

AHA Medical/Scientific Statement

Special Report

Cardiovascular Disease in Women

Special Writing Group

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Action must be taken to prevent cardiovascular disease in women and men before signs and symptoms of the disease appear or a myocardial infarction or stroke is experienced. Prevention is critical because 40% of all coronary events in women are fatal, 67% of all sudden deaths in women occur in those without a history of coronary heart disease,¹ and stroke is one of the leading causes of severe disability among women. Much is known about the risk factors for cardiovascular disease in women, but much less is known about the effect modification of these risk factors has on the reduction of risk in women. However, given the knowledge available, much can be done to prevent or control risk factors in women.

Prevention of morbidity and death from cardiovascular diseases must start in the young. Although healthy living habits should begin in childhood, this report focuses on cardiovascular diseases among postmenopausal women entering the coronary heart disease- and stroke-prone years. The discussion is extended to younger women where applicable: for example, in the sections on oral contraceptives and prevention and control of risk factors.

Because of the growing number of older women in the population and those at risk for cardiovascular disease, the diagnosis and treatment of heart disease, stroke, and peripheral arterial disease are vital.

General Considerations

Cardiovascular diseases, especially coronary heart disease and cerebrovascular disease, are the leading causes of death in women in the United States and claim more black women's and white women's lives than do cancer, accidents, and diabetes combined.² Each year more than 236 000 women die of a heart attack, and more than 87 000 women die of a stroke. The age-adjusted death rates from diseases of the heart in women are four times higher in white women and six times higher in black women than the death rates for breast cancer. From 1980 to 1989 there was a 27% decline in age-adjusted death rates from coronary heart disease and a 65% decline in death rates

from cerebrovascular diseases from 1960 to 1989 among white women. In black women there was a 22% and 68% decline, respectively. Despite these substantial declines in mortality, coronary heart disease and stroke still rank first and third as the causes of death for middle-aged and older women, with substantially higher rates in black women. With each decade of life, the rate of death from coronary heart disease increases threefold to fivefold. By the ages of 75 to 84, the death rate in white women is more than 1290 per 100 000 population and in black women it is more than 1300 per 100 000 population.²

Cardiovascular diseases are also a leading cause of disability in women.³ Estimates of the percentage of women with ischemic heart disease who were disabled by their illness in 1980 ranged from 36% in women aged 55 to 64 to 55% in women aged 75 and older. Women who survive a stroke fare even worse: 62% of female stroke survivors aged 55 to 64 had some form of disability and 61% of those aged 75 and older were disabled.⁴

Another indication of the impact of a disease on society is its cost. In 1991 the cost of cardiovascular disease was estimated to be \$117.4 billion,⁵ including lost productivity resulting from disability. Women incur more than half of the yearly health care costs related to cardiovascular diseases (about 58%), although their death rate from cardiovascular disease ranges from one fourth to almost equal that of men, depending on the age group.^{6,7}

By the year 2000, 38% of all women in the United States will be 45 years old or older. By the year 2015, this proportion will increase to 45%.⁸ With this increase in a population of older women, cardiovascular disease is likely to be even more of a major health problem in the future. Because of the relatively large population of older women in the United States, in 1990 cardiovascular disease caused a greater proportion of all deaths in women than in men: 46% and 40%, respectively.⁹ Death rates from cardiovascular disease, however, are only the tip of the iceberg; one in nine women aged 45 to 64 has some form of cardiovascular disease, and after age 65 the ratio increases to one in three.⁵ While death rates from cardiovascular disease are declining, the number of women dying from cardiovascular disease continues to grow each year.⁵

Physicians should be aware that women perceive their risk of cancer as much greater than that of heart disease or stroke. Before women can reduce their cardiovascu-

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lar risk, they must understand their risk of death or disability from these diseases.

Risk Factors

A number of cohort studies examining various risk factors for cardiovascular disease have included women. In these studies the risk factors for cardiovascular disease in women are similar to those in men.¹⁰⁻¹⁶ In the Framingham Heart Study, risk factors for definite coronary disease (ie, excluding angina pectoris) included glucose intolerance, cigarette smoking, elevated systolic or diastolic blood pressure, increased total serum cholesterol or low-density lipoprotein levels, decreased high-density lipoprotein levels, older age, and deprivation of estrogen after natural or surgical menopause.¹⁰ These studies have also indicated that certain risk factors may affect women differently than they do men. For example, diabetes, hypertriglyceridemia, and low levels of high-density lipoprotein appear to be stronger risk factors for women than for men. Sedentary lifestyle and obesity are also important risk factors for coronary disease in women.¹⁷⁻¹⁹ In one study, fitness (as measured by maximal treadmill exercise test) was significantly related to decreased total mortality in women, primarily because of lower rates of cardiovascular disease and cancer.²⁰ More data are needed to determine whether such factors as elevated triglyceride level, alcohol intake, and postmenopausal progestin use are risk factors for cardiovascular disease in women. There is evidence that aspirin may protect against first myocardial infarction in women; further research is needed.²¹

