

# Coronary Artery Disease in Association with Depression or Anxiety

among Patients Undergoing Angiography  
to Investigate Chest Pain

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*In search of associations between coronary artery disease and symptoms of depression and anxiety, we conducted a prospective cross-sectional study of 314 patients (age range, 19–79 yr) who had presented with chest pain. Coronary angiographic findings were classified into 5 categories (0–4), in which higher numbers indicated more severe disease. Symptoms of depression and anxiety were evaluated by the Beck depression and anxiety inventories, in which higher scores indicated more severe symptoms.*

*Older age, male sex, diabetes mellitus, hypercholesterolemia, and high income were found in association with coronary artery disease. Woman patients exhibited significantly higher depression and anxiety scores ( $P < 0.001$ ), even though they had coronary artery disease infrequently ( $P = 0.003$ ). At first, no significant correlation was found between coronary artery disease levels 0, 1, 2, 3, or 4 and scores of depression or anxiety.*

*After controlling for sex differences and other confounding variables, however, we found that every 1-point increase in the depression score was associated with an average 5% to 6% increase in abnormal coronary angiographic findings or definitive coronary artery disease, respectively ( $P = 0.01$  and  $P = 0.002$ ). Although there was no such association between anxiety score and coronary artery disease, the highest anxiety scores were encountered in patients with slow coronary flow. (Tex Heart Inst J 2009;36(1):17-23)*

**E**pidemiologic studies have shown that depression or anxiety disorder can predict the incidence of coronary artery disease (CAD) in healthy populations.<sup>1</sup> Moreover, depression or anxiety disorder can also influence the course and prognosis of known CAD.<sup>2-4</sup> Although one study reported similar psychological variables in groups of patients with chest pain who had angiographically normal or abnormal coronary arteries,<sup>5</sup> several other studies<sup>6-9</sup> reported that patients who had chest pain and normal coronary arteries exhibited more psychiatric illnesses than did patients with definitive CAD.

Because we expected that symptoms of depression and anxiety would be associated with CAD in a consecutive population that had been referred for selective coronary angiography, we compared coronary angiographic findings with depression and anxiety scores that had been estimated in accordance with symptom scales. Our findings are discussed herein.

## Patients and Methods

### Study Population

This prospective, cross-sectional study comprises 1,064 consecutive patients who were referred to Avrupa Safak Hospital from April through May 2006 for coronary angiography to investigate stable angina pectoris or severe chest pain that probably arose from CAD. Slightly more than 60% of these patients came from our institution, and the rest were referred from 6 other hospitals. Our institutional review board approved the study, and we obtained informed consent from all patients.

From the 1,064 referred patients, we enrolled 314 (152 men and 162 women; mean age,  $56.26 \pm 11.68$  yr [range, 19–79 yr]). The inclusion criteria were age greater than 18 years, a coronary angiogram clear enough to enable evaluation of the cause of stress-induced chest pain, and the patient's consent. The exclusion criteria were current preg-

nancy, cardiomyopathy, previous myocardial infarction or any revascularization procedures (whether percutaneous transluminal coronary angioplasty or coronary artery bypass grafting), unstable angina pectoris, history of congenital heart disease, chronic renal failure, follow-up visits or medical treatment for chronic psychosis, recent medical treatment for depression, insufficient cooperation, and incomplete study forms.

The study population was chiefly from Gaziosmanpasa, most of whose inhabitants migrated within the last century from elsewhere in Turkey (northern, middle, and eastern Anatolia and the Marmara region), and from various Balkan countries. We believe that our sample is a good representation of the Turkish population.

All patients underwent physical examination, coronary angiography, assessment of atherosclerosis risk factors via questionnaire, New York Heart Association (NYHA) functional classification, and a semi-structured psychiatric interview. Atherosclerosis risk factors, as established by the Turkish Society of Cardiology, include older age (>45 yr in men; >55 yr in women, or earlier in the event of premature menopause), family history of atherosclerosis, current smoking, hypertension (>140/90 mmHg or use of antihypertensive drugs), hypercholesterolemia (total cholesterol >200 mg/dL or low-density lipoprotein [LDL] cholesterol >130 mg/dL), high-density lipoprotein (HDL) cholesterol level <35 mg/dL, and diabetes mellitus. All of these coronary risk factors, except for the HDL level, were analyzed in this study sample.

