Coronary Artery Disease Prevention: What's Different for Women?

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Cardiovascular disease is the leading cause of death in women, as well as an important cause of disability, although many women and their physicians underestimate the risk. Exercise, hypertension treatment, smoking cessation and aspirin therapy are effective measures for the primary prevention of coronary artery disease in women. The roles of lipid-lowering agents and hormone replacement therapy in primary prevention are not well established. In secondary prevention, hormone replacement therapy has not been effective in lowering the risk of recurrent myocardial infarction, but several lipid-lowering agents have been shown to reduce this risk and to lower mortality rates in women with known coronary artery disease. Other secondary prevention measures, including aspirin, beta blockers, angiotensin-converting enzyme inhibitors, revascularization and rehabilitation, have proven benefits in women but are underused, especially in minority women. Family physicians should emphasize the use of proven treatments, with particular attention given to underserved populations. (Am Fam Physician 2001;63:1393-400,1405-6.)

O *A patient information handout on preventing heart attacks in women, written by the authors of this article, is provided on page 1405.*

Members of various medical faculties develop articles for "Practical Therapeutics." This article is one in a series coordinated by the Department of Family and Community Medicine at the Medical College of Wisconsin, Milwaukee. Guest editors of the series are Linda N. Meurer, M.D., M.P.H., and Douglas Bower, M.D.

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Coronary artery disease has been widely considered a "man's disease" and not a major concern for women. Yet cardiovascular disease is the leading cause of death in adult women in the United States. A 1995 Gallup poll found that one in three primary care physicians in this country, as well as four out of five women, was unaware of this fact.[1(p3)]

Women's age-adjusted mortality rates from heart disease are four to six times higher than their mortality rates from breast cancer. Yet, because public campaigns have emphasized breast cancer risks in the effort to promote screening mammography, many women are more afraid of breast cancer than of coronary artery disease.

Over the past two decades, public education efforts related to cardiovascular disease prevention have been aimed primarily at male populations. As a result, the prevalence of coronary risk factors and the number of cardiovascular deaths have decreased in men—but not in women.[1(pp4,6)]

Lipid-lowering medications and hormone replacement therapy have raised great hopes for primary prevention of coronary artery disease (i.e., prevention of a first myocardial infarction or the onset of symptomatic coronary artery disease). However, in caring for women, physicians await evidence from randomized, controlled trials to support the effectiveness of these measures, while sorting among conflicting sets of recommendations. In secondary prevention, which includes measures to prevent reinfarction and cardiovascular death, there is good evidence for the effectiveness of many therapies. However, studies indicate that women may not be prescribed beneficial therapies as frequently as men.

This article reviews the characteristics of coronary artery disease, the prevalence and significance of coronary risk factors, and the evidence for the effectiveness of preventive strategies in women. Approaches to targeting preventive efforts to women's special needs are also addressed.

Characteristics of Coronary Disease in Women

When women present with myocardial infarction, they are more likely than men to be misdiagnosed, and they are also more likely to die of their first infarction[2] *(Table 1)*.[1-9] Chest pain in perimenopausal women is often difficult to diagnose because it may present atypically. Shoulder or neck pain, nausea, fatigue or

Women are less likely than men to be offered treatment that could prevent reinfarction.

dyspnea are more likely to signal myocardial infarction in women than in men.[1] Classic substernal pressure symptoms are comparatively less predictive of myocardial infarction in women.[2-4]

Because studies have shown that women with coronary artery disease present with a mix of typical and atypical symptoms, it is important that physicians consider risk factors when evaluating chest pain syndromes in women.[4] An approach that uses risk-factor scoring to guide an appropriate assessment of chest pain in women without known coronary artery disease is presented in *Figure 1*.[4]

Coronary risk factors are more prevalent in women who are older, poor, African American, Hispanic or Native American. Primary and secondary prevention in these underserved populations requires particular attention to the context of these women's lives. There is evidence that several preventive measures can reduce the risk of coronary disease *(Table 2)*.[10-17]

TABLE 1
Coronary Artery Disease: What's Different for Women?

