

# Scared to Death? Generalized Anxiety Disorder and Cardiovascular Events in Patients With Stable Coronary Heart Disease

## *The Heart and Soul Study*

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**Context:** Anxiety is common in patients with coronary heart disease (CHD), but studies examining the effect of anxiety on cardiovascular prognosis and the role of potential mediators have yielded inconsistent results.

**Objectives:** To evaluate the effect of generalized anxiety disorder (GAD) on subsequent cardiovascular events and the extent to which this association is explained by cardiac disease severity and potential behavioral or biological mediators.

**Design:** Prospective cohort study (Heart and Soul Study).

**Setting:** Participants were recruited between September 11, 2000, and December 20, 2002, from 12 outpatient clinics in the San Francisco Bay Area and were followed up until March 18, 2009.

**Participants:** One thousand fifteen outpatients with stable CHD followed up for a mean (SD) of 5.6 (1.8) years.

**Main Outcome Measures:** We determined the presence of GAD using the Diagnostic Interview Schedule. Proportional hazards models were used to evaluate the association of GAD with subsequent cardiovascular events

and the extent to which this association was explained by potential confounders and mediators.

**Results:** A total of 371 cardiovascular events occurred during 5711 person-years of follow-up. The age-adjusted annual rate of cardiovascular events was 9.6% in the 106 participants with GAD and 6.6% in the 909 participants without GAD ( $P = .03$ ). After adjustment for demographic characteristics, comorbid conditions (including major depressive disorder), cardiac disease severity, and medication use, GAD remained associated with a 62% higher rate of cardiovascular events (hazard ratio, 1.62; 95% confidence interval, 1.11-2.37;  $P = .01$ ). Additional adjustment for a variety of potential behavioral and biological mediators had little effect on this association (hazard ratio, 1.74; 95% confidence interval, 1.13-2.67;  $P = .01$ ).

**Conclusions:** In outpatients with CHD, a robust association between GAD and cardiovascular events was found that could not be explained by disease severity, health behaviors, or biological mediators. How GAD leads to poor cardiovascular outcomes deserves further study.

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**A**MPLE EVIDENCE HAS DEMONSTRATED a strong and consistent association between psychological factors, such as stress and cardiovascular health.<sup>1,2</sup> These factors are important contributors to health decrements in initially healthy patients and in patients with established coronary heart disease (CHD).<sup>3</sup> Efforts have been made to understand how these factors contribute to CHD onset, progression, and prognosis. Most of these efforts have been directed toward depression, with several meta-analyses demonstrating that depression is an independent risk factor for the development of CHD in the general population<sup>4,5</sup> and a prognostic risk factor in pa-

tients with CHD.<sup>6,7</sup> It is less clear whether this increased risk of cardiac events extends to patients with other symptoms of negative affect, such as anxiety.<sup>8,9</sup>

Compared with the extensive literature on depression in patients with CHD, relatively few studies have examined the role of anxiety. Symptoms of anxiety are common in patients with CHD, with prevalence rates ranging from 24% to 31%.<sup>10-15</sup> Several studies<sup>14,16,17</sup> have found that anxiety symptoms are predictive of disability, increased physical symptoms, and worse functional status and quality of life in patients with CHD. However, studies examining anxiety as a risk factor for future CHD events have yielded conflicting results. Some studies have reported anxiety symp-

toms to be predictive of subsequent cardiac events, mortality, and in-hospital complications<sup>11,18-21</sup> in patients with CHD, whereas others have found no association<sup>15,22-24</sup> or even a protective effect.<sup>25,26</sup> In addition, the extent to which this increased risk is independent of potential confounding factors and the role of potential mediators has not been determined. Moreover, only 1 previous study<sup>21</sup> has evaluated the cardiac prognostic importance of generalized anxiety disorder (GAD); others have relied on self-report measurement of anxiety symptoms. GAD is common and treatable and could, therefore, be an important modifiable risk factor in patients with CHD.

In a prospective cohort study of 1015 participants with stable CHD, we evaluated the independent effect of GAD on subsequent cardiovascular events and the extent to which this association was explained by differences in demographic characteristics, comorbid conditions, cardiac disease severity, and potential behavioral and biological mediators.

