



Coronary artery disease in young women: risk factor analysis and long-term follow-up

ANITA ZEILER ARNOLD, DO, AND DOUGLAS S. MOODIE, MD

- **BACKGROUND** Heart disease is the leading cause of death in women of all ages in the United States, but data on coronary disease in young women remains sparse.
- **OBJECTIVE** To identify and follow up a cohort of young women referred for the evaluation of coronary disease.
- **METHODS** Retrospective review of the medical records.
- **RESULTS** Thirty-two women younger than 31 years met the entry criteria. The average age was 28 ± 2.4 years, 28% had insulin-dependent diabetes mellitus, 38% had hypertension, 6% had congenital heart disease, 38% had a family history of coronary artery disease, 72% were smokers, and 28% used oral contraceptives. Serum cholesterol levels were > 5.17 mmol/L (200 mg/dL) in 71%, and the mean cholesterol level was 6.70 ± 2 mmol/L (259 ± 78 mg/dL). Resting electrocardiographic results were abnormal in 28 women (88%), 22 of whom had evidence of transmural myocardial infarction. Follow-up averaged 9.8 ± 6.4 years. Five patients died, all of whom had hypertension, and 4 of whom had diabetic nephropathy and required dialysis.
- **CONCLUSIONS** Risk factors for coronary disease in young women include hypertension, hypercholesterolemia, diabetes mellitus, familial coronary disease, and smoking. Long-term prognosis is excellent for those without advanced diabetes mellitus and renal failure.

■ **INDEX TERMS:** CORONARY DISEASE; RISK FACTORS; FEMALE; FOLLOW-UP STUDIES
 ■ CLEVE CLIN J MED 1993; 60:393-398

From the Departments of Cardiology and Pediatrics,
 The Cleveland Clinic Foundation.

Address reprint requests to D.S.M., Department of Pediatrics,
 A120, The Cleveland Clinic Foundation, 9500 Euclid Avenue,
 Cleveland, OH 44195.

R EPORTS OF CORONARY disease in young persons appeared as early as 1951.¹ During the Korean war, Enos and colleagues² reported a 77.3% prevalence of gross coronary atherosclerosis in an autopsy series of 300 American soldiers aged 18 to 48 years (mean age 22.1 years).

■ See editorial, p. 411

Before this report in 1953, coronary atherosclerosis had been considered a disease of middle-aged and older men. Since then, numerous authors have examined coronary atherosclerosis in young adults.³⁻⁶ Definitions of "young" have varied from less than 65 years old in the Framingham study⁷ to 21 to 30 years old in other studies.⁸ However, all these reports describe risk factor profiles and angiographic data for a population of predominantly male subjects. There is a paucity of data concerning coronary artery disease in women in general, and in young women in particular. This is despite World Health Organization data showing that more women in the United States die of heart disease than of any other cause.⁹

This study describes a group of women younger than 31 years old who were referred to our institution for the evaluation of coronary artery disease or documented myocardial infarction between 1970 and 1991. Some were followed up for almost 20 years, and all were evaluated with coronary angiography. We summarize their risk factor profiles and follow-up data.

METHODS

Using a computerized database of discharge diagnoses, we identified all female patients aged 30 years or younger who had coronary atherosclerosis as their discharge diagnosis from 1970 through 1991. There was no specific lower age limit. Only women who had evidence of myocardial infarction or coronary artery disease without congenital anomalies of the coronary arteries were included. We defined coronary artery disease as stenosis greater than 50% in at least one major epicardial artery, and we defined myocardial infarction by World Health Organization criteria, which include characteristic enzyme elevations, chest pain, and electrocardiographic changes. All patients had undergone coronary arteriography as part of their evaluation.

We reviewed the medical records and abstracted information on age, weight, blood pressure, cholesterol level, smoking history, and family history of coronary artery disease. We noted the presence or absence of hypertension, diabetes mellitus, and chronic renal failure, and whether the patient used oral contraceptives. We coded the resting electrocardiographic results, and reviewed the angiographic data. We also noted the presence of single-vessel or multivessel disease, as well as which vessels were affected. Left ventricular function had been evaluated by angiography and assessed qualitatively in all cases, and if the films were of suitable quality, left ventricular ejection fractions were calculated.