Presentation
Women present at a later age.[1(p3)-3]
In women, typical angina is less predictive of coronary artery disease (pretest probability is 50 to 60 percent in women versus 80 to 99 percent in men).[3,4]
Women may present with shoulder or jaw pain, dyspnea or nausea.[1(p316),4]
Risk factors
Diabetes has a stronger influence in women.[3,5]
High HDL cholesterol levels, which lower the risk of coronary artery disease, are more common in women.[6]
The roles of total cholesterol, LDL cholesterol and lipoprotein(a) in women are unclear.[7]
The risk of coronary artery disease increases after menopause.
Prognosis
Women are more likely to die of a first myocardial infarction.[2]
Women experience more long-term disability.[1(p25)]
Women have more comorbidity (because they are usually older on presentation).
Primary prevention
There is insufficient evidence for the benefits of cholesterol-lowering drugs in women.
There is insufficient evidence for the benefit of estrogen replacement therapy.
Secondary prevention
Women are less likely to undergo angioplasty or bypass surgery.[8]
Fewer women receive cardiac rehabilitation.[1(p213)]
Fewer women receive therapy with aspirin, beta blockers or angiotensin-converting enzyme inhibitors.[9]

HDL = high-density lipoprotein; LDL = low-density lipoprotein.

Information from references 1 through 9.

PHYSICAL INACTIVITY, OBESITY AND DIABETES

Sedentary lifestyle is the most common risk factor for coronary artery disease in women. Data from the National Center for Health Statistics indicate that 39 percent of white women and 57 percent of women of color do not get enough physical exercise.[18] Rates of physical inactivity are highest among poor women.

Physical inactivity contributes to obesity and is an independent risk factor for myocardial infarction.[13] Conversely, modest exercise has been strongly associated with risk reduction in observational studies. Investigators in the Nurses' Health Study[19] found that 30 to 45 minutes of walking three times weekly reduces the risk of myocardial infarction by 50 percent in women (even older women). Exercise has also been found to reduce the risk of type 2 diabetes (formerly known as non–insulin-dependent diabetes, and also a risk factor for coronary artery disease), even in women with obesity and a family history of diabetes.[20]

Obesity is an independent risk factor for all-cause mortality. It is highly associated with diabetes, hyperlipidemia and hypertension.[21] According to the National Center for Health Statistics,[18] 33 percent of African American women and 17 percent of white women are obese (i.e., body mass index [BMI] greater than 30). The risk of cardiovascular disease becomes higher with increasing weight, even at lower BMIs. Central obesity (a waist-to-hip

ratio greater than 0.8) is associated with a disproportionate increase in coronary risk. The most effective treatment for obesity in women has not been determined, and exercise appears to be less effective in promoting weight loss in women than in men.[22]

Obesity is also a major risk factor for the development of type 2 diabetes, which is the most important risk factor for coronary disease in women. Coronary artery disease generally presents at an older age in women than in men, but diabetes wipes out this gender-protective effect. Furthermore, coronary disease is more likely to be fatal in women with diabetes.[5] Native Americans and African Americans have higher rates of diabetes and its cardiovascular sequelae.

Although there is a dose-response relationship between the level of hyperglycemia and the incidence of coronary artery disease, studies have not clearly shown that tight control of type 2 diabetes reduces the risk of cardiovascular disease. However, secondary prevention trials have found that aggressive control of hypertension and hyperlipidemia does reduce the risk of reinfarction in women with diabetes.[17]

In some patients, central obesity, hypertension, impaired glucose metabolism and hyperlipidemia are clustered in the insulin resistance syndrome, which, in women, also overlaps with the polycystic ovary syndrome.[1(p78)] Both syndromes are associated with increased cardiovascular risk. Drugs that alter insulin resistance, such as metformin (Glucophage) and rosiglitazone (Avandia), may be useful for primary prevention in patients with this pattern of metabolic dysfunction, but their long-term effect on cardiovascular morbidity and mortality is yet to be determined.

Given that inactivity and obesity are major contributors to cardiovascular disease, increased physical activity is clearly important in the primary and secondary prevention of heart disease. Exercise rehabilitation after myocardial infarction increases functional capacity. However, women are less likely than

Chest Pain in Women Without Known Coronary Artery Disease

Assign appropriate points for each of the patient's risk factors. Add the points to obtain the total score, which guides the diagnostic strategy.