Although progress is being made in decreasing some known risk factors, much more can be done. For example, in 1980-1991 almost 20% of all women had serum cholesterol levels that were considered high (≥ 240 mg/dl); the proportion was more than 50% in women more than 55 years old.² However, in 1988 only 28% of women in the United States had been told their cholesterol level and only 13.5% of women reported knowing their cholesterol level.²² Although high-density lipoprotein cholesterol and low-density lipoprotein cholesterol levels are better markers for risk than is total serum cholesterol, there are no national estimates for these fractions.² After the age of 45 years, 60% of white women and 79% of black women in the United States have hypertension (ie, they are taking antihypertensive medication or have a systolic pressure ≥ 140 mm Hg or a diastolic pressure ≥ 90 mm Hg).² It is estimated that only 54% of all hypertensive people are aware they are hypertensive and only 11% receive adequate therapy.⁵ In 1988, almost 50% of black women and 30% of white women in the United States were obese,² and almost six of every 10 women had a sedentary lifestyle.²³ The trend toward inactivity is increasing in the United States.²² There has been a decrease in cigarette smoking by white women and black women of 30% and 36% respectively from 1965 to 1990²; however, nearly 23% of women 18 and older (almost 22 million women) still smoke cigarettes.⁵ Contrary to what might be expected, national cross-sectional data indicate that from 1965 to 1990 the age group with the greatest increase in the percentage of women who smoked were those 65 and older (a 45% increase). Women with the greatest reduction in proportion of smokers were those aged 18 to 44. This most likely reflects a cohort effect of women

who started to smoke during the 1940s and continued into older age and a smaller proportion of younger women (18 to 44) who smoked in 1987 compared with 1965.²

Prevention

Because of the magnitude of the problem of heart disease and stroke in women and the evidence that risk can be decreased by a healthy lifestyle, action clearly must be taken before women show symptoms of coronary disease or have a myocardial infarction. One reason is that some studies indicate that a higher proportion of initial heart attacks are fatal in women (39%) than in men (31%).¹ In one recent study, the proportion of women with myocardial infarction who died in the hospital (15.8%) was higher than that of men who died in the hospital (10.3%); however, when age was taken into account, the survival rates of women and men were similar.²⁴ In addition, women are one and one half to four times more likely than men to die after coronary artery bypass surgery.²⁵

Women's cardiovascular health can be improved if the following efforts are made:

1. Public education and awareness are crucial. *Women must understand their vulnerability before they will make personal changes and accept environmental changes (eg, no-smoking environments). The three most important health-related behaviors for women are to avoid smoking, eat a balanced, low-saturated-fat diet to control blood lipid levels, and maintain a moderate level of physical activity to help control weight.* If these behaviors do not also control high blood pressure and diabetes, medical interventions are needed; diabetes negates the protective effect that being female has on the risk of developing coronary heart disease. Although it is never too late to begin risk reduction, the importance of starting it early in life must be emphasized.

2. Education of health care providers is essential. Providers must understand the risks associated with cardiovascular disease in women as well as the importance of a) prevention or control of these risk factors, b) recognition of symptoms (by women themselves as well as health care providers), and c) timely referral with appropriate diagnosis and intensive treatment.

3. Studies are needed to help clarify the process of behavior adaptation and change in women if viable and effective prevention and intervention efforts are to be made. What strategies are conducive to healthy lifestyles in women? Is environmental change or health education more effective?

4. Studies on the effects of risk modification should include women and provide answers to such questions as why mortality in white women, compared with that in black women, does not decrease when antihypertensive medication is taken.

5. As more women survive heart attack, stroke, coronary artery bypass surgery, or coronary angioplasty, their prognosis must be better understood to prevent recurrent attacks and disability. Do women usually care for themselves after a heart attack or stroke, or do they need caregivers? What type of medical care or rehabilitation do they need and what are they receiving now? Do they return to their normal activities and have an improved quality of life?

6. Health care providers must be familiar with community resources for referral for smoking cessation, dietary counseling, weight control, and physical activity. There are windows of opportunity when behavioral interventions might be most useful (eg, during pregnancy to prevent smoking or during menopause to encourage exercise and prevent weight gain).

Diagnosis, Treatment, Prognosis, and Rehabilitation in Women With Coronary Heart Disease

Chest Pain

Although angina was the predominant initial presentation of coronary heart disease in women in the Framingham Heart Study (based on clinical history),¹ almost 50% of women with chest pain had normal coronary arteriograms in studies using invasive techniques.^{26,27} Women with angina in the Framingham Study were considered to have a favorable prognosis, with rare progression to myocardial infarction,^{27,28} but these data predate the use of coronary arteriography for confirmation of coronary heart disease, and some of these women may have had chest pain of noncoronary origin. Unfortunately, these early findings contributed to the perception among physicians that angina was not a serious prognostic indicator in women.