## METHODS

The Heart and Soul Study was designed to determine how psychological disorders lead to cardiovascular events in outpatients with stable CHD.<sup>27</sup> Patients in California were recruited from 2 Department of Veterans Affairs (VA) medical centers (San Francisco VA Medical Center and the VA Palo Alto Health Care System), 1 university medical center (University of California, San Francisco), and 9 public health clinics in the Community Health Network of San Francisco. Patients were eligible to participate if they had at least 1 of the following: a history of myocardial infarction, angiographic evidence of at least 50% stenosis in 1 or more coronary vessels, previous evidence of exercise-induced ischemia using treadmill or nuclear testing, a history of coronary revascularization, or a diagnosis of CHD documented by an internist or cardiologist. Between September 11, 2000, and December 20, 2002, a total of 1024 participants were enrolled: 240 from the public health clinics, 346 from the university medical center, and 438 from the VA medical centers.

All the participants completed a baseline examination that included an interview, fasting venous blood sample collection, a psychiatric interview, a questionnaire, echocardiography, exercise treadmill testing, 24-hour ambulatory electrocardiography, and 24-hour urine collection. Of the 1024 participants who completed the baseline examination, 3 did not complete the diagnostic interview for anxiety, and we could not contact 6 individuals (<1%) during follow-up, leaving 1015 for this analysis. The protocol was approved by the appropriate institutional review boards (Committee on Human Research, University of California, San Francisco; Research and Development Committee, VA Medical Center, San Francisco; Medical Human Subjects Committee, Stanford University, Stanford, California; Human Subjects Committee, Veterans Affairs Palo Alto Health Care System, Palo Alto, California; and the Data Governance Board of the Community Health Network, San Francisco). All participants provided written informed consent.

## GENERALIZED ANXIETY DISORDER

We determined the presence of GAD during the past year using the computerized Diagnostic Interview Schedule for DSM-IV.<sup>28</sup> Computerized versions of the Diagnostic Interview Schedule have previously demonstrated acceptable validity and reliability.<sup>29,30</sup> We also ascertained the presence of major depressive disorder (MDD) using the computerized Diagnostic Interview Schedule

for DSM-IV. Participants with a major depressive episode in the past month were informed of this diagnosis, were instructed to discuss their symptoms with their primary care physician, and were provided a list of local resources available for treatment.

## BASELINE CARDIAC DISEASE SEVERITY AND RISK FACTORS

Fasting venous blood samples were collected to determine low- and high-density lipoprotein cholesterol levels. Participants completed an exercise treadmill test according to a standard Bruce protocol. Those who could not continue the standard Bruce protocol were switched to slower settings and were encouraged to exercise for as long as possible. Exercise capacity was calculated as the total number of metabolic equivalent tasks achieved. We performed resting and stress echocardiograms using an ultrasound system (Acuson Sequoia; Acuson Siemens, Mountain View, California) with a 3.5-MHz transducer. Before exercise, standard 2-dimensional parasternal long- and short-axis and apical 2- and 4-chamber views were obtained and planimetric using a computerized digitization system to determine end diastolic and end systolic left ventricular volume and to calculate left ventricular ejection fraction. At peak exercise, parasternal long- and short-axis and apical 2- and 4-chamber views were used to detect the development of left ventricular wall motion abnormalities. Inducible ischemia was defined as the presence of new wall motion abnormalities at peak exercise that were not present at rest.

## POTENTIAL BEHAVIORAL MEDIATORS

Smoking and alcohol use were determined by self-report questionnaire.<sup>31</sup> To assess medication adherence, we asked, "In the past month, how often did you take your medications as the doctor prescribed?" Possible responses were "all of the time (100%)," "nearly all of the time (90%)," "most of the time (75%)," "about half the time (50%)," or "less than half the time (<50%)." We defined medication nonadherence as taking prescribed medications 75% of the time or less.<sup>32</sup> To assess physical activity, we asked, "Which of the following statements best describes how physically active you have been during the past month, that is, done activities such as 15 to 20 minutes of brisk walking, swimming, general conditioning, or recreational sports?" Participants chose 1 of the following 6 categories: not at all active, a little active (1-2 times per month), fairly active (3-4 times per month), quite active (1-2 times per week), very active (3-4 times per week), or extremely active ( $\geq 5$  times per week). Participants who reported that they were not at all or a little active were considered physically inactive. Self-report has been shown to be a reliable, valid, and accurate method of assessing physical activity.<sup>33-36</sup> In particular, single-response items have demonstrated excellent construct validity.<sup>35-37</sup>

