Self-reported anxiety and the risk of clinical events and atherosclerotic progression among patients with Coronary Artery Bypass Grafts (CABG)

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Background Symptoms of anxiety are associated with increased risk of coronary artery disease and potentially poor prognosis among patients with existing coronary artery disease, but whether symptoms of anxiety influence atherosclerotic progression among such patients is uncertain. Accordingly, we evaluated the hypotheses that symptoms of anxiety are associated with adverse clinical outcomes and progression of atherosclerosis among individuals with previous coronary artery bypass graft (CABG) surgery and saphenous vein grafts enrolled in the Post-CABG Trial.

Methods The Post-CABG Trial randomized patients with a history of CABG surgery to either aggressive or moderate lipid lowering and to either warfarin or placebo. Patients were followed up for clinical end points and coronary angiography was conducted at enrollment and after a median follow-up of 4.3 years. Anxiety symptoms were assessed at enrollment using the state portion of the Spielberger State-Trait Anxiety Inventory (STAI) in 1317 patients.

Results In models adjusting for age, sex, race, treatment assignment and years since CABG surgery, a STAI score ≥40 was positively associated with risk of death or myocardial infarction (MI) (OR 1.55, 95% CI 1.01-2.36, P = .044). This association was attenuated slightly when depressive symptoms were included in the model, but lost statistical significance (P = .11). There was a dose-response relationship between STAI score and risk of death or MI. There was no association between self-reported anxiety and atherosclerotic progression of grafts.

Conclusions Anxiety symptoms are associated with increased risk of death or MI among patients with saphenous vein grafts, but this risk does not appear to be mediated by more extensive atherosclerotic progression. (Am Heart J 2009;158:867-73.)

Anxiety and symptoms of anxiety are a risk factor for coronary artery disease in healthy populations.[1,2] However, the role of anxiety in predicting adverse cardiac events in those already diagnosed with coronary artery disease (CAD) is unclear,[3-5] with a recent review suggesting that there is little evidence to suggest any role at all.[2] Among CAD patients undergoing CABG surgery, anxiety is common and is associated with an increased all-cause mortality risk.[6-8] However, little is known about possible pathways that might explain this association. In particular, the relationship between anxiety and the progression of atherosclerosis is unclear, and the few studies that have been published show conflicting results.[9,10] Although we recently showed that the presence of depressive symptoms is associated with progression of atherosclerosis among individuals with previous CABG surgery, the effect of anxiety on atherosclerotic progression in these grafts is not known.[11] Therefore, we evaluated the hypotheses that symptoms of anxiety are associated with adverse clinical outcomes and progression of atherosclerosis among individuals with previous CABG surgery and saphenous vein grafts enrolled in the Post-CABG trial.[12]

Methods

Study population and design

The Post-CABG Study is a completed multicenter clinical trial that compared the effects of 2 lipid-lowering strategies and low-dose anticoagulation versus placebo on the progression of atherosclerosis in saphenous vein grafts, as documented by assessment of angiograms obtained at baseline and 4 to 5 years after study entry. Participants were aged 21 to 74 years at enrollment, had undergone CABG surgery 1-11 years before enrollment and had ≥2 patent saphenous vein grafts in men and ≥1 in women. Participants also had an low-density lipoprotein

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cholesterol (LDL-C) of 130 to 175 mg/dL, plasma triglycerides <300 mg/dL, and left ventricular ejection fraction ≥30%. Specific exclusion criteria included unstable angina, decompensated heart failure, New York Heart Association class III and IV heart failure, life-threatening arrhythmias, large left ventricular aneurysm, life-threatening cerebrovascular disease, systemic hypertension refractory to drug therapy, and severe renal or hepatic dysfunction. Subjects with MI within the previous 3 months, percutaneous coronary intervention within the previous 6 months, gastrointestinal hemorrhage or diagnosis of active gastrointestinal ulcer within 2 years, major psychiatric disorders, or absolute contraindications to treatment with any study medications were excluded. In total, 1351 patients were enrolled between March 1989 and August 1991. Of these, 1317 completed a quality of life questionnaire and form the cohort for the present study. All participants provided written informed consent.

