mammogram, so that takes women out of the group who would be likely to have had breast cancer diagnosed within the next 8 years (if you believe the data on mammogram latency to a clinical diagnosis). That also may make estrogen appear to be safer with respect to breast cancer than it really is.

Most women who use estrogen over the long term have had an early oophorectomy. Early oophorectomy is very protective against breast cancer; again, this would make estrogen look safer than it really is.

Women of upper social classes, who tend to be thinner, use estrogens more often, and being thin reduces breast cancer risk. This is yet another factor that would tend to make estrogen look safer than it really is for breast cancer.

On the other hand, women who are taking estrogen are examined more frequently by a physician and have more frequent mammograms. This would artificially increase the risk because more cancer would be diagnosed.

**Long-Term Estrogen Use**

Long-term estrogen use increases gallbladder disease and increases deep vein thrombosis and pulmonary embolus two- to fourfold. The chance of having a hysterectomy is increased two- to threefold because women on estrogen bleed. The risk of developing carcinoma of the uterus is increased in proportion to the duration of estrogen use, and progestins may not completely eradicate this effect, probably because of incomplete compliance in taking the progestins.

In addition, there have been several case reports of retinal hemorrhage and anecdotal reports of increased risk of asthma with long-term estrogen use. Two papers have suggested an increased risk of ovarian cancer, and at least two good studies have indicated that estrogen users have more migraines (although other studies have suggested that they have fewer migraines). Those are some side effects of long-term estrogen that women may wish to consider.

On the other hand, there are other benefits of long-term use. Estrogens reduce the risk of osteoporotic fractures. Several papers suggest a reduced risk of colon cancer. The literature on stroke and dementia is mixed.
Undoubtedly, some women have a very miserable quality of life without estrogen; there are probably an equal number of patients who feel truly miserable while taking estrogen and cannot wait to stop it.

**Alternatives to Estrogen: The Statins and SERMs**

The consideration of alternatives to estrogen presents another very important issue. Regarding estrogen and the heart, the statins (Table 2) can serve as an alternative and have been shown to prevent heart disease in women in clinical trials.[49] Actually better clinical trial data exist for the statins than for estrogen. With regard to osteoporosis prevention, other options also exist.

The ideal situation would be to have one drug that had all of the beneficial actions but without adverse effects. Do the SERMs meet these criteria? Both tamoxifen and raloxifene can be considered SERMs, and many other SERMs are currently in development. Tamoxifen lowers LDL cholesterol and increases triglycerides without altering HDL cholesterol (Table 3).[50]

The dose of raloxifene approved for clinical use is 60 mg/d. This provides an LDL-lowering effect that is not as great as the effect produced by conjugated estrogens. Perhaps more worrisome is the fact that raloxifene does not significantly change total HDL-cholesterol levels, although it does favorably alter HDL2, which is probably the most protective part of the HDL. Raloxifene has an effect on lipoprotein(a) that the statins probably do not have, and that could be a benefit. The drug also has a positive effect on fibrinogen. Unlike estrogen alone or combined with a progestin, raloxifene does not appear to raise tri-glyceride levels, and no one is quite sure how important that might be.

In summary, raloxifene has a positive effect on lipids, which is probably not quite as strong as the effect of estrogen (certainly, not with regard to HDL) but is otherwise rather similar. Dr. Clarkson’s data regarding raloxifene showed no vasoactive effects and no protection in the monkey model. In the rabbit model, raloxifene appeared to have direct vascular effects.[51] At present, the effects of raloxifene on CV disease are unknown.

For breast cancer data, the numbers look very different. Data presented at the 1998 American Society of Clinical Oncology (ASCO) meeting[52] suggest that raloxifene reduces the risk of breast cancer. This would be a useful addition to our armamentarium because women are looking for a drug without the effects of tamoxifen on the uterus that they can use to prevent breast cancer. These data are exciting but are not yet sufficient to make recommendations. Raloxifene doesn’t prevent one from gaining weight. That happens when one gets older and does not relate to menopause. Raloxifene has no effect on blood pressure or pulse.