Elucidation of the etiology of chest pain in women poses a challenge. An exercise-based diagnostic test with exercise of adequate intensity is more likely to be successfully completed by younger women, but the lower prevalence of coronary disease in young women engenders a greater likelihood of a false-positive result. On the other hand, a negative, or normal, test has great predictive accuracy for the absence of disease. Women without significant disability from associated disease with definite or probable angina should undergo appropriate exercise testing. Radionuclide imaging, coronary angiography, or both should be used as indicated for diagnosis, prognosis, and assessment for possible revascularization. For women with minimal symptoms or atypical chest pain with a normal resting electrocardiogram, exercise electrocardiography is recommended to rule out disease. If results are normal at an adequate exercise heart rate or workload, no other testing is required. If results of the exercise test electrocardiogram are abnormal (eg, ST segment depression), stress radionuclide myocardial perfusion studies or stress echocardiography can be performed to help separate false-positive from true-positive responses. Alternatively, some recommend combining exercise electrocardiographic testing with a functional test of perfusion or function from the outset when there is a low to intermediate pretest likelihood of coronary artery disease.

Although the prevalence of coronary heart disease among older women makes the ordering of an exercise-based test reasonable, many older women are unable to exercise adequately because of other illnesses or general deconditioning. Specific information about the amount of physical activity performed by women in their daily routines should be sought because a low activity level attained at exercise testing may lead to a false-negative diagnosis of angina pectoris. There is promising information on the value of pharmacological stress perfusion imaging with thallium-201 and pharmacological stress

echocardiography for detection of myocardial ischemia and determination of prognosis in patients unable to exercise adequately. Agents such as dipyridamole, adenosine, and dobutamine have been successfully used for this purpose. Coronary arteriography is an initial diagnostic procedure used in women with unstable pain syndromes for whom exercise testing is inappropriate. Because most coronary heart disease occurs in elderly women, the approach should be to identify patients who are either highly symptomatic or at high risk for coronary heart disease (ie, those with evidence of myocardial ischemia) for more invasive diagnostic and therapeutic interventions.

Myocardial Infarction

The average age of death from myocardial infarction is lower for men than for women. However, by age 65 and over, the number of deaths from ischemic heart disease is 11% higher for women than for men (American Heart Association, personal communication, National Center for Health Statistics, 1993). It is estimated that the onset of any initial manifestation of coronary heart disease is 7 to 10 years later in women than in men. Although the clinical presentation of myocardial infarction is similar in men and women (except that women have a higher incidence of non-Q-wave myocardial infarction), it is more often fatal in women, both in hospital and during the first year after infarction.^{1,29-31} despite better ejection fraction at hospital discharge in women with myocardial infarction.³⁰ The prognosis is even worse for black women than for white women. It has been speculated that this decreased early and late survival in women may be due to increased mean age at the time of infarction, increased complications of myocardial infarction, and/or comorbidity compared with men.^{32,33} In one study, however, it was demonstrated that excess mortality in women was not a function of age at the time of infarction.³¹ Women also have unrecognized infarction more frequently than men; for example, 35% of infarctions were unrecognized in women compared with 28% in men in the Framingham Heart Study.^{1,29} This may also be related to older age and/or associated diabetes and hypertension at the occurrence of infarction. Although the Framingham Study data show that unrecognized infarction occurs more frequently in women, there is little information on silent ischemia in women, and data are needed. Forty percent of women, compared with 13% of men, have reinfarction during the first year after infarction.^{1,34} Women are also more likely than men to have a stroke after myocardial infarction and less likely to have postinfarction pericarditis. In the Coronary Artery Surgery Study, heart failure was reported more in women than in men, despite better ventricular systolic function³⁵; this probably reflects diastolic dysfunction.³⁶ In the Framingham Study, the percentage of women aged 65 to 94 who died suddenly (37%) was similar to that of men (40%) in the same age group.¹ The Rochester Coronary Heart Disease Project also shows a similar mortality from sudden unexpected death among men (13.7%) and women (13.4%) aged 30 years or older.²⁴ Further research is needed to explain these similarities and differences between the sexes.

Treatments

Coronary thrombolysis has comparable benefits for women and men,³⁷ despite the higher rate of bleeding complications (particularly intracerebral bleeding) in women; it is unknown whether a relative increase in dosage of a thrombolytic drug (because women have a lesser body mass) is contributory. β -Blocking drugs and aspirin, given to patients after myocardial infarction, are of equal benefit in women and men^{38,39}; other drugs have not been systematically compared. Because women have smaller coronary arteries, vasodilator drugs may theoretically confer more benefit than for men; however, because Raynaud's phenomenon is more frequent in women, use of nonselective β -blocking drugs may be unwise.⁴⁰ If the decreased mortality risk from postinfarction ventricular arrhythmias in women⁴¹ is confirmed, the need for antiarrhythmic therapy after infarction should be reduced.