Risk determinants

Major risk factors (3 points each)

Typical anginal pain ____
Postmenopausal status without hormone replacement therapy ____
Diabetes ____
Peripheral vascular disease ____

Intermediate risk factors (2 points each)

Hypertension ____
Smoking ____
Total cholesterol level > 265 mg per dL (6.85 mmol per L) ____

Minor risk factors (1 point each)

Patient age > 65 years ____
Obesity ____
Sedentary lifestyle ____
Family history of coronary artery disease ____
Stress ____

Total score: ____

Diagnostic strategy

≤ 2 points	Low likelihood of coronary artery disease (< 20%): no tests indicated
3 or 4 points	Moderate likelihood of coronary artery disease (20% to 80%): exercise tolerance test or imaging study
≥ 5 points	Strong likelihood of coronary artery disease (> 80%): exercise tolerance test, with cardiac catheterization performed if test is inconclusive or positive

FIGURE 1. Approach to the assessment of chest pain in women not known to have coronary artery disease.

Information from Douglas PS, Ginsburg GS. The evaluation of chest pain in women. N Engl J Med 1996;334:1311-5.

TABLE 2

Measures for Primary and Secondary Prevention of Coronary Artery Disease

Primary prevention	Secondary prevention
Proven benefit in controlled trials[10,11]	Proven benefit in controlled trials
Hypertension control	Hypertension control
Beta blockers	Beta blockers
Thiazide diuretics	Aspirin
Aspirin[12]	Angiotensin-converting enzyme inhibitors[16]
Benefit in observational studies	Aggressive cholesterol-lowering therapy[17]
Exercise[13]	Angioplasty
Smoking cessation[14]	Coronary artery bypass surgery
Proven benefit in men but controversial in women	Benefit in observational studies
Drug therapy to lower cholesterol levels[15]	Smoking cessation
Insufficient evidence of benefit	Exercise rehabilitation*
Estrogen replacement therapy	

**—Functional improvement; no studies on mortality reduction.*

Information from references 10 through 17.

men to be referred for this therapy.[1(p213)] Even when referred, they are less likely to remain enrolled.

Barriers to physical activity in women include lack of leisure time because of household and care-taking responsibilities, comorbid conditions such as arthritis, and lack of appropriate programs and access to facilities. Lack of access is especially severe among low-income women, who have the highest rates of obesity and cardiovascular morbidity and mortality. Even a walking program can be difficult and dangerous in a neighborhood where the streets are not safe.

It is important that physicians encourage the development of accessible, appropriate exercise options for women. For instance, walking clubs provide safety and social support for exercise, and water exercise programs are helpful for patients with arthritis. Cardiac rehabilitation programs should track successful participation of women as a measure of their effectiveness. Taking the longer view, a holistic approach to cardiovascular disease prevention among women includes the promotion of sports and other types of physical activity for girls and young women, perhaps increasing the likelihood of lifelong physical activity.

HYPERTENSION

Fortunately, major trials of hypertension treatment, such as the Hypertension Detection and Follow-up Program (HDFP)[10] and the Systolic Hypertension in the Elderly (SHEP)[11] trial, included adequate numbers of African American and white women, and demonstrated the benefits of treatment. Hypertension treatment reduced the incidence of coronary artery disease by 15 percent in HDFP and by 33 percent in SHEP.

Because major long-term trials have demonstrated the efficacy of beta blockers and thiazide diuretics in reducing coronary artery disease and stroke, these agents should be considered as initial therapy in all patients who have not lowered their blood pressure with diet and exercise. Thiazide diuretics have a favorable effect on calcium excretion and, thus, may be especially appropriate for use in women who are at risk for osteoporosis.

HYPERLIPIDEMIA

In women, low-density lipoprotein (LDL) cholesterol and total cholesterol levels increase after the age of 55 years and peak between 55 and 65 years of age, about a decade later than in men. A meta-analysis of pooled observational data demonstrated an increased risk of coronary artery disease in women younger than 65 years who had hyperlipidemia,[7] with a much weaker association in women (and men) older than 65 years.