Follow-up data were obtained through telephone contact with the patient or with a relative if the patient was dead. If the patient had died in the follow-up period, a cause of death was determined from autopsy reports or clinical information, when available. We classified the cause of death as cardiac or noncardiac for the purposes of follow-up. The patient's history of intervening procedures (repeated coronary angiography, coronary bypass grafting, angioplasty) or cardiac events (myocardial infarction, angina pectoris) was also reviewed.

Definitions

We considered hypertension to be present if the patient had two or more systolic readings higher than 140 mm Hg or two or more diastolic readings higher than 90 mm Hg, or if she was currently undergoing treatment for hypertension. Diabetes mellitus was considered present if the patient was taking insulin or an oral hypoglycemic agent at the time of evaluation, if she had a history of abnormal glucose tolerance tests, or if her initial fasting blood glucose level was greater than 140 mg/dL. A positive family history of coronary disease was defined as a diagnosis of coronary atherosclerosis in a first-degree relative before the age of 60. Patients were considered smokers if they had ever smoked, and we calculated the number of pack-years. A history of myocardial infarction was recorded if there was electrocardiographic evidence of transmural myocardial infarction or if the medical records documented chest pain, characteristic enzyme changes, and abnormal electrocardiographic results as defined by the World Health Organization. The coding categories for the resting electrocardiographic results were "normal," "evidence of myocardial infarction" (pathologic Q waves), "nonspecific ST-T wave changes," and "other," which included atrioventricular or bundle branch blocks or other arrhythmias. Chronic renal failure indicated dialysis dependence.

Statistics

All values are presented as the mean $\pm$ one standard deviation.

RESULTS

Thirty-two patients met the study entry criteria. Their average age was 28 ± 2.4 years (range 18 to 30 years). At baseline, 9 (28%) had insulin-dependent diabetes mellitus for a mean duration 18 ± 8.2 years (range 15 to 22 years), 12 (38%) had hypertension for a mean duration of 8 ± 4 years (range 4 to 14 years), and 2 (6%) had congenital heart disease (one had a repaired atrial septal defect 20 years prior to our evaluation, and one had a bicuspid aortic valve). Twenty-three patients (72%) smoked, and they had an average of 12 ± 10 pack-years of exposure (range 1 to 45 pack-years). Oral contraceptives were used by 9 women (28%) for an average of 4 ± 2.5 years (range 1 to 10 years). Most of the patients (69%) were initially in Canadian functional class I or II. A history of familial coronary artery disease

TABLE
CHARACTERISTICS OF WOMEN WHO DIED DURING FOLLOW-UP

Age (y)	Hypertension	Chronic renal failure	Diabetes mellitus	Family history of coronary disease	Smoker	Follow-up (y)	Cholesterol level (mg/dL)	Left ventricular dysfunction	Ejection fraction(%)
29	Yes	Yes	Yes	No	Yes	1.8	180	Severe	33
30	Yes	Yes	Yes	Yes	No	0.3	263	Moderate	23
24	Yes	No	No	No	Yes	0.7	309	Moderate	...
26	Yes	Yes	Yes	Yes	No	2.0	305	Normal	69
26	Yes	Yes	No	No	No	2.0	215	Mild	...

was found in 12 of the patients (38%).

Cholesterol data were available for 28 of the patients (88%). The mean fasting serum cholesterol level was 6.70 ± 2 mmol/L (259 ± 78 mg/dL), the range was 4 to 12.9 mmol/L (155 to 500 mg/dL), and 20 of the 28 patients (71%) had serum cholesterol levels greater than 5.17 mmol/L (200 mg/dL).

