Depression, C-reactive Protein and Two-year Major Adverse Cardiac Events in Men after Acute Coronary Syndromes

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Background: We investigated the impact of depression and inflammatory markers, assessed 2 months after acute coronary syndrome (ACS), on major adverse cardiac events over 2 years (MACEs; cardiac death, survived myocardial infarction, survived cardiac arrest, and nonelective revascularization).

Methods: Depression symptoms (Beck Depression Inventory-II; BDI-II), major depression, C-reactive protein (CRP), interleukin-6, and soluble intercellular adhesion molecule were assessed in 741 ACS patients (including 602 men).

Results: Some 102 (78 men) experienced at least one MACE. Beck Depression Inventory-II scores of ≥14 predicted MACEs ($p = .007$). The increase in risk was marked in men (hazard ratio [HR] = 1.96, 95% confidence interval [CI] = 1.24–3.09, $p = .004$), with little evidence of a relationship in women ($p = .85$). Subsequent analyses were limited to men. Results were similar after covariate adjustment (HR = 1.72, 95% CI = 1.07–2.77, $p = .024$). C-reactive protein levels were also associated with increased MACE risk (adjusted HR for CRP ≥ 2.0 mg/L = 1.67, 95% CI = 1.07–2.62, $p = .025$). C-reactive protein levels and BDI-II scores interacted in predicting MACEs. Men with both BDI-II scores of ≥14 and CRP of ≥2.0 mg/L experienced an increase in risk similar to those with only one of these factors.

Conclusions: In men assessed 2 months after ACS, depression and CRP are overlapping prognostic risks. Patients with either risk may benefit from similar therapies.

Key Words: CRP, depression, depressive disorder, inflammation, myocardial infarction, prognosis

There is strong observational evidence that both major depression and elevated levels of depression symptoms assessed during hospitalization for an acute coronary event predict poor long-term prognosis (Lett *et al.* 2004). The majority of studies suggest that this association is independent of cardiac disease severity. Measures of subchronic inflammation also are increasingly implicated as prognostic factors in patients with coronary artery disease (CAD; Liuzzo and Biasucci 2003; Ridker *et al.* 2005). However, there has been little research simultaneously evaluating the prognostic importance of depression and inflammatory markers in these patients.

Depression and inflammation likely combine in complex ways to influence CAD. Animal and clinical studies suggest that chronic stress and depression augment innate inflammatory responses, leading to increases of C-reactive protein (CRP), interleukin-6 (IL-6), and soluble intercellular adhesion molecule (sICAM-1; Black 2002). Alternatively, systemic inflammation itself may give rise to symptoms of depression (Dantzer *et al.* 1993; Miller *et al.* 2003; Motivala *et al.* 2005). We previously observed that major depression is associated with higher sICAM-1 levels in patients with recent acute coronary syndromes (ACSs; Lespérance *et al.* 2004). We also found major depression to be related to increased CRP levels, but primarily in those patients not treated with statins.

The present study involves an expanded sample of patients who were assessed for depression and inflammatory markers approximately 2 months after discharge for ACS and were followed for major adverse cardiac events (MACEs) over 2 years. We chose to assess patients some time after discharge, rather than during hospitalization, to allow for resolution of the acute stresses of the coronary event. We hypothesized that both elevated levels of depression symptoms and inflammatory markers would be associated with higher levels of events but that the relationship between elevated depression symptoms and inflammatory markers would account largely for any depression-related differences in outcomes.

Methods and Materials

Subjects

The Epidemiological Study of Acute Coronary Syndromes and the Pathophysiology of Emotions (ESCAPE) received approval from the Research Ethics Committees of the Montreal Heart Institute and Hôpital du Sacré Coeur de Montréal. Patients from both hospitals who underwent a coronary angiogram during admission for a suspected acute myocardial infarction (MI) or episode of unstable angina with elevated troponin-T levels (based on each hospital's laboratory standards) between August 31, 1999 and August 2, 2001 were evaluated for study eligibility ($n = 2715$). Exclusions included having ACS secondary to another disease, having conditions likely limiting survival to less than 2 years, being cognitively unable to collaborate or provide informed consent, living too far to come for evaluation, and having insufficient knowledge of French or English to complete

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Received July 13, 2006; revised September 13, 2006; accepted September 29, 2006.

