Coronary artery disease in women: a risk-factor analysis

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■ **BACKGROUND** Risk factor modification is important in preventing coronary artery disease; however, risk factors for coronary artery disease have been studied mostly in men, not women.

■ **OBJECTIVE** To examine risk factors for coronary artery disease in women.

■ **METHODS** We retrospectively reviewed the records of all adult women who underwent their first-ever cardiac catheterization at our institution in 1983. Risk factors in women with angiographic evidence of coronary atherosclerosis were compared with risk factors in women without angiographic evidence of coronary artery disease.

■ **RESULTS** Risk factors identified included age, diabetes mellitus, hypertension for more than 5 years, hyperlipidemia, smoking, and familial coronary artery disease.

■ **CONCLUSIONS** Risk factors for coronary artery disease in women are similar to those of men.

■ INDEX TERMS: CORONARY DISEASE; RISK FACTORS; FEMALE
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MEN HAVE BEEN THE focus of most studies of coronary artery disease (CAD). However, investigations in the last 10 years have identified issues about coronary atherosclerosis in women and have raised concerns about the validity of applying to women the same conclusions drawn from studies in men.[1,2]

■ *See editorial, p.411*

While coronary atherosclerosis has long been considered a disease of men, the World Health Organization in 1990 reported that heart disease remains the leading cause of death for women of all ages in the United States.[3] Although treatment options have improved significantly, prevention of disease by modification of risk factors is a primary goal. Our report describes a group of women with angiographically documented CAD and compares them with a group of women with angiographically normal coronary arteries to determine a risk-factor profile based on a population of women referred to a tertiary care facility during a single year.

TABLE
RISK FACTORS FOR CORONARY ARTERY DISEASE (CAD) IN WOMEN

Risk factor	Women with CAD	Women without CAD	P value
Age	59 ± 8	55 ± 9	< .001
Weight (kg)	68 ± 14	74 ± 16	< .001
Systolic blood pressure (mm Hg)	139 ± 25	136 ± 20	Not significant
Diastolic blood pressure (mm Hg)	81 ± 12	83 ± 11	< .05
Hypertension			
Percentage with hypertension	49.3%	41.5%	Not significant
Duration (years)	4.8 to 7.9	2.5 to 4.7	< .001
Diabetes			
Percentage with diabetes	20.6%	11%	< .01
Duration (years)	2.1 to 5.6	0.9 to 3.9	< .001
Family history of CAD	57%	34%	< .001
Smokers	36%	14%	< .001
Mean cholesterol (mg/dL)	260 ± 66	255 ± 61	< .01
Typical angina			
Percentage with typical angina	75.5%	23%	< .001
Duration of symptoms (years)	1.99 to 2.8	2.9 to 3.9	< .001
Postmenopausal status	97%	84.9%	Not significant

METHODS

From January 1 through December 31, 1983, 6130 patients underwent coronary arteriography at our institution; 26.3% of them were women. Women who constituted our study population met the following criteria: (1) no congenital or valvular heart disease; (2) the cardiac catheterization analyzed was the first ever performed on the patient; and (3) complete angiographic data with respect to coronary anatomy and left ventriculography were available.

Medical records were retrospectively reviewed for the following criteria: age, weight, systolic and diastolic blood pressures, total serum cholesterol, family history of CAD, hypertension (including duration), diabetes mellitus (and duration), smoking, and medications at the time of catheterization. Postmenopausal state and oral contraceptive or estrogen use in the year preceding catheterization were noted, as were the findings on the resting electrocardiogram (ECG), the reason for catheterization, and the presenting symptoms.

Definitions

In our study, we defined significant CAD as a greater than 50% decrease in the luminal diameter of at least one major epicardial artery. Hypertension was considered present if (1) there was a diagnosis of hypertension with ongoing treatment; (2) the patient had two or more systolic readings greater than 140 mm Hg; or (3) the diastolic pressure was greater than 90 mm Hg. Diabetes mellitus was considered present if (1) the patient was taking insulin or an oral hypoglycemic agent at the time of catheterization; (2) there was a history of abnormal glucose tolerance tests; or (3) the initial fasting blood glucose was greater than 140 mg/dL. Cholesterol values were obtained after an overnight fast; as was the practice at that time, the values were not routinely fractionated.

A positive family history was defined as coronary atherosclerosis in a first-degree relative before age 60. Patients were classified as smokers, nonsmokers, or former smokers (those who had not smoked for at least 3 months prior to angiography). A history of myocardial infarction was considered present if evidence of Q-wave myocardial infarction was noted on initial ECG, or if the medical record indicated characteristic enzyme changes with an abnormal ECG. The resting ECG was coded as follows: "normal" (Minnesota code), "evidence of myocardial infarction" (pathologic Q waves), "nonspecific changes," or "other" (bundle branch block or idiopathic conduction abnormalities).

Statistical analysis

Values are presented as the mean plus or minus one standard deviation. Continuous variables were compared by means of Student's *t* test; discrete variables were compared by the chi-square method. *P* values less than .05 were considered significant.