### Evaluation of Socioeconomic Status

Two indicators of socioeconomic status were education and annual household income. Patients' levels of education were defined as "less than high school graduation," "high school graduation," or "beyond high school." Economic status was classified according to the following annual household income levels: less than \$8,500 (U.S.), between \$8,500 and \$42,500, and more than \$42,500. These 3 values are in accordance with the regional economic and social status of the residents of Gaziosmanpasa, which is the most populous county of Istanbul. We numbered these education and income indices progressively, as 1, 2, and 3.

### Psychological Tests

The authors constructed a semi-structured psychiatric interview that began with the Beck Depression Inventory (BDI) and Beck Anxiety Inventory (BAI). The BDI is a 21-item scale developed by Beck and colleagues<sup>10</sup> that is widely used to measure the severity of depression. Each item was scored from 0 to 3, in increasing order of severity. The scores for each of these 21 items were totaled at the end of the psychological evaluation. Accuracy and reliability studies of the BDI have been con-

ducted by Hisli,<sup>11</sup> who accepted a score of 17 or above as indicative of major depression in the Turkish population; we accepted this same value as our indicator of major depression. To distinguish patients with depression, Carney and associates<sup>12</sup> used a BDI score equal to or greater than 10, which revealed a moderate sensitivity (78%) and specificity (90%). The BAI is applied in a manner similar to that of the BDI. The validity and reliability of the BAI have been studied in the Turkish population by Ulusoy.<sup>13</sup> After completion of the symptom scales and tabulation of the results, we performed a clinical psychiatric interview of every patient. This interview was performed before angiography, so neither the psychiatrist nor the patient was aware of the clinical status or angiographic results.

### Coronary Angiography

Before diagnostic coronary angiography, all patients underwent stress electrocardiography, myocardial perfusion scintigraphy, or (for high-risk patients) symptomatic assessment. Selective coronary angiography by means of the conventional Judkins technique and left ventriculography were performed in all patients. Each angiogram was interpreted by 2 cardiologists who were not aware of the psychiatric diagnosis. A significant obstructive atherosclerotic lesion was defined as stenosis equal to or greater than 50% of the luminal diameter in 1 or more coronary arteries. Any differences were resolved by a 3rd cardiologist. The coronary angiographic findings were classified into 5 categories in accordance with their severity (Table I). Groups 0 and 1 (normal coronary arteries and noncritical stenosis, respectively) served as controls when patients were regrouped to facilitate statistical analysis. Groups 2, 3, and 4 were also defined in accordance with the simple and widely used system of coronary angiography risk stratification established for the management of stable angina pectoris.<sup>14</sup>

### Statistics

Patients' characteristics are summarized as mean  $\pm$  SD or as percentages; the CAD groups are compared with one another in regard to age by means of Student's *t* test, in regard to depression and anxiety scores by means of the Mann-Whitney U test or the Kruskal-Wallis test, and in regard to categorical variables by means of the  $\chi^2$  test. Multivariate logistic regression was processed to control the possible confounding effects of age, sex, varying income and education indices, varying NYHA scores, personal histories of psychiatric visits and treatment for depression or anxiety, and the presence of hypertension, hypercholesterolemia, diabetes mellitus, or smoking. All analyses were performed with SPSS (Statistical Package for the Social Sciences) version 15.0 (SPSS Inc.; Chicago, Ill). Statistical significance was defined as  $P < 0.05$ .

## Results

Table II summarizes some of the demographic and clinical characteristics of patients with and without CAD. Our patients with CAD had significantly higher age, higher ratio of male to female, and higher income in-

dices, and an increased prevalence of hypercholesterolemia and diabetes mellitus ( $P < 0.05$ ). On the other hand, depression and anxiety scores, education indices, NYHA scores, and the prevalence of smoking, hypertension, and family history of atherosclerosis were similar in patients with CAD and without CAD ( $P > 0.05$ ).