Data on lipoprotein fractions were available for 12% of the patients (38%). The mean high-density lipoprotein (HDL) level was 1.26 ± 0.38 mmol/L (49 ± 15 mg/dL), and the range of HDL levels was 0.74 to 2 mmol/L (29 to 78 mg/dL). The mean LDL level was 4.6 ± 1.65 mmol/L (178 ± 64 mg/dL), and the range of LDL levels was 3.1 to 7.88 mmol/L (120 to 305 mg/dL). Triglyceride data were available for 28 of the patients (88%). The mean serum triglyceride level was 164 ± 86 mg/dL, and the range of triglyceride levels was 44 to 465 mg/dL.

Resting electrocardiographic results were abnormal in 27 patients (84%), 21 of whom (78%) had evidence of myocardial infarction, which was the most common abnormality.

Fourteen patients (44%) had angiographic evidence of single-vessel disease: 10 (71%) had left anterior descending coronary artery stenosis, 2 (14%) had right coronary artery stenosis, and 2 (14%) had circumflex coronary artery stenosis. There were 14 patients (44%) with multivessel disease, 8 of whom (57%) had two vessels affected (all involving the left anterior descending coronary artery), and 6 of whom (42%) had triple-vessel disease. Normal coronary arteries were seen in 4 patients (13%), even though these women had documented evidence of myocardial infarction by World Health Organization criteria.

Left ventricular function was normal in 4 patients (13%), and it was not documented in 1 patient. The remainder had left ventricular dysfunction, which was mild in 14 (44%), moderate in 8 (25%), and

severe in 4 (12%). An ejection fraction had been calculated in 18 cases (56%). The average ejection fraction was $53 \pm 18\%$, and the range was 20% to 80%. Thirteen of these patients (72%) had ejection fractions greater than 40%, and 5 (28%) had ejection fractions less than 40%. Initial treatment included coronary artery bypass grafting for 14 patients (40%), 13 of whom (93%) had internal mammary artery grafts.

Long-term results

Follow-up was available for 29 patients (91%) and averaged 9.8 ± 6.4 years (range 3 months to 19.5 years). Five patients died during the follow-up period, 3 (60%) of cardiac causes (second myocardial infarction with subsequent cardiac arrest), 1 of sepsis (the patient had brittle diabetes mellitus and severe triple-vessel disease), and 1 of a presumed cardiac cause (the patient died in her sleep a few months after a second myocardial infarction). The patients who died had significant medical problems: 4 (80%) had chronic renal failure from diabetes mellitus, and all of them had hypertension. Three of the patients (60%) had multivessel disease and 4 (80%) had ventricular impairment at initial presentation. The characteristics of the patients who died are summarized in the Table.

Including the patients who died of cardiac causes, there was a 44% incidence of progression of coronary atherosclerosis evidenced by myocardial infarction, second cardiac catheterization, need for coronary artery bypass surgery, or hospitalization for angina pectoris. As would be expected, the patients who did the worst over the follow-up period had other significant medical problems including diabetes mellitus, systemic lupus erythematosus (1 patient), and Takayasu's arteritis (1 patient). We attempted to stratify the patients according to their number of risk factors on initial presentation. Of the

patients for whom follow-up was available, only one had no risk factors. She underwent single-vessel bypass surgery 12 years ago, and is presently alive and well without further cardiac events. Seven patients had four risk factors; four of them had successful bypass surgery and are alive and well at follow-up, and three were treated medically and have died. We were unable to find any correlation between the number of risk factors on initial presentation and subsequent outcomes.

All the patients who underwent bypass surgery were alive and well at the time of follow-up, and all were in functional class I or II. All of the patients who died during follow-up had been medically treated. It is possible that these women, because of their severe underlying medical diseases, were not felt to be good surgical candidates.

DISCUSSION

As reported by the World Health Organization in 1991, more women in the United States die of heart disease than of any other cause.⁹ It has long been known that women are relatively protected against coronary artery disease at least until the menopause,¹⁰ but reports of young women with coronary artery disease are appearing more frequently.¹¹⁻¹⁴

Although we can compare our results with those of similar studies, most of those studies involved patients older than those in our group, and for the most part, they involved men. Our study also included angiographic documentation of coronary artery disease as part of the patient's evaluation, which the other studies did not.