RESULTS

The study group consisted of 653 women; 494 had angiographic evidence of CAD, and 159 did not. The risk-factor profiles of the two populations are shown in the *Table*. Most of the women in both groups were white homemakers. The mean age for women with CAD was 59 ± 8 years and 55 ± 9 years for those without CAD ($P < .001$). In addition, 14.5% of women with CAD and 27% of women

without CAD were below age 50.

Women with CAD did not have a higher prevalence of obesity. In fact, on average they weighed less than women without CAD. This finding may be related to the fact that more women with CAD were smokers. While systolic blood pressure did not differ significantly between the two groups, diastolic blood pressures were lower in women with CAD. The incidence of hypertension did not differ between the two groups, but duration of hypertension was longer in women with CAD ($P < .001$). The CAD group contained more diabetic patients than the group without CAD (20.6% vs 11%, $P < .01$), and the mean duration of diabetes was longer ($P < .001$) in the group with CAD.

Cholesterol values after overnight fast were obtained in all but 11 women (7 with CAD, 4 without). Mean serum cholesterol was significantly higher in women with CAD (260 ± 66 mg/dL) compared with those without CAD (225 ± 61 mg/dL) ($P < .01$). Further subdividing the groups, 151 women (31%) with CAD and 43 women (27.7%) without CAD had cholesterol levels of 251 to 300 mg/dL; 78 women (16%) with CAD and 10 (6.4%) without CAD had levels of 301 to 350 mg/dL; and 27 women (5.5%) with CAD and only 1 (0.6%) without CAD had cholesterol levels greater than 351 mg/dL.

A positive family history was noted more often in women with CAD (57%) than in those without CAD (34%, $P < .001$), and more women with CAD had a history of smoking (36%) when compared with the group without CAD (14%, $P < .001$).

Of women with CAD, 40% had a history of myocardial infarction, but only 20% of these had electrocardiographic evidence of a transmural myocardial infarction. In the group without CAD, such a history was noted in only three cases (2%), with only one (0.6%) having an ECG indicating prior myocardial infarction.

Three patients in each group reported the use of oral contraceptives, but these numbers are too small to draw conclusions about the influence of oral contraceptive use on CAD in these groups. Most women in both groups were postmenopausal (97% of women with CAD, 84.9% of those without CAD); however, the significance of this factor is unknown, since most of the women reported surgical menopause without knowing their ovarian status.

Most (85.4%) of the women with CAD were studied because of complaints of chest pain, with 75.5% reporting typical angina pectoris. In women without CAD, 81% were studied because of chest pain, but only 23% reported typical anginal pain. The duration of symptoms before catheterization was statistically different: women with CAD were symptomatic for 2 to 3 years, whereas women without CAD were symptomatic for 3 to 4 years ($P < .001$).

The risk factors identified by univariate analysis were entered into a stepwise logistic regression equation, which was then used to determine the sensitivity and specificity of the factors in determining risk for coronary atherosclerosis. Using a random sample of half the women in each subset (those with and those without CAD), the presence or absence of coronary atherosclerosis was best predicted by smoking, age, family history, cholesterol level, and duration of hypertension. The sensitivity of the model was 94%, and the specificity was 27%.

DISCUSSION

This study examined clinical features of 653 adult women in order to formulate a risk-factor profile for CAD. In our patients, risk factors for CAD included age, long-standing hypertension, diabetes mellitus, elevated total serum cholesterol level, family history of CAD, and smoking. Our data agree with other epidemiologic reviews of risk factors for women.

Cholesterol

Welch[4] reported that women with angiographically documented CAD had higher mean cholesterol levels than women without CAD. In the group with total cholesterol levels less than 200 mg/dL, only 10% of women had significant disease by coronary angiography, whereas in the group with total cholesterol levels greater than 275 mg/dL, 44% had CAD. In our study, 52.5% of women with coronary atherosclerosis had total cholesterol levels greater than 250 mg/dL, whereas 34% of women without CAD had total cholesterol levels over 250 mg/dL.

Obesity

The Framingham data have clearly established obesity as an independent risk factor for cardiovascular disease in both men and women.[5] This conclusion is supported by several other investigators in long-term follow-up studies.[6–8] The weight gain that occurs after the young adult years also appears to increase the risk of CAD in both sexes; this risk cannot be attributed either to the initial weight or to the changes in risk factors associated with weight

gain.[8] It has been suggested that the risk of CAD is related to the distribution of adipose tissue rather than to the absolute amount. The direct access of abdominal adipose tissue to the portal circulation may be an important factor in the development of CAD. Freedman[9] suggests that the role of body fat distribution (as assessed by the ratio of waist circumference to hip circumference) can explain differences in lipoprotein levels between the sexes. After controlling for waist-hip ratios in several types of analyses, sex differences in levels of lipoproteins and lipids were greatly reduced. Although we did not have access to waist-hip ratios in our patients, we did not find that women with CAD had a higher incidence of obesity; in fact, they weighed less on average than their counterparts without CAD. This is probably related to confounding variables (such as smoking) in the group without CAD.