**TABLE I.** Depression and Anxiety Scores of the Patients

Group	No.	Angiographic Findings	BDI Score (mean)	BAI Score (mean)
0	159	Normal coronary arteries	12.8 ± 8.6	17.7 ± 11.0
1	49	Nonobstructive CAD or significant stenosis in nonsignificant (<2 mm) side branch(es) or slow coronary flow with normal coronary arteries or nonobstructive CAD	14.0 ± 9.0	19.5 ± 13.6*
2	50	Significant (≥2 mm) side-branch disease(s) or 1 main-vessel disease at any level, except for ostial or proximal LAD lesion	13.2 ± 9.0	14.9 ± 12.0
3	28	Significant stenosis in 2 main coronary arteries or significant ostial or proximal LAD lesion alone	16.3 ± 11.2	16.4 ± 14.1
4	28	Obstructive 3-vessel disease or significant left main coronary artery lesion	16.7 ± 11.4*	19.2 ± 15.7
Kruskal-Wallis ANOVA ( $P$ value)			KW- $\chi^2 = 4.3$ (0.36)	KW- $\chi^2 = 4.8$ (0.30)

\* = highest depression or anxiety scores; ANOVA = analysis of variance; BAI = Beck Anxiety Inventory; BDI = Beck Depression Inventory; CAD = coronary artery disease; KW = Kruskal-Wallis; LAD = left anterior descending coronary artery

**TABLE II.** Patient Characteristics and Clinical Data by Univariate Testing

Characteristics of Patients	Patients without CAD (n=159)	Patients with CAD (n=155)	Test Statistics	P Value
Age (yr)	53.2 ± 10.2	58.7 ± 9.1	$t=4.97$	<0.001
Women/men	95 / 64	67 / 88	$\chi^2=8.5$	0.003
Family history, n (%)	65 (41)	69 (44)	$\chi^2=0.42$	0.54
Smoking, n (%)	39 (24)	27 (17)	$\chi^2=1.9$	0.16
Hypercholesterolemia, n (%)	57 (35)	77 (49)	$\chi^2=6.1$	0.013
Hypertension, n (%)	83 (52)	82 (52)	$\chi^2=0.01$	0.9
Diabetes mellitus, n (%)	32 (20)	47 (30)	$\chi^2=4.33$	0.037
Previous psychiatric visit, n (%)	36 (22)	28 (18)	$\chi^2=1.01$	0.31
Education index (1 / 2 / 3)	117 / 29 / 4	100 / 36 / 8	$\chi^2=2.94$	0.23
NYHA score (1 / 2 / 3)	46 / 94 / 10	39 / 89 / 15	$\chi^2=1.54$	0.46
Income index (1 / 2 / 3)	115 / 31 / 4	93 / 37 / 14	$\chi^2=8.29$	0.016
Mean BDI score	12.8 ± 8.6	14.69 ± 9.9	$z=1.49$	0.13
Mean BAI score	17.4 ± 11.0	17.7 ± 11.0	$z=1.02$	0.31

BAI = Beck Anxiety Inventory; BDI = Beck Depression Inventory; CAD = coronary artery disease (including nonsignificant atherosclerotic lesions); NYHA = New York Heart Association;  $\chi^2$  = chi-square test;  $t$  = Student's  $t$  test;  $z$  = Mann-Whitney U test

**TABLE III.** Depression and Anxiety Scores of the Patients When Regrouped

Angiographic Findings	No. Pts.	Mean BDI Score	Mann-Whitney Test (P value)	Mean BAI Score	Mann-Whitney Test (P value)
Normal angiogram (Group 0)	159	12.8 ± 8.6	z = 1.49 (0.13)	17.7 ± 11.0	z = 1.02 (0.31)
Abnormal angiogram (Groups 1, 2, 3, and 4)	155	14.6 ± 9.9		17.4 ± 11.0	
No or nonsignificant CAD (Groups 0 and 1)	208	13.1 ± 8.7	z = 1.27 (0.20)	18.1 ± 11.7	z = 1.85 (0.06)
Definitive CAD (Groups 2, 3, and 4)	106	14.9 ± 10.3		16.4 ± 13.6	

BAI = Beck Anxiety Inventory; BDI = Beck Depression Inventory; CAD = coronary artery disease; z = Mann-Whitney U test

Previous psychiatric follow-up for depression or anxiety disorders was documented in 36 patients without CAD and in 28 patients with CAD ( $P=0.31$ ).

Depression and anxiety scores were similar in the 5 groups of patients (see summaries, Table I). Depression scores had only insignificant increases from Group 0 to Group 1 and from Group 2 to Group 4 ( $P=0.36$ ; Kruskal-Wallis analysis of variance). Furthermore, we could not find significant differences in depression or anxiety scores after patients had been regrouped in various ways ( $P>0.05$ ; Table III).