0006-3223/07/$32.00
doi:10.1016/j.biopsych.2006.09.029

interviews. Brief letters describing the study were sent to the 1815 potentially eligible patients soon after discharge. The letters provided a telephone number to call for those who did not want to be contacted further. Beginning about 6 weeks after discharge, multiple attempts were made to telephone all eligible patients to explain the study and obtain preliminary participation. Of these, 1576 were contacted, with 964 agreeing to a research appointment. Informed consent was obtained and baseline interviews were completed with 811 of these patients (654 men). Overall, 51.5% of eligible patients accepted and completed study participation (55.3% of men, 40.4% of women). Major reasons for not participating were the fasting blood draw and the time needed for assessments (approximately 3 h on a weekday morning). There were technical difficulties with blood processing for 30 subjects (19 men). Because of our focus on inflammation, we did not include those who were taking antibiotics ($n = 20$) or who had current alcohol abuse or dependence ($n = 20$), resulting in a final sample of 741 (602 men).

Procedures

Patients brought their medications to the research institute after an overnight fast. After informed-consent procedures, a nurse assessed vital signs and recorded medications. After a brief rest period, antecubital blood samples were drawn for glucose, insulin, lipids, and inflammatory markers. Patients then had a light breakfast, completed brief tests of cognitive function, and responded to self-report questionnaires, including the Beck Depression Inventory-II (BDI-II; Beck *et al.* 1996). On the basis of our prior research, the BDI-II was selected as our primary depression measure. As suggested in the BDI-II manual, a score of at least 14 out of 63 was used to identify individuals with at least mild to moderate symptoms of depression (elevated depression symptoms). To assess current major unipolar depression, a trained psychologist, blind to self-report results, administered the Structured Clinical Interview for the DSM-IV (SCID; First *et al.* 1996).

Blood samples were taken between 8:15 and 10:40 AM, and for 95% of patients, this occurred before 10:00 AM. Citrated tubes were used to collect samples for IL-6 and sICAM-1. Immediately after the blood draw, tubes were processed by centrifuge at 4°C, with the resulting plasma frozen at −80°C before analysis. Blood for CRP was collected in plain tubes, with serum frozen at −80°C. After thawing, stored aliquots were assayed in a manner blinded to patients' depression status; commercially available ELISA kits for inflammatory markers were used. The Dade Behring N High Sensitivity CRP assay (Dade Behring Diagnostics, Marburg, Germany) on the BN ProSpec was used to determine CRP levels. Levels of IL-6 and sICAM-1 were assessed in duplicate with commercially available ELISA kits (R&D Systems, Minneapolis, Minnesota). The mean coefficients of variation were 7.2% for IL-6 and 5.1% for sICAM-1.

An experienced cardiac radiologist, blind to information about depression, applied established criteria (Bypass Angioplasty Revascularization Investigation Investigators 1991) to code the number of major coronary vessels with ≥50% blockage on coronary angiograms after revascularization procedures during the index admission. Additional cardiac-history data was abstracted from hospital charts. The study outcome was the time to the first MACE occurrence (cardiac death, survived MI, survived cardiac arrest, and nonelective revascularization). Patients were phoned every 6 months for 2 years to obtain information about readmissions and vital status. When readmissions were reported at hospitals other than study hospitals, or we learned that a patient had died, patients or their next of kin were mailed chart-access forms that they signed and returned to the research center. Records for all such admissions were obtained from the archives departments of the hospitals in question. In addition, a total review also was made of participants' admissions and outpatient contacts at the two study hospitals for the 2 years after baseline. Finally, we examined Quebec Medicare records for hospitalization and procedure information, as well as the dates of most recent contacts with physicians to establish evidence of survival beyond the 2-year point. During the 2-year period, only six patients (7%; 1 woman) were lost to follow-up.

