Advanced Studies in Medicine

Nanette K. Wenger, MD, is a recognized authority on women and coronary heart disease. She chaired the US National Heart, Lung, and Blood Institute conference on Cardiovascular Health and Diseases in Women and has served on the national board of the American Heart Association (AHA). In 1998 she received the AHA Physician of the Year Award. She is professor of medicine (Division of Cardiology) at the Emory University School of Medicine and Chief of Cardiology at Grady Memorial Hospital.

The Advanced Studies in Medicine (ASiM) senior contributing editor for this issue interviewed Dr Wenger about coronary heart disease and its diagnosis and management in postmenopausal women.

ASiM: Current studies indicate that coronary heart disease (CHD) is significantly underdiagnosed in postmenopausal women. What has been your experience with CHD in women?

Dr Wenger: CHD is the leading cause of death for US women. However, survey data indicate that 4 of 5 US women and 1 of 3 primary care physicians are not aware of women's vulnerability to CHD. As a result, women and their physicians often fail to relate chest pain to CHD, and another cause is frequently sought. Complaints of chest pain are not as appropriately or aggressively evaluated as they are in men, and women are more likely than men to delay seeking attention for the severe chest pain of myocardial infarction (MI) after the onset of symptoms. Physicians caring for women must evaluate patient complaints of chest pain, particularly when the pain is precipitated by exertion or emotion, and must undertake diagnostic procedures for recognition and risk stratification. These are typically exercise-based tests with or without radionuclide or echocardiographic imaging.

ASiM: How do coronary risk factors for postmenopausal women compare with those of the general population?

Dr Wenger: Menopausal women have the same coronary risk factors as premenopausal women and the general population. The only aspect that may differ for these women relates to menopausal status, and this has not been shown unequivocally to be a specific risk factor for cardiovascular disease. Coronary risk factors predominate and cluster in older women; thus, this high prevalence of risk factors and menopausal status occur concomitantly as women age.

ASiM: Why is primary prevention of CHD such an important issue for postmenopausal women?

Dr Wenger: Coronary risk factors are more common in women after menopause. While men are more likely to develop hypertension during middle age—40 to 60 years old—women are more likely to develop hypertension at older ages. In addition, isolated systolic hypertension is more prominent among elderly women than elderly men. Diabetes is more common in older women than older men, with the older women far more likely to develop de novo diabetes. Finally, low-density lipoprotein cholesterol levels in women increase after middle age, more so than in men of the same age.

ASiM: In the Multiple Outcomes of Raloxifene Evaluation (MORE) trial, raloxifene was shown to be beneficial in the prevention of osteoporosis, and outcome measures indicated that an early increase in cardiovascular events was not seen in the patients taking raloxifene. How can clinicians use this information in treating postmenopausal patients?

Dr Wenger: The MORE trial evaluated the effect of raloxifene, a selective estrogen receptor modulator, in women at risk for osteoporosis. These women were not selected as being either at risk for breast cancer or at risk for cardiovascular disease. The MORE trial showed that raloxifene is beneficial in the prevention of osteoporosis, in improving bone density, and in the treatment of osteoporotic fractures. For physicians treating menopausal women, this means that estrogen is not the only option for the prevention of osteoporosis; raloxifene, as well as the bisphosphonates, can be considered. (Reprint of MORE trial article can be found on page 721.)
CLINICIAN INTERVIEW

ASiM: Results of the MORE trial showed no evidence of early increased risk for cardiovascular events. In your opinion, how should that be interpreted by clinicians?

Dr Wenger: While raloxifene therapy did not significantly affect the risk for cardiovascular events in the overall cohort, which was comprised of women who were not at increased cardiovascular risk, raloxifene therapy did significantly reduce the risk for cardiovascular events in the subset of women at increased risk based on the Raloxifene Use for the Heart (RUTH) score. This is a post hoc analysis and justifies a clinical trial, which is currently in progress. Whether raloxifene affects the risk for cardiovascular events in postmenopausal women with documented coronary disease or at increased risk for its occurrence is currently being tested prospectively in the RUTH trial, although results will not be available for several years.

The primary objectives of RUTH are to determine whether raloxifene at a dosage of 60 mg daily lowers the risk for coronary events, such as coronary death, nonfatal myocardial infarction, or hospitalized acute coronary syndrome other than myocardial infarction, and whether it reduces the risk for developing invasive breast cancer in postmenopausal women at risk for a major coronary event.

The suggestive data from the MORE trial should not be construed to document that raloxifene provides cardiovascular protection or protection from breast cancer. As noted, the issue of cardiovascular protection and breast cancer risk reduction is being evaluated in the randomized placebo-controlled RUTH trial, and the comparison of raloxifene with tamoxifen is being studied in the Study of Tamoxifen and Raloxifene (STAR) trial, which is still enrolling patients at this time.

ASiM: Hormone replacement therapy (HRT) was once thought to potentially reduce CHD risk in postmenopausal women. However, recently published reports of current clinical trials indicate that HRT is no longer considered appropriate for primary prevention of cardiovascular disease. One of these trials was part of the Women's Health Initiative (WHI). Can you provide some information on this study?

