Depressive Symptoms and the Risk of Atherosclerotic Progression Among Patients With Coronary Artery Bypass Grafts

Gregory A. Wellenius, ScD; Kenneth J. Mukamal, MD, MPH; Ambar Kulshreshtha, MB, MPH; Sharon Asonganyi, MPH; Murray A. Mittleman, MD, DrPH

Background—Depressive symptoms have been associated with increased risk of coronary artery disease and poor prognosis among patients with existing coronary artery disease, but whether depressive symptoms specifically influence atherosclerotic progression among such patients is uncertain.

Methods and Results—The Post-CABG Trial randomized patients with a history of coronary bypass graft surgery to either an aggressive or a moderate lipid-lowering strategy and to either warfarin or placebo. Coronary angiography was conducted at enrollment and after a median follow-up of 4.2 years. Depressive symptoms were assessed at enrollment with the Centers for Epidemiologic Studies Depression scale (CES-D) in 1319 patients with 2496 grafts. In models that adjusted for age, gender, race, treatment assignment, and years since coronary bypass graft surgery, a CES-D score \( \geq 16 \) was positively associated with risk of substantial graft disease progression (OR 1.50, 95% CI 1.08 to 2.10, \( P = 0.02 \)) and marginally associated with a 0.11-mm (95% CI 0.22 to 0.01 mm, \( P = 0.07 \)) decrease in minimum lumen diameter, but not with risk of graft occlusion (\( P = 0.30 \)). Additional adjustment for past medical history, blood pressure, and renal function did not materially alter these results. This association was virtually absent among participants randomly assigned to aggressive lipid-lowering therapy.

Conclusions—These findings suggest that depressive symptoms are associated with a higher risk of atherosclerotic progression among patients with saphenous vein grafts and that aggressive lipid lowering can minimize this increased risk. Whether depressive symptoms increase progression in other types of coronary atherosclerosis and whether aggressive lipid lowering attenuates such progression will require additional study. (Circulation. 2008;117:2313-2319.)

Key Words: depression ▪ coronary disease ▪ atherosclerosis ▪ coronary artery bypass grafting ▪ saphenous vein

Depression and depressive symptoms are highly prevalent among patients with coronary artery disease (CAD) and independently predict adverse cardiovascular events. In patients with CAD, depression has been associated with recurrent myocardial infarction, angina, ventricular arrhythmias, and mortality. Depression is also specifically associated with a higher risk of cardiac events after coronary artery bypass graft (CABG) surgery. Patients with depression before CABG are more often depressed after the surgery and have worse physical function and higher comorbidity. Surprisingly, whether treatment for depression improves clinical outcomes among patients with CAD remains uncertain.

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Several mechanisms may mediate the observed association of depression with adverse outcomes among patients with CAD. Depression has been associated with decreased adherence to treatment, with a variety of potentially unfavorable lifestyle characteristics such as obesity and smoking, and with higher levels of inflammatory and prothrombotic markers. There have been few studies investigating the potential link between depressive symptoms and progression of atherosclerosis per se, despite the association between depression and clinical outcomes. Accordingly, we evaluated the hypothesis that depressive symptoms are associated with progression of atherosclerosis among individuals with previous CABG surgery and saphenous vein grafts enrolled in the Post-CABG Trial.

Methods

Study Population and Design
The Post-CABG Study is a completed clinical trial designed to compare the effects of 2 lipid-lowering strategies and low-dose warfarin on progression of atherosclerotic disease among patients with a history of coronary artery bypass graft surgery. The study enrolled 2507 patients from 15 centers in the United States, and the primary end point was the occurrence of major adverse cardiovascular events, including myocardial infarction, stroke, or death. Patients were randomly assigned to either an aggressive lipid-lowering strategy or a moderate strategy, and to either warfarin or placebo. Coronary angiography was conducted at enrollment and after a median follow-up of 4.2 years. Depressive symptoms were assessed at enrollment with the Centers for Epidemiologic Studies Depression scale (CES-D) in 1319 patients with 2496 grafts. In models that adjusted for age, gender, race, treatment assignment, and years since coronary bypass graft surgery, a CES-D score \( \geq 16 \) was positively associated with risk of substantial graft disease progression (OR 1.50, 95% CI 1.08 to 2.10, \( P = 0.02 \)) and marginally associated with a 0.11-mm (95% CI 0.22 to 0.01 mm, \( P = 0.07 \)) decrease in minimum lumen diameter, but not with risk of graft occlusion (\( P = 0.30 \)). Additional adjustment for past medical history, blood pressure, and renal function did not materially alter these results. This association was virtually absent among participants randomly assigned to aggressive lipid-lowering therapy.