High triglyceride levels seem to increase the risk of coronary artery disease in women, but this association has been difficult to separate from the effects of obesity and diabetes. Although high lipoprotein(a) levels are associated with an increased risk of cardiovascular disease in men, limited studies in women have found an increased risk only in young women who did not have other coronary risk factors.

Compared with men, women have slightly higher high-density lipoprotein (HDL) cholesterol levels, and these levels tend to remain steady throughout life. Several studies have demonstrated the protective effects of high HDL cholesterol levels, even in patients with high total cholesterol levels. An HDL cholesterol level higher than 60 mg per dL (1.55 mmol per L) is considered a "negative risk factor" (i.e., it offsets one of the other coronary risk factors).

Almost all major trials on primary prevention of coronary artery disease using cholesterol-lowering medications have not included women. The exception is the Air Force/Texas Coronary Atherosclerosis Prevention Study.[23] Although this trial showed a reduction in cardiac events when men and women were analyzed together, careful examination of the data presented on the female patients does not unequivocally demonstrate a benefit in women. The role of lipid-lowering medications in primary prevention is still controversial. However, in secondary prevention in

women with known coronary disease, evidence from clinical trials[17] that included women is adequate to support their use.

The cholesterol screening and treatment recommendations summarized in *Table 3*[6,24,25] reflect differences in the thresholds for evidence of benefit as determined by various expert panels. The National Cholesterol Education Program (NCEP)[6] goes farthest in extrapolating to women the evidence of benefit for cholesterol-lowering medications in men. In contrast, the American College of Physicians (ACP)[25] acknowledges the lack of evidence that treatment of hyperlipidemia in asymptomatic women is effective. The NCEP, ACP and U.S. Preventive Services Task Force[24] all recommend risk factor assessment, prudent diet and exercise.

The natural history of serum lipid levels and the risk of coronary artery disease reflect the influence of female hormones and their decline after menopause. Theoretically, estrogen acts to reduce cardiac risk by, among other mechanisms, dilating coronary arteries, decreasing platelet aggregation and fibrinogen levels, serving as an antioxidant, raising HDL cholesterol levels and lowering LDL cholesterol levels.

TABLE 3
Recommendations on Cholesterol Screening and Treatment for Women: Primary Prevention of Coronary Artery Disease*

	Screening		*Treatment*	
Group	*Normal risk*	*High risk†*	*Normal risk*	*High risk†*
USPS Task Force[24]	Total cholesterol level in women 45 to 65 years of age	Total cholesterol level obtained earlier in women at high risk	Low-fat diet Exercise	Consider drug therapy.
ACP[25]	Total cholesterol level "appropriate but not mandatory" in women 45 to 65 years of age Unknown value in women 65 to 75 years of age Not recommended in women older than 75 years	Total cholesterol level obtained earlier in women at high risk Not recommended in women older than 75 years	Drug therapy not necessary in premenopausal women	No recommendation
NCEP[6]	Total and HDL cholesterol levels in all persons 20 years and older	Consider obtaining total and HDL cholesterol levels in children and adolescents.	Drug therapy if LDL cholesterol level is higher than 190 mg per dL (4.90 mmol per L)	Drug therapy if LDL cholesterol level is higher than 160 mg per dL (4.15 mmol per L). The goal is an LDL cholesterol level below 130 mg per dL (3.35 mmol per L).

USPS = U.S. Preventive Services; ACP = American College of Physicians; NCEP = National Cholesterol Education Program; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

**—These recommendations apply to women with no history of myocardial infarction, angina pectoris or known coronary artery disease (primary prevention). Women with a previous myocardial infarction or known coronary artery disease should be treated aggressively to achieve an LDL cholesterol level below 100 mg per dL (2.60 mmol per L) to lower their risk of a second cardiac event (secondary prevention).*

†*—Women should be considered at high risk if they have diabetes or other macrovascular disease, a family history of premature coronary artery disease or two of the following: a family history of coronary artery disease, smoking, hypertension, older than 55 years, severe hyperlipidemia or an HDL cholesterol level below 35 mg per dL (0.90 mmol per L).*

Information from references 6, 24 and 25.

The role of hormone replacement therapy in the prevention of coronary artery disease in women remains unclear.