Dr Wenger: The WHI, the largest study of menopausal women ever undertaken, was developed specifically for better understanding of women's health issues, including an improved understanding of cardiovascular disease (CVD) in postmenopausal women. WHI was initiated in 1993 and was intended to continue over a 15-year period to ascertain information in a number of areas of health, with the goal of incorporating study findings into interventions to enhance the health of postmenopausal women. WHI includes several randomized clinical trials as well as an observational cohort. Among these trials were studies involving the use of hormones, both unopposed estrogen and HRT, with the goal of the researchers to determine the effects of these hormones on risk for cardiovascular disease, osteoporosis, breast, and colorectal cancer.

The randomized hormone trials involved the assignment of women, who underwent hysterectomy, to conjugated equine estrogen (CEE) 0.625 mg daily versus placebo and the randomization of women with an intact uterus to CEE combined with medroxyprogesterone acetate (MPA) 2.5 mg daily versus placebo. The overall WHI enrolled about 160 000 postmenopausal women who were aged 50 to 79 years; the hormone program included 27 000 predominantly healthy women, with about 10 000 women in the estrogen versus placebo arm and 17 000 in the estrogen/progestin versus placebo arm.

ASiM: In April 2000, the Data Safety and Monitoring Board (DSMB) of WHI recommended that all women in the hormone program be informed of an increase in cardiovascular events. How did this affect continuation of the study?

Dr Wenger: Based on review of the preliminary 2-year data, an unanticipated increase in cardiovascular events, including MI and stroke, was encountered in both hormone groups (conjugated equine estrogen [CEE] and conjugated equine estrogen plus medroxyprogesterone acetate [CEE + MPA]) but not the placebo groups. These events were seen in about 1% of the women in the study and occurred in addition to the increased risk for venous thromboembolism (VTE) that had already been anticipated. The DSMB requested participants be notified because the excess of cardiovascular events was unanticipated and that aspect was not included in their informed consent document. With the potential for later benefit as the driving force behind continuing the studies, the DSMB recommended continuation. I would like to emphasize that the extent of the occurrence of cardiovascular events did not reach...
the preset stopping boundaries for the trial. The risk for these cardiovascular events persisted into years 3 and 4 of the study, but the trial was still continued based on DSMB recommendations.

In May 2002, the DSMB identified that the increase in invasive breast cancer in the estrogen/progestin group exceeded the preset trial stopping boundaries, although this effect was not seen in women who were taking only estrogen. The preset trial stopping boundaries were more stringent for the risk of breast cancer, an anticipated possible adverse event for the study, than they were for the beneficial effects that were anticipated in the trial for heart disease and stroke. Stopping boundaries in a clinical trial are designed to protect the participants in the study from further adverse events if they seem to be at risk by an intervention, which usually necessitates more stringent stopping rules. Benefit stopping grounds also exist for beneficial effects that should be extended to the general community, but more robust evidence often is required to terminate a trial for benefit. The findings at this point were significant: 26% increase in invasive breast cancer, 29% increase in CHD events, 41% increase in stroke, and a doubled risk for VTE. However, the same study also showed benefit: 37% decrease in colon cancer, 33% decrease in hip fracture, and 24% decrease in total fracture. The effect on all-cause mortality was neutral. For overall scoring, risk exceeded benefit.

**ASIM:** How can the practicing clinician apply the information from this study to the management of patients who are already taking combination HRT?

Dr Wenger: While the absolute risk for an individual woman is very low, with over 97% of women in the study experiencing no adverse events, the population risk is substantial if this therapy is applied as a widespread primary prevention intervention. For example, if 10,000 women were treated for 1 year with the CEE/MPA combination, the increase in events compared with placebo-treated women would be an additional 7 CHD events, 8 strokes, 8 pulmonary emboli, 18 VTE episodes, and 8 instances of invasive breast cancer. In contrast, the total number of colorectal cancers would decrease by 6, and hip fractures would decrease by 5. The risk-benefit ratio is inappropriate for a population-based primary prevention strategy, where the goal is to promote health and prevent disease. The estrogen-only arm did not show the increased risk for invasive breast cancer, so the estrogen-versus-placebo arm of the hormone study is continuing. Results of this study suggest that this particular estrogen/progestin combination should not be instituted or continued for the primary prevention of CHD. Decisions about continuation of HRT must be made on an individual basis, unrelated to CHD issues.

**ASIM:** About the same time the WHI began, the Heart and Estrogen/Progestin Replacement Study (HERS) was recruiting patients. What were the goals of HERS, and how did the findings affect researchers’ recommendations?

Dr Wenger: HERS was a landmark clinical trial designed to examine the effect of estrogen plus progestin on coronary risk in women with documented CHD. The study included 2763 menopausal women randomized to hormone therapy or placebo. The hormones and doses used were the same as those for the WHI HRT hormone arm: CEE 0.625 mg plus MPA 2.5 mg daily. This combination was chosen, as was the case with WHI, because it was the preparation used by most US women on HRT.

