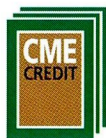


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# Addressing coronary heart disease risk in women

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### ABSTRACT

Contrary to popular perceptions, coronary heart disease (CHD) is a serious and widespread problem in US women. Public education, preventive interventions, and better data on CHD risk and prevention in women are needed.

**Postmenopausal women are 10 times more likely to die of CHD than of breast cancer**

**C**ORONARY HEART DISEASE (CHD) traditionally has been considered a problem of men. Although it is the leading cause of death for US women, resulting in more than 250,000 deaths annually, until recent years most data used for the care of women derived from studies conducted predominantly or exclusively in middle-aged men. Initial efforts to prevent CHD through risk factor modifications have focused more on men than on women. Only in 1993 did Congress mandate that clinical trials supported by the National Institutes of Health include women in numbers sufficient to define gender differences.

CHD is an equal opportunity killer, and since half of our patients are women, we have to be familiar with CHD risk factors and presentations in this suboptimally addressed segment of the population. The only way to improve the situation is through intensive preventive interventions (TABLE 1), educational campaigns, earlier evaluation, and accumulation of data on CHD prevention and treatment in women.

TABLE 1

### Cornerstones of reducing coronary heart disease risk in women

Smoking cessation

Pharmacologic and nonpharmacologic control of lipid abnormalities and hypertension

Regular physical activity of moderate intensity

Healthy diet

Weight control

### COMMON MISPERCEPTIONS

Doctors and the public misperceive the prevalence and the impact of CHD in women.

CHD is highly prevalent and lethal in women. According to current estimates, one of every three US women age 65 and older has CHD. Disability due to CHD is a major problem: one third of women in their 50s and 60s with coronary disease are disabled by their symptoms. After age 75, the rate is more than 55%.

Forty percent of all coronary events in women are fatal. Moreover, women who have a myocardial infarction or a myocardial revascularization procedure do less well than their male counterparts.<sup>1,2</sup>

Yet surveys show that most women and many primary care clinicians believe that breast cancer is the major women's health concern, not CHD. In reality, a postmenopausal woman is 10 times more likely to die of CHD than of breast cancer.<sup>2</sup> We need major public education to shift this misperception and teach women how to prevent CHD.

### CORONARY HEART DISEASE TRENDS IN WOMEN VS MEN

Cardiovascular and coronary mortality continues to decline in the United States, but the



decline is less prominent for women than for men. At the same time, demographically, coronary risk factors have decreased more prominently for men than for women, because risk reduction messages have been aimed predominantly at men.

### Prevalence of risk factors in women

Risk factors are highly prevalent in women in this country in all racial and ethnic groups. Only 33% of US women do not have at least one major risk factor for CHD, and that percentage decreases with older age.

According to data from the National Center for Health Statistics,<sup>3</sup> more than a fourth of women aged 20 to 75 smoke cigarettes, more than a third have hypertension, more than a fourth have hypercholesterolemia, more than a fourth are overweight, and 6 out of 10 are sedentary.

Risk factors tend to predominate and cluster in lower socioeconomic groups and in groups with less education—two factors that commonly coexist.

### ■ CIGARETTE SMOKING

In earlier years, more men than women in this country smoked cigarettes. But today, because smoking cessation has been more successful in men than in women, and because more young women than young men currently smoke, equal numbers of men and women smoke cigarettes. In fact, more than 3,000 young people start smoking each day, and half of them are girls.

Smoking patterns among women have changed: women now start smoking at a younger age and tend to smoke more cigarettes daily. Today, 23% of US women over age 18 smoke.

### Smoking and coronary heart disease risk

The prevalence of smoking among women is a national tragedy, for the reasons given below.

**Smoking triples the risk of myocardial infarction**, even for premenopausal women,<sup>4</sup> and is an important contributor to sudden death in young women. Smoking's coronary risk is amplified by the use of oral contraceptives. In addition, smoking lowers the age at initial myocardial infarction more for women than it does for men.

