Knowledge about the natural history of coronary heart disease in women was limited until recent years. Few studies included women, despite the fact that heart disease is the No. 1 cause of death in women older than 50 years and the cause of about 500,000 deaths annually. Over the past decade, knowledge has increased owing to a combination of greater participation of women in medical studies, improved medical technology, and political pressure. While much remains to be learned, researchers have found that coronary artery disease in women typically follows a different course than it does in men. Women’s risk factors also differ from men’s, in part owing to the key protective role played by estrogen. Increasing knowledge about women and heart disease can provide new tools for physicians caring for women at risk of heart disease.

Women’s health issues that did not concern reproduction received little attention and little research funding prior to 1986. This was particularly unfortunate in the area of heart disease, which was long considered to be a greater threat to men than to women. Researchers have found more recently that, while men typically develop heart disease earlier in life than women, women have a worse prognosis than men once they have had a myocardial infarction.3 Women also face a worse prognosis than men once they have had a myocardial infarction.3 In addition, African American women face mortality rates from heart disease that are double those of white women, leaving CAD to be the leading cause of death in African American women aged 30 to 39 years.4 The delay in addressing heart disease in women as a distinct condition resulted in years of treating men and women at risk of heart disease equally, overlooking women’s special needs.

Until a decade ago, men were the model subjects in most funded biomedical studies. The National Institutes of Health (NIH), Bethesda, Md, the major source of research funding in this country, had no policy about the inclusion of women in large trials addressing heart disease, cancer, and stroke.5 It was then assumed that whatever the findings, the results would hold true in women. Since then, it has become apparent that this generalization was incorrect in many situations.6

The Food and Drug Administration (FDA) policy through the early 1990s prohibited women in their childbearing years from participating in phase 1 drug trials, which test the efficacy, safety profiles, and dosages of new drugs.7 Guidelines also limited women in their childbearing years from participating in the more advanced phase 2 trials. Also, the US General Accounting Office found that in the more advanced phase 2 and 3 trials, adequate analysis of the data looking at sex differences of safety and effectiveness occurred only 50% of the time between 1988 and 1991.7 However, once a new drug was approved and on the market, physicians prescribed these drugs to women as well as men, assuming that women and men would require similar dosages, that the efficacy would be similar, and that side effects would be the same.

Guidelines of the FDA not only prevented women in their childbearing years from participating in clinical trials but also raised questions about the appropriate dosage of approved medications for women.8

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from participating in clinical trials, but also prevented women who were unlikely to become pregnant, such as women using birth control, women who were sexually inactive, or those with partners with varicocelies, from participating. In excluding women from these early clinical trials, researchers risked missing sex-related differences in adverse effect profiles and in appropriate dosing of drugs. As a result, phase 3 trials often were not designed to account for these differences.

Women were excluded from drug trials during their childbearing years for 2 reasons. There was concern about birth defects after the well-publicized thalidomide tragedy in the 1950s and 1960s. In addition, there was concern that women who were postmenopausal, who had undergone a hysterectomy, or who were using estrogen replacement therapy would show variations in estrogen and progesterone levels that would affect the efficacy of the trial drugs.

FROM TECUMSEH TO FRAMINGHAM

A review of early longitudinal studies beginning in the 1950s shows that heart disease was initially considered a more significant problem for men than for women. Many studies did not include women. Others included women in their study population but omitted them from data reports. Still others added women to their study population after the studies had been conducted for some time.

The Western Collaborative Group Study is one of many prospective studies that omitted women entirely. The study, whose final report was issued in 1975, followed up 257 men beginning in 1960 or 1961 for 8 or 9 years. Researchers examined risk factors for coronary heart disease (CHD) and reported a significant link between type A behavior and CHD. Another study, the Los Angeles Heart Study, included women in its study population, with 1859 men and 393 women. However, women were not included in the data reported in the first 10 years of follow-up, published in 1964. The study only reported on the prevalence of coronary disease among white men.