There have been no randomized clinical trials of either percutaneous transluminal coronary angioplasty or coronary artery bypass grafting in women. Registry and report series data indicate that women who undergo these procedures are older, have more severe and unstable angina,^{35,42,43} and are more likely to have urgent or emergency procedures. Although the number of coronary arteriograms has nearly doubled and the number of coronary artery bypass graft procedures nearly tripled in women during the last decade, hospital discharge data indicate that these procedures are still used less in women than in men.^{44,45} Because the outcome of increased use of coronary arteriography and coronary artery bypass grafting in women has not been studied, the advantages or disadvantages of these procedures remain unknown.

Women treated with coronary artery bypass graft surgery in the Coronary Artery Surgery Study³⁵ and other studies⁴³ were older, were more likely to have hypertension and diabetes, and had more severe or unstable angina, more cardiac enlargement, and more severe mitral regurgitation than did men; however, they had less severe and extensive coronary artery disease, less preoperative infarction, and better ventricular function.³⁶ Women had greater operative and postoperative mortality from coronary artery bypass grafting^{35,42,45} despite long-term survival rates similar to those of men.^{25,42} Graft patency appears to be lower for women, but because these data are derived from angiography performed for clinical indications, the actual patency rate is unknown. Postoperative improvement is less favorable than for men,⁴⁶ with less relief of angina,²⁵ and fewer women return to work.⁴⁷ In earlier surgical studies, smaller body size (and therefore smaller coronary artery size) was thought to be associated with excess coronary artery bypass grafting mortality^{35,42}; this may contribute to the poorer results of coronary artery bypass grafting in women.

In the initial National Heart, Lung, and Blood Institute Percutaneous Transluminal Coronary Angioplasty Registry, percutaneous transluminal coronary angioplasty in women was less successful and had increased complications, procedural mortality, and hospital mortality than in men; on the other hand, with successful percutaneous transluminal coronary angioplasty, long-term survival was better for women, with less restenosis

and less additional revascularization.^{48a} More recent data show comparable procedure success rates and no increased procedural mortality.^{48b,48c}

Rehabilitation

Data on rehabilitation for women after a coronary event are limited, and most guidelines are derived from studies of men. Women are referred for exercise rehabilitation less frequently by their physicians, although women's functional improvement is comparable to men's when exercise rehabilitation is undertaken; however, their program attendance is lower and dropout rates are greater.^{49,50} Whether this reflects timing, settings, or programs designed for the predominant population of middle-aged working men (with little relevance for older women) is unknown. After a coronary event, women have more depression, anxiety, and guilt feelings about their illness than men^{35,51}; their return to remunerative work is delayed and work is resumed at a lower intensity compared with men's, despite an early return to high-intensity household tasks.³⁵

Stroke in Postmenopausal Women

Stroke is the leading cause of severe disability in the United States for both women and men and is the third leading cause of death. In the United States stroke is estimated to cost \$15.3 billion annually for medical care, including rehabilitation, and the estimated additional costs due to loss of earning capacity and lost output bring the total to \$18 billion.⁵

Mortality

Stroke mortality has declined in the United States^{52,53} and in most western countries since 1900.^{53,54} The decline in stroke mortality was observed through the 1970s^{53,55} and into the 1980s.⁵²⁻⁵⁴ Mortality rates in women were almost uniformly 10% to 20% lower than in men, and where it has been studied, the rate of decline in mortality has been similar in women and men.⁵⁶ Mortality rates are generally higher in black men than in white men and in black women than in white women.⁵⁷

The trends for mortality from cerebral infarction follow the trends for all stroke, because cerebral infarction accounts for about 80% of all strokes. There are no satisfactory data on mortality trends in patients with primary intracerebral hemorrhage because of its low incidence and the uncertainty of diagnoses made before the common use of computed tomography brain scans. Mortality rates for subarachnoid hemorrhage increased dramatically from 1950 to 1970 and were always higher in women, but this increase was probably due to improvements in diagnosis made possible by increased use of cerebral angiography. Since 1970 the mortality rate for subarachnoid hemorrhage has decreased by 50% or more in both sexes.

Incidence

The occurrence of stroke is best determined by studying the incidence of first stroke in a population because of the potential biases in stroke mortality data due to changes in coding practices, changes in diagnostic procedures and perceptions, low autopsy rates, and inaccuracies in death certificate diagnoses.^{58,59} In the early 1950s the incidence of stroke in Rochester, Minn,

was similar in men and women, at a little more than 200 per 100 000 population per year. After that, the incidence in women decreased by more than 50% until the end of the 1970s and decreased in men by about one third in the same period. In the early 1980s stroke incidence increased again by about 15% in both men and women.⁶⁰ In Soderhamn, Sweden, between the late 1970s and the mid-1980s there was also a significant increase in the incidence of stroke among women and a modest but not statistically significant increase in incidence among men.⁶¹ The trend in incidence for cerebral infarction is similar to that for all stroke.