Statistical Analyses

SPSS for Windows (version 14.0) was used for analyses. Values of p of ≤ .05 were considered significant. Plots of the log cumulative hazards for MACE-free survival times in patients with and without elevated (≥14) BDI-II scores, and with and without current unipolar major depression, were inspected visually. All plots appeared to support the assumption of proportional hazards, and Cox proportional hazards regressions were used to assess the impact of BDI-II scores and current unipolar depression on MACEs over 2 years. Censoring took place on the day of loss to follow-up or the occurrence of the earliest MACE. Patients with bipolar disorder were excluded from analyses concerning the importance of unipolar depression.

Background characteristics and inflammatory markers in patients with and without BDI-II scores of ≥14 were compared by using χ^2 tests for categorical variables and t tests for continuous variables. Because of skewed distributions, analyses for inflammatory markers involved natural-log transformations, and those involving the continuous BDI-II score were based on standardized scores (Z scores). Although there is no clear guidance in the literature about appropriate cutoffs for sICAM-1 and IL-6 as predictors of prognosis in stable ACS patients, Ridker *et al.* (2005) recently found that the approximate median cutoff of ≥2.0 mg/L for CRP, measured 30 days after an ACS, was a significant predictor of recurrent coronary events. We used this cutoff in addition to analyzing continuous, log-transformed CRP levels.

Cox proportional hazards regression analyses were used to assess the impact of individual baseline measures and inflammatory markers on MACEs over 2 years. For analyses assessing the interactions betweens pairs of variables, the interaction term was added to a model including the main effects involved in the interaction, with model improvement assessed by using the partial likelihood-ratio test.

To select background variables for statistical adjustment, we used the approach suggested by Steyerberg *et al.* (2000). All baseline variables other than antidepressant medication (because of its low frequency and high association with depression) and aspirin (because 90% of patients were prescribed it) were entered together into a Cox proportional-hazards regression analysis to predict cardiac events. Because of the high degree of interrelationship between body mass index (BMI) and waist circumference ($r = .89$), and the fact that waist circumference was not available for two participants, BMI was used as the measure of adiposity in these analyses. Those variables with adjusted p values of <.50 were retained as covariates and entered together on the first step of a Cox proportional-hazards regression analysis, followed by the variables for which covariate adjustment was needed. All analyses were repeated omitting patients receiving antidepressant medication.

Results

Sample Characteristics

The sample of 741 included 602 (81.2%) men. Patients ranged in age from 24 to 90 years (mean = 59.8 y). Overall 201 participants (27.1%) had BDI-II scores of ≥14 (25.2% of men, $n = 152$; 35.3% of women, $n = 49$; $p = .017$). Results of the SCID showed that 46 subjects met criteria for current unipolar major depression (4.5% of men, $n = 27$; 13.7% of women, $n = 19$; $p < .001$).

Depression and MACEs

A total of 102 patients (78 men, 24 women; $p = .41$) experienced at least one MACE during the 2-year follow-up period (10 cardiac deaths [9 men], 49 survived MIs [40 men], 2 survived cardiac arrests [1 man], and 39 nonelective revascularizations [28 men]). In the overall sample, BDI-II scores of ≥14 were significantly linked to MACEs (hazards ratio [HR] = 1.74, 95% confidence interval [CI] = 1.17–2.59, $p = .007$), as were standardized continuous BDI-II scores (HR = 1.20 per SD increase, 95% CI = 1.01–1.42, $p = .041$). However, because there were five times as many men as women in the sample, the impact of depression in men easily could have obscured the degree of relationship in women. Therefore, we assessed the interactions between depression and sex in predicting MACEs. Although the interaction between sex and BDI-II scores of ≥14 did not reach significance ($p = .22$), there was evidence of an interaction between the continuous BDI-II score and sex ($p = .053$). In men, there was a significant increase in risk of MACEs associated with increases in the BDI-II score, but in women there was no evidence that depression scores increased risk of MACEs. Results were similar for elevated BDI-II scores (Table 1).