HORMONE REPLACEMENT THERAPY

Investigators in observational studies such as the Nurses' Health Study[26] found decreases in coronary artery disease outcomes among women receiving hormone replacement therapy. However, observational studies suffer from "healthy user" bias: women who are receiving hormone replacement therapy are more likely to be of higher socioeconomic status, to be healthier, to seek medical care and to exercise. These studies were not designed to detect the possible adverse effects of hormone therapy. In the Prospective Estrogen-Progesterone Interventions (PEPI) trial,[27] estrogen replacement improved lipid profiles. However, the PEPI trial was not designed to evaluate the effects of this treatment on the incidence and mortality of coronary artery disease.

The Women's Health Initiative,[28] a randomized, controlled trial of hormone replacement therapy for the prevention of coronary artery disease, is expected to yield definitive information about the value of estrogen replacement as primary prevention. The results of this trial are expected in 2006.

The Heart and Estrogen/Progestin Replacement Study (HERS)[29] was a randomized, controlled trial of combined continuous hormone replacement therapy as secondary prevention in women with known coronary artery disease. In the HERS hormone replacement group, the rate of coronary events increased in the first two years and decreased in the third and fourth year, with no net benefit over the study period.

The possible increased risk of breast cancer in women who receive hormone replacement therapy remains a concern.[30] Estrogen replacement has proven benefits for reducing perimenopausal symptoms and preventing osteoporosis. At present, however, there is insufficient evidence to recommend hormone replacement therapy for the prevention of coronary artery disease.

SMOKING

Smoking is a major risk factor for the development of cardiovascular disease in women. More than 60 percent of myocardial infarctions in women younger than 50 years are attributable to smoking, as are 21 percent of all deaths from coronary artery disease. All women benefit from quitting smoking. Investigators in the Nurses' Health Study[14] found that the risk of coronary artery disease decreases by one third two years after smoking cessation.

In the United States, fewer women than men currently smoke, and the prevalence of smoking among women has declined over the past three decades. However, tobacco use has decreased more dramatically in men than in women. Compared with male smokers, women more often smoke to relieve stress, anger, boredom or depression. Women are more likely than men to cite smoking as a strategy for weight loss, and they more often give weight gain as a major reason for relapsing after quitting.[31]

Compared with men, women find it harder

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to quit smoking initially, with and without treatment, and are also more likely to relapse. Some evidence shows that nicotine replacement appears to be more effective in men.[32] In women seeking to quit smoking, combination therapy with bupropion (Zyban) and the nicotine patch appears to produce the best long-term results.[33]

Because of gender-based differences in reasons for smoking, reasons for quitting and responses to pharmacologic agents, research on gender-specific smoking cessation strategies is needed. For example, it might be helpful for women to quit smoking early in their menstrual cycle (when withdrawal symptoms are not overlapping with premenstrual symptoms), to use bupropion to minimize weight gain and to address psychosocial stressors. Consideration of factors unique to women may help physicians be more successful in treating women smokers.

ASPIRIN AND CARDIOACTIVE DRUGS

Investigators in the Nurses' Health Study[34] observed a decreased risk of first myocardial infarction and death in women who took one to six aspirins per week. In the Hypertension Optimal Treatment (HOT) study,[12] men (53 percent) and women (47 percent) were randomized to receive 75 mg of aspirin per day or placebo, in addition to hypertension treatment. The HOT study showed an association between aspirin use and reductions in major cardiovascular events and myocardial infarctions.

The use of aspirin therapy for primary prevention of cardiovascular disease appears to be justified in women with hypertension. However, further studies are needed to determine the optimal aspirin dose and whether other groups of women are likely to benefit from this treatment. Aspirin therapy is clearly beneficial in women with chronic stable angina, unstable angina and evolving myocardial infarction, and for the prevention of recurrent infarction.

Women, especially if older, African American or Hispanic, are less likely than white men to receive aspirin, beta blockers, angiotensin-converting enzyme inhibitors and lipid-lowering drugs after myocardial infarction, despite evidence of benefit.[9,35] These patients are also less likely to be referred for revascularization procedures[8,36] and cardiac rehabilitation. Family physicians have an important role in ensuring that their patients have access to these therapies.

The potential effect of preventive interventions is not as clearly defined in women as it is in men.

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