In some studies the incidence of stroke during pregnancy and the puerperal period was relatively high for the subjects' age group, but these studies were probably flawed by selection bias. A recent population-based study indicated that the incidence of stroke in women during pregnancy and the puerperal period was similar to the rate for all women aged 15 to 39 in the population.⁶²

The average annual incidence of transient ischemic attack is 30 to 50 per 100 000 population and may be slightly lower in women than in men.⁶³⁻⁶⁵ There is no good evidence of a decline in the incidence of transient ischemic attack in men or women.

The incidence of primary intracerebral hemorrhage has declined since the early 1950s in men and women and was about the same for men and women through the 1970s at about 10 per 100 000 population per year.⁶⁶ Subarachnoid hemorrhage is unique in that its incidence has not changed over a 40-year period of observation. The annual incidence of subarachnoid hemorrhage due to aneurysm is about 12 per 100 000 in women and about 7 per 100 000 in men.⁶⁷

Risk Factors

Studies of risk factors for stroke have usually included women and men, but few have reported the relative risks of these factors specifically for women. Hypertension is the risk factor with the highest relative risk for stroke, estimated at about 4.0. The relative risk for transient ischemic attack is also about 4.0, although some studies consider transient ischemic attack evidence of first stroke. Age is an important risk factor; risk almost doubles for each 10 years of increasing age. Several other risk factors are important, each with a relative risk of about 2.0; these include ischemic heart disease, hypertensive heart disease, congestive heart failure, diabetes mellitus, cigarette smoking, and family history of myocardial infarction. Atrial fibrillation also has a high relative risk, but the extent to which it is independent of hypertension and heart disease is not entirely clear.⁶⁸⁻⁷⁰ Nevertheless, atrial fibrillation often identifies a patient at increased risk of stroke.

The risk factors for stroke appear to be the same for women and men. However, men between the ages of 50 and 59 have twice the risk of stroke that women of the same age have after controlling for other significant risk factors.^{68,70} At older ages, the rates in men and women are more similar (eg, at age 80 to 84 the rate of stroke in men is 22.3 per 100 000 and in women 23.9 per 100 000 over a 10-year follow-up in the Framingham Study⁷⁰). Several prospective studies indicate that postmenopausal estrogen replacement therapy protects against stroke.^{71,72}

The incidence of intracranial hemorrhage is low, and there are few studies of associated risk factors. Primary risk factors for intracerebral hemorrhage, other than age, are hypertension and use of oral anticoagulants.^{73,74} Cigarette smoking is a risk factor for subarachnoid hemorrhage, but it is unclear whether preexisting hypertension is a significant risk factor.⁷⁵⁻⁷⁷ From an ecological perspective, it is difficult to associate hypertension with risk of subarachnoid hemorrhage because the incidence of subarachnoid hemorrhage has not changed over time^{67,77} and hypertension rates have decreased substantially in the same populations. This observation should be verified in population-based longitudinal studies. There is no indication of whether these risk factors are more or less important in women, but the incidence of subarachnoid hemorrhage is significantly higher in women than in men.

Prevalence of risk factors. The contribution of a risk factor to occurrence of stroke is determined by the strength of its association with outcome and the prevalence of the condition in the population at risk. Hypertension carries the highest relative risk for stroke and is also the most prevalent risk factor, being present in about 30% of men and women over the age of 35 in Rochester, Minn.⁷⁸ Transient ischemic attack without prior stroke has a prevalence of about 2% in men and women. Among the other risk factors associated with a significant independent increased risk of stroke in persons over the age of 35, ischemic heart disease has a prevalence in the population of 7%, and diabetes mellitus of about 6%. Congestive heart failure has a low prevalence, about 1%. Each of these risk factors increases in prevalence with increasing age.⁷⁹

Hypertension, transient ischemic attack, congestive heart failure, and diabetes mellitus have similar prevalence rates in men and women, and ischemic heart disease and atrial fibrillation are much less prevalent in women than in men.⁷⁹ Cigarette smoking is slightly less prevalent in adult women than in adult men,^{5,80} but projections for the year 2000 indicate that smoking will be more prevalent in women than in men.⁸¹