Finally, among the 722 patients who did not meet criteria for bipolar disorder, there was an overall link between unipolar major depression and MACEs (HR = 2.38, 95% CI = 1.33–4.26, $p = .004$). As for depression symptoms, this link was primarily a result of the relationship in men. However, both the number of patients with unipolar depression and the number of MACEs among them were too small to allow covariate adjustment (9 events in 27 depressed men, 4 events in 19 depressed women). In fact, even when considering patients with elevated BDI-II scores, there were only nine events in women. In combination with the relatively small number of women included, this reduced study power to draw conclusions about the relationship between depression and outcomes in women. Therefore, subsequent analyses involving covariate control and the inflammatory markers were limited to men and our primary measure of depression, the BDI-II.

Baseline Characteristics Associated with Elevated BDI-II Scores in Men

Table 2 includes the levels of inflammatory markers and background characteristics of men with BDI-II scores of ≥14, in comparison to those with lower scores. Men with BDI-II scores of ≥14 were more likely to be sedentary, to smoke, and to have a previous cardiac history, and they had significantly higher fasting triglyceride and glucose levels than did those with lower scores. They also were more likely to be taking antidepressants than men with lower BDI-II scores. Finally, there were significantly higher CRP and sICAM-1 levels in those with elevated BDI-II scores, but little difference in IL-6 levels. As in our previous work, the increase in CRP associated with BDI scores of ≥14 was greater in those not receiving statins than in those receiving statin treatment (p for interaction = .019). There was no evidence of statin-related differences in the link between continuous, log-transformed BDI-II scores and sICAM-1 ($p = .98$) or IL-6 ($p = .17$).

Elevated BDI-II Scores and MACEs in Men after Adjustment for Covariates

The baseline characteristics associated with BDI-II scores of ≥14 suggest that men with elevated depression symptoms may have been at greater risk of MACEs than those with lower scores. However, when baseline covariates were controlled using the method of Steyerberg *et al.* (2000), BDI-II scores of ≥14 continued to significantly predict cardiac events (Table 3). After adjustment for the covariates shown in Table 3, the p value for the continuous standardized BDI-II score's ability to predict MACEs increased to .11 (adjusted HR = 1.18; 95% CI = .97–1.44). The pattern of results for both elevated BDI-II scores and the standardized continuous score were similar when the 43 patients taking antidepressants were eliminated from the analyses (Supplement 1).

Inflammatory Markers and MACEs in Men

When analyzed as continuous, log-transformed variables, both sICAM-1 (HR = 2.63, 95% CI = 1.08–6.43, $p = .034$) and CRP (HR = 1.32, 95% CI = 1.09–1.60, $p = .005$) were significantly related to MACEs in men, but IL-6 was not (HR = 1.21, 95% CI = .91–1.61, $p = .19$). Similar results were obtained by using the predetermined cutoff of CRP of ≥2.0 mg/L, which identified the upper 45.7% of men in our sample (HR = 1.67, 95% CI = 1.07–2.62, $p = .025$). After adjustment for the covariates shown in Table 3, CRP levels remained a significant predictor of MACEs both when considered as a continuous, log-transformed measure (HR = 1.36, 95% CI = 1.11–1.66, $p = .003$), and when using the cutoff of CRP ≥ 2.0 mg/L (HR = 1.68, 95% CI = 1.04–2.71, $p = .034$). Covariate adjustment for the variables shown in Table 3