## POTENTIAL BIOLOGICAL MEDIATORS

Three-channel 24-hour ambulatory Holter electrocardiography was used to assess heart rate variability,<sup>38</sup> including the standard deviation of 5-minute mean NN intervals (SDANN) and the natural log of very low frequency power. We collected 24-hour urine samples to measure norepinephrine and cortisol excretion. Norepinephrine was assessed by means of gas chromatography-mass spectrometry at Associated Regional and University Pathologists Inc (Salt Lake City, Utah). Cortisol was analyzed using radioimmunoassay or (owing to a change at the Associated Regional and University Pathologists Inc laboratory) high-performance liquid chromatography-tandem mass spectrometry.<sup>39,40</sup>

**Table 1. Baseline Characteristics of 1015 Participants With Stable Coronary Heart Disease by Generalized Anxiety Disorder Status<sup>a</sup>**

Variable	Anxiety (n=106)	No Anxiety (n=909)	P Value
Demographic characteristics			
Age, mean (SD), y	60 (11)	68 (11)	<.001
Male sex, No. (%)	71 (67)	761 (84)	<.001
White race, No. (%)	60 (57)	551 (61)	.42
High school graduate, No. (%)	94 (89)	789 (87)	.62
BMI, mean (SD)	29.3 (6.0)	28.3 (5.2)	.07
Comorbid conditions, No. (%)			
Major depressive disorder	85 (80)	137 (15)	<.001
Hypertension	81 (76)	637 (70)	.18
Myocardial infarction	50 (47)	495 (55)	.16
Diabetes mellitus	34 (32)	231 (25)	.14
Congestive heart failure	16 (15)	162 (18)	.50
Stroke	13 (12)	134 (15)	.51
Cardiac disease severity and risk factors			
Resting left ventricular ejection fraction, mean (SD)	0.64 (0.07)	0.61 (0.10)	.01
Exercise capacity, mean (SD), MET	7.9 (3.6)	7.2 (3.3)	.06
LDL-C, mean (SD), mg/dL	108.8 (37.8)	103.7 (33.2)	.16
HDL-C, mean (SD), mg/dL	44.2 (15.0)	46.1 (14.0)	.19
Inducible ischemia, No. (%)	18 (17)	210 (23)	.18
Medication use, No. (%)			
Aspirin	83 (78)	705 (78)	.86
β-Blocker	68 (64)	521 (57)	.18
Renin-angiotensin system inhibitor	45 (42)	477 (52)	.05
Selective serotonin reuptake inhibitor	27 (25)	70 (8)	<.001
Other antidepressant	26 (25)	52 (6)	<.001
Anxiolytic, benzodiazepine	19 (18)	64 (7)	<.001
Tricyclic antidepressant	12 (11)	32 (4)	<.001
Anxiolytic, nonbenzodiazepine	8 (8)	29 (3)	.02
Potential biological mediators, mean (SD)			
Heart rate variability, SDANN, ms	112.1 (36.7)	108.6 (36.0)	.37
Heart rate variability, lnVLF, ms <sup>2</sup>	6.3 (0.8)	6.3 (0.9)	.93
Serotonin in non-SSRI users, ng/mL	122.8 (72.8)	119.5 (67.7)	.69
Cortisol, μg/d	34.5 (21.9)	39.0 (30.1)	.17
Norepinephrine, μg/d	51.2 (25.3)	51.8 (26.7)	.82
Log C-reactive protein, mg/L	0.65 (1.21)	0.72 (1.31)	.64
Log ω-3 fatty acid, % DHA+EPA	1.25 (0.49)	1.34 (0.43)	.05
Potential behavioral mediators, No. (%)			
Regular alcohol use	32 (30)	259 (28)	.70
Current smoking	29 (27)	170 (19)	.05
Medication nonadherence	19 (18)	64 (7)	<.001
Self-reported physical activity, No. (%)			
Not at all active	19 (18)	169 (19)	.03
A little active, 1-2 times/mo	31 (29)	151 (17)	
Fairly active, 3-4 times/mo	15 (14)	140 (15)	
Quite active, 1-2 times/wk	15 (14)	139 (15)	
Very active, 3-4 times/wk	14 (13)	202 (22)	
Extremely active, ≥5 times/wk	12 (11)	105 (12)	

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; lnVLF, natural log of very low frequency power; MET, metabolic equivalent task; SDANN, standard deviation of 5-minute mean NN intervals; SSRI, selective serotonin reuptake inhibitor.

SI conversion factors: To convert cholesterol to millimoles per liter, multiply by 0.0259; cortisol to nanomoles per liter, multiply by 27.588; C-reactive protein to nanomoles per liter, multiply by 9.524; and norepinephrine to picomoles per liter, multiply by 5.911.

<sup>a</sup>Numbers may not sum to their respective subtotals due to missing data, and percentages may not sum to 100% due to rounding.

