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Preventive Cardiology

In this issue of Clinical Cardiology we are initiating a new section entitled "Preventive Cardiology." Reviews, editorials, and original work will appear from time to time throughout the year. Articles will cover an array of topics focused on primary and secondary prevention of cardiac events in patients with cardiovascular disease.

Hormones and the Cardiologist

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Summary: Cardiologists must become more involved in discussing and recommending hormone replacement in postmenopausal women with established coronary artery disease, and those individuals at high risk of coronary events. A large amount of epidemiologic and observational data, as well as new research in vascular biology, strongly support the benefits of estrogen on the development and progression of coronary atherosclerosis. While breast and uterine cancer are valid concerns, selected high-risk women with and without established coronary disease should be counseled by an informed cardiologist to consider hormone replacement therapy.

Key words: menopause, estrogen, hormone replacement, coronary artery disease

Introduction

Hormone replacement therapy, as well as a broader focus on women's cardiovascular issues, has received considerable attention over the past decade. The recognition that women have not been included in many important clinical trials dealing with coronary artery disease (CAD) has stimulated widespread concern and publicity, and has been, in part, responsible for the development of the Women's Health Initiative.[1] The lay media, including magazines and television, frequently feature health-related stories on women as a unique and often medically underserved population. In this editorial commentary, I would like to address a single aspect of this dialogue: postmenopausal hormone replacement therapy (HRT) for women with overt coronary disease or at high risk for the development of CAD.

The Argument

It is my contention that cardiologists should more frequently recommend HRT for women with vascular disease, either initiating HRT treatment themselves or making sure that a primary care provider or gynecologist reviews in detail the pros and cons of HRT with the patient. I believe that HRT is indicated in all postmenopausal women with established CAD, including asymptomatic subjects who are not overtly at risk for breast cancer development. In the absence of a relative or specific contraindication to estrogen therapy, such women should be encouraged to consider strongly the use of HRT, especially combined estrogen-progesterone therapy in those women with an intact uterus. Treatment is recommended for women willing to use hormones. Many will refuse HRT for a variety of reasons, particularly for fear of breast or uterine cancer. At the very least, women with CAD who are estrogen deficient should be carefully counseled as to the potential benefits of HRT and provided an opportunity to have a relevant discussion with an appropriate health care provider, including the cardiologist. This recommendation is concordant with published guidelines on HRT established by a select committee of the American College of Physicians.[2]

I suggest that the status of HRT today, with respect to prevention of CAD morbidity and mortality, is somewhat similar to that of cholesterol-lowering recommendations prior to publication of the major clinical trials with the statins, beginning with the Scandinavian Simvastatin trial in 1994.[3] There

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are remarkable similarities in the benefits of estrogen therapy and lipid reduction regarding effects on the arterial wall and platelet-thrombosis phenomena; there are also many positive outcomes in animal and human experiments and a large array of epidemiologic and observational data. Nevertheless, the hazards of breast and uterine cancer with estrogen therapy have no downside counterpart with cholesterol lowering. Extrapolation of individual observational studies as well as meta-analyses indicating a reduction of CAD with estrogen replacement parallels many earlier lipid-lowering predictions. The Women's Health Initiative,[1] the Angiographic Trial in Women, and the Heart and Estrogen/Progestin Replacement Study (HERS), although not yet completed, are likely to confirm a significant decrease in CAD progression, morbidity, and mortality in the HRT cohorts, although probably not as great as is suggested in the observational studies published thus far.[4–6]