Table 1. Depression-related Hazards Ratios for Time to First Major Adverse Cardiac Event, Assessed 2 Months after Acute Coronary Syndrome

	Men ($n = 602$; 78 Events)			Women ($n = 131$; 24 Events)		
Measure	Hazards Ratio	95% CI	*p* Value	Hazards Ratio	95% CI	*p* Value
BDI-II Score ≥ 14	1.96	1.24–3.09	.004	1.08	.47–2.48	.85
Continuous BDI-II Score[a]	1.31	1.08–1.59	.006	.87	.56–1.34	.52
Unipolar Major Depression[b]	3.17	1.58–6.36	.001	1.24	.43–3.63	.69

BDI-II, Beck Depression Inventory-II.
[a]Hazards ratio per SD increase.
[b]Based on 722 patients without bipolar disorder; men, $n = 584$, 76 events; women, $n = 138$, 24 events.

Table 2. Inflammatory Markers and Baseline Characteristics in Relation to Elevated Levels of Depression Symptoms in Men Assessed 2 Months after Acute Coronary Syndrome

Characteristics	Not Depressed (BDI-II < 14; *n* = 450)	At Least Mild to Moderate Depression (BDI-II ≥ 14; *n* = 152)	*p* Value
Inflammatory Markers[a]			
sICAM-1 (ng/mL)	179.1 (156.5–210.2)	192.6 (166.9–233.3)	.001[b]
IL-6 (pg/mL)	2.03 (1.41–3.14)	2.22 (1.41–3.64)	.30[b]
CRP (mg/L)	1.66 (.91–3.87)	2.02 (1.02–4.91)	.042[b]
Demographic Variables			
Age (y)	59.8 ± 10.3	58.7 ± 10.0	.24
Education (y)	11.7 ± 4.5	11.1 ± 4.4	.20
Married	81.6%	77.6%	.29
Risk Factors and Cardiac History (%)			
Sedentary	45.6	55.9	.027
Current Daily Smoker	13.1	23.0	.004
Previous MI, Coronary Bypass, or Angioplasty	31.6	45.4	.002
Left Ventricular Ejection Fraction <45%	20.0	25.0	.19
Intervention at Index Hospitalization (%)			
Coronary Bypass Surgery	21.6	17.8	.32
Coronary Angioplasty	61.8	62.5	.87
≥1 Coronary Vessels with ≥50% Blockage after Index Revascularization	51.1	59.2	.084
Baseline Indicators of Metabolic Syndrome			
Body Mass Index (kg/m^2)	28.1 ± 4.1	28.6 ± 4.6	.19
Waist (cm)	101.9 ±10.4 (*n* = 449)	103.1 ± 11.4 (*n* = 151)	.23
Fasting Triglyceride Level (mmol/L)	1.78 ± .97	2.11 ± 1.15	.001
Fasting High-density Lipoprotein Level (mmol/L)	1.06 ± .21	1.04± .23	.40
Fasting Glucose Level (mmol/L)	6.19 ± 1.69	6.57 ± 2.00	.023
Systolic Blood Pressure (mm Hg)	134.3 ± 23.0	136.6 ± 22.7	.30
Diastolic Blood Pressure (mm Hg)	74.7 ± 10.9	75.3 ± 9.7	.53
Medications at Baseline Interview (%)			
Aspirin	89.8	90.8	.72
Beta-blockers	78.0	75.7	.55
Angiotensin-converting Enzyme Inhibitors	52.9	46.1	.15
Hypoglycemics	19.3	21.1	.65
Calcium-channel Blockers	18.2	22.4	.26
Statins	74.2	71.7	.54
Long-acting Nitrates	12.9	17.8	.14
Antidepressants	4.4[c]	15.1	<.001

Unless otherwise noted, data are mean ± SD for continuous variables.

BDI-II, Beck Depression Inventory-II; CRP, C-reactive protein; IL-6, interleukin-6; MI, myocardial infarction; sICAM-1, soluble intercellular adhesion molecule-1.