The Pooling Project 5, whose final report was issued in 1978, drew from 5 epidemiological studies to evaluate risk factors for CAD. Three of the studies were all-male studies, and 2 included women: the Framingham, Mass, and Tecumseh, Mich, studies. Yet, researchers only considered white men in this analysis. The study evaluated risk factors for CAD alone and in combination with one another. The study used fatal and nonfatal myocardial infarction and sudden death as end points. Such studies advanced general knowledge about CHD, but did little to establish how best to treat women at risk of heart disease or female patients with CAD.

Other studies were launched as all-male studies and changed their study population as time progressed. The Baltimore (Baltimore, Md) Longitudinal Study of Aging is a prospective community-based study of normative aging that started in 1958. However, women were not enrolled until 1978. When risk factors for exercise-induced silent ischemia were assessed beginning in 1984, few women were being evaluated. This made it difficult to link certain risk factors to an increased incidence of silent ischemia or CAD.

One study that included women was the Tecumseh study, one of several prospective longitudinal studies undertaken in the United States during the 1950s and 1960s to evaluate cardiac risk factors in a given community. The Tecumseh study was a longitudinal study launched in 1959 to evaluate and compare risk factors in the farm community of Tecumseh. The study looked at the prevalence of hypertension and hypercholesterolemia in men and women and the prevalence of cardiac heart disease. The study of 9800 people produced a great deal of information, documenting that hypertension and obesity are risk factors for CAD. The study also documented in 1965 that women of childbearing age showed lower cholesterol levels than older women.

Other prospective studies that included women were the Framingham study and the Rochester (Rochester, Minn) Coronary Heart Disease Project. The Framingham study was launched in 1948. Since then, the study has produced a wealth of information about CHD in men and women. In 1980, researchers using Framingham data found that working women did not have a higher incidence rate of CHD than housewives.

The Rochester Coronary Heart Disease Project, which enrolled its first subjects in 1950, examined a variety of coronary risk factors in women. A 1980 report examining data from 1960 through 1982 found that the use of steroidal estrogens reduced CHD in women aged 40 to 59 years and that cigarette smoking and hypertension boosted rates of CHD.

Both the Framingham and Rochester studies concluded that women with angina had a benign course compared with men with angina and a much more favorable outcome, with fewer events such as myocardial infarction. In part, this stemmed from technological differences between contemporary and past studies. Routine coronary angiography was not part of the evaluation in the Framingham and Rochester studies. The diagnosis of angina was made based on clinical presentation and electrocardiographic findings only. In a subset analysis of the Coronary Artery Surgery Study, it was shown that up to 50% of women with chest pain had no significant epicardial CAD, compared with only 17% of the men with similar symptoms and normal coronary anatomy. This finding suggested that the clinical presentation of chest pain in women is not specific as an indicator of CHD in women. Many of the women in both previous studies probably had noncardiac chest pain. The limited epidemiological data available about women and heart disease during the 1950s to the 1970s contributed to this overly positive portrait of women and heart disease. In the late 1970s and early 1980s, several important clinical trials approved by the NIH included no women. One such study, the Physicians Health Study, started in 1981, looked at the efficacy of aspirin in reducing the incidence of heart disease.
widespread view that women were not enrolled, it is not known if they achieve the same reduction in myocardial infarction as men. As a result, no conclusions could be drawn as to whether aspirin was beneficial to women. Other large epidemiological studies, such as the Multiple Risk Factor Intervention Trials of CAD, which began in 1973, also did not enroll women.22

CHANGING THE NIH

Official policy concerning women and clinical trials began to change in 1986. That year, the NIH established a policy requiring researchers to state whether or not women were included in a study. If women were not included in a study, the researchers needed to explain why they were not. The new policy, adapted on the recommendation of a Public Health Service Task Force,3 was intended to encourage researchers to evaluate sex differences in their studies. However, concerns developed that the policy was not being followed. In 1990, a group of elected women legislators pushed successfully for an investigation of the NIH by the House Subcommittee on Health and Environment. Congresswomen Olympia Snowe, a Republican from Maine (R-Maine), and Patricia Schroeder, a Democrat from Colorado (D-Colorado), now retired, played leading roles in the investigation. Mark V. Nadel, the associate director of the General Accounting Office, accused the NIH of ignoring its own policy.4 William F. Raub, who was acting director of the NIH at that time, conceded that the policy was loosely worded and had not been enforced for several years.5

