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Clustering of traditional risk factors and precocity of coronary disease in women

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Abstract

Background: Women usually develop coronary artery disease (CAD) 10 years later than men do. CAD in women is associated with menopausal status and the number and intensity of risk factors. But, when the age gap between men and women narrows, less is known about the influence of risk factors on CAD. *Methods*: We assessed the prevalence of traditional risk factors in 850 men and 468 women with stable CAD who had mean age, 58.3±8.6 and 58.8±10.3 years (P=NS), respectively. *Results*: Univariate analysis of risk factors showed that body mass index (BMI), hypertension (all three stages), diabetes, triglycerides (≥2.8 mmol/l), cholesterol (≥6.2 mmol/l) and family history were more prevalent in women. Smoking and previous myocardial infarction (MI) were more prevalent in men. Multivariable analysis disclosed hypertension, diabetes, dyslipidemia and family history as independent risk factors for women with stable CAD and smoking and previous MI as independent risk factors for men. *Conclusion*: Clustering of traditional risk factors may explain the precocity of CAD in women who are near in age to men. © 2001 Elsevier Science Ireland Ltd. All rights reserved.

Keywords: Menopause; Coronary artery disease; Risk factors; Myocardial infarction; Dyslipidemia; Revascularization

1. Introduction

Cardiovascular diseases are the main cause of death in women in industrialized countries [1]. Women have a 7–10 year advantage over men in the incidence of cardiovascular diseases however [2]. This gap is in part explained by women's years of exposure to the protective effects of estrogen before menopause. It is well-known that estrogen has salutary effects on lipid plasma levels and also directly on the endothelium. Therefore, the high incidence of cardiovascular disease in women is only seen two decades after women have passed through menopause.

Risk of coronary artery disease in women and men increases with the number of risk factors present [3]. But when women are approximately the same age as men with coronary disease, less is known about the differences between them that influence the development of atherosclerosis. To explore this further, we analyzed after adjusting for age a large select group of women and men with stable coronary artery disease receiving treatment at our tertiary hospital.

2. Methods

We analyzed data on 1318 consecutive age-ad-

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justed outpatients with stable coronary artery disease (CAD), 850 men and 468 women, ages 33 to 84 years. The diagnosis of stable CAD was made according to clinical history and documented by coronary angiography (>50% reduction in lumen size in any subepicardial coronary artery) in 1181 (89.6%) patients. Previous history of surgical myocardial revascularization or typical nuclear exercise stress test changes for CAD associated with stable typical angina were used to include the remaining 137 patients in the stable group.

Clinical data involved analysis of standard risk factors, such as body mass index (BMI) [weight(kg)/height(m [2])], family history, hypertension, smoking, dyslipidemia, diabetes and previous myocardial infarction. Surgical myocardial revascularization and coronary disease severity were also assessed. Family history of CAD was defined as CAD occurring in parents (before age 55 for men and 65 for women) and siblings. Hypertension was classified according diastolic blood pressure (DBP) in stages I (90–99 mmHg), II (100–109 mmHg) and III (≥110 mmHg) [4]. Dyslipidemia was divided into hypertriglyceridemia (triglycerides≥2.8 mmol/l) and hypercholesterolemia (total cholesterol≥6.2 mmol/l) [5]. Plasma lipid levels were obtained from venous blood after a 12-h overnight fast. Total cholesterol and triglycerides were determined by standard enzymatic methods. Diabetes was diagnosed when patient was under hypoglycaemic drug or blood glucose levels were greater than 7.0 mmol/l [6]. Coronary artery disease severity was based on the number of major epicardial coronary arteries affected.

3. Statistical analysis

Age, BMI and lipid profiles were analyzed using Student's *t*-test. The chi-square statistical test was used for categorical variables, such as prevalence of hypertension, smoking, dyslipidemia, diabetes, family history, previous myocardial infarction and myocardial revascularization, and coronary artery disease severity. A P value of <0.05 was considered statistically significant. Using sex as a dependent variable, we carried out a backward stepwise multiple logistic regression. Independent variables included all the variables mentioned above.