[a]Data are median (25th, 75th percentiles).

[b]Values of *p* for inflammatory markers based on log-transformed data.

[c]SCID results showed the 20 patients with BDI-II < 14 taking antidepressants included the following: 8, in remission or partial remission from an episode of major depression; 1, subthreshold depression; 1, bipolar disorder; 1, generalized anxiety disorder; 1, panic disorder; 2, past alcohol abuse or dependence; 5, taking antidepressants to stop smoking; and 1, unclear reason for antidepressant use.

increased the *p* value for the link between continuous, log-transformed sICAM-1 levels to .12 (HR = 2.17, 95% CI, .83–5.68).

Inflammatory Markers, BDI-II Scores, and MACEs in Men

Given the main effects of BDI-II scores and CRP levels on MACEs, we evaluated the degree of interaction between these two measures as well as the extent to which this interaction might improve the model for predicting time to first MACE. As illustrated in Figure 1, there was evidence of an interaction between elevated BDI-II scores and CRP levels of ≥2.0 mg/L in predicting MACEs in men ($p = .079$; *p* adjusted for covariates in Table 3 = .086). In fact, when both BDI-II score and CRP levels were analyzed as continuous measures, the interaction was significant ($p = .012$; $p = .020$ after adjustment for the covariates shown in Table 3).

Both higher levels of depression symptoms and CRP were associated with increases in the risk of MACEs, but the impact was not additive. Only men with both lower BDI-II scores and lower levels of CRP remained at comparatively low risk over 2 years. In short, men with either elevated depression symptoms or higher CRP levels were at significantly increased risk, but there was a ceiling effect, with no added risk from the combination of the two. Elimination of those on antidepressants did not change the pattern of results (Supplement 2).

Discussion

This prospective study was designed to confirm the negative impact of depression on cardiac prognosis in patients after an ACS admission and to investigate the relationships between depression and markers of inflammation in predicting subsequent cardiac events. Even though depression was assessed several weeks after hospital discharge, both elevated scores on

Table 3. Multivariable Model of Time to First Major Adverse Cardiac Event in Men Assessed 2 Months after Acute Coronary Syndrome ($n = 602$; 78 events)

Predictor	Hazards Ratio	95% CI	*p* Value
Years of Education[a]	.84	.66–1.07	.16
Married	1.39	.75–2.57	.29
Current Daily Smoker	1.68	.94–3.00	.080
Coronary Bypass Surgery during Index Hospitalization	.68	.29–1.55	.35
≥1 Coronary Vessel with ≥50% Blockage after Index Revascularization	3.37	1.81–6.29	<.001
Body Mass Index[a]	.81	.63–1.03	.087
Fasting Triglyceride Level[a]	1.15	.94–1.40	.18
Fasting Glucose Level[a]	.80	.62–1.05	.10
Fasting High-density Lipoprotein Level[a]	1.09	.87–1.36	.47
Diastolic Blood Pressure[a]	1.23	.98–1.56	.078
Beta-blockers	.87	.49–1.53	.63
Calcium Channel Blockers	1.49	.88–2.52	.14
Angiotensin-converting Enzyme Inhibitors	1.33	.82–2.16	.25
Statins	.63	.39–1.01	.054
Long-acting Nitrates	1.93	1.13–3.29	.016
BDI-II Score ≥ 14	1.72	1.07–2.77	.024

BDI-II, Beck Depression Inventory-II.
[a]Hazards ratio per SD increase.

the BDI-II scale and current major unipolar depression were significantly related to MACEs over 2 years. We also observed a tendency for less impact of depressive symptoms and major depression on cardiac events in women than in men. However, previous studies have demonstrated a link between depression during hospitalization and cardiac events in women with CAD (Frasure-Smith *et al.* 1999; Penninx *et al.* 2001), and both the number of women in the current study and the frequency of events that occurred in women were too small to draw conclusions.