The results of this study, published in 1998, reported no difference between the hormone-treated and placebo-treated groups in the occurrence of nonfatal MI or coronary death, the primary trial outcome. Furthermore, no benefit was seen for a variety of secondary cardiovascular outcomes, including coronary artery bypass graft surgery, percutaneous coronary revascularization, hospitalization for unstable angina or congestive heart failure, nonfatal ventricular arrhythmia, sudden death, stroke or transient ischemic attack, and peripheral arterial disease. A 52% increase in risk for coronary events was noted during the first year, with a probable decreased risk in years 3 through 5. The risk for VTE increased 3-fold, and an increase of almost 50% was seen in incidence of gallbladder disease requiring surgery. Thus, initiation of HRT was not recommended for the secondary prevention of CHD. However, at that time, researchers suggested that women already taking HRT might achieve late benefit.

**ASIM:** If HERS showed no benefit for the secondary prevention of CHD overall, what is the significance of HERS II?

Dr Wenger: HERS II was designed to determine whether the risk reduction in coronary events seen
during years 3 to 5 would persist with additional follow-up. HERS II included 93% of the surviving women from HERS (2321 individuals). This was an open-label study with women encouraged to remain on their original drug assignment; follow-up was by telephone contact only. The overall mean observation period was 6.8 years; in that time, no reduction in coronary events (MI or coronary death) or secondary cardiovascular events was seen in the HRT group compared with the placebo group for either HERS, HERS II, or for the total follow-up of almost 7 years. Even with adjustment for potential confounders and other factors such as statin use, the findings were not altered. Nor were they altered with analysis by an “as-treated” rather than an “intention-to-treat” basis.

Other notable findings included a 2-fold increase in VTE and a nearly 50% increase in gallbladder disease requiring surgery in the hormone-treated group. Breast cancer, other cancers, hip fracture, or other fractures did not show any significant differences between the placebo and hormone-treated groups.

**AsI M:** You suggest, based on the WHI results, that the combined hormone regimen should not be instituted or continued for the primary prevention of CHD. HERS and HERS II study participants already had CHD. How would you utilize the results of this study to advise postmenopausal women with CHD on the use of HRT?

**Dr Wenger:** The HERS II findings, comparable to those from the WHI hormone study, indicate that menopausal hormone therapy should not be used to reduce the risk for cardiovascular events. This holds true for women who have CHD and are seeking secondary prevention as well as healthy women who are seeking primary prevention. The estrogen/progestin therapy does not provide CHD benefit and may actually increase risk.

**AsI M:** Do you have any recommendations to offer the practicing clinician who treats postmenopausal women currently taking HRT?

**Dr Wenger:** The ultimate decision rests with the patient, but only after careful discussion and consultation with her physician. This discussion should address the reasons for which menopausal hormone therapy was initiated and whether these reasons persist. Most commonly, therapy is initiated for menopausal symptoms. For these patients, the physician must ascertain whether therapy should be continued to relieve symptoms. If hormonal therapy was initiated for lipid lowering during the years when this was the recommended therapy, physicians should advise their patients that
the current recommendations for lipid lowering include statin use, as noted in the National Cholesterol Education Program Adult Treatment Panel III guidelines. If hormone therapy was instituted because of low bone mineral density for the prevention of osteoporosis, the use of hormone therapy versus alternatives, such as bisphosphonates or raloxifene, and their specific risks and benefits, should be explored. Currently, no evidence supports that hormone therapy improves urinary incontinence, and it actually may cause this condition to worsen. I particularly want to emphasize that all of the information on which current decisions are being made were derived since 1998, the date of publication of the initial HERS study. Physicians and their patients must make decisions relative to 4 years of new and evolving information.

**ASIM:** To date, have any additional notable new studies or publications other than the ones we have discussed shown harm or benefit from HRT?

**Dr. Wenger:** Until very recently, physicians have been dependent on information provided by a large number of observational studies and the meta-analyses of these studies that suggested cardiovascular benefit from HRT, which is why they had recommended hormone therapy for cardiovascular benefit in the past. In addition to the recent WHI and HERS II clinical trial data, newly published meta-analyses differ from the previous meta-analyses. One of these meta-analyses evaluates the value of HRT in the primary prevention of cardiovascular disease and coronary artery disease (CAD) by studying the potential explanatory variables of the relationship between HRT, CVD, and CAD. This meta-analysis adjusted for socioeconomic status, as well as other major CAD risk factors, and shows that with these adjustments, no benefit in the secondary or primary prevention of CVD events is seen. This meta-analysis differs from traditionally cited studies, but most importantly, its results are consistent with those of the recent randomized trials that have shown no cardiovascular benefit from HRT.

Essentially, it highlights that differences previously described related to the characteristics of the women who were hormone users rather than to hormone use per se. Another recent meta-analysis produced comparable results.

We are dealing with a rapidly changing landscape. Good scientific information continues to emerge from rigorous, ongoing clinical trials. Thus, physicians should counsel women regarding hormone therapy based on the most current and appropriate scientific information.
REFERENCES