Management of risk factors for stroke. Proper management of heart disease and diabetes mellitus is prudent, but the extent to which treatment of most of these disorders affects the risk of stroke has not been determined. However, treatment of patients with nonvalvular atrial fibrillation with warfarin or aspirin reduces risk of stroke in women and men.⁸² Treatment of hypertension also reduces risk of stroke in women and in men, and by more in black women than in white women.^{83,84} Women and men with isolated systolic hypertension also benefit from treatment.⁸⁵ Cessation of cigarette smoking reduces the effects of smoking on the arteries⁸⁶ as well as the frequency of stroke.^{87,88} Aspirin treatment in patients with transient ischemic attack reduces the frequency of stroke in women and men,⁸⁹ and when recent-onset transient ischemic attack is associated with high-grade carotid artery stenosis on the same side of the brain, carotid endarterectomy is effective in reducing stroke in both women and men.^{90,91}

Peripheral Arterial Occlusive Disease

In the United States peripheral arterial occlusive disease is an important cause of morbidity and health care expenditures among older people. Incidence in-

creases sharply with age. From 1985 to 1987, an estimated 229 000 men and 184 000 women per year were discharged from hospitals with the diagnosis of chronic peripheral arterial occlusive disease. Arteriography was performed during 88 000 hospitalizations per year and aortoiliac femoral bypass during 31 000 hospitalizations per year. The discharge diagnosis of acute peripheral arterial occlusive disease was made in 60 000 men and 50 000 women per year, and 28 000 embolectomies or thrombectomies of lower limb arteries were done per year. However, few deaths were attributed to peripheral arterial occlusive disease.⁹²

Coronary artery disease is strongly associated with peripheral arterial occlusive disease and is the primary cause of death in patients who have the latter, which may be asymptomatic or result in intermittent claudication. Hospitalization for peripheral arterial occlusive disease is usually due to severe occlusive disease with accompanying thrombotic occlusion, ischemic skin ulceration, or gangrene that causes pain during rest. Severe occlusive disease causing limb loss is uncommon unless patients continue to smoke or have diabetes mellitus.

Peripheral arterial occlusive disease, as diagnosed by absence of peripheral pulses or by peripheral arterial bruits, has a lower prevalence in women than in men; it is uncommon in women unless they smoke or have diabetes mellitus, and the age at onset of peripheral arterial occlusive disease is greater in women than in men.⁹³ In the Systolic Hypertension in the Elderly Program, in which the subjects were 60 years old or older and had systolic blood pressure greater than 160 mm Hg, the prevalence of peripheral arterial occlusive disease (arm-ankle index <0.90) was 26.7% (50 of 187 subjects). The incidence of peripheral arterial occlusive disease in women increased with age and was associated with smoking and lower levels of high-density lipoproteins.⁹⁴ Signs of peripheral arterial occlusive disease, such as arterial bruits and nonpalpable peripheral pulses, are predictors of an associated atherosclerotic process.⁹⁵ Revascularization of peripheral arterial occlusive disease by angioplasty or bypass surgery depends in part on the disability due to claudication, the underlying pathoanatomic characteristics, and the needs and desires of the patient.

Severe coronary artery disease increases the risk of perioperative complications among patients undergoing revascularization. Therefore, preoperative patients who are unable to exercise sufficiently may require pharmacologic radionuclide testing to assess limitations in myocardial perfusion. Those with a moderate or large defect suggesting potential myocardial ischemia may require coronary angiography for determination of the extent and severity of coronary artery disease and the need for coronary revascularization before surgery for peripheral arterial occlusive disease.

Hormones and Cardiovascular Disease in Women

Because of past controversies and lack of clinical trial data, women and their health care providers need particular information about hormone use and the risk of cardiovascular disease.

Oral Contraceptives

Studies conducted when doses of estrogen and progestin in oral contraceptives were higher than they are now indicated that users had an increased risk of vascular disease, particularly if they were heavy smokers.⁹⁶⁻⁹⁸ The rates of myocardial infarction and stroke were also adversely affected. Nonsmokers or light smokers had little or no increase in risk due to oral contraceptive use, although smoking itself increases risk of myocardial infarction. Oral contraceptive use was also associated with increased risk of stroke, but only in women who smoked and were hypertensive. Early indications from newer studies suggest that cardiovascular risk is lower with use of low-dose oral contraceptives than with previous preparations, and the newer oral contraceptives may even be protective.⁹⁹⁻¹⁰² The reduction in risk is reasonable, because the adverse effects of oral contraceptives (raising low-density lipoprotein cholesterol levels, lowering high-density lipoprotein cholesterol levels, increasing blood pressure, and enhancing coagulation) are dose dependent. The effect of low-dose oral contraceptive use on cardiovascular risk among smokers and women more than 35 years old is not clear; however, increased risk of cardiovascular disease associated with oral contraceptives ends if their use is discontinued. A meta-analysis of 10 case-control and eight prospective studies found an overall relative risk of 1.01 (confidence interval, 0.91-1.18) for myocardial infarction for past users compared with those who had never used oral contraceptives.¹⁰³