Studies in samples without CAD have shown that both major depression and elevated depression symptoms are associated with CRP (Danner *et al.* 2003; Empana *et al.* 2005; Ford and Erlinger 2004; Ladwig *et al.* 2005; Liukkonen *et al.* 2006; Miller *et al.* 2002; Penninx *et al.* 2003) and IL-6 (Empana *et al.* 2005; Miller *et al.* 2002; Penninx *et al.* 2003). Our study confirms the association between elevated depression symptoms and CRP in male CAD patients, but we were unable to confirm a similar association with IL-6. In addition, we observed a link between sICAM-1 and depression symptoms, which also was recently reported in men without CAD (Empana *et al.* 2005).

To our knowledge, our study is the first to examine the prognostic importance of depression symptoms and inflammatory risk factors together in stable CAD patients. We observed an interaction between depression symptoms and CRP in predicting cardiac events; only those men with low levels of depression and low levels of CRP evidenced low risk of MACEs. Furthermore, in men with CAD, we observed that the impact of CRP was largely restricted to the nondepressed and that the impact of elevated depression symptoms was primarily in those with lower levels of CRP. This does not support the interpretation that the prognostic impact of depression is explained by inflammation, nor does it suggest that depression and CRP levels are independent risk factors in stable CAD patients. Instead, CRP and depression appear to be at least partially overlapping risks (Kraemer *et al.* 2005).

Although it has been suggested that antidepressants, particularly SSRIs, may influence levels of inflammatory markers (Castanon *et al.* 2002), as well as cardiac outcomes (Glassman 2005), removing patients on antidepressants from our data set did not change the pattern of results. However, the number of patients on antidepressants was too small to determine whether or not the observed risks associated with depression and CRP levels differed according to use of antidepressants. The only way to find out whether antidepressants alter inflammation in post-ACS patients would be by conducting a randomized trial.

Only two studies have evaluated the joint prognostic impact of depression and inflammatory markers in non-CAD patients. Ladwig *et al.* (2005) recently reported the results of more than 7 years of follow-up for 3021 CAD-free men in the MONICA-KORA Augsburg Cohort study. Depression symptoms were unrelated to baseline CRP levels. However, there was a significant interaction between CRP and depression in predicting cardiac events. Levels of CRP predicted events to a greater extent among the depressed than the nondepressed, leading the investigators to suggest that CRP and depression may have a synergistic effect in the development of CAD in men. In the Prospective Epidemiological Study of Myocardial Infarction, a case–control study involving men only, Empana *et al.* (2005) found that depression, CRP, IL-6, and sICAM-1 were each associated with the incidence of cardiac events, independently of each other and after adjustment for major CAD risk factors. However, tests for the interactions between depression and inflammatory markers were not reported.

There is evidence that depression and inflammation share many physiologic processes and that each can precede and influence the other. For example, in women acting as caregivers to Alzheimer's patients, the naturally occurring stress of changing residences was associated with increases in plasma IL-6, suggesting that psychological stress itself may precede activation of the inflammatory response (Lutgendorf *et al.* 1999). Conversely, the development of depressive symptoms and major depression after interleukin-alpha treatment for cancer or hepatitis C (Capuron and Miller 2004) implies that a rise in pro-inflammatory cytokines