The Congressional Caucus for Women’s Health Issues, organized in 1989, forced the NIH to reexamine its record and to enforce the policy it had established in 1986. The Congressional Caucus was also responsible for supporting the NIH Reorganization Act in 1993. Potential differences in outcomes between the sexes must now be explored in all research funded by the NIH.5,6

EMERGING RESEARCH

Well before the involvement of public officials, the medical community was becoming more interested in the special nature of women and heart disease. The first National Heart, Lung, and Blood Institute workshop examining CHD in women took place in 1986.23 Led by Nanette Wenger, MD, the workshop represented the first time that researchers from several disciplines gathered to discuss current findings about heart disease in women. One of their goals was to identify future needs and directions for research. They reviewed risk factors that are important to women and considered whether the differences between men and women were truly sex differences or whether they stemmed from other factors.

Pressure from women concerned about the emerging knowledge about the adverse effects of heart disease in women helped to persuade a group of public officials of the importance of funding research related to women and heart disease. The 1990 guidelines from the NIH for funding of grant proposals related to women and heart disease came about, in part, from pressure from the Congressional Caucus and House Subcommittee on Health and the Environment. The caucus, which included female legislators such as Mary O’Keefe (D-Ohio), Pat Schroeder, Senator Barbara Boxer (D-California), and Marilyn Lloyd (D-Tennessee), pursued legislation that would shift research funding away from reproductive health issues alone and would include problems such as heart disease and breast and ovarian cancer. That same year, the federal government appropriated $2 million to establish the Office of Research on Women’s Health at the NIH, to monitor the inclusion of women in clinical trials funded by the agency.6,24

A second National Heart, Lung, and Blood Institute conference examining women and heart disease took place in 1992.23 Led by Dr. Wenger, Leon Speroff, MD, and Barbara Packard, MD, the conference addressed risk factors and risk factor modification, including the use of estrogen replacement therapy. Participants also discussed the different presentations of heart disease in women compared with men and the difficulties of diagnostic testing. They also examined the risks and efficacy of medical therapy, interventional treatment, and coronary artery bypass surgery.

In 1993, another barrier to effective testing of drugs for heart disease in women toppled when the FDA rewrote its 16-year-old policy.7 The policy required women of childbearing potential who use accepted means of birth control to be included in early clinical trials. Also, the FDA was required to tell drug developers at pharmaceutical firms that they must use adequate numbers of women to be able to detect differences in drug actions, dosages, and adverse effects in both sexes.

A NEW FOCUS

The new attention being paid to women and heart disease has greatly expanded knowledge in the field. Because of a plethora of both small and large studies examining women and CAD, physicians know much more about the presentation of CAD and risk factors that are most important in women. We also know how best to proceed with diagnostic testing and what to expect after women receive interventional procedures such as angioplasty and coronary bypass surgery.

For example, researchers have determined that women develop CAD approximately 10 years later than men.23 To a great extent, this is because of the favorable effects of significant levels of circulating estrogens, which confer an excellent cholesterol profile in women that is not seen in men. This benefit begins in puberty and does not end until menopause. Both the total cholesterol and low-density lipoprotein (LDL) levels remain lower in women than in men until after menopause.17 Thereafter, the levels slowly rise. Likewise, the high-density lipoprotein (HDL) level remains higher in women than in men and begins to decrease after menopause.17
Women face particular risk factors, although some risk factors are similar for both sexes. Elevated triglyceride levels and a low HDL level confer the greater risk for CAD in women, compared with the elevated total cholesterol and LDL levels seen in men. An HDL level lower than 1.15 mmol/L (45 mg/dL) appears to impart a significant risk of CAD in women. The Framingham study was the first study to show that hypercholesterolemia in women is a significant risk factor. Women with a total cholesterol level above 6.85 mmol/L (265 mg/dL) were approximately twice as likely to develop CAD than those with cholesterol levels of 5.30 mmol/L (205 mg/dL) or lower.