### Confounding Variables

We came to realize that sex was the chief confounding factor in these analyses. Both depression ( $15.5 \pm 9.4$  vs  $11.8 \pm 8.8$ ;  $P<0.0001$ ) and anxiety scores ( $21.7 \pm 12.8$  and  $13.1 \pm 10.1$ ;  $P<0.0001$ ) were found to be significantly higher in female patients. On the other hand, female patients were less frequently found to have CAD than were male patients ( $P=0.003$ ). In addition, there were confounding factors other than sex: we discovered significant associations ( $P<0.05$ ) between depression and anxiety scores and atherosclerosis risk factors such as diabetes mellitus, hypertension, and hypercholesterolemia.

The possible confounding variables discussed above were adjusted during further analyses. After multivariate logistic regression, significant associations were found between depression scores and abnormal coronary angiographic findings or definitive CAD in 2 different analyses (Tables IV and V). A 1-point increase in depression score was associated with an average 5%-to-6% increase in the risk of abnormal coronary angiographic findings or definitive CAD ( $P=0.01$  and  $P=0.002$ ). In contrast, there was no association between anxiety score and coronary angiographic findings. However, the

highest BAI score was found in Group 1, which comprised patients with slow coronary flow, nonobstructive CAD, or both (Table I).

### Discussion

Several investigators have considered possible associations between psychological variables and CAD in patients who have undergone coronary angiography, and the results have been conflicting.<sup>5,9,15,16</sup> In our study, the depression score in patients who had CAD was at first not significantly different from the depression score in patients who did not have CAD. However, the paradoxical effect of female sex was chiefly responsible for this finding; after controlling for sex and other variables, we found that the depression score was strongly correlated to CAD in our sample. We estimated that every 5-point increase in depression score was associated with a 25%-to-30% increase, on average, in the risk of abnormal coronary angiography findings or definitive CAD.

The associations between CAD and the factors of age, sex, diabetes mellitus or hypercholesterolemia or both, and higher ratio of men to women are not unique to our patients: they can be found elsewhere in the medical literature. The association that we found between CAD and high income level could be coincidental and needs further evaluation. Another interesting finding was the similarity in the NYHA scores of our patients with and without CAD. We speculate that sociocultural factors—agoraphobia, social isolation, and a sedentary life style induced by moderate depression or higher anxiety—could have contributed to the poor physical condition of patients who did not have CAD.

It is known that patients with stable angina pectoris and normal coronary angiography usually have cardiac

**TABLE IV.** Results of Multivariate Logistic Regression Analysis of Coronary Artery Disease as a Dependent Variable (Group 0 vs Groups 1, 2, 3, and 4)

Characteristics of Patients	Beta	P Value	Odds Ratio	95% CI of Odds Ratio	
				Lower	Upper
Age (yr)	0.07	<0.001	1.07	1.04	1.10
Male sex	0.55	<0.001	1.74	1.28	2.35
Family history	0.20	0.157	1.22	0.93	1.60
Smoking	-0.11	0.547	0.90	0.64	1.27
Hypercholesterolemia	0.30	0.044	1.35	1.01	1.81
Hypertension	0	0.995	1.00	0.75	1.34
Diabetes mellitus	0.40	0.016	1.49	1.08	2.06
Previous psychiatric visit	-0.13	0.466	0.88	0.62	1.24
Education index	-	0.384	-	-	-
2 versus 1	-0.09	0.777	0.91	0.49	1.72
3 versus 1	0.51	0.339	1.66	0.59	4.72
Income index	-	0.017	-	-	-
2 versus 1	-0.54	0.064	0.58	0.33	1.03
3 versus 1	1.24	0.005	3.46	1.44	8.32
NYHA score	-	0.391	-	-	-
2 versus 1	-0.11	0.604	0.90	0.60	1.35
3 versus 1	0.42	0.201	1.52	0.80	2.88
BDI score	0.05	0.011	1.05	1.01	1.09
BAI score	-0.02	0.146	0.98	0.95	1.01

Model  $\chi^2=68.70$ ;  $P < 0.001$ ; overall classification, 67.2%

BAI = Beck Anxiety Inventory; BDI = Beck Depression Inventory; CI = confidence interval; NYHA = New York Heart Association

**TABLE V.** Results of Multivariate Logistic Regression Analysis of Coronary Artery Disease as a Dependent Variable (Groups 0 and 1 vs Groups 2, 3, and 4)