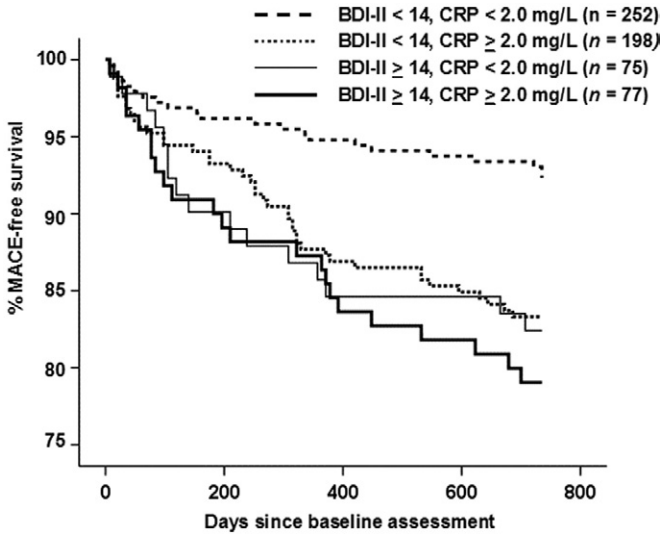

Figure 1. Two-year major adverse cardiac event-free survival by levels of depression symptoms (Beck Depression Inventory-II; BDI-II) and C-reactive protein (CRP) in 602 men assessed 2 months after acute coronary syndrome. MACE, major adverse cardiac event.

can precede mood disorder. Animal studies show that the HPA axis and noradrenergic activation associated with depression and chronic stress promotes the inflammatory response (Black and Garbutt 2002) and that subchronic inflammation can also produce symptoms that resemble depression (Dantzer *et al.* 1993).

Within hours of an MI, these are simultaneous plasma increases in proinflammatory cytokines, CRP, and adhesion molecules that last at least several days in human beings (Pudil *et al.* 1999) and up to 4 weeks in rats (Francis *et al.* 2004). These increases are accompanied by rises in cytokines in the hypothalamus, which may explain some of the behavioral correlates of inflammation. Wann *et al.* (2006) recently reported that in a rat model, the brain cytokine increase after acute MI induces apoptosis in the amygdala, a limbic structure involved in the regulation of mood, as well as cardiovascular autonomic function. This suggests that at least some depressive symptoms in the post-MI period may be secondary to cytokine-induced brain changes and, thus, may not lead to any additional risk of cardiac events beyond that associated with elevated inflammatory markers.

Our study has limitations. Although we would have liked to evaluate the impact of depression and inflammation on cardiac mortality, our sample size was far too small to provide adequate power. However, the definition we used for our composite outcome of MACEs (cardiac deaths, survived MIs, survived cardiac arrests, and emergency revascularizations) involved events that are all likely related to worsening atherosclerosis. In fact, patterns of results paralleling that for the composite outcome appeared when the most common events, recurrent MIs and emergency revascularizations, each were considered separately. Women were less likely to accept study participation than men, and their relatively small number, combined with their low rate of cardiac events, prevent conclusions about the apparent lack of relationships in women. Inflammatory markers were assessed only once and at the same time as depression, so we cannot infer cause-and-effect relationships. We performed multiple statistical tests, and some of the significant results may be falsely positive. Similarly, lack of significant results in some subgroups may be related to the sample sizes in those groups.

Conclusions

When multiple risk factors co-occur in the same individuals, untangling their separate contributions can be very difficult (Kraemer *et al.* 2005). The current study underscores this complex bidirectional relationship between depression and inflammation. Given our finding of overlap between depression and inflammation in predicting prognosis in stable ACS patients, it would be of interest to determine the extent to which patients with elevated inflammatory markers, with depression, or with both could benefit from similar interventions. Regular exercise (Blumenthal *et al.* 1999), a Mediterranean diet (Esposito *et al.* 2004), and antidepressants (Castanon *et al.* 2002), combined with statins (Jialal *et al.* 2002), may not only successfully control inflammation but also could potentially be efficacious in treating depression in CAD patients.

This research was supported by the Medical Research Council of Canada and an unrestricted grant from GlaxoSmithKline (POP-37744), the Charles A. Dana Foundation, the Montreal Heart Institute Research Fund, the Pierre David Fund, and the Fondation du Centre Hospitalier de l'Université de Montréal. NFS and FL have received nonrestricted grant support from IsodisNatura. Lundbeck, Canada supplied placebo and medication to FL and NFS for