Conclusions—These findings suggest that depressive symptoms are associated with a higher risk of atherosclerotic progression among patients with saphenous vein grafts and that aggressive lipid lowering can minimize this increased risk. Whether depressive symptoms increase progression in other types of coronary atherosclerosis and whether aggressive lipid lowering attenuates such progression will require additional study. (Circulation. 2008;117:2313-2319.)

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Other Covariates

At enrollment, participants reported their smoking history (grouped as never, former, <20 cigarettes per day, and ≥20 per day), physical activity level relative to others of their age and sex (grouped to create 3 levels of activity), and alcohol consumption (grouped as none or 1 to 6, 7 to 13, and ≥14 drinks per week). Body mass index was measured at enrollment and grouped into 3 categories (<25, 25 to 29.9, and ≥30 kg/m²). Serum creatinine was measured at enrollment, and we estimated glomerular filtration rate using the abbreviated Modified Diet and Renal Disease study equation.24 Participants were grouped according to estimated glomerular filtration rate in 3 categories (<60.0, 60.0 to 74.9, and ≥75.0 mL·min⁻¹·1.73 m⁻²).

Statistical Analysis

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.25 We used a logit link function for binary outcomes and an identity link function for change in minimal lumen diameter, and we assumed an exchangeable correlation matrix in all models. We created sequentially adjusted models to examine the effects of confounding and potentially mediating factors. We first examined the association of CES-D scores with outcome in models adjusted for age (in quartiles), years since CABG (as a continuous variable), gender, race (white versus other), and treatment assignment (4 categories). We then developed additional models that further adjusted for systolic blood pressure, use of antihypertensive medication, estimated glomerular filtration rate, history of myocardial infarction and stroke, and type 2 diabetes mellitus that required pharmacological treatment with sulfonylureas or insulin. We lastly adjusted for behavioral determinants that may be on a causal pathway between depressive symptoms and graft disease progression, including body mass index, former or current smoking, alcohol intake, physical activity, total cholesterol, high-density lipoprotein cholesterol, and triglycerides.

In stratified analyses, we evaluated whether the effect of depressive symptoms varied by age (<65 versus ≥65 years) using generalized estimating equation models that included an age-by–CES-D interaction term and controlled for lipid-lowering strategy, warfarin assignment, gender, race, and years since CABG. Similarly, we evaluated whether the effect of depressive symptoms varied by lipid-lowering strategy (moderate versus aggressive) using generalized estimating equation models that included a strategy-by–CES-D interaction term and controlled for warfarin assignment, age, gender, race, and years since CABG. These models assume no interaction between the warfarin and lipid-lowering strategy treatment arms. This assumption is supported by the published primary analysis of the Post-CABG trial.15

Cox proportional hazards models were used to evaluate the association between depressive symptoms and risk of clinical events. We controlled for similar covariates as in generalized estimating equation models and assessed the validity of the proportional hazards assumption graphically using plots of Schoenfeld residuals for each covariate.26 The number of clinical events was insufficient to support robust stratified analyses by age or treatment assignment.

CES-D scores were available in 1319 (97.6%) of patients. The exclusion of subjects with missing values from analyses can lead to biased results. Multiple imputation is an effective method for dealing with the missing data under certain assumptions. This method replaces each missing value with a set of plausible values that represent the uncertainty about the right value to impute. The imputed data sets are then analyzed with standard regression techniques, and the overall results are obtained by combining the results from analysis on each imputed data set.