We used high-pressure liquid chromatography with electrochemical detection to assay whole-blood serotonin levels.<sup>41</sup> High-sensitivity C-reactive protein (CRP) levels were measured using the Integra assay (Roche, Indianapolis, Indiana) in the first 229 participants and (owing to a change at the laboratory) the Extended Range assay (Beckman Coulter Ireland Inc, Galway, Ireland) in the remaining samples.<sup>42</sup> Blood levels of 2 ω-3 fatty acids, docosahexaenoic acid and eicosapentaenoic acid, were measured using capillary gas chromatography as the percentage composition of total fatty acid methyl esters in the red blood cell membranes.<sup>43</sup>

## OTHER PATIENT CHARACTERISTICS

Age, sex, race, educational achievement, and medical history were determined by means of self-report questionnaire. We measured height and weight and calculated body mass index (calculated as weight in kilograms divided by height in meters squared). Participants were instructed to bring their medication bottles to their appointment, and study personnel recorded all current medications. Medications were categorized using Epocrates Rx (Epocrates Inc, San Mateo, California).

**Table 2. Cardiovascular Events During Follow-up by Generalized Anxiety Disorder Status**

Event	Events, Age-Adjusted Annual Rate, No. (%) <sup>a</sup>		Age-Adjusted Hazard Ratio (95% CI)	P Value
	Anxiety (n=106)	No Anxiety (n=909)		
Myocardial infarction	15 (3.4)	97 (1.9)	1.71 (0.98-2.99)	.06
Stroke or transient ischemic attack	7 (1.5)	42 (0.8)	1.83 (0.81-4.15)	.15
Heart failure	9 (2.0)	137 (2.5)	0.75 (0.38-1.48)	.40
All-cause mortality	24 (5.0)	242 (4.1)	1.29 (0.85-1.98)	.24
Any of these outcomes	39 (9.6)	332 (6.6)	1.43 (1.03-2.00)	.03

Abbreviation: CI, confidence interval.

<sup>a</sup>Values represent the number of persons with anxiety and any of these specific events.

## CARDIOVASCULAR EVENTS

Between the baseline examination and the last day of follow-up on March 18, 2009, we conducted annual follow-up interviews with participants (or their proxies) by telephone asking specifically about hospitalization for "heart trouble." For any reported event, medical records, electrocardiograms, death certificates, and coroner's reports were retrieved and reviewed by 2 independent blinded adjudicators. In the event of disagreement, the adjudicators conferred, reconsidered their classification, and requested consultation from a third blinded adjudicator as necessary.

The outcome events were stroke, heart failure, myocardial infarction, transient ischemic attack, and death. Heart failure was defined as hospitalization for a clinical syndrome involving at least 2 of the following: orthopnea, third heart sound, pulmonary rales, paroxysmal nocturnal dyspnea, elevated jugular venous pressure, and cardiomegaly or pulmonary edema on chest radiography. These signs and symptoms must have represented a clear change from the usual clinical status.<sup>44</sup> Stroke was defined as a new neurologic deficit not known to be secondary to brain trauma, tumor, infection, or another cause.<sup>45,46</sup> Nonfatal myocardial infarction was defined based on the presence of symptoms, electrocardiographic changes, and cardiac enzymes using standard criteria.<sup>47,48</sup> Transient ischemic attack was defined as a focal neurologic deficit (in the absence of head trauma) lasting more than 30 seconds and no longer than 24 hours, with rapid evolution of the symptoms to the maximal level of deficit in less than 5 minutes and with subsequent complete resolution.<sup>45,46</sup> Deaths were confirmed by review of death certificates and coroner's reports.

## STATISTICAL ANALYSIS

Baseline differences in characteristics between participants with and without GAD were compared using *t* tests and  $\chi^2$  tests. Levels of CRP and  $\omega$ -3 fatty acid were log transformed because they were not normally distributed. We estimated the risk of cardiovascular events associated with anxiety disorder using Cox proportional hazards models.

