Estrogen, Selective Estrogen Receptor Modulation, and Coronary Heart Disease: Something or Nothing

V. Craig Jordan

In terms of lifetime risk, one in three women will die of heart disease and one in six of stroke; in contrast, one in nine women will develop breast carcinoma, and only one in 25 will eventually die of it (1). It is, therefore, clear that a successful therapeutic intervention to improve death rates for coronary heart disease (CHD), however modest, will have a disproportionately large benefit on women’s health. Lipid-lowering drugs produce clear-cut benefits in the primary prevention of CHD (2). Although the population currently being evaluated is primarily male, the successful treatment strategy is invariably for 5–7 years. Duration of therapy is an important consideration for a successful intervention.

Women have less heart disease than men up to the age of 50 years but catch up to men after menopause, so there has been a tendency to ascribe an elevated risk for women to a loss of sex steroids, notably estrogen. For 50 years, estrogen replacement therapy or hormone replacement therapy (HRT)—i.e., a combination of estrogen and a progestin (to avoid a modest increase in endometrial cancer risk)—have been prescribed to protect against a number of diseases associated with advancing age. The evidence to support estrogen use for the prevention of osteoporosis is good; however, in the case of CHD, the benefit from estrogen was inferred from observational studies [reviewed in (3)]. It is now clear that observational studies are misleading and only randomized prospective clinical trials can provide evidence for or against the benefit of HRT without bias. High-risk women must be recruited to record a statistically valid result, with sufficient events in a short period. Long-term (5–10 years) therapy is also necessary to stop or reverse existing CHD pathology. This issue is extremely important, since only 40% of the women who were prescribed HRT continue after 1 year (4). In a clinical trial, compliance would be aided by support from health care professionals (5).

Unfortunately, the early results from the first randomized clinical trial in high-risk women showed no differences between placebo versus HRT in the primary outcome of nonfatal myocardial infarction (MI) or death from CHD (6). The Heart and Estrogen/progesterin Replacement Study (HERS) trial (6) recruited a total of 2763 women with coronary disease, with a mean age of 66.7 years. A total of 172 women in the hormone group and 176 women in the placebo group had MI or CHD death, with an average follow-up of 4.1 years. However, there was a statistically significant time trend, with more CHD events in the hormone group in year 1 but less in years 4 and 5. This trend occurred despite a net lowering of low-density lipoprotein (LDL) cholesterol of 11% and a 10% elevation in high-density lipoprotein cholesterol. One has to wonder why the trial was stopped prematurely in light of the trend toward improvement in cardiovascular health.

A major concern about the use of long-term HRT is the link between estrogen and the development of breast cancer. In an analysis of 51 studies, the relative risk of breast cancer was 1.35 (95% confidence interval = 1.21 to 1.49) for women who currently or recently (i.e., within the past 4 years) used HRT for 5 years or more (7). In the Breast Cancer Detection and Demonstration Project, the risk of breast cancer increased by 8% per year of HRT (8). Clearly, therapeutic agents that have the benefits of estrogen but without the carcinogenic actions in the breast should be developed and evaluated in clinical trial.

Tamoxifen produces an assortment of estrogenic and antiestrogenic activities in tissues, which is not surprising from a pharmacologic point of view, since the drug was originally classified as a partial agonist and not a pure antiestrogen (9). However, the recognition of selective estrogen receptor modulation (SERM), with the so-called nonsteroidal antiestrogens in the mid-1980s (10–13), raised the possibility that drugs could be targeted to prevent breast cancer, osteoporosis, and CHD. At the meeting of the American Association for Cancer Research in San Francisco in 1989, Dr. Leonard Lerner and I suggested that the nonsteroidal antiestrogens had enormous potential as preventives, not just as treatments, for breast cancer:

Is this the end of the possible applications for antiestrogens? Certainly not. We have obtained valuable clinical information about this group of drugs that can be applied in other disease states. Research does not travel in straight lines and observations in one field of science often become major discoveries in another. Important clues have been garnered about the effects of tamoxifen on bone and lipids so it is possible that derivatives could find targeted applications to retard osteoporosis or atherosclerosis. The ubiquitous application of novel compounds to prevent diseases associated with the progressive changes after menopause may, as a side effect, significantly retard the development of breast cancer. The target population would be postmenopausal women in general, thereby avoiding the requirement to select a high-risk group to prevent breast cancer (14).