We used Markov chain Monte Carlo multiple imputation methods27 to create 5 simulated data sets in which CES-D scores were available in all subjects. All analyses on angiographic and event end points were performed on each simulated data set. Results for each analysis from the imputed data sets were combined with an accounting for both the within-imputation and between-imputation variances. This procedure yields SEs, CIs, and probability values that reflect the uncertainty in the imputed values.

Outcome Measurements

Baseline and follow-up angiograms were obtained with catheterization techniques that permitted computer-assisted quantitative measurement (CAAS system, PIE Medical Imaging, Maastricht, Netherlands).23 The primary 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 preexisting 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 analyses. Additional prespecified angiographic trial end points included complete occlusion of grafts that were patent at baseline and change in minimum lumen diameter.

In addition, participants were followed up for a prespecified composite end point of death, myocardial infarction, stroke, recurrent bypass surgery, or angioplasty. As in the past,22,23 we also examined an end point of death or myocardial infarction alone (ie, excluding revascularizations).
All probability values are 2-tailed and all CIs computed at the 95% level. Analyses were performed with SAS 9.1 (SAS Institute, Cary, NC). This analysis was approved by the Beth Israel Deaconess Medical Center Committee on Clinical Investigations.

The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

Baseline Characteristics

Participants had a mean age of 61.5 years, and were predominantly white (94%) and male (92%). CES-D scores were available in 1319 (97.6%) of patients and ranged from 0 to 56, with a median score of 5 (Figure). The 127 participants (9.6%) with CES-D scores ≥16 tended to be younger, more often women, and more likely to have cardiovascular risk factors (Table 1).

Angiographic Outcomes

Data on substantial progression of atherosclerosis and graft occlusion were available for 1192 participants (88%; Table 2). Of 213 grafts in participants with depressive symptoms, 34.3% developed substantial progression of atherosclerosis, and 9.4% became occluded. Data on change in minimum lumen diameter were available for 1091 participants (81%).

We used multiple imputation methods to simulate CES-D scores for subjects with missing values. In regression models that controlled for age, gender, race, years since CABG surgery, and treatment assignment, the presence of depressive symptoms was associated with a 50% (95% CI 8% to 210%, \( P=0.02 \)) greater risk of substantial graft disease progression and was marginally associated with a 0.11-mm (95% CI -0.22 to 0.01 mm, \( P=0.07 \)) greater decrease in minimum lumen diameter (Table 3). Depressive symptoms were not associated with significantly greater risk of graft occlusion, a less common outcome. Additional adjustment for potential confounders did not materially alter these results. Inclusion of potential mediators reduced the OR for significant graft progression from 1.49 to 1.41, a 13.8% decrease in the regression coefficient for depressive symptoms. In sensitivity analyses, no increased risk was observed for any outcome for participants with a CES-D score between 8 and 15.

We repeated these analyses excluding subjects for whom the CES-D score was missing (rather than imputing the missing values). Use of the complete-case analysis did not materially change the results, although the probability value for the association between CES-D score and change in minimum lumen diameter from the base model became statistically significant (\( P=0.05 \)).

Table 4 shows the effect of depressive symptoms on progression of graft disease among participants randomized to aggressive or moderate lipid-lowering strategies. The association of depressive symptoms with progression was consistently more apparent among subjects randomized to the moderate lipid-lowering strategy, with essentially completely null associations among those assigned to aggressive lipid lowering, although formal tests of interaction were not