Primary prevention trials have been scarce, but the members of the Expanded Clinical Evaluation of Lovastatin Study did look at the efficacy of lovastatin in women. They found the total cholesterol and LDL levels decreased as much in women taking the drug as in men. The HDL level also increased equally in both sexes. The Scandinavian Simvastatin Survival Study was a secondary prevention trial that included women. The trial found that the risk of nonfatal coronary events was significantly reduced in women as well as men taking simvastatin compared with those taking placebo. Mortality was not significantly reduced in women. This is most likely because of the small number of fatal events in this group.

It is clear that diabetes is a worse risk factor for CAD in women than in men. Once women with diabetes develop CAD, they do poorly. In the Nurses’ Health Study, there was up to a 7-fold increase in cardiovascular events in women with diabetes. Women with diabetes lose their premenopausal estrogen advantage. Therefore, they are at equal risk as men of developing CAD in their 40s.

Smoking is a major risk factor for women as well as men, but women may sacrifice even more when they smoke than men. Smoking seems to negate the estrogen advantage seen in nonsmoking premenopausal women. Female smokers have the same risk of developing CAD as men at the same age. The Nurses’ Health Study showed that the number of cigarettes per day correlated with the risk of myocardial infarction and fatal CAD. Even as few as 3 to 5 cigarettes per day increased the risk for all women, but particularly young women, of developing CAD. This added risk can be eliminated if women stop smoking. By 3 years after smoking cessation, the risk of developing CAD is equivalent to that of someone who never smoked.

A sedentary lifestyle also is a risk factor for women with CAD. In 1995, the Harvard Alumni Health Study, which included only men, showed that even modest amounts of exercise improved their survival rate and significantly lowered their risk of CAD. The same year, Kokkinos et al showed that women with moderate to high levels of fitness had significantly reduced levels of triglycerides, LDL, blood glucose, and blood pressure and also showed a higher HDL compared with women at a low level of fitness.

Another prevention trial was the Group Health Cooperative of Puget Sound study. All participants were postmenopausal women who had sustained a nonfatal myocardial infarction and were compared with healthy controls. The risk of myocardial infarction was significantly reduced in the women who exercised regularly, even at low to moderate levels of exercise, compared with those who did not exercise.

Because of findings from the Nurses’ Health study, the Postmenopausal Estrogen/Progestin Intervention Trial, and others, it is clear that estrogen replacement therapy is beneficial in preserving premenopausal cholesterol profiles and thereby in reducing a woman’s risk of CAD. The Nurses’ Health Study, funded by the NIH, was a prospective study that followed up 48,470 nurses for more than a decade. None of the women had CAD or cancer at the beginning of the study. Researchers found an almost 50% reduction in the incidence of CAD and a 52% lower mortality rate in women using estrogen replacement therapy when compared with postmenopausal women who were not using hormone replacement therapy. The Postmenopausal Estrogen/Progestin Intervention Trial, also funded by the NIH and published in 1995,
women. This prospective 9-year study will follow up 1400 women.

Other key studies include the Angiographic Trial in Women and the Estrogen Replacement and Atherosclerosis Study, both of which will assess the efficacy of hormone replacement therapy in altering the course of CAD in women.36 Another trial, the Evaluation of Ischemic Heart Disease in Women, will attempt to determine if diagnostic testing in women can be improved.36 These 3 studies are all expected to be completed before the year 2000.

As knowledge about women and heart disease increases, practitioners will gain new tools to combat and help prevent heart disease in women. While much progress has been made, many questions still need to be answered. Physicians in the future can expect to gain increasing knowledge about tailoring their prevention and treatment efforts to the particular needs of women from the results of research currently in progress.

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