Participants were randomly assigned in a 2 × 2 factorial design to either aggressive LDL-C lowering with lovastatin 40 to 80 mg/d to achieve an LDL-C of 60 to 85 mg/dL or moderate LDL-C lowering with lovastatin 2.5 to 5 mg/d to achieve an LDL-C of 130 to 140 mg/dL and either warfarin 1 to 4 mg/d to achieve an international normalized ratio of 1.8 to 2.0 or warfarin-placebo. All prospective participants received active warfarin treatment 1 month before randomization. Only participants who consumed over 90% of the prescribed medication were randomized. Participants' adherence to prescribed treatment with lovastatin during the trial was excellent; 85% to 90% took the medication as prescribed.[12]

Anxiety symptoms

Self-reported anxiety symptoms were assessed at study enrollment using the state component of the widely used and extensively validated Spielberger State-Trait Anxiety Inventory (STAI).[13-15] The state portion of the STAI is a 20-item self-administered instrument designed to measure the presence of anxiety symptoms at the present moment. The two STAI subscores (ie, the state and trait) have high concordance in people with diagnosed Generalized Anxiety Disorder as well as people without diagnosed anxiety.[13] The STAI does not capture information on patients' clinical or treatment history. State-Trait Anxiety Inventory scores range from 20 to 80, with higher scores indicating more severe symptoms. To permit comparability with previous studies, we dichotomized the STAI scores using scores of <40 to indicate no or minimal symptoms and ≥40 to indicate the presence of moderate or severe symptoms.[15,16]

Outcome measurements

We considered angiographic and clinical end points as determined by the Post-CABG investigators.[12] As previously,[11,17,18] we examined an end point of death or MI alone. Participants were also followed for a prespecified composite end point of death, MI, stroke, recurrent bypass surgery, or angioplasty.

The primary angiographic end point of the trial was significant worsening of initially patent grafts, defined as a decrease of ≥0.6 mm in lumen diameter at the site of greatest change at follow-up. It included worsening of pre-existing lesions, new lesions in previously intact grafts, and occlusion. All initially patent grafts were considered to have developed graft worsening in patients who died before follow up angiography. Surviving participants who did not have follow-up or interim angiograms and who did not undergo repeated bypass surgery or angioplasties were excluded from angiographic analyses. Additional prespecified angiographic trial end points included complete occlusion of grafts patent at baseline and change in minimum lumen diameter. Baseline and follow-up angiograms were obtained with catheterization techniques that permitted computer-assisted quantitative measurement (CAAS system, PIE Medical Maastrecht).[19]

Other covariates

At enrollment, participants reported their smoking history (grouped as never, former, <20 cigarettes per day, and ≥20 per day) and alcohol consumption (grouped as none, 1-6, 7-13, and ≥14 drinks per week). Serum creatinine was measured at enrollment, and we estimated glomerular filtration rate (eGFR) using the abbreviated Modified Diet and Renal Disease study equation.[20] Participants were grouped according to eGFR in 3 categories (<60.0, 60.0-74.9, and ≥75.0 mL/min per 1.73 m^2). Depressive symptoms were measured with the Centers for Epidemiologic Studies Depression scale (CES-D), a 20-item self-administered instrument designed to measure the presence of depressive symptoms over the previous week in community studies.[21] The CES-D, which has been widely used and extensively validated, does not capture information on patients' clinical or treatment history and is not a diagnostic tool for depression.[22-25] To ensure comparability with other studies,[26] we chose a priori to use scores of <16 to indicate no or minimal depressive symptoms and ≥16 to indicate the presence of moderate or severe symptoms.

Statistical methods

Cox proportional hazards models were used to evaluate the association between symptoms of anxiety and risk of clinical events. We first examined the association of STAI score with outcomes in models adjusted for age (in quartiles), years since CABG (as a continuous variable), sex, race (white versus other), and treatment assignment (four categories). Next, we additionally adjusted for CAD risk factors including current smoking, systolic blood pressure, history of type 2 diabetes mellitus requiring treatment with sulfonylureas or insulin, eGFR, and alcoholic beverage consumption. In the third model, we added history of MI or stroke. Finally, in our last model we additionally adjusted for depressive symptoms. We assessed the validity of the proportional hazards assumption using Schoenfeld residual plots for each covariate.[27]