To evaluate whether a covariate changed the strength of association between anxiety disorder and cardiovascular events, we calculated the percentage change in the effect size (log hazard ratio [HR]) for anxiety disorder before and after adjustment for the potential confounder or mediator. To avoid any artifact due to different sample sizes between the 2 nested models, participants missing the covariate of interest were excluded from each comparison. We sequentially considered demographic variables, including depression, comorbid conditions, cardiac disease severity, use of medications, and potential behavioral and biological mediators.<sup>49</sup> Variables that re-

sulted in a more than 5% change in the effect size (log HR) for GAD were considered confounders or potential mediators and were included in the final multivariable models.<sup>50</sup>

We verified the proportional hazards assumption of these models using log-minus-log survival plots and by checking for secular patterns in scaled Schoenfeld residuals. We used Wald tests to check for interactions of anxiety disorder with age, sex, and MDD in age- and multivariable-adjusted models. Analyses were performed using a statistical software program (SAS version 9.2; SAS Institute Inc, Cary, North Carolina).

## RESULTS

Of the 1015 participants, 106 (10.4%) met the criteria for GAD in the past year. Compared with participants who did not have GAD in the past year, those with GAD were younger, more likely to be female, and more likely to have MDD (**Table 1**). GAD was associated with a better left ventricular ejection fraction and greater renin-angiotensin system inhibitor, anxiolytic, and antidepressant drug use. Participants with GAD had lower  $\omega$ -3 fatty acid levels and were more likely to smoke, were less physically active, and were less adherent to medications.

A total of 371 cardiovascular events occurred during 5711 person-years (mean [SD] of 5.6 [1.8] person-years) of follow-up. The age-adjusted annual rate of cardiovascular events was 9.6% in the 106 participants with GAD and 6.6% in the 909 participants without GAD (HR, 1.43; 95% confidence interval [CI], 1.03-2.00; *P* = .03) (**Table 2**). After excluding the 222 patients with MDD, the age-adjusted annual rate of cardiovascular events was 9.2% in 21 participants with GAD and 6.9% in 772 participants without GAD (HR, 1.33; 95% CI, 0.69-2.59; *P* = .39).

## POTENTIAL MEDIATORS

Several variables, including male sex, comorbid conditions, left ventricular function, exercise capacity, renin-angiotensin system inhibitor and antidepressant drug use, medication nonadherence, physical activity level, heart rate variability, and CRP level, met the criteria for potential confounding or mediation (**Table 3**). Variables that did not change the effect size for GAD by 5% or more included MDD, use of selective serotonin reuptake inhibitors or anxiolytics, body mass index, smoking, and levels of serotonin,  $\omega$ -3 fatty acids, and 24-hour excretion of norepinephrine and cortisol (Table 3).

**Table 3. Change in the Strength of Association Between Generalized Anxiety Disorder and Cardiovascular Events<sup>a</sup> After Adjustment for Potential Confounders and Mediators**

Covariate	Change in Effect Size After Adjustment, % <sup>b</sup>
Demographic characteristics	
Male sex	19.7
White race	-0.2
High school graduate	0.8
Body mass index	0
Comorbid conditions	
Hypertension	-1.4
Myocardial infarction	6.4
Stroke	-2.1
Congestive heart failure	4.5
Diabetes mellitus	-9.3
Major depressive disorder	0.4
Cardiac disease severity and risk factors	
Resting left ventricular ejection fraction	31.4
Exercise capacity, MET	-13.5
LDL-C level	-0.2
HDL-C level	-2.8
Inducible ischemia	3.2
Medication use	
Aspirin	-1.2
β-Blocker	0
Renin-angiotensin system inhibitor	12.0
Tricyclic antidepressant	-10.9
Selective serotonin reuptake inhibitor	-2.5
Other antidepressant	-10.5
Anxiolytic, benzodiazepine	3.7
Anxiolytic, nonbenzodiazepine	-1.0
Potential behavioral mediators	
Regular alcohol use	-0.2
Smoking, current	-1.2
Medication nonadherence	-13.0
Physical inactivity	-17.5
Potential biological mediators	
Heart rate variability, SDANN	14.8
Heart rate variability, lnVLF	-1.4
Serotonin level, among nonusers of SSRIs	1.6
Cortisol excretion	1.9
Norepinephrine excretion	0.4
Log C-reactive protein level	10.1
Log ω-3 fatty acid level	-0.4

Abbreviations: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; lnVLF, natural log of very low frequency power; MET, metabolic equivalent task; SDANN, standard deviation of 5-minute mean NN intervals; SSRI, selective serotonin reuptake inhibitor.

<sup>a</sup>Expressed as the percentage change in the age-adjusted log hazard ratio.

<sup>b</sup>Changes greater than 5% were considered clinically important and were included in subsequent multivariate regression models.