The purpose of this commentary is not to defend individual estrogen studies or discuss in detail the many questions relating to the published data on HRT. It has been repeatedly emphasized that women who choose to take HRT, and particularly those who stay on such therapy, are health conscious and likely to engage in a variety of behaviors beneficial to longevity and an enhanced quality of life. Thus, "prevention bias" remains a major factor in interpretation of the estrogen replacement literature,[7] as does "compliance bias;" individuals who continue on a therapy, even if placebo, tend to do better than those who do not, suggesting that compliance or acceptance of treatment is a marker for other behaviors that result in better overall health. Nevertheless, there is a strong scientific rationale for estrogen replacement, and virtually no data exist that refute the hypothesis that HRT will decrease vascular events and improve survival in high-risk women. There is no doubt that estrogens promote uterine hyperplasia and the potential for endometrial cancer, a risk that is markedly attenuated by the concomitant use of a progestin. It does appear that there is a modest increase risk of breast cancer, possibly as much as 1.5–2 fold, with long duration of estrogen therapy.[8,9] Nevertheless, calculations regarding the overall population benefit from prevention of myocardial infarction and symptomatic coronary disease indicate that the vascular effects of HRT are substantially more beneficial than the more dramatic but lesser projected risk from an increase in the incidence of breast cancer death,[8,9] particularly in women with major CAD risk factors.[10] This argument is likely to continue for years, but it is important that health professionals understand these various issues and keep the breast cancer versus heart disease dialogue in a broad perspective. Coronary artery disease is the most significant health problem that postmenopausal women are likely to encounter.

A variety of large observational HRT studies has been reported, as has a number of meta-analyses.[5–11] The published literature underscores an approximate halving of CAD morbidity and mortality in women with history of HRT compared with those who have never used estrogen; however, most experts predict that the actual benefit in prospective studies will be considerably less than a 40–50% reduction in CAD events.

Some Recent Studies

Several recent reports substantiate older data and are worthy of mention. Ettinger *et al.* performed an interesting prospective analysis of two groups of women enrolled in the Kaiser Permanente Health Plan in northern California.[8] One primary prevention cohort consisted of 232 postmenopausal Caucasian women who used estrogen for at least 5 years and were born between 1900 and 1915. All had documentation of the date of menopause or loss of ovarian function and began HRT within 3 years of menopause. The estrogen users were carefully matched to 222 subjects of similar age who did not or never had used estrogen, and medical charts and death certificates were serially reviewed in detail. Data analysis tracked all cancers, hospital admissions, and deaths. The study began in 1980, and follow-up was terminated in 1992 or by death. The groups were well matched with respect to demographic variables. The estrogen users were followed up to a mean of 27 years after the menopause and on average continued to take estrogen for approximately two-thirds of this time period. The non-HRT users were followed-up to a mean of 28 years following menopause; a small proportion took estrogen briefly, none for more than 1 year. The HRT cohort consisted predominantly of estrogen users, and only 6% had taken a progestin. Previous reports from this study have focused on estrogen efficacy for gynecologic complications and hip fractures, demonstrating in part that bone loss and fracture incidence were substantially reduced in the estrogen users.[12] The results demonstrate that the sustained use of estrogen was associated with a reduction in all-cause mortality that began to be manifest at 10 years after menopause, with survival curves continuing to separate by completion of the study, with a mean 23-year follow-up. These women were quite elderly (mean 77 years of age) at the termination of the long observation period. Risk reduction assessment demonstrates that estrogen use was associated with a 46% lower age-adjusted death rate, and, after adjustments for multiple risk factors, there was still a 43% risk reduction.[8] There was a greater survival benefit with longer versus shorter use of estrogen. The reduction in mortality from cardiovascular and coronary disease accounted for the majority of the survival benefit. Estrogen use was associated with a significantly increased relative risk of breast cancer death of 1.9. The authors conclude that current use and long duration of estrogen were important, although prior observational studies have not shown a clear-cut survival relationship with duration of estrogen therapy. Furthermore, even in those subjects where long-term use was stopped (HRT women were exposed to estrogen for approximately 17 years), a survival benefit was seen.[8] The recent report from the huge Nurses Health Study also demonstrated a robust decrease in total mortality as well as an increase in breast cancer in long-term HRT users, with a possible attenuation of benefit after 10 or more years of HRT.[9]