Smoking was one of the most common risk factors found in our study, as 72% of our patients smoked. This finding is consistent with other reports.^{15,16} Glover et al¹⁵ found an 89% prevalence of smoking in 120 patients who had a myocardial infarction before age 36, but only 11 of their patients (8%) were women. Similarly, Al-Yusuf and colleagues¹⁶ found an 89% prevalence of smoking in 37 patients younger than 40 years, but only 2 of the patients (5.4%) were women. Smoking appears to be as powerful a risk factor for the development of coronary atherosclerosis in young women as it is in young men.

A positive family history of coronary artery disease (defined in most studies as premature coronary atherosclerosis in a first-degree relative) has been reported to be a risk factor in studies of young pa-

tients with coronary atherosclerosis,^{17,18} but the incidence appears to vary considerably. Uhl and Farrell⁶ found familial coronary artery disease to be the most important risk factor in their study of 165 patients younger than 40 years with documented myocardial infarction. This contrasts with the findings of Al-Yusuf and colleagues,¹⁶ who reported that none of their young patients with documented myocardial infarction had a family history of coronary artery disease. Other estimates fall between 29%¹⁹ and 48%.¹⁵ Our results are within this range, with 37% of our young women reporting familial coronary artery disease.

Although obesity has been reported in some studies to be a risk factor for the development of coronary artery disease,²⁰⁻²² our patients' average weight was 58 ± 9 kg (range 50 to 86.8 kg) and they were not significantly overweight. Because obesity is often related to hypertension, hyperlipidemia, and diabetes mellitus, it is difficult to assess the role of weight as an independent risk factor.²³

Diabetes mellitus is a well-established risk factor for coronary atherosclerosis,^{24,25} and our results support this. Twenty-eight percent of our patients were diabetic (all insulin-dependent), with an average duration of diabetes of 18 years. It has been theorized that women with juvenile-onset insulin-dependent diabetes do not have the protection that being premenopausal confers against the development of coronary atherosclerosis.²⁴ The disease was severe in all patients, and most had evidence of retinopathy, nephropathy, and neuropathy. Three of the five patients who died had severe diabetes mellitus, and four had renal failure.

Hypertension is a well-established risk factor reported in numerous studies.^{15,23} Our group had a 38% prevalence of hypertension for an average duration of 8 ± 4 years. Two patients had hypertension related to vasculitis; the remainder presumably had essential hypertension. The duration of hypertension may be as important as the absolute elevation of pressure: in another study at our institution, which compared risk factors in women with and without angiographic evidence of coronary disease (average age 59 ± 8 years for the women with coronary artery disease and 55 ± 9 years for the women without coronary artery disease), hypertension per se was not statistically significant as a risk factor but the duration of hypertension between the two groups was significant ($P < 0.001$).²⁶

Hyperlipidemia has been recognized as an impor-

tant risk factor for coronary artery disease in younger patients.^{4,19} In studies of young patients with angiographic documentation of coronary artery disease, the prevalence of hyperlipidemia ranged from 14% in Weinberger's series²⁷ (in which 83% of the patients underwent angiography) to 68% in Davia's series³ (in which all of the patients underwent angiography). Our patients had an average serum cholesterol level of 6.70 ± 2 mmol/L (259 ± 78 mg/dL), and 20 of 28 patients had serum cholesterol levels greater than 5.17 mmol/L (200 mg/dL). Hyperlipidemia (serum cholesterol level greater than 6.5 mmol/L; 250 mg/dL) and smoking occurred together in 62% of our patients and may be additive risk factors in young women.

Oral contraceptives have been implicated in myocardial infarction; vasospasm and subsequent thrombus formation are the proximate etiologic factors.¹² Underwood and colleagues⁸ described 13 young women aged 21 to 30 years with symptomatic coronary artery disease and found that 61.5% had been using oral contraceptives. Other studies with smaller numbers of women did not report the prevalence of oral contraceptive use. We found that 28% of our patients used oral contraceptives. Of this group, only one patient had angiographically normal coronary arteries, suggesting vasospasm was a cause of her documented myocardial infarction.