We conducted exploratory analyses to examine potential dose-response relationships. We created quintiles of STAI score and assigned each quintile the median value of the quintile and then tested for linear trend, adjusting for all of the above covariates. In addition, we analyzed for dose-response relationship using the STAI score as a continuous variable. We also analyzed the risk of death or MI associated with having high STAI score alone, a high CES-D score alone, or both, compared to scoring low on both scales, and then analyzed the potential interaction between presence of anxiety symptoms and presence of depressive symptoms. As a sensitivity analysis, we centered the anxiety symptoms and depressive symptoms scores by subtracting the mean for each and then repeated the interaction analysis. This approach avoids biases that may arise from examining the interaction between 2 categorical variables.

As described by the Post-CABG investigators, we analyzed graft progression on a per-graft basis using generalized estimating equations to account for the clustering of grafts within participants.[28] We used a logit link function for binary outcomes (substantial progression of atherosclerosis and graft occlusion) and an identity link function for change in minimal lumen diameter and assumed an exchangeable correlation matrix in all models. We created sequentially adjusted models using the covariates described above to examine the effects of potential confounding factors. Finally, we examined potential dose-response relationships as above.

P values are 2-tailed, and CIs were computed at the 95% level. Analyses were carried out using SAS 9.1 (SAS Institute, Cary, NC). This analysis was approved by the Beth Israel Deaconess Medical Center Committee on Clinical Investigations. The Post-CABG Study was conducted and supported by the National Heart, Lung, and Blood Institute, National Institutes of Health (Bethesda, MD) and Merck and Company in collaboration with the Post-CABG Study Investigators. This manuscript was prepared using a limited access dataset obtained from the National Heart, Lung, and Blood Institute. The project was supported by grant no. ES015774 from the National Institute of Environmental Health Sciences (Bethesda, MD). Dr Mittleman held an Established Investigator Grant from the American Heart Association (AHA 0140219N) (Dallas, TX). The authors are solely responsible for the design and conduct of this study, all study analyses, and drafting and editing of the manuscript.

Results

Baseline characteristics

Participants had a mean age of 61.5 years and were predominantly white (94%) and men (93%). STAI scores ranged from 20-76, with a median of 29. The 226 participants with scores ≥40 tended to be younger with more cardiovascular risk factors (Table I). They were also more likely to exhibit depressive symptoms. The Pearson correlation between self-reported anxiety score and self-reported depressive symptoms score was 0.55 ($P < .0001$).

Table I. Baseline characteristics of Post-CABG participants according to self-reported anxiety score

	Self-reported anxiety score		
	≥40	<40	Missing
	(n = 226)	(n = 1091)	(n = 34)
Age (y, mean ± SD)	60.3 ± 7.7	61.8 ± 7.2	60.6 ± 7.3
Male sex (%)	91.2	92.2	85.3
White race (%)	91.6	94.9	97.1
Time since CABG (y)	5.0 ± 2.7	4.8 ± 2.5	5.2 ± 2.5
Systolic blood pressure (mm Hg)	135.5 ± 20.4	134.0 ± 17.1	135.9 ± 14.2
Diastolic blood pressure (mm Hg)	80.3 ± 10.3	79.6 ± 8.7	81.8 ± 8.3
Estimated glomerular filtration rate (mL/min per 1.73 m^2)	74.0 ± 14.3	73.0 ± 15.0	74.8 ± 15.0
Medical history (%)			
Myocardial infarction	50.0	48.5	58.8
Stroke	0.9	3.1	2.9
Hypertension	41.2	34.5	29.4
Diabetes mellitus	9.7	8.5	2.9
Smoking history (%)			
Current	15.9	10.3	2.9
Former	63.7	63.2	79.4
Body mass index (kg/m^2)	27.7 ± 4.1	27.7 ± 4.6	27.9 ± 4.1
Alcohol consumption (drinks/week)	2.5 ± 4.7	2.9 ± 5.0	2.4 ± 7.5
Number of SVGs (mean, range)	2.6 (1-6)	2.6 (1-8)	2.5 (1-5)
Self-reported Depression Score ≥16 (%)	35.0	4.3	Missing

SVG, Saphenous vein graft.