Table 1
Clinical characteristics of the patients[a]

	Men	Women	*P*
N (1318)	850(65)	468(35)	
Age (years)	58.3±8.6	58.8±10.3	0.347
BMI (Kg/m2)	26.7±1.8	27.6±2.4	<0.0001
Family history	272(32)	192(41)	0.001
Hypertension	408(48)	323(69)	<0.0001
Stage I	208(24)	136(29)	0.080
Stage II	184(22)	142(30)	<0.001
Stage III	12(1)	36(8)	<0.0001
Smoking	488(54)	168(36)	<0.0001
Diabetes	225(26)	162(35)	0.002
Type 1	36(4)	39(8)	0.032
Type 2	189(22)	123(26)	0.113
Triglycerides (2.8 mmol/l)	171(22)	140(30)	<0.0001
Cholesterol (6.2 mmol/l)	257(37)	192(41)	<0.0001

[a] Mean±S.D. Values in parenthesis mean percentage. BMI, body mass index; DID, diabetes insulin-dependent; DNID, diabetes non-insulin-dependent.

4. Results

4.1. Clinical characteristics of the patients were shown in Tables 1 and 2

Mean age was similar in women and men (58.8±10.3 vs. 58.3±8.6; $P=0.347$). Compared with men, women had greater BMI (27.6±2.4 vs. 26.7±1.8; $P<0.0001$), prevalence of family history [41 vs. 32%; $P=0.001$. *RR* 1.48 (95%CI: 1.16±1.88)], hypertension [69 vs. 48%; $P<0.0001$. *RR* 2.41 (95%CI: 1.89–3.08)], diabetes [35 vs. 26%; $P=0.002$. *RR* 1.12 (95%CI: 1.04±1.21)], hypertri-

Table 2
Myocardial infarction, congestive heart failure (CHF), coronary artery bypass graft (CABG) and catheterization prevalence in patients with stable coronary artery disease[a]

	Men	Women	*P*
N (1318)	850(65)	468(35)	
Myocardial Infarction	621(74)	265(57)	<0.0001
Non-Q-wave	76(9)	32(7)	0.220
Q-wave	545(64)	233(50)	<0.0001
CHF (class II to IV)	174(20)	90(20)	0.641
Class II	136(16)	75(16)	0.947
Class III and IV	38(4)	15(3)	0.405
CAGB	319(38)	148(31)	0.037
Mammary + Saphenous	158(19)	65(14)	0.036
Saphenous	161(19)	83(18)	0.642
Catheterization	778(92)	351(76)	<0.0001
One-vessel	189(22)	122(26)	0.113
Two-vessels	265(31)	109(23)	0.003
Three-vessels	324(38)	120(26)	<0.0001

[a] Values in parenthesis mean percentage.

glyceridemia [30 vs. 22%; $P<0.0001$. *RR* 1.14 (95%CI: 1.06±1.22)], and hypercholesterolemia [41 vs. 37%; $P<0.0001$. *RR* 1.18 (95%CI: 1.08±1.29)]. Stage III hypertension was more prevalent in women, 8 vs. 1% ($P<0.0001$), and similar distribution existed for stages I and II between the sexes. Insulin-dependent diabetes were more prevalent in women ($P=0.031$) and non-insulin-dependent diabetes were similar in women and men ($P=0.113$). Smoking [54 vs. 36%; $P<0.0001$. *RR* 1.60 (95%CI:1.40±1.83)], previous myocardial infarction [74 vs. 57%; $P<0.0001$. *RR* 2.08 (95%CI: 1.63±2.65)] and surgical myocardial revascularization [38 vs. 31%; $P=0.037$. *RR* 1.30 (95%CI:1.02±1.66)] were greater in men. Also more men underwent cardiac catheterization (92 vs. 76%; $P<0.0001$). Prevalence of Q-wave myocardial infarction was greater in men ($P<0.0001$) and non-Q wave was equal in both sexes ($P=0.220$). The prevalence of congestive heart failure ($P=0.641$), functional classes II to IV, was similar in women and men. Surgical myocardial revascularization occurred more in men ($P=0.037$). Occurrence of saphenous vein graft implantation was similar in women and men ($P=0.642$) but mammary artery implantation was greater in men ($P=0.036$). Coronary artery disease severity was greater in men with more two- and three-vessel involvement than in women ($P<0.01$). Left main artery involvement was observed in 3 (0.3%) men and 8 (2%) women ($P=0.02$). Patients medication were shown in Tables 3. Aspirin (78 vs. 72%, $P=0.018$), cholesterol-lowering (26 vs. 18%, $P=0.001$) and antiarrhythmic drugs (5 vs. 1%, $P<0.001$) were more frequent in men and hypoglycemic drugs (25 vs. 32%, $P=0.008$) in women. Hormone replacement therapy with estrogen plus progestin was observed in only 12 (2.6%) women. Previous use of oral contraceptives were observed in 19 (4%) women.