Congenital heart disease (other than coronary artery anomalies) is usually not reported in studies of young patients with coronary atherosclerosis, suggesting a rare association. In the population we studied, only 2 patients (6%) had a history of congenital heart disease: one had an atrial septal defect repaired 20 years earlier, and the other had a bicuspid aortic valve.

Angiography

Equal numbers of our patients had single-vessel coronary artery disease or multivessel coronary artery disease (44% each), and 12% of our patients had normal coronary arteries. In contrast, other studies report that single-vessel disease is far more common than multivessel disease in younger patients.²³ The left anterior descending artery was by far the most commonly involved vessel; it was stenotic in 71% of the patients with single-vessel disease and in all of the patients with multivessel disease. Pahlajani reported left anterior descending artery involvement in 78% of 92 patients less than 40 years of age, but only two subjects (2.1%) were

female.⁵ Weinberger found left anterior descending artery involvement in 64% of patients less than 30 years of age studied with angiography after myocardial infarction; however, only four subjects (13.3%) were women.²⁷ In our series, the left anterior descending artery was the vessel most commonly involved, followed by the right coronary artery and the circumflex coronary artery. Only one of our patients had left main trunk involvement, which is rarely reported in young patients.²⁸

Left ventricular function was normal or mildly impaired in 18 of the 31 patients for whom this information was available (58%); the remainder had moderate or severe left ventricular dysfunction. This distribution is somewhat different from other reports, as left ventricular function is not uniformly reported. Underwood⁸ commented that 30% of 88 men aged 21 to 30 years with coronary artery disease had normal function while 70% had abnormal function, but did not differentiate the degree of abnormality.

Limitations

The limitations of our study are those inherent in any retrospective analysis, particularly one that includes 20-year follow-up. The database of discharge diagnoses from which the study population was identified may have concealed additional patients who would have fit the entry criteria. We tried to avoid this by searching for the diagnoses of "coronary atherosclerosis," "myocardial infarction," or "cardiac catheterization." The data may also have been influenced by a referral bias to a tertiary care facility and may not represent coronary artery disease in young women in the general population. Nevertheless, this group of young women helps to clarify risk factors in women for coronary artery disease, and defines their long-term prognosis.

CONCLUSIONS

Heart disease is the leading cause of death in women today, and we must identify and institute measures to alter risk factors for this population. In our study we have examined a large group of young women with angiographically documented coronary artery disease and found that smoking, family history, complicated diabetes mellitus, hyperlipidemia, and hypertension are associated with the development of coronary atherosclerosis. Although the use of oral contraceptives has been implicated in coronary spasm and myocardial infarction, only one of

the four women in our series with normal coronary arteries and documented myocardial infarctions used oral contraceptives.

Follow-up data show that women with advanced disease at presentation that is accompanied by severe underlying medical illnesses have a limited sur-

vival. In the remainder of our study population, despite the markedly young age at which these women exhibited coronary atherosclerosis, the natural history of the disease suggests a good prognosis, even for women who have bypass surgery at an early age.