Last year, another update from the Nurse's Health Study was published that assessed the possibility that concomitant progestin therapy might diminish the favorable cardiovascular effects of postmenopausal estrogen.[13] This study, previ-

ously reported for estrogen use of at least 10 years[6] and recently updated,[9] analyzed almost 60,000 women who were 30–35 years old at baseline and were followed for 16 years. There was a marked decrease in the risk of major CAD events among women on combination therapy of 61% (multivariate risk adjusted), and a 40% decrease in multivariate adjusted relative risk of CAD in women who used conjugated estrogen alone, compared with those who never used HRT. Stroke was not affected by HRT. Current or recent use of HRT appeared to decrease CAD risk more than in those patients who had not used HRT within 3 years of study entry. Thus, adding a progestin did not appear to attenuate estrogen benefits; nevertheless available data on combination therapy versus estrogen alone are minimal. These authors discuss the issue of whether "hormone users are different from nonusers in ways that may influence heart disease," and observe that "women who take hormones are a self-selected group who usually have healthier life styles with fewer risk factors than women who do not take hormones."[13]

A recent small retrospective secondary prevention trial, published in the cardiology literature,[14] parallels these much larger data bases. This was an actuarial analysis of 337 women who underwent elective angioplasty at the Mid-America Heart Institute in Kansas City and were then followed for a mean of 65 months. The treatment group consisted of 137 women who underwent revascularization between 1982 and 1994 and received long-term estrogen therapy, and who were computer matched to 200 controls who did not receive estrogen. The baseline chararacteristics were comparable except for a greater incidence of diabetes in the controls. While there was no difference in need for subsequent revascularization between the two angioplasty cohorts, cardiovascular end points were significantly different. The incidence of death, nonfatal myocardial infarction, or nonfatal stroke was reduced by 70% during the 7 years after angioplasty in the estrogen group. The event curves began to separate within the first 6 months. During the follow-up period, 8% of the estrogen users and 22% of the control women died, mostly from myocardial infarction. The 7-year survival rate was 93% for the estrogen cohort versus 75% for the controls. Multivariate analysis identified diabetes, estrogen therapy, and ejection faction as independent predictors of myocardial infarction or cardiac death during study follow-up.[14]

These three trials, while widely different in design, resonate with a large amount of previously published observational data, indicating that, for whatever reasons, postmenopausal women with or without CAD who use HRT demonstrate a robust decrease in cardiovascular deaths as well as in other significant cardiac events compared with non-hormone users. Nevertheless, no large prospective randomized clinical trial exists to support these favorable data.

Vascular Biology

Many publications demonstrate a beneficial effect of estrogen on the vascular wall both in in vitro and in vivo experiments; this commentary will not extensively review these reports. In addition to the well known effects of hormone replacement on lipid status (decreased low-density lipoprotein cholesterol, increased high-density lipoprotein cholesterol),[15, 16] recently confirmed by the Post Menopausal Estrogen/Progestin Intervention (PEPI) Trial,[17] and a small rigorous study of HRT and/or pravastatin,[18] it is known that estrogens have beneficial effects on fibrinolytic activity, decreasing PAI-1 levels, and impairing platelet-thrombosis activation. Furthermore, a variety of investigations suggests that 17 beta-estradiol improves endothelial dysfunction associated with CAD in women (but not in men). Many studies have shown that abnormal coronary artery vasomotor responses are improved in the presence of estrogen, modulated through several mechanisms, including augmentation of nitric oxide activity. Estrogens appear to protect against LDL oxidation[19] and may have a direct antioxidant effect within the vessel wall, which could relate to the beneficial actions on endothelial dysfunction.[20] Estrogen may favorably affect the function of vascular smooth muscle and alter the proportion of collagen and elastin and collagen subtypes in the extracellular matrix of the vessel wall.[20] Estrogens may play a role in enhancing collateral coronary channels and impede adhesion molecule expression and cytokine activation.[21]

Hormone Replacement Therapy in Women with Coronary Artery Disease

Clinical reports have indicated exercise time improvement to angina in postmenopausal women with CAD who received acute estradiol administration.[22] A recent preliminary report demonstrated that chronic administration of 17-beta estradiol by patch in women with angina increased exercise time to 1 mm ST-segment depression at 8 weeks, although not at 4 weeks.[23]

Another preliminary study demonstrated that postmenopausal women without clinical CAD (primary prevention), who were HRT users for at least 4 years had a remarkedly reduced prevalence of coronary calcification as measured by fast CT when compared with an age-matched group of middle-aged women who had never used estrogen.[24] This suggests that estrogen impedes the development of atherosclerosis and subsequent vessel wall calcification.