Clinical events

During a median follow-up of 4.3 years, 122 participants developed the end point of death or MI (Table II). In survival analyses controlling for age, sex, race, years since CABG, and treatment assignment, the presence of anxiety symptoms (STAI ≥40) was associated with a hazard ratio of 1.55 (95% CI 1.01, 2.36, $P = .044$). In addition, controlling for systolic blood pressure, diabetes mellitus, eGFR, current smoking, and alcohol consumption attenuated this association, and it lost statistical significance ($P = .08$) (Table III). When controlling further for history of MI or stroke, the association remained the same but, again, was not statistically significant ($P = .06$) (Table III). Finally, the association remained similar when additionally controlling for presence of depressive symptoms, ($P = .11$) (Table III). In interaction analyses in the final model, there was no evidence to suggest that the effect of anxiety differed by lipid-lowering group (aggressive vs moderate, $P_{\text{homogeneity}} = .77$), or assignment to warfarin versus placebo ($P_{\text{homogeneity}} = .86$). There was a statistically significant dose-response relationship between self-reported anxiety score in quintiles and risk of death or MI in the base and full models, and the *P* value for linear trend in the full model was .007. In the dose-response model treating STAI score as a continuous variable, the hazard ratio was 1.022 (95% CI 1.00-1.04, $P = .048$). This means that for every 10-point increase in STAI score, the risk of death or MI increased by 24%.

We also analyzed the risk of death or MI associated with having high STAI score alone, a high self-reported depression score (CES-D ≥16) alone, or both, compared to scoring low on both scales. In this model, which included age, sex, race, years since CABG surgery, and treatment assignment, the hazard ratio for anxiety alone (n = 147) was 1.37 (95% CI 0.82-2.27, $P = .22$), and for depression alone (n = 47), the hazard ratio was 1.18 (95% CI 0.43-3.25, $P = .74$). In those having both self-reported depressive and anxiety symptoms (n = 79), the

Table II. Crude clinical event rates by self-reported anxiety score

	Self-reported anxiety score ≥40	Self-reported anxiety score <40	*P*
No. of participants	226	1091	
Death or MI			
Number of events	30	92	
Person-years	908	4497	
Rate/1000 person-years	33.0	20.5	.021
Composite end point*			
Number of events	38	160	
Person-years	887	4316	
Rate/1000 person-years	42.9	37.1	.42

*Composite end point is death, MI, stroke, recurrent bypass surgery, or angioplasty.

Table III. Association between anxiety symptoms (self-reported anxiety score ≥40) and clinical outcomes among Post-CABG participants*

	Death or MI end point		Composite end point of death, MI, stroke, recurrent bypass surgery, or angioplasty	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Base model*	1.55 (1.01-2.36)	.04	1.05 (0.73-1.50)	.81
Model B†	1.47 (0.96-2.26)	.08	1.00 (0.70-1.45)	.99
Model C‡	1.52 (0.99-2.34)	.06	1.02(0.71-1.48)	.90
Model D§	1.47 (0.92-2.35)	.11	0.94 (0.63-1.40)	.76

*Referent group is patients with self-reported anxiety score <40. Base model is adjusted for age, sex, race, treatment assignment, and years since CABG surgery.
†Model B is the base model additionally adjusted for current smoking, systolic blood pressure, diabetes, eGFR, and alcohol consumption.
‡Model C is additionally adjusted for history of MI or stroke.
§Model D is additionally adjusted for presence of depressive symptoms.

hazard ratio was 2.04 (95% CI 1.08, 3.89, $P = .029$). We found no evidence to suggest that the effect of anxiety symptoms differed by the presence of depressive symptoms ($P_{\text{homogeneity}} = .72$), but our statistical power to detect such a difference was limited. Treating depressive symptoms and anxiety symptoms scores as continuous variables did not materially alter the results ($P_{\text{homogeneity}} = .11$).