Hypertension

We did not find hypertension to be an independent risk factor for CAD in women; this is contrary to findings in other studies.[1] This difference is most likely due to the large number of hypertensive women without CAD in our study, a bias that may have been introduced at the time of selection for angiography. However, the duration of hypertension was significantly longer in women with CAD, supporting the belief that the duration of hypertension plays a role in the development of coronary atherosclerosis.

Smoking

In men, smoking is a powerful risk factor for the development of coronary atherosclerosis.[10,11] The same has been shown for women in several population-controlled studies.[12,13] Our results agree with these studies. Smoking is associated with increased platelet aggregability, increased fibrinogen levels, and a decrease in the fraction of high-density lipoprotein levels. Willett[14] reported that women smoking even one to four cigarettes per day had an increased risk for the development of fatal coronary heart disease, nonfatal myocardial infarction, and angina pectoris. The Mayo group reported an increased risk of CAD in female smokers that was not offset by the addition of steroidal estrogens.[13]

Diabetes mellitus

Glucose intolerance has been reported to be a significant predictor of coronary heart disease in women as well as men.[15] In the Framingham data[15] for patients ages 50 to 59, glucose intolerance was a more significant risk factor for women than for men. Even when corrected for diabetes-associated obesity, hyperlipidemia, and hypertension, the risk of coronary events in diabetic women was double that of nondiabetic women, a finding supported by other investigators as well.[16]

Familial coronary atherosclerosis

Studies of young patients with coronary atherosclerosis have reported that a positive family history of CAD (defined in most studies as premature coronary atherosclerosis in a first-degree relative) is a risk factor,[17,18] but the incidence appears to vary considerably. Most studies report a range of 29%[19] to 48%.[20] Our study showed that 54% of the women who had CAD also had a family history of CAD. In an elegant study of twins, Austin[18] identified a number of inherited cardiac risk factors, the most significant of which was the association of low-density lipoprotein cholesterol. This association held, even after adjusting for environmental factors.

Hormonal factors

The major physiologic difference between men and women is hormonal status; therefore, analyses of risk factors between the sexes should include the effects of menopause. It has already been established that women develop symptoms of CAD an average of 10 years later than men, and it is presumed that estrogen is "coronary-protective" until menopause. Postmenopausal women have a rate of CAD similar to that seen in men.[21] The Framingham analysis found no episode of myocardial infarction or coronary death recorded in premenopausal women in 8500 person-years of follow-up.[22]

The question to be answered in this regard is whether estrogen supplementation will delay the appearance of CAD in postmenopausal women. The data from the literature are difficult to interpret because many of the studies were observational, with no attempt to control for hormonal preparations used by the women. Furthermore, factors such as obesity and cigarette smoking need to be controlled before the effects of estrogen replacement can be interpreted. Nevertheless, several conclusions may be drawn from available data.

First, nearly all studies confirm that unopposed oral estrogen decreases low-density lipoprotein levels and increases high-density lipoprotein levels, creat-

ing a favorable cardiovascular risk profile.[23,24] Unopposed estrogen clearly works to lower blood pressure, which also decreases cardiovascular risk. Luotola et al[25] used a crossover study design to evaluate the effects of estrogen replacement on systolic blood pressure in postmenopausal women. They found that all blood pressure levels fell while the patients received estrogen (in both normotensive and hypertensive populations) and that this reversed when the patient entered the placebo phase. They were able to correlate the blood pressure changes with significant changes in serum estrone levels.

Second, early reports of estrogen use noted that large doses of estrogen alter clotting factors and increase the risk of a thrombotic event. These effects were attributed to increased factors VIII, IX, and X, and to a decrease in antithrombin III; they might have been related to higher doses of estrogens, since recent reports have not confirmed this finding. Chetkowski et al[26] reported no changes in fibrinogen A, high-molecular-weight fibrinogen, or antithrombin III. Lind and coworkers[27] similarly reported no change in fibrin degradation products, prothrombin time/partial thromboplastin time, factors V, VIII, or X, platelet count, or platelet aggregability in postmenopausal women using estrogen supplements.

Third, ovarian status is important in the postmenopausal state: surgical oophorectomy results in an abrupt loss of hormones while natural menopause produces a more gradual loss.[28] Whether the rate of hormone loss plays a role in the development of CAD is yet to be proven, but it may enter into the risk-factor profile of postmenopausal women.

Williams[29] has suggested a possible mechanism relating estrogens and coronary heart disease: he proposes that estrogens inhibit the growth of atherosclerotic plaques, and decrease the prevalence of myocardial ischemia via a vasomotor modulation of arterial tone. He noted that acetylcholine, normally a potent arterial dilator, caused paradoxical constriction in estrogen-deficient animals. Although the data regarding the value of estrogen replacement in postmenopausal women conflict, apparently only the Framingham data[30] suggest that estrogen replacement has a detrimental effect on the cardiovascular system. The rest of the data suggest it is beneficial.[31]

Our study is limited by its retrospective nature, and patient-entry bias which occurred because our institution is a tertiary referral center. Nevertheless, our results further clarify the risk-factor profile for a large cohort of women with CAD.

CONCLUSION

Our results suggest that risk factors for women are similar to those reported for men, and that these risk factors need to be considered when counseling women for prevention of CAD.

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