| Table 1. Baseline Characteristics of Post-CABG Participants According to CES-D Score |
|-----------------|-----------------|-----------------|
|                | ≥16             | <16             |
| (n=127)        | (n=1192)        | Missing (n=32)  |
| Age, y, mean±SD| 60.4±7.2        | 61.7±7.3        | 60.5±7.5        |
| Male gender, % | 87.4            | 93.2            | 84.4            |
| White race, %  | 91.3            | 94.6            | 96.9            |
| Time since CABG, y | 4.3±2.3        | 4.9±2.6        | 5.3±2.5        |
| Systolic blood pressure, mm Hg | 135.5±21.3 | 134.2±17.3 | 134.8±13.4 |
| Diastolic blood pressure, mm Hg | 79.5±11.0 | 79.8±8.8 | 81.5±8.3 |
| Estimated glomerular filtration rate, mL·min⁻¹·1.73 m⁻² | 74.1±14.6 | 73.0±14.9 | 75.5±14.4 |
| Past medical history, % | 127 (n=127) | 1192 (n=1192) | 32 (n=32) |
| Myocardial infarction | 55.9 | 48.0 | 59.4 |
| Stroke | 1.6 | 2.9 | 3.1 |
| Hypertension | 39.4 | 35.2 | 28.1 |
| Diabetes mellitus | 13.4 | 8.2 | 3.1 |
| Smoking history, % | 19.7 | 10.3 | 3.1 |
| Current | 62.2 | 63.3 | 81.3 |
| Former | 28.2±4.6 | 27.7±4.5 | 28.0±4.3 |
| Body mass index, kg/m² | 2.3±5.0 | 2.9±4.9 | 2.5±7.7 |
| Alcohol consumption, drinks/wk | 6.9±2.0 | 6.5±1.8 | 6.3±1.2 |
| White blood cell count, \times10⁹/L | 229.6±25.5 | 231.1±25.4 | 232.8±29.9 |
| Total cholesterol, mg/dL | 177.0±79.7 | 161.2±73.4 | 164.0±60.2 |
| Triglycerides, mg/dL | 155.8±21.0 | 159.0±20.6 | 158.6±20.4 |
| LDL-C, mg/dL | 38.5±9.3 | 40.0±9.9 | 41.3±12.1 |
| HDL cholesterol, mg/dL | 2.5 (1–5) | 2.6 (1–8) | 2.5 (1–5) |

HDL indicates high-density lipoprotein.
statistically significant. When subjects with missing CES-D scores were excluded, the test for interaction was statistically significant for change in minimum lumen diameter ($P_{H11005} 0.04$).

We found no evidence of effect modification by age.

**Clinical Events**

During a median follow-up of 4.2 years, 208 participants developed a recurrent clinical event. We used Markov chain Monte Carlo multiple imputation methods to simulate CES-D scores for subjects with missing values. In the base model, depressive symptoms were associated with a hazard ratio of 1.50 (95% CI 0.96 to 2.36, $P_{H11005} 0.08$). Additional adjustment for potential confounders reduced the hazard ratio to 1.37 (95% CI 0.87 to 2.17, $P_{H11005} 0.18$). In a sensitivity analysis, no increased risk was observed for participants with a CES-D score between 8 and 15.

With an end point of death or myocardial infarction, with 132 events, depressive symptoms were associated with a hazard ratio of 1.69 (95% CI 1.00 to 2.87; $P=0.05$) in the base model and 1.50 (95% CI 0.88 to 2.56, $P=0.13$) in the full model. In a sensitivity analysis, the hazard ratio was linearly associated with CES-D score ($P_{H11004} 0.01$). Specifically, the hazard ratios were 1.46 (95% CI 0.94 to 2.27) for participants with a CES-D score between 8 and 15 and 1.91 (95% CI 1.10 to 3.29) for participants with a CES-D score $\geq 16$.

We repeated these analyses excluding subjects for whom the CES-D score was missing. In all cases, the results based on the complete-case analysis were not materially different from the original results.

**Discussion**

In this study of clinical trial participants with previous CABG surgery, the presence of depressive symptoms was associated with a higher risk of substantial progression of graft atherosclerosis and decrease in minimum lumen diameter over 4 to 5 years of follow-up. This association was virtually eliminated by random assignment to aggressive lipid lowering with high-dose lovastatin.