When we considered the composite end point of death, MI, stroke, recurrent bypass surgery, or angioplasty, there was no association between anxiety symptoms and risk of the composite end point. Controlling for smoking, systolic blood pressure, diabetes, eGFR, history of MI or stroke, and depressive symptoms did not materially alter these results (Table III). In analysis by STAI quintiles, there was no dose-response relationship. In the fully adjusted model, the hazard ratio for revascularization procedures alone (ie, the composite end point excluding death, MI, and stroke) was 0.63 (95% CI 0.36, 1.13, $P = .12$).

Angiographic outcomes

Data on substantial progression of atherosclerosis and graft occlusion were available for 1174 participants (89%) in the study population. Of 407 grafts in participants with anxiety symptoms, 129 (31.7%) developed substantial progression of atherosclerosis, and 32 (7.9%) became occluded. Data on change in minimum lumen diameter were available for 1077 participants (82%).

In regression models controlling for age, sex, race, years since CABG surgery, and treatment assignment, the presence of anxiety symptoms was not associated with an increase in odds of substantial graft disease progression (OR 1.15, 95% CI 0.87-1.51, $P = .34$) (Table IV). Addition of further covariates did not alter this finding. There was no evidence of an association between the presence of anxiety symptoms and either graft occlusion or change in minimum lumen diameter (Table IV). These results were not materially altered in the sensitivity analysis comparing participants in the top tenth percentile for anxiety (self-reported anxiety score ≥43) with the rest. There was no clear dose-response pattern.

Discussion

In this study of clinical trial participants with previous CABG surgery, the presence of anxiety symptoms was significantly associated with a higher incidence rate of death or MI after a median follow-up time of 4.3 years. After controlling for the presence of depressive symptoms and other covariates, the association remained although it was no longer statistically significant, and a significant dose-response relationship persisted. The risk of death or MI in those with both depressive and anxiety symptoms was what would be expected from the combination of the independent effects. Anxiety symptoms had no detectable effect on any of our measures of atherosclerotic progression of saphenous vein grafts and were not associated with revascularization procedures during follow-up.

These results are in keeping with previous studies that have shown that anxiety is an independent risk factor for all-cause mortality in patients who have undergone CABG surgery[7,8] and suggest that the presence of anxiety symptoms is cause for concern in these patients. The observed dose-response relationship between STAI score and risk of death or MI indicates that even at lower levels of anxiety attention is warranted. Some[2] but not all prior studies in patients with stable CAD[5] have found that anxiety is associated with worse prognosis. However, patients who have undergone CABG surgery are a distinct subset of patients with CAD and may be affected differently by anxiety.

Table IV. Association between anxiety symptoms (self-reported anxiety score ≥40) and angiographic outcomes among Post-CABG Participants*

	Substantial progression of atherosclerosis		Graft occlusion		Change in minimum lumen diameter	
	OR (95% CI)	P	OR (95% CI)	P	Δ (95% CI)	P
Base model*	1.15 (0.87-1.51)	.34	0.96 (0.63-1.47)	.86	–0.011 (–0.098 to 0.074)	.79
Model B†	1.11 (0.84-1.47)	.47	0.92 (0.60-1.42)	.72	–0.0064 (–0.092 to 0.079)	.88
Model C‡	1.14 (0.87-1.51)	.35	0.94 (0.61-1.44)	.77	–0.011 (–0.097 to 0.075)	.80
Model D§	1.00 (0.74-1.37)	.99	0.86 (0.54-1.38)	.53	0.022 (–0.073 to 0.11)	.65

Δ, Mean change in mm.
* Referent group is patients with self-reported anxiety score <40. Base model is adjusted for age, sex, race, treatment assignment, and years since CABG surgery.
† Model B is the base model additionally adjusted for current smoking, systolic blood pressure, diabetes, eGFR, and alcohol consumption.
‡ Model C is additionally adjusted for history of MI or stroke.
§ Model D is additionally adjusted for presence of depressive symptoms.