When adjusted for male sex, comorbid conditions, cardiac disease severity, and medication use, GAD remained associated with a 62% greater rate of cardiovascular events (HR, 1.62; 95% CI, 1.11-2.37;  $P=.01$ ). Additional adjustment for potential behavioral and biological mediators, including medication nonadherence, physical inactivity, heart rate variability (SDANN), and log CRP level, did not substantially change this association (**Table 4**). In the final model, GAD was associated with a 74% greater rate of cardiovascular events (HR, 1.74; 95% CI, 1.13-2.67;  $P=.01$ ) (**Table 5** and **Figure**). We found no evidence that the association between GAD and cardiovascular events varied by age, sex, or MDD ( $P$  for interaction  $\geq .1$  for all).

**Table 4. Association Between Generalized Anxiety Disorder and Subsequent Cardiovascular Events<sup>a</sup> With Sequential Adjustment for Potential Confounders and Mediators**

Adjusted Variable <sup>b</sup>	Hazard Ratio (95% CI)
Age, per 10-y increase	1.43 (1.03-2.00)
Plus male sex	1.54 (1.10-2.15)
Plus history of myocardial infarction and diabetes mellitus	1.56 (1.11-2.19)
Plus left ventricular ejection fraction (per 10% decrease) and exercise capacity, MET (per SD decrease)	1.72 (1.19-2.48)
Plus use of renin-angiotensin system inhibitor, tricyclic antidepressant, and other antidepressant	1.62 (1.11-2.37)
Plus potential behavioral mediators: medication nonadherence and physical inactivity	1.52 (1.04-2.24)
Plus potential biological mediators: heart rate variability (SDANN, per SD decrease) and log C-reactive protein (per SD increase)	1.74 (1.13-2.67)

Abbreviations: CI, confidence interval; MET, metabolic equivalent task; SDANN, standard deviation of 5-minute mean NN intervals.

<sup>a</sup>Cardiovascular events were heart failure, myocardial infarction, stroke, transient ischemic attack, or death.

<sup>b</sup>Each model includes the variables from the preceding row so that the final model includes all the variables listed in this table.

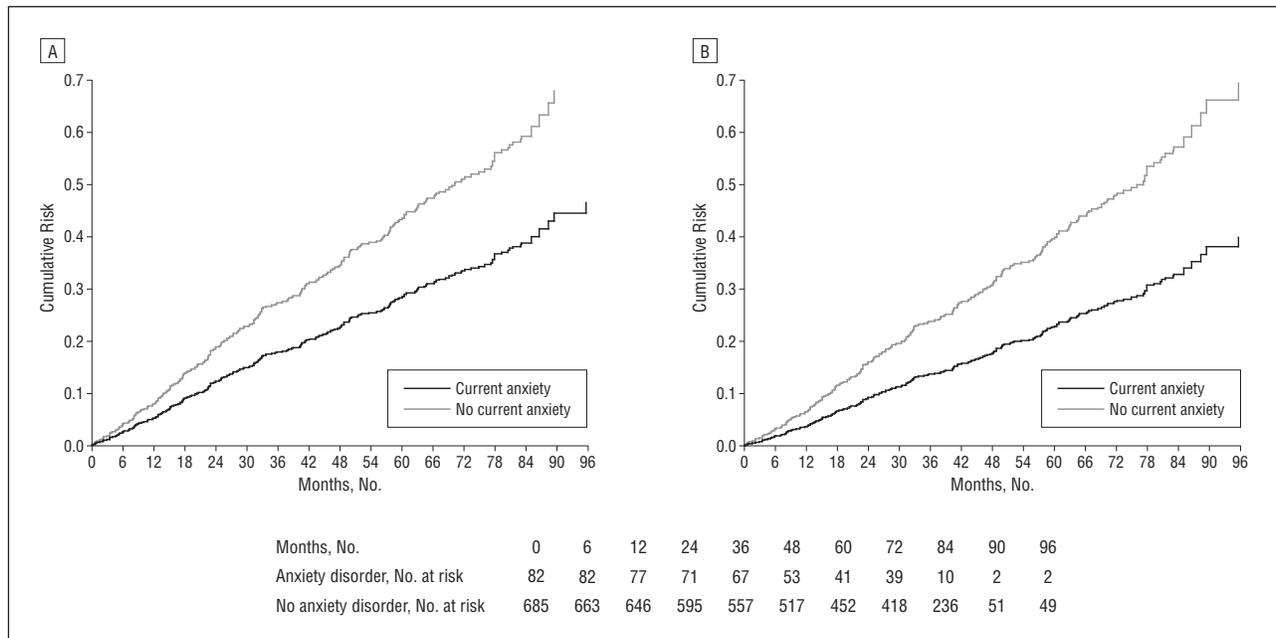
**Table 5. Fully Adjusted Model of the Association Between Generalized Anxiety Disorder and Subsequent Cardiovascular Events<sup>a</sup> in 767 Participants With Complete Data on All Covariates**