Oral contraceptive use has substantial effects on the plasma lipoprotein risk factors for cardiovascular disease. The magnitude and direction of effects depend on whether the preparation has an overall estrogenic or progestogenic action and on the androgenicity of the progestin. The estrogenic component raises triglyceride and high-density lipoprotein levels and decreases low-density lipoprotein levels, whereas certain progestins with androgenic actions, such as norgestrel and norethindrone, have opposite effects.¹⁰⁴⁻¹⁰⁷ Most commonly used low-dose oral contraceptives containing levonorgestrel or norethindrone raise plasma triglyceride levels¹⁰⁶⁻¹⁰⁹ by increasing the production of triglyceride-rich very low-density lipoproteins.¹¹⁰ Oral contraceptives with levonorgestrel usually produce greater adverse effects on low-density lipoprotein and high-density lipoprotein levels than norethindrone-containing preparations.^{105-109,111,112} Oral contraceptives with fixed very low-dose norethindrone (0.5 mg per dose or less) lower low-density lipoprotein levels and raise high-density lipoprotein levels.^{107,112,113} Apparently the androgenicity of this low dose of norethindrone is overcome by the action of the concomitant estrogen. Some oral contraceptives long available in Europe contain the progestins gestodene, desogestrel, or norgestimate, which have favorable estrogenic effects on low-density lipoprotein and high-density lipoprotein levels.^{107,114-116} Desogestrel- and norgestimate-containing oral contraceptives are now available in the United States. The effect on cardiovascular disease of these oral contraceptives that favorably affect low-density lipoprotein and high-density lipoprotein levels is unknown, but a beneficial action is plausible. Use of this type of oral contraceptive is preferable for women who have other risk factors for cardiovascular disease.

Recommendations. Women who smoke, particularly those who smoke more than 10 cigarettes per day, should not use oral contraceptives. An oral contraceptive that lowers low-density lipoprotein levels and raises high-density lipoprotein levels should be used by patients with high-risk lipid profiles. It is not known whether oral contraceptives that lower low-density lipoprotein levels and raise high-density lipoprotein levels are safe for smokers, because it is speculated that the immediate cause of increased coronary morbidity may be more related to thrombosis than to atherogenesis. A wide range of current low-dose agents can be prescribed for women who do not smoke and who lack other risk factors for cardiovascular disease.

Postmenopausal Hormone Use

Millions of women in the United States use estrogen after menopause. In 1986 alone 20 million prescriptions were dispensed. Traditionally estrogen has been prescribed to relieve symptoms of menopause. Risk of osteoporosis and bone fractures can be reduced by estrogen, which restores calcium balance.¹¹⁷ The majority of case-control and prospective epidemiological studies show that postmenopausal women who take estrogen have a lower incidence of cardiovascular disease than women who do not use estrogen.^{118,119} Overall, estrogen use is associated with a risk reduction of 50% for coronary heart disease,^{118,119} and risk of stroke is similarly decreased.¹²⁰ The beneficial effect of taking estrogens may extend for years after their use is stopped.^{119,120} However, caution is needed in interpreting these studies because they were not randomized trials and could have been affected by selection bias; that is, physicians may tend to prescribe estrogen for healthier women.

In the 1970s, concern about thrombotic complications from high doses of estrogens in oral contraceptives, as well as studies of hormone use in men with myocardial infarction, led to withholding of estrogen replacement therapy from women who had existing cardiovascular disease. However, on further investigation, estrogen appears to improve survival in these women even more than in women without cardiovascular disease.¹²⁰⁻¹²²

The recommended dose of postmenopausal estrogen was decreased during the 1970s and 1980s to the minimum necessary to relieve menopausal symptoms and reduce osteoporosis. Recent studies indicate that a low dose of estrogen, such as 0.625 mg/day of conjugated equine estrogens, lowers risk of cardiovascular disease^{119,120} in part because it lowers low-density lipoprotein levels and raises high-density lipoprotein levels to the same degree as does 1.25 mg.¹²³ Most women in all studies of estrogen replacement and cardiovascular disease took estrogen orally, and it is not known whether transdermal administration of estradiol (by skin patch) reduces cardiovascular disease risk. However, because transdermal estradiol has little of the favorable effects of oral estrogens on plasma low-density lipoprotein and high-density lipoprotein levels,¹²³⁻¹²⁵ reduction of cardiovascular disease risk cannot be assumed.