The nonsteroidal antiestrogen strategy provided the scientific rationale for raloxifene (originally named either LY156,758 or keoxifene in the literature during the previous decade) (11,12,15,16), which was evaluated subsequently to prevent osteoporosis (17,18) but with the beneficial side effect of lowering the incidence of breast cancer (19). These preliminary data are the basis for the ongoing study of tamoxifen and raloxifene (STAR) to determine the reduction of breast cancer incidence prospectively as the primary endpoint. Unlike raloxifene, tamoxifen has already been tested in high-risk premenopausal...
and postmenopausal women to determine its worth in reducing the incidence of invasive and noninvasive breast cancer. The P-1 trial showed about a 50% decrease in reducing invasive breast cancer for all age groups and for all levels of risk (20). Secondary endpoints were safety issues of fractures and ischemic heart disease. Overall, there was a 19% reduction in the incidence of fractures, which almost reached statistical significance. There was a 45% decrease in hip fractures. In contrast, there was no difference in ischemic heart events. Of the total number of events related to ischemic heart disease, 57 occurred in the placebo group in women more than 50 years of age and 61 occurred in women more than 50 years of age who were treated with tamoxifen (20).

In this issue of the Journal, Reis et al. (21) analyze the data from the National Surgical Adjuvant Breast and Bowel Project Breast Cancer Prevention Trial P-1 to determine whether there is any time-related cardiovascular effect of tamoxifen. This is a safety issue for the use of tamoxifen as a chemopreventive agent in light of the HERS results that show an increase in early mortality for HRT (6).

Cardiovascular follow-up was available for 13,194 women, 1,048 of whom had prior CHD. Among women without CHD, risk ratios for tamoxifen were 1.75 for fatal MI and 1.11 for nonfatal MI. For women with CHD, risk ratios for tamoxifen users were 0 for fatal MI and 1.25 for nonfatal MI. There was no evidence of an early increased risk for MI followed by a late decrease, as observed in the HERS trial. This is the good news; tamoxifen for the chemoprevention of breast cancer provides a better safety profile than HRT use in women at risk of CHD. Nevertheless, is it reasonable to compare a secondary endpoint in the P-1 trial with the results from HERS, which is a prospective randomized trial? In the high-risk categories, there were three times as many women in HERS, and the mean age was 10 years older (66.7 versus 57.7 years) for the HERS volunteers. Not all answers to questions can be derived from a single trial.

Important issues need to be addressed by medical scientists. For 50 years, there has been a belief that estrogen protects women from CHD. The HERS trial seems to recommend that, if you survive the first year, the use of HRT for secondary prevention could benefit women at risk if you take it long enough. The Women’s Health Initiative Study Group (22), which has randomly assigned 27,348 women to receive HRT, could establish whether estrogen protects against CHD. A total of 10,739 women without a uterus are receiving either unopposed conjugated equine estrogen (CEE) at a dose of 0.625 mg daily or placebo, and 16,609 women are receiving CEE at a dose of 0.625 mg daily plus 2.5 mg medroxyprogesterone acetate or placebo. The primary study outcome is fatal and nonfatal ischemic cardiovascular events, but only those occurring during an average of 4 years of follow-up. In addition, we need to discover why estrogen can successfully prevent osteoporosis but its beneficial effect on CHD is much harder to demonstrate. There is clearly a good opportunity for advancement with SERMs. Tamoxifen (23) and raloxifene (24) both lower LDL cholesterol, so important advances in cardiovascular prevention are possible. For tamoxifen, there will be no trials in women at risk for CHD, but the STAR trial of 22,000 postmenopausal women randomly assigned to receive tamoxifen (20 mg) or raloxifene (60 mg) will also provide a critical comparison of cardiovascular events. An important test for SERMs and CHD will come with an ongoing trial, Raloxifene Use for the Heart (RUTH). Ten thousand high-risk postmenopausal women are being randomly assigned to receive either raloxifene (60 mg) or placebo for 5 years. The results from RUTH could reveal that SERMs are truly multifunctional medicines (25).

References

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NOTE

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