In this study, the combined effect of depressive and anxiety symptoms was not statistically higher than the effect of each alone. Our results are consistent with the findings of Frasure-Smith and Lesperance, who recently studied a cohort of patients with stable CAD and found that patients with comorbid clinical diagnoses of both anxiety and depression did not have a higher risk of major adverse cardiac events than those who carried only one diagnosis.[5]

We found that presence of anxiety symptoms was not associated with atherosclerotic progression in saphenous vein grafts. This finding corroborates the recent finding that anxiety symptoms have no effect on atherosclerotic progression in carotid arteries in healthy individuals.[10] On the other hand, symptoms of anxiety have been associated with endothelial dysfunction in healthy elderly men, which may indicate that anxiety affects the process of atherogenesis.[29] Our findings are further bolstered by the fact that anxiety symptoms were not associated with increased risk of revascularization procedures in these patients. Although it is possible that anxious patients are under-treated, the fact that they had no more risk of atherosclerotic progression of saphenous vein grafts may indicate that there are other mechanisms besides atherosclerosis contributing to death or MI in these patients.

The question remains, then, by what mechanism might anxiety affect long-term outcome in patients with CAD? Chronic stress provokes MI in people with underlying heart disease through a number of proposed mechanisms,[3] including vasomotor abnormalities in epicardial coronary arteries, abnormally high production of catecholamines in response to stress resulting in higher myocardial oxygen demand and risk of sudden death, and abnormalities in thrombosis and hemostasis.[3] Anxiety could indirectly alter control of other clinical risk factors through its effects on weight, smoking, alcohol use, and exercise. In models presented here, we controlled for smoking, assuming it to be a potential confounder. If instead smoking is an intermediate, it would be inappropriate to adjust for it. However, removing smoking from the full model of death or MI did not change either the point estimate or the p-value (data not shown). Alternatively, anxiety may be a risk marker of other psychiatric states or more severe underlying disease.

Specific strengths and limitations of the Post-CABG trial warrant discussion. The trial was large and based in multiple centers, and the assessment of graft progression was uniform and systematic with prespecified angiographic end points. Robust data on potential confounders were available, and both angiographic and clinical outcomes were assessed. Adherence to medication was a prerequisite for entry, so the effects of anxiety symptoms independent of this potential pathway could be studied. On the other hand, exclusion of noncompliant patients limits the generalizablily of this study, and limits our ability to evaluate the effects of medication non-compliance. Finally, the STAI is a widely accepted instrument with well-established reliability and validity.

At the same time, this study has some important limitations. First, the state anxiety component of the STAI does not indicate the presence of major affective disorders nor does it capture clinical diagnoses or treatment. In fact, people with severe psychiatric illness were excluded from the study. Furthermore, we used the state component of the STAI, which does not measure trait anxiety directly. However, these two measures are highly correlated.[13] Second, patients were recruited into this study up to 11 years after CABG surgery, resulting in large variations in the degree of graft atherosclerosis at baseline and possibly obscuring the effects of anxiety symptoms on atherosclerotic progression. Third, as this was a clinical trial with restrictive inclusion criteria, the results of this study may not be generalizable to different patient populations. For example, whether anxiety symptoms alter atherosclerotic progression in arterial grafts or native coronary arteries requires further study. The generalizability of the trial is further limited by its restriction to predominantly white and male clinical trial participants. Although this restriction limited the variability among

participants and reduced potential confounding, similar longitudinal angiographic studies are needed in broader populations. Fourth, depression and anxiety often overlap and the instruments used to assess them are not specific.[5] A review of the literature recently concluded that there is much confusion in measuring different negative affective dispositions.[2] However, we compared those who had only anxiety symptoms, only depressive symptoms, and the two conditions together, which should result in better differentiating the conditions. It is possible that having any negative affective disposition confers risk for death or MI. Finally, the study data were collected over a decade ago, which could limit its clinical use. Regardless of changes in treatment modalities, however, these data still allow elucidation of the biological relationship between anxiety symptoms and progression of atherosclerosis in saphenous vein grafts.

In summary, among patients who had undergone previous CABG surgery, anxiety symptoms were associated with higher risk of death or MI, although this relationship lost statistical significance after controlling for the effect of depressive symptoms. However, there was no increased risk of atherosclerotic progression in saphenous vein grafts. Despite advances in surgical and medical management of CABG patients, the prognostic import of anxiety symptoms on death or MI provides a potentially valuable opportunity to elucidate mechanisms of this relationship and to reduce adverse outcomes among patients with saphenous vein grafts. We encourage further studies to determine whether treating anxiety will impact the risk of death or MI in such patients.

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