Oral estrogen replacement therapy affects plasma lipoprotein levels.¹²⁵ Three actions are well known. Estrogens lower plasma low-density lipoprotein levels and raise high-density lipoprotein levels each by about

15%.¹²³ The mechanisms of action are accelerated catabolism of low-density lipoprotein particles¹²³ and probably increased synthesis of high-density lipoprotein particles.¹²⁶ Estrogens increase the liver's production of triglycerides and very low-density lipoprotein particles that raise plasma triglyceride levels.^{123,126} The effect of usual doses of oral estrogens, such as micronized estradiol (2 mg per dose) or conjugated estrogens (0.625 mg per dose), is to raise plasma triglyceride levels by about 25%.¹²³ Therefore, estrogens should be used cautiously in patients with hypertriglyceridemia. A higher dose of conjugated estrogen (1.25 mg per dose) has only minimal additional effects on low-density lipoprotein and high-density lipoprotein levels but nearly doubles the increase in levels of very low-density lipoprotein and triglyceride particles.¹²³ The effects of very low doses of estrogens such as conjugated estrogens (0.3 mg per dose) are not well characterized. However, these doses may not be effective for alleviation of menopausal symptoms in many women. The use of low-dose oral estrogens could be considered for the therapy of plasma lipoprotein disorders characterized by high levels of low-density lipoprotein or low levels of high-density lipoprotein. Compared with the high cost of most hypolipidemic drugs, oral estrogens are a relatively inexpensive way to favorably affect low-density lipoprotein and high-density lipoprotein levels.

The beneficial effects of estrogen replacement therapy on low-density lipoprotein and high-density lipoprotein levels could explain the reduced rates of cardiovascular disease in women taking it. However, epidemiological studies have suggested that only part of the beneficial effects on cardiovascular disease associated with estrogen replacement can be explained by the effects on low-density lipoprotein and high-density lipoprotein levels.^{121,122} Other plausible mechanisms include decreased lipid uptake in the vessel wall, improved glucose and insulin levels,¹²⁷ and vasodilation.¹²⁸ Estrogens do not affect blood pressure.¹²⁹ In rabbits¹³⁰ and monkeys,¹³¹⁻¹³³ estrogen with or without progestins retarded diet-induced coronary atherosclerosis, apparently by a mechanism other than improved serum lipid levels.

High doses of estrogens increase the risk of endometrial cancer, but there is insufficient information about presently used doses. Because progestational hormones substantially reduce the adverse effect of estrogen replacement on endometrial hyperplasia and cancer, a progestin is often taken with estrogen to protect the endometrium; however, certain synthetic progestins, such as norgestrel, norethindrone, and medroxyprogesterone acetate (the progestin most commonly used by postmenopausal women), have detrimental androgenic effects that lower serum high-density lipoprotein levels, as does testosterone. Oral progesterone, the natural hormone, does not seem to have an androgenic action, indicating that the progestational action to protect the endometrium is an effect separate from the androgenic action that lowers high-density lipoprotein levels. Experts do not agree on whether or how to use progestins, only that women who have had a hysterectomy do not need them.

Researchers do not agree about whether estrogen replacement therapy increases breast cancer rates. There is remarkable inconsistency between studies on the effects of duration of use and dose on breast cancer

risk.¹³⁴⁻¹³⁸ One recent meta-analysis found no overall effect of estrogen use,¹³⁵ while another found an increase in risk for breast cancer after 5 years of estrogen use.¹³⁸ Concern about an adverse effect of concomitant progestin use has also been raised.^{136,137} Further study is needed before firm conclusions can be drawn.

Recommendations. A clinical trial in women has not been conducted to examine the effects of postmenopausal replacement hormones on risk of cardiovascular disease, but there is strong epidemiological evidence that estrogen is beneficial in reducing the risk of several diseases (eg, coronary heart disease and osteoporosis) in many populations of women. However, the decision to use estrogen replacement to reduce risk of cardiovascular disease should be individualized. Women who have a high risk of cardiovascular disease because of adverse lipid profiles or who have preexisting disease are particularly good candidates for estrogen replacement therapy. Women with lower than average risk factor levels have less need for estrogen's protective effects, and the decision to use estrogen replacement therapy should be based on other considerations, such as menopausal symptoms and osteoporosis. The decision about whether to use a progestin is complex. Some experts believe that the benefits of estrogen given alone outweigh the potential adverse effects, because cardiovascular disease is far more prevalent than endometrial cancer. If estrogens are prescribed without a progestin, the health of the endometrium must be evaluated before and during therapy. If concomitant progestin therapy is chosen, a low dose of medroxyprogesterone acetate (eg, 2.5 mg) should be used. Pharmaceutical companies should be urged to take steps to market for postmenopausal women approved progestational hormones (eg, desogestrel, norgestimate) that do not lower high-density lipoprotein levels.

Conclusion

By the year 2015 almost half of all women in the United States will be 45 years of age or older, and a large cohort will be in the coronary heart disease- and stroke-prone years.¹³⁹ To ensure the health of an older population, we must begin to prevent high-risk behaviors in younger women now. Health care providers play a pivotal role in ensuring that the appropriate diagnosis is made and treatment prescribed and in educating women about risk for cardiovascular disease. Women must have access to knowledge, a healthy environment, health care, and the skills they need to prevent and reduce risk from cardiovascular disease.

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