Characteristics of Patients	Beta	P Value	Odds Ratio	95% CI of Odds Ratio	
				Lower	Upper
Age (yr)	0.05	<0.001	1.05	1.02	1.09
Male sex	1.27	<0.001	3.56	1.98	6.39
Family history	0.30	0.27	1.35	0.79	2.30
Smoking	-0.17	0.62	0.84	0.43	1.65
Hypercholesterolemia	0.33	0.24	1.39	0.80	2.41
Hypertension	-0.03	0.90	0.97	0.55	1.69
Diabetes mellitus	0.19	0.54	1.21	0.66	2.20
Previous psychiatric visit	-0.50	0.17	0.60	0.29	1.24
BDI score	0.06	0.002	1.06	1.02	1.10
BAI score	-0.03	0.09	0.97	0.95	1.00

Model  $\chi^2=49.93$ ;  $P < 0.001$ ; overall classification, 69.7%

BAI = Beck Anxiety Inventory; BDI = Beck Depression Inventory; CI = confidence interval



“syndrome X.” We think it likely that most of our patients in Groups 0 and 1 had syndrome X. In our sample, patients with slow coronary flow (Group 1) had the highest anxiety score. Slow coronary flow has been identified as a definite subset within the wide spectrum of syndrome X and can be used as a marker for myocardial ischemia.<sup>17</sup> In another study, Ketterer and coworkers<sup>18</sup> showed that syndrome X patients might be more emotionally distressed than healthy controls, indeed as distressed as patients with CAD. In the present study, patients with slow coronary flow also had unexpectedly higher depression symptoms.

We observe that the indications for coronary angiography among our patients arose largely from symptomatic assessment, and that chest pain was chief among these symptoms. Chest pain, we should point out, can also be a symptom of panic disorder, depression, hypochondriasis, somatization disorder, and generalized anxiety disorder.<sup>19,20</sup> We should also emphasize the importance of diagnosis, treatment, and follow-up of depression and anxiety disorder in order to prevent unnecessary diagnostic cardiac catheterization, long before these conditions can result in CAD. In fact, 50.6% of our patients had normal coronary angiographic results. On the other hand, we thought that the symptomatic assessment of our patients increased the strength of our study by providing a balanced population. In this manner, we avoided the spectrum bias inherent in a population skewed toward severe or late-stage disease.<sup>21</sup>

Several hypotheses have been proposed to explain the association between symptoms of depression and anxiety and CAD: increased platelet reactivity, endothelial dysfunction, decreased variability in heart rate, accelerated atherogenesis, and poor adherence to therapies.<sup>22,23</sup> Symptoms of depression and anxiety have also been associated with atherosclerosis risk factors.<sup>24-27</sup> We have also shown, in a previous study,<sup>28</sup> that diabetes mellitus, hypertension, and hypercholesterolemia, which are known to be causally related to CAD, were associated with depression and anxiety symptoms in the same sample. These findings are compatible with the results of our present study. We believe that depression and anxiety symptoms can interact with major atherosclerosis risk factors in many complicated and long-term processes, at present mostly undefined, in the development of CAD.

### Limitations

By its nature, a cross-sectional study cannot show a definite causal relationship between CAD and depression or anxiety disorder. However, we think that our findings are clinically relevant because we also showed, in the same sample, some associations between atherosclerosis risk factors and symptoms of depression and anxiety. We classified coronary angiographic findings into 5 categories for the sake of simplicity. The final 3 subclasses (Groups 2, 3, and 4) were in general compati-

ble with coronary angiographic risk stratifications used in well-known guidelines<sup>14</sup> and clinical trials,<sup>29</sup> but we defined them slightly differently. For control, we used Group 0 patients (normal coronary arteries) either by themselves or in combination with Group 1 patients (nonobstructive atherosclerotic lesions or slow coronary flow or both).

### Conclusions

Our sample shows some correlations between depression score and abnormal coronary angiographic findings, definitive CAD, or both. Patients with higher depression scores (estimated before the procedure) had a significantly increased risk of abnormal coronary angiographic findings or definitive CAD. This is compatible with our previous report in which depression and anxiety symptoms were associated with major atherosclerosis risk factors in the same sample. Anxiety symptoms were found to be extreme only in patients with slow coronary flow. Future research with better study designs is needed for definitive conclusions.

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