**Smoking lowers the age of menopause** by 1.5 to 2 years, and a longer time in menopause may also increase CHD risk.

**Smoking lowers HDL** (high-density lipoprotein) levels, for both women and men. It also raises fibrinogen levels and increases platelet aggregability.

**Smoking intensity.** The Nurses' Health study, a self-report observational study of 120,000 nurses, showed that the intensity of smoking—ie, the number of cigarettes smoked—correlates with all coronary events. However, even smoking fewer than 5 cigarettes daily doubles coronary risk.

Moreover, women may underreport the amount they smoke. When a woman says she smokes one, two, or three cigarettes a day, it is better to interpret that as meaning she is not smoking a full pack a day. Clinicians should inform women who smoke even a few cigarettes daily that their risk of coronary events is doubled, and that risk is not lower if they smoke low-nicotine and low-tar cigarettes.

**Smoking compounds coronary risk.** Smoking also increases the risk of coronary events in women already at risk because of a prevalence of other risk factors.

**Smoking cessation reduces CHD risk.** The good news is that smoking cessation is enormously effective. Within 2 years of cessation, women decrease their risk of dying from a cardiovascular event by 24%, independent of the amount or duration of smoking or the age at which smoking cessation occurred. Within 3 to 5 years their risk will approach that of a woman who has never smoked.<sup>5</sup> This benefit is also seen in women who have had a myocardial infarction or bypass surgery.

However, because more women than men smoke for weight control, smoking cessation programs for women that do not incorporate weight control with diet and exercise are bound to fail. This may explain why traditional smoking cessation programs have been less successful for women than for men.

### ■ HYPERTENSION

For a number of coronary risk factors there is an age-related male-female risk crossover.

For example, more young and middle-

**Clinicians should tell smokers even a few cigarettes a day doubles CHD risk**



aged men than women have hypertension, but after age 65 this pattern reverses. After age 50, twice as many women as men will develop hypertension. In the United States, 50% of Caucasian women and almost 80% of African American women over age 45 have hypertension.<sup>3</sup>

In addition, obesity—particularly central obesity—is a more important contributor to hypertension for women than for men, especially for older women.

**Systolic hypertension.** In men the systolic blood pressure peaks in middle age, but in women it continues to increase until beyond age 80, which is where our data set ends. Thus, isolated systolic hypertension is predominantly a disease of women.

Women made up 57% of the cohort in the Systolic Hypertension in the Elderly Program (SHEP).<sup>6</sup> Of importance: the trial showed that control of isolated systolic hypertension with chlorthalidone and low-dose beta-blockers, if needed, decreased the risk of stroke by a third and reduced fatal and nonfatal coronary events by a fourth. Subsequent heart failure was lessened as well.

#### ■ LIPID ABNORMALITIES

The same pattern of age-related male-female risk crossover is seen with lipid abnormalities. At young and middle age, total cholesterol and its major component, low-density lipoprotein (LDL) cholesterol, are higher in men. But in women the total cholesterol and LDL levels increase with age, particularly after menopause, at least to age 70. In the elderly, LDL levels are higher for women than they are for men.

High-density lipoprotein (HDL) levels are about 10 mg/dL higher in women than men across the life span, and these levels decrease only minimally at menopause and later. Based on Framingham data, an increase of 10 mg/dL in the HDL cholesterol level in women decreases their coronary risk by 40% to 50%.

Whether triglycerides are an independent risk factor for heart disease in women is not known: they are not for men. But the combination of a high triglyceride level and a low HDL level appears to be more important as a risk attribute in women than in men.

#### Effects of lipid-lowering therapy in women

Until a few years ago, no data were available about lipid-lowering therapy in women because women were not included in pharmacologic research studies; data on nonpharmacologic intervention are also limited. But data for women have dramatically increased.

**The Scandinavian Simvastatin Survival Study (4S),<sup>7</sup>** a study of secondary prevention in which women constituted almost a fifth of the study population, showed that women who underwent lipid-lowering therapy had a decrease in major coronary events comparable to that of men. Benefit was evident both in elderly and in diabetic patients.