Table 3
Medication distribution in patients with stable coronary artery disease[a]

	Men	Women	*P*
N (1318)	850(65)	468(35)	
Nitrates	408(48)	239(51)	0.325
Beta-blockers	331(39)	159(34)	0.082
Calcium channel blockers	357(42)	215(46)	0.179
Aspirin	663(78)	337(72)	0.018
ACE inhibitors	391(46)	201(43)	0.322
Diuretics	297(35)	173(37)	0.506
Cholesterol-lowering drugs	221(26)	84(18)	0.001
Digoxin	85(10)	61(13)	0.116
Antiarrhyithmics drugs	42(5)	5(1)	<0.001
Hypoglycemic drugs	214(25)	151(32)	0.008
Insulin	36(4)	39(8)	0.032
Oral	178(21)	112(24)	0.235

[a] Values in parenthesis mean percentage. ACE, angiotensin-converting enzyme.

4.2. Multivariate regression

Using sex as a dependent variable, backward stepwise multiple logistic regression disclosed hypertension ($P<0.0001$), diabetes ($P=0.037$), dyslipidemia (hypertriglyceridemia plus hypercholesterolemia) ($P=0.008$), and family history ($P<0.0001$) as independent variables for women. For men the independent variables selected were smoking ($P<0.0001$) and previous myocardial infarction ($P=0.016$). Age was not selected as an independent variable.

5. Discussion

Our study analyzed a large population of patients with established stable coronary artery disease and brought out three important points. First, women have 7 to 10 years protection against coronary artery disease compared with men [7], but when this gap does not exist through adjusting by age less is known about the differences in risk factors between men and women that significantly influence the expression of coronary disease. Because of estrogen protection, coronary disease is rare in premenopausal women but increases slightly in almost 15-year intervals after menopause and exponentially in the late 7th decade. In our study women and men with coronary disease had the same mean age, but women had a greater number of risk factors (hypertension, diabetes, hypertriglyceridemia, hypercholesterolemia, family history) than men (smoking, previous myocardial infarction). This clustering of risk factors probably reduces estrogen protection in a great scale precociously favoring coronary disease expression. It is well-known that clustering of risk factors negatively influences the atherosclerotic process starting in young persons [8].

It is important to note that except for family history all the above risk factors in women are easily

trackable in most cases. This clustering of risk factors may explain the higher incidence of sudden death in women with no previous symptoms of coronary disease [9] and 60% higher in-hospital mortality in women than in men after acute myocardial infarction [10]. Studies document a significant benefit of antihypertensive therapy in reducing coronary heart disease and stroke in both sexes [11,12]. This point is very important because stroke is the main cause of death in our population [13]. Potential benefits have also been seen with statins in reducing coronary events in secondary and primary prevention [14]. Previous observational studies have suggested that estrogen replacement may reduce cardiovascular events [15,16]. This was not supported by the recently published Heart and Estrogen/Progestin Replacement Study (HERS) where no protection was observed for cardiovascular events [17,18]. In fact HERS investigators observed an increase in thromboembolic events.

Second, despite the greater number of risk factors less severe coronary disease was observed in women supporting the idea that in spite of clustering of risk factors, women still had the natural protection for atherosclerosis development. The beneficial effect of estrogen is the factor most cited that protects women and even so after menopause clustering of risk factors does not equalize risk between women and men.

Third, in our study men underwent a greater number of myocardial revascularization procedures. One explanation was the greater severity of coronary disease in men but raises an ancient question about possible inadequate treatment of coronary disease in women.

In conclusion, women at almost the same age as men with coronary disease have clustered but modifiable risk factors that promote earlier expression of coronary artery disease.

6. Limitations of the study

This study analyzed a very special population of patients. Only outpatients with stable coronary artery disease who sought treatment in our tertiary hospital were included. This study included patients who survived an acute myocardial infarction or in-hospital patients with acute myocardial infarction.

Angioplasty was not assessed in this population because some patients who underwent angioplasty or stent placement were a very selected group. Because they must have suitable atherosclerotic lesions for angioplasty these patients probably do not have the same clinical characteristics and risk factors distribution as observed in general patients with stable coronary artery disease. Though, including them in our analysis would have soiled our data.

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