Variable	Hazard Ratio (95% CI)	$P$ Value
Anxiety disorder	1.74 (1.13-2.67)	.01
Age, per 10-y increase	1.57 (1.36-1.83)	<.001
Male sex	2.47 (1.57-3.90)	<.001
History of myocardial infarction	1.50 (1.15-1.97)	.003
History of diabetes mellitus	1.38 (1.03-1.84)	.03
Left ventricular ejection fraction, per 10% decrease	1.32 (1.17-1.49)	<.001
Exercise capacity, MET, per SD decrease	1.46 (1.23-1.73)	<.001
Renin-angiotensin system inhibitor	1.13 (0.87-1.48)	.35
Tricyclic antidepressant	1.44 (0.85-2.42)	.17
Other antidepressant	1.40 (0.88-2.22)	.16
Medication nonadherence	2.83 (1.87-4.30)	<.001
Physical inactivity	1.24 (0.95-1.62)	.12
Heart rate variability, SDANN, per SD decrease	1.15 (1.00-1.33)	.05
Log C-reactive protein level, per SD increase	1.19 (1.04-1.37)	.01

Abbreviations: CI, confidence interval; MET, metabolic equivalent task; SDANN, standard deviation of 5-minute mean NN intervals.

<sup>a</sup>Cardiovascular events were heart failure, myocardial infarction, stroke, transient ischemic attack, or death.

Given that smoking is a known major cardiovascular risk factor, we conducted a sensitivity analysis by including current smoking in the final model. This did not result in a change in the effect size of GAD. In addition, adjustment for previous smoking did not change the effect of GAD. We conducted a second sensitivity analysis by including left ventricular ejection fraction as a dichotomous variable (as <45% and as <55%) in the final model.



**Figure.** Cumulative risk of cardiovascular events stratified by the presence or absence of generalized anxiety disorder in an age-adjusted model (A) and in a model fully adjusted for potential confounders and mediators (B) in 767 participants with complete data on all covariates.

This did not result in a significant change in the effect size of GAD.

#### COMMENT

In this prospective cohort study of more than 1000 outpatients with stable CHD, participants with baseline GAD had a greater rate of subsequent cardiovascular events (stroke, heart failure, myocardial infarction, transient ischemic attack, or death) than did participants without GAD. Despite evaluating a variety of potential mediators, including cortisol, norepinephrine, and CRP levels; heart rate variability; smoking; medication nonadherence; and physical inactivity, the association between GAD and cardiovascular events could not be explained. Even after adjustment for these and other variables, GAD remained associated with a 74% greater rate of cardiovascular events.

This study is unique in its focus on the relationship of GAD to cardiovascular events in outpatients with stable CHD. We are aware of only 1 previous study that has evaluated the cardiac prognostic importance of GAD. Frasurre-Smith and Lespérance<sup>21</sup> demonstrated that GAD independently predicted cardiac events in 804 patients with acute coronary syndrome, but the extent to which the association was explained by potential behavioral and biological mediators was not assessed. Other studies<sup>11,15,18-26</sup> examining the impact of anxiety on cardiac prognosis have relied on self-report measurements of anxiety symptoms and have varied in patient populations, sample size, length of follow-up, and ability to control covariates.

We previously found that the association between depressive symptoms and cardiovascular events was largely explained by poor health behaviors, especially physical inactivity, in depressed patients with CHD.<sup>28</sup> However, despite an exhaustive search for potential mediators, we did not identify the reason for an increased risk of cardiovas-

cular events associated with anxiety disorder. Several studies have demonstrated that anxiety is linked to pathologic mechanisms involved in CHD events,<sup>51</sup> including indicators of autonomic dysfunction, such as reduced baroreflex cardiac control and reduced heart rate variability,<sup>52-55</sup> increased catecholamine levels<sup>56</sup> and platelet activity,<sup>57</sup> dysregulation of the serotonin system,<sup>58</sup> and markers of inflammation and coagulation.<sup>59</sup> Thus, we were surprised that biological mediators, such as heart rate variability (SDANN), norepinephrine level, and inflammation (CRP level), did not explain the increased risk associated with anxiety disorder in the present study. Similarly, important health behaviors, including smoking, medication adherence, and physical activity, were not responsible for the increased risk of cardiovascular events.