**The Cholesterol and Recurrent Events (CARE) study<sup>8</sup>** was a secondary prevention study in persons with average cholesterol levels. In women, who made up 14% of the study population, the decrease in death and reinfarction was more prominent than in men.

Given these indications that lipid-lowering therapy can lower CHD risk in women, baseline data from the Heart and Estrogen Replacement Therapy Study (HERS),<sup>9</sup> an ongoing intervention trial of hormone therapy in postmenopausal women with defined coronary disease, are cause for concern: at baseline almost half the women were taking lipid-lowering drugs, yet most had LDL levels well above the National Cholesterol Education Program treatment guidelines<sup>10</sup>—ie, they were being treated with appropriate drugs, but not at appropriate dosages.

**The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS),<sup>11</sup>** a placebo-controlled primary prevention trial of lipid-lowering therapy in persons with no prior coronary event, included 997 women among its 6,605 participants (17%). At 5.2 years, treatment reduced the incidence of first coronary events compared to placebo, and this decrease was more marked in women than in men.

The lipid entry criteria included an HDL level of 50 mg/dL or less for women. Interestingly, only 17% of the group that attained the treatment benefit would have qualified for treatment under the current National Cholesterol Education Program guidelines. Data such as these are likely to lead to new goals for lipid-lowering therapy.

**Women are more likely than men to become diabetic, hypercholesterolemic, and hypertensive in older age**





## ■ DIABETES MELLITUS

Diabetes is a powerful risk factor for CHD in women, essentially negating the gender-protective effect, even for premenopausal women.

When diabetic patients have a myocardial infarction, their hospital and long-term prognosis is less favorable than for nondiabetic patients. But this is far more the case for diabetic women. The diabetic woman has a doubled risk of recurrent infarction and a fourfold increase in the risk of heart failure. And since so many of these women have intact ventricular systolic function, heart failure manifestations are likely to reflect diastolic dysfunction.

**Age-related risk crossover.** Age-related male-female risk crossover is also an issue in diabetes and CHD. Beyond age 45, more women than men develop diabetes. Thus, a woman who has had few risk factors during young and middle age is far more likely than her male counterpart to become diabetic, hypercholesterolemic, and hypertensive at older age and, not surprisingly, to develop clinical manifestations of CHD.

**Blood glucose control.** More and more, we are learning that precise control of the blood glucose concentration lowers the risk of both microvascular and macrovascular complications.

**Exercise and diabetes risk.** The Nurses' Health Study showed that diabetes increases the risk of cardiovascular events by threefold to sevenfold.<sup>12</sup> But at the same time, the Nurses' Health Study showed a decreased incidence of diabetes among women who exercise regularly. This indicates that, for women at high risk of diabetes based on family history or a history of gestational diabetes, a regular exercise program is an important component of their preventive care.

## ■ OBESITY

We are becoming a nation of obese individuals, both men and women.<sup>3</sup> For women, obesity predominates among minority women and those with lower education and income levels.

The obese patient of either sex has high total cholesterol, triglyceride, and LDL levels, low HDL levels, insulin-resistance, hyperuricemia, and hypertension. In short, the obese patient is a walking risk factor for CHD.

Central obesity—a waist-to-hip ratio of 0.8 or greater—is one of the major risk factors for CHD in older women. The Nurses' Health Study showed that an increase in body weight was directly associated with an increase in all-cause mortality. However, no excess mortality was seen in lean women when smokers were excluded. The lowest mortality rate was in women who weighed at least 15% less than the US average, who never smoked, and whose weight had been stable across their lives.<sup>5</sup> The yo-yo pattern of weight gain and weight loss is associated with an increased risk of CHD.

## ■ SEDENTARY LIFESTYLE

Most US women are sedentary, even though exercise and physical fitness have been shown to decrease the risk of mortality. The more favorable coronary risk profile associated with physical fitness is especially true for women.