REFERENCES

1. Yater MW, Welsh PP, Stapelton JE. Comparison of clinical and pathologic aspects of coronary artery disease in men of various age groups: study of 950 autopsied cases from the Armed Forces Institute of Pathology. *Ann Intern Med* 1951; 34:352-392.
2. Enos WF, Holmes RH, Beyer J. Coronary disease among United States soldiers killed in action in Korea. *JAMA* 1953; 256:2859-2866.
3. Davia JE, Halial FJ, Cheitlin MD, Gregoratos G, McCarty R, Foote W. Coronary artery disease in young patients: angiographic and clinical review of 40 cases aged 35 and under. *Am Heart J* 1974; 87:689-696.
4. Riecan sky I, Melichercik J, Kasper J, Zelenay J, Havlinova K. Myocardial infarction at a young age. *Czech Med* 1988; 11:123-130.
5. Pahlajani DB, Chawla MH, Kapashi KA. Coronary artery disease pattern in the young. *J Assoc Physicians India* 1989; 37:312-314.
6. Uhl GS, Farrell PW. Myocardial infarction in young adults: risk factors and natural history. *Am Heart J* 1983; 105:548-553.
7. Gordon T, Kannel WB. Premature mortality from coronary heart disease: The Framingham Study. *JAMA* 1971; 215:1617-1625.
8. Underwood DA, Proudfit WL, Lim J, MacMillan JP. Symptomatic coronary artery disease in patients aged 21 to 30 years. *Am J Cardiol* 1985; 55:631-634.
9. World Health Statistics Annual. Vital statistics and cause of death. Geneva: World Health Organization, 1991.
10. Gordon T, Kannel WB, Hjortland MC, McNamara PM. Menopause and coronary heart disease: The Framingham Study. *Ann Intern Med* 1978; 89:157-161.
11. Proudfit WL, Welch CC, Siqueira C, Morcerf FP, Sheldon WC. Prognosis of 1000 young women studied by coronary angiography. *Circulation* 1981; 64:1185-1190.
12. Coma-Canella I, García AG, Jadraque M, Daza NS. Repetitive myocardial infarction in a young woman with vasospastic coronary artery disease. *Eur Heart J* 1985; 6:710-713.
13. Janosik DL, Labovitz AJ, Kennedy HL. Anterior and inferior myocardial infarction in a young woman with angiographically normal coronary arteries. *Am Heart J* 1986; 112:606-609.
14. Haik BJ, Haft JL. Coronary artery disease in a young woman with SLE. *N J Med* 1988; 85:295-297.
15. Glover MU, Kuber MT, Warren SE, Vieweg WVR. Myocardial infarction before age 36: risk factor and angiographic analysis. *Am J Cardiol* 1982; 49:1600-1603.
16. Al-Yusuf AR, Hasmi J, Kolar J. Myocardial infarction in the young—a long term follow-up study. *Indian Heart J* 1985; 37:275-279.
17. Mody R. Coronary artery disease in young. *J Assoc Physicians India* 1989; 37:303-304.
18. Austin MA, King MC, Bawol RD, Hulley SB, Friedman GD. Risk factors for coronary heart disease in adult female twins. *Am J Epidemiol* 1987; 125:308-318.
19. Maity AK, Chatterjee SS, Dutta S, Guha S. Prognostic significance of risk factors in acute myocardial infarction in young. *Indian Heart J* 1989; 41:288-291.
20. Lapidus L, Bengtsson C, Larsson B, Pennert K, Rybo E, Sjöström L. Distribution of adipose tissue and risk of cardiovascular disease and death: a 12 year follow up of participants in the population study of women of Gothenburg, Sweden. *Br Med J* 1984; 289:1257-1261.
21. Gillum R. The association of body fat distribution with hypertension, hypertensive heart disease, coronary heart disease, diabetes and cardiovascular risk factors in men and women aged 18-79 years. *J Chronic Dis* 1987; 40:421-428.
22. Hubert HB, Feinleib M, McNamara PM, Castelli WP. Obesity as an independent risk factor for cardiovascular disease: a 26 year follow up of participants in the Framingham heart study. *Circulation* 1983; 67:968-977.
23. Jalowiec DA, Hill JA. Myocardial infarction in the young and in women. *Cardiovasc Clin* 1989; 20:197-206.
24. Wenger NK. Coronary disease in women. *Annu Rev Med* 1985; 36:285-294.
25. Barrett-Connor E, Cohn BA, Wingard DL, Edelstein SL. Why is diabetes mellitus a stronger risk factor for fatal ischemic heart disease in women than in men? The Rancho Bernardo Study. *JAMA* 1991; 265:627-631.
26. Arnold AZ, Underwood DA. Coronary artery disease in women: a risk-factor analysis. *Cleve Clin J Med* 1993; 60:387-392.
27. Weinberger I, Rotenberg Z, Sagy A, Friedmann J, Agmon J. Myocardial infarction in young adults under 30 years: risk factors and clinical course. *Clin Cardiol* 1987; 10:9-15.
28. Lobo FV, Cairns JA, Stolberg HO, Heggveit A. Death following coronary angiography in a young woman with isolated left coronary ostial stenosis. *Can J Cardiol* 1989; 5:149-154.