It is interesting that, compared with the women who took placebo, significantly fewer women taking raloxifene had an accidental injury. When one looks at hundreds of variables, which one does when examining the safety of new drugs, some strange findings arise—some of which may be important and some of which may be due to chance alone. There is also an increased risk of leg cramps in women who take raloxifene, as occurs in some patients on estrogen. Compared with women receiving raloxifene, women taking placebo had fewer headaches, more diarrhea, and were more likely to have bronchitis. It is unclear whether any of these observations are clinically relevant. Hot flashes were significantly more common in the raloxifene group. It appears that the great majority of women will have no side effects while receiving raloxifene, but women who have symptoms such as hot flashes may not find relief from this drug.

The only cognitive function study on raloxifene assessed two doses administered for 1 year in 48 women each. The study participants were older women who were not mentally impaired when the trial started or when it ended. Raloxifene produced no detectable effect on cognition.[53] This outcome is what I would expect in studies of estrogen replacement. If you take older women who are not mentally impaired, give them estrogen, and follow them for 1 year, you will not find any change in their cognitive function tests either.

**Other Considerations**

Thrombotic events are a problem with estrogen. Three papers published in the Lancet in December 1996 showed a relative risk between 2 and 3 for hormone replacement therapy. The raloxifene clinical trial results show that raloxifene acts like an estrogen with respect to venous thrombotic events, the risk being > 2 in all four available studies. In the study with the largest number of patients enrolled, the relative risk was 4.5. Thus, raloxifene, like all drugs, has risks associated with it, and venous thrombotic events represents one of those risks.

Without a controlled clinical trial, the effect of hormone therapy (now including raloxifene and other SERMs) on heart disease prevention will remain unknown. Whether or not to use estrogen is a fundamental question faced by all postmenopausal women. If estrogen does prevent heart disease, it would outweigh all of the other known risks and benefits in women who do not have heart disease. (This is not true for women who have breast cancer.) We clearly need more research to help women...
with and without breast cancer make this decision.

**Discussion**

Dr. Kathy Helzlsouer suggested that there are additional potential biases regarding increased risk of breast cancer and choice of estrogen use. These include socioeconomic status, obesity, level of education, and amount of alcohol intake, which are consistently found to increase, although to a small degree, the risk of breast cancer. Dr. Helzlsouer agreed with Dr. Barrett-Connor that there are biases, but she felt that they do not always work to underestimate the risk of breast cancer.

**Effects of Tamoxifen on Lipids and CV Disease**

**Dr. Olsen:** In the Wisconsin trial, tamoxifen caused a reduction in total cholesterol even after 5 years of administration. Triglycerides tended to be higher in the tamoxifen group, although this did not reach statistical significance. Levels of LDL cholesterol fell within 3 months in tamoxifen recipients and remained lower for the entire time they were measured. There was a tendency for HDL cholesterol to fall slightly in the tamoxifen group, but this effect was not statistically significant. Additional data indicate that tamoxifen significantly reduced lipoprotein(a).[54] Fibrinogen and platelets also decreased in the tamoxifen-treated patients, and there was a trend toward a reduction in homocysteine. No significant differences were noted between women receiving tamoxifen and those given placebo for 10 years with respect to CV deaths. However, the numbers are not large enough to draw meaningful conclusions. As described previously, overall survival at the 16-year time point was improved in patients originally randomized to tamoxifen—a difference which reached statistical significance.

**Perspective of a Patient Advocate**

Barbara Parker: I am a breast cancer survivor who has experienced symptoms of and had concerns about urogenital atrophy, hot flashes, insomnia, osteoporosis, and CV disease. I have tried to determine whether women surviving breast cancer for > 5 years face a greater subsequent risk of death from breast cancer or from CV disease and could not find the answers to these questions. Participants at this conference should consider that such factors as motivation, compliance, and willingness to change one's lifestyle are less compelling in the asymptomatic patient facing potential risks than they are in women who currently are experiencing symptoms.

**References:**


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