In studies that provided gender-specific data, coronary disease risk decreased by 50% in physically active vs inactive women, not only for young women, but also for middle-aged and elderly women.<sup>13</sup>

The level of activity need not be intense: walking 30 to 45 minutes three times a week reduces risk by 50%. In older women who have osteoporosis and are prone to musculoskeletal injury, exercise regimens should be low-impact and of low-to-moderate intensity aerobic activity.

## ■ POSTMENOPAUSAL HORMONE THERAPY

Hormone replacement therapy is of interest in CHD prevention because of the increased CHD risk in the postmenopausal years.

### Cardiovascular benefits

Estrogen has lipid-related benefits: it increases HDL levels and lowers LDL levels, and lipid uptake is decreased in the vascular wall. An unfavorable effect is an increase in triglyceride levels. However, the lipid benefits are only part of the spectrum of benefits. Likely mediated by hormone receptors in the vascular endothelium, estrogen can restore the vasodilator capacity of atherosclerotic vessels. This improvement in endothelial function was seen initially

**Walking 30 to 45 minutes three times per week reduces risk by 50%**



in animal models and more recently in postmenopausal women. Estrogen is associated with lower fibrinogen levels, lower levels of plasminogen activator-1 (PAI-1), and lower levels of adhesion molecules. Estrogen also has a favorable antioxidant effect, limiting the oxidation of LDL cholesterol, which may partly mediate the restoration of vasodilator capacity, even in atherosclerotic coronary arteries.

### Other benefits

Estrogen therapy has noncoronary benefits as well, including a decrease in bone loss and amelioration of menopausal symptoms.

### Studies of postmenopausal hormone replacement

A large number of observational studies of estrogen use suggest a substantial decrease in the risk of coronary events. But observational studies have serious limitations, such as selection bias, since healthy women are typically prescribed estrogen. Package inserts had suggested that estrogen should not be given to women who smoke or who have hypertension, diabetes, claudication, stroke, angina, heart failure, or a history of myocardial infarction. Also, women who take estrogen have a more favorable risk profile and are more likely to exercise, to be diet conscious, and to be nonsmokers.

Data from the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial,<sup>14</sup> an intermediate outcomes trial of more than 800 women randomized to estrogen and several estrogen-progestin combinations vs placebo, show that all regimens increased the HDL cholesterol concentration, lowered the LDL cholesterol concentration, and lowered the fibrinogen level. All regimens raised the triglyceride level, and none increased blood pressure or body weight. So estrogen therapy seems to have a favorable coronary risk profile. What we don't know is whether this will translate into a decrease in clinical events.

Based on observational studies, if there is benefit from hormone use, the women most likely to benefit are those with defined coronary disease or at high risk of it. Those least likely to benefit are those at risk for breast cancer or venous thromboembolism. However, the recently published Heart and

Estrogen/Progestin Replacement Study (HERS)<sup>15</sup> showed no decrease in CHD events in women with established CHD taking estrogen plus progestin. These data should not be extrapolated to healthy women or to other hormone regimens. Until randomized trials are completed, there are only limited data that we can use to make clinical decisions.

### Risks of hormone replacement


According to several meta-analyses, estrogen use increases the risk of breast cancer, and the risk is greater with older age and with longer duration use. Another problem not yet well appreciated in clinical practice is the increased risk of venous thromboembolism, although the absolute risk is low.

### COMMON DRUGS AND CHD RISK: UNANSWERED QUESTIONS

#### Aspirin

The benefit of aspirin to prevent coronary events is well established in men, but data on its use in women are conflicting. This is most likely because, particularly for young and middle-aged women, the risk of stroke is greater than the risk of infarction, and stroke occurring in the setting of aspirin use is more likely to be hemorrhagic.<sup>16</sup> For now it is perhaps more prudent to await further clinical trial data before routinely prescribing aspirin to prevent CHD.

#### Antioxidants

The data on preventive use of antioxidants are conflicting for both sexes. 

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**IN THIS ISSUE  
PAGE 491**