Several pathophysiological mechanisms have been proposed to underlie the associations of depression and depressive symptoms with CAD and its prognosis. The association of depressive symptoms with graft atherosclerosis observed

<table>
<thead>
<tr>
<th>CES-D Score</th>
<th>≥16</th>
<th>&lt;16</th>
<th>Missing</th>
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<tbody>
<tr>
<td>Substantial progression of atherosclerosis</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Subjects/grafts, n</td>
<td>101/213</td>
<td>1074/2283</td>
<td>17/37</td>
</tr>
<tr>
<td>Grafts with outcome, n (%)</td>
<td>73 (34.3)</td>
<td>662 (29.0)</td>
<td>15 (40.5)</td>
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<tr>
<td>Subjects having ≥1 graft with outcome, n (%)</td>
<td>53 (52.5)</td>
<td>473 (44.0)</td>
<td>8 (47.1)</td>
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<tr>
<td>Mean per-patient percent of grafts with outcome</td>
<td>33.8</td>
<td>28.8</td>
<td>35.3</td>
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<td>Graft occlusion</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Subjects/grafts, n</td>
<td>101/213</td>
<td>1074/2283</td>
<td>17/37</td>
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<tr>
<td>Grafts with outcome, n (%)</td>
<td>20 (9.4)</td>
<td>186 (8.2)</td>
<td>6 (16.2)</td>
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<tr>
<td>Subjects having ≥1 graft with outcome, n (%)</td>
<td>17 (16.8)</td>
<td>160 (14.9)</td>
<td>4 (23.5)</td>
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<tr>
<td>Mean per-patient percent of grafts with outcome</td>
<td>8.3</td>
<td>7.8</td>
<td>13.7</td>
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<tr>
<td>Change in minimum lumen diameter</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Subjects/grafts, n</td>
<td>89/187</td>
<td>989/2070</td>
<td>13/29</td>
</tr>
<tr>
<td>Mean±SD change, mm</td>
<td>−0.33±0.73</td>
<td>−0.28±0.71</td>
<td>−0.74±1.21</td>
</tr>
<tr>
<td>Intraclass correlation coefficient</td>
<td>0.17</td>
<td>0.16</td>
<td>0.32</td>
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$\Delta$ indicates mean change in millimeters.

*Referent group is patients with CES-D score <16. Base model is adjusted for age, gender, race, treatment assignment, and years since CABG surgery. Full model is additionally adjusted for systolic blood pressure, estimated glomerular filtration rate, history of myocardial infarction, stroke, hypertension, and diabetes mellitus. Adjustment for mediators further included body mass index, smoking history, alcohol intake, physical activity, total cholesterol, HDL cholesterol, and triglycerides. Multiple imputation methods were used in all analyses to account for participants for whom CES-D scores were not available.
here suggests that progression of atherosclerosis per se may be responsible at least in part for the observed effects of depression on clinical outcomes, rather than just differences in plaque vulnerability or predisposition to thrombosis or arrhythmias.

Depression is associated with an increase in sympathetic nervous system activity, reflected in decreased heart rate variability,28,29 which may itself increase activation of the renin-angiotensin and corticosteroid axes and, subsequently, atherosclerosis. Depression is clearly associated with markers of systemic inflammation in population-based studies,12,30 but the direction of this association and whether it exists among patients with CAD who already have elevated levels is less certain.31–33 Endothelial function is also impaired during and after episodes of depression,34–37 even among patients with CAD,38 perhaps via effects of depression on cortisol release.39 Depression could indirectly alter control of other atherosclerotic risk factors through its effects on weight, smoking, alcohol use, and exercise, and the present results suggested that addition of these factors might indeed account for a portion of the observed association of depressive symptoms with atherosclerosis.

In the present study, the association between depressive symptoms and graft atherosclerosis was virtually eliminated by random assignment to intensive lipid lowering, with a goal LDL-C of 60 to 85 mg/dL. This finding suggests that depression and statins may have opposing actions on common pathways in their influence on atherosclerosis. For example, as noted above, depression could influence atherosclerosis by increasing levels of systemic inflammation, whereas statins have pleiotropic antiinflammatory effects that could ameliorate this.40–42