This leaves the question of why GAD is associated with adverse outcomes in patients with CHD. One possibility is that anxiety may be associated with surges in catecholamines, which are, in turn, related to poor CHD prognosis. Although we collected urine samples to measure levels of catecholamines and found no association with GAD, it is possible that using 24-hour specimens did not allow us to capture these fluctuations. Another possibility is that anxious patients with CHD may be less likely to seek preventive medical care, possibly due to an avoidant coping strategy. Benninghoven et al<sup>60</sup> found that patients with higher anxiety levels had worse medication compliance and less contact with their cardiologists. Patients who are less likely to seek preventive care could be at increased risk for subsequent events. Alternatively, patients with anxiety could be more likely to seek care and receive a diagnosis of stroke or myocardial infarction, and, thus, the increased risk of events could be due to greater ascertainment in patients with anxiety. However, this would not explain their increased mortality. It is also possible that there exists a common background origin to GAD symptoms

and risk of cardiovascular disease. The interplay of genetic factors or the programming effects of fetal or postnatal growth patterns may play a role. Further research to determine the mechanisms responsible for the relationship between GAD and prognosis is warranted.

We also considered the possibility that depression could have interacted with anxiety and, thus, affected the relationship found between GAD and cardiovascular events. Anxiety and depression are highly comorbid disorders in psychiatric populations and in individuals with chronic medical conditions, including heart disease.<sup>61-64</sup> In the present study, 80% of patients with GAD had comorbid depressive disorder. However, adjusting for major depression did not change the effect of GAD on cardiovascular events, and we found no evidence of an interaction between GAD and depression. Therefore, the prognostic value of GAD seems to be independent of depressive disorder. This finding is consistent with 2 previous studies<sup>11,19</sup> that found anxiety to be a significant predictor of cardiovascular events after adjustment for depression.

Finally, GAD was associated with lower  $\omega$ -3 fatty acid levels. There is a clear association between dietary factors resulting in lower levels of  $\omega$ -3 fatty acids and increased CHD risk.<sup>65,66</sup> In addition, a recent study<sup>43</sup> found a strong association between low  $\omega$ -3 fatty acid levels and depression in outpatients with stable CHD. Although  $\omega$ -3 fatty acid levels did not affect the strength of association between GAD and cardiovascular events, this is a potentially interesting avenue to explore.

This study has several strengths, including detailed assessments of GAD and cardiac disease severity, careful measurement of potential behavioral and biological mediators, and comprehensive assessment of cardiovascular events. However, several limitations must also be considered. First, most of the participants were older men, and almost half were recruited from VA medical centers. Therefore, these results may not generalize to women or to other patient populations. Second, the associated risk with GAD may have been the result of greater cardiac disease severity. We attempted to address this possibility by carefully measuring and adjusting for comorbid conditions and cardiovascular disease severity. However, no observational study can completely eliminate confounding, and it remains possible that the effect of GAD on cardiovascular outcomes may have been affected by worse underlying cardiac disease severity that was not otherwise accounted for in the models. Third, this study was limited to outpatients with stable CHD, and, thus, we cannot comment on the mechanisms of association between anxiety and cardiovascular outcomes in healthy populations or in patients after acute coronary syndrome. Fourth, we did not account for other anxiety disorders, such as specific phobias, panic disorder, or posttraumatic stress disorder. In addition, the high comorbidity between GAD and MDD could also mean that minor variants of depression are prevalent that we did not account for in the analyses. Fifth, we had no information on the time frame between the qualifying CHD event and the assessment of GAD except that it was at least 6 months before enrollment.

Despite these limitations, these findings have implications for clinical practice and research. GAD may be considered a prognostic factor in patients with CHD and could

be used in risk stratification. Evaluation and treatment of anxiety may also be considered as part of the comprehensive management of patients with CHD. Research programs designed to advance our understanding of the impact of GADs on medical prognosis and biobehavioral mechanisms that link anxiety to mortality in the context of CHD are needed to develop evidence-based approaches to improving patient care. In particular, randomized clinical trials will be necessary to determine whether pharmacologic and behavioral interventions to reduce anxiety will result in better CHD outcomes. The management of anxiety in patients with CHD may also require the development of collaborative and integrative approaches combining medical and psychological expertise.

In summary, we found a strong and robust association between GAD and cardiovascular events that could not be explained by disease severity, health behaviors, or biological mediators. The results of this study indicate the need for future research to identify the underlying processes by which GAD contributes to adverse events in patients with CHD and to test interventions to alleviate this increased risk.

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