While the issue of prevention and compliance bias cannot be resolved, a recent report with respect to women's views of HRT is of interest.[25] One thousand postmenopausal women from Washington state, all members of a large HMO, were queried about their attitudes with respect to the likelihood of developing coronary heart disease and the potential of protection against this risk by hormone use. Even in women who were current users of HRT, there was considerable confusion and lack of clarity regarding self-rated CAD risk, as well as the role of estrogen replacement as a protective measure. Current HRT users, when compared with those not on HRT, were more likely to believe that HRT is protective, but overall "58% of women were uncertain, misinformed, or dis-

agreed with the scientific evidence suggesting that HRT protects against CAD."[25] In this presumably relatively well educated and healthy group of individuals, it was clear that available information had not been adequately absorbed by these women with respect to decision making. This supports my contention that physicians have not done and are not doing an adequate job communicating with postmenopausal women.

Conclusions

Which women are at greater risk? At the present time, there is insufficient evidence to recommend that all postmenopausal women go on estrogen replacement.[2] Clearly, those individuals with contraindications, especially with a family history of breast cancer or those who have serious doubts about personal estrogen use, should not be considered for HRT. Any woman who no longer has a uterus is a good candidate for estrogen replacement, as there is no risk of endometrial cancer or postmenopausal bleeding. While the benefits of HRT for prevention of osteoporosis and fractures, cardiovascular disease, and favorable effects on gynecologic and genital-urinary symptoms are well substantiated, and while they appear to provide a sufficient rationale for prescribing hormones in many women, the priority for the cardiologist must be women with established vascular disease and who have had natural or surgical menopause. Those individuals who have had premature cessation of ovarian function should be targeted aggressively. Recent analysis of the Scandinavian Simvastatin Survival Study (4S) and Cholesterol and Recurrent Events (CARE) lipid lowering trials suggest that women have as good or better response to lipid lowering with respect to protection against CAD events than men.[3, 26] Hormone use in these trials has not been reported, but it would appear likely that hypercholesterolemic postmenopausal women with or without CAD should be targets for HRT. The concept of multiple risk factors substantially increasing the likelihood of development of CAD is an important one, and in non-CAD postmenopausal women who have other major CAD risk factors (smoking, diabetes, hypertension, hypercholesterolemia), HRT would appear to be appropriate. The 1992 American College of Physicians Guidelines support this view.[2] The latest report from the Nurses Health Study also confirms this concept,[9] as does a recent decision analysis using a Markov model.[10] One target group for special consideration is the postmenopausal woman who has not suffered a vascular event and who has diabetes. The ravages of diabetes on the vascular system are well known, and it is reasonable to assume that any protection derived from estrogen replacement would be particularly important in these individuals. It is hoped that the results from HERS and the Women's Health Initiative will provide useful data on subsets of women who may benefit more with HRT.

Breast cancer remains the major negative aspect of HRT. A recent meta-analysis of breast cancer and hormone use, combining 51 studies estimated to represent 90% of the existing literature, confirmed a graded relationship of breast cancer risk with increasing HRT duration, with a loss of this risk 5 years after cessation of estrogen use.[27] The increased risk appears to be 20 to 50% for current or recent users.

At the very least, the subject of HRT should be discussed more widely by cardiovascular physicians with their patients. Who should prescribe HRT remains unclear. Most cardiologists feel more comfortable referring their postmenopausal patients to a gynecologist, internist, or family practitioner for institution of estrogen replacement.[9] There is a variety of issues for women to consider, including choice of agent and regimen, and the fact that an experienced primary care physician may be more proficient in this area than most cardiologists; however, the stamp of approval for consideration of HRT from the cardiologist would appear to be an important first step for many individuals. Familiarity with the problems of HRT and the ability to communicate openly regarding the many issues involved is imperative for the cardiologist who is truly concerned about the postmenopausal patient with vascular disease.

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