Our work may have specific clinical implications. First, depressive symptoms appear to be an important and easily measured risk factor for progression of graft disease, and hence, their measurement may contribute to risk stratification after CABG. Second, the association of depressive symptoms with subsequent atherosclerotic progression appears to be substantially attenuated by high-dose statin therapy, and this provides further impetus to ensure all such patients are treated appropriately and intensively. Third, the present results provide continued support for efforts to identify effective methods to address depression and depressive symptoms in patients with CAD. Although cognitive-behavioral therapy for depression after acute myocardial infarction has not specifically been shown to reduce clinical events in randomized

<table>
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<tr>
<th>Table 4. Association Between Depressive Symptoms (CES-D Score ≥16) and Angiographic Outcomes According to Randomized Treatment Assignment*</th>
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<tbody>
<tr>
<td>Substantial Progression of Atherosclerosis</td>
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<td>---------------------------------</td>
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<tr>
<td>Moderate lipid-lowering strategy</td>
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<td>Aggressive lipid-lowering strategy</td>
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MLD indicates minimum lumen diameter; Δ, mean change in millimeters.

*ORs and mean change adjusted for warfarin assignment, age, gender, race, and years since CABG surgery. Multiple imputation methods were used in all analyses to account for participants for whom CES-D scores were not available.
needed in broader populations. Fourth, as expected from the entry criteria for the trial, the prevalence of depressive symptoms among Post-CABG participants was low, which limited the precision of our estimates. Fifth, although robust data on a number of potential confounders were available, the possibility of residual confounding by lifestyle or other risk factors remains.

In summary, among patients who had undergone previous CABG surgery, depressive symptoms were associated with higher risk of atherosclerotic progression in saphenous vein grafts. Our analysis provides prospective evidence for a direct association between depressive symptoms and atherosclerotic progression as a potential mechanism for the corresponding association of depressive symptoms with clinical prognosis. Despite advances in surgical and medical management of patients after CABG, the prognostic import of depressive symptoms on atherosclerotic progression provides a potentially valuable opportunity to elucidate mechanisms of graft atherosclerosis and to reduce adverse outcomes among patients with saphenous vein grafts. We encourage further studies to determine whether interventions that target depression and related symptoms will impact the progression of graft atherosclerosis or clinical prognosis of such patients.

Sources of Funding
The Post-CABG Study was conducted and supported by the National Heart, Lung, and Blood Institute (NHLBI), National Institutes of Health, in collaboration with the Post-CABG Study Investigators. This article was prepared with use of a limited-access data set obtained from the NHLBI. The project described was supported by grant No. F32-ES013804 from the National Institute of Environmental Health Sciences (NIEHS). Dr Mittleman holds an Established Investigator Grant from the American Heart Association (AHA 0140219N). The contents of this report are solely the responsibility of the authors and do not necessarily represent the official views of the NIEHS, NHLBI, National Institutes of Health, or American Heart Association.

Disclosures
None.

References
wellenius et al depressive symptoms and atherosclerosis


**CLINICAL PERSPECTIVE**

Depression and depressive symptoms are highly prevalent among patients with coronary artery disease and independently predict adverse cardiovascular events. Several mechanisms have been proposed to explain this association, including decreased adherence to treatment and increased prevalence of unfavorable lifestyle characteristics, among others; however, few studies have investigated the potential link between depressive symptoms and progression of atherosclerosis. Accordingly, we evaluated the hypothesis that depressive symptoms are associated with progression of atherosclerosis among individuals with previous coronary artery bypass graft surgery and saphenous vein grafts enrolled in the Post-CABG Trial. Depressive symptoms over the previous week were assessed at trial enrollment, and quantitative coronary angiography was conducted at enrollment and 4 to 5 years later. We found that the presence of depressive symptoms was associated with a higher risk of substantial progression of saphenous vein graft atherosclerosis and a decrease in minimum lumen diameter and that this association was virtually eliminated by random assignment to aggressive lipid lowering with high-dose lovastatin. Our analysis provides prospective evidence for a direct association between depressive symptoms and atherosclerotic progression as a potential mechanism for the corresponding association of depressive symptoms with clinical prognosis.
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Circulation. 2008;117:2313-2319; originally published online April 21, 2008; doi: 10.1161/CIRCULATIONAHA.107.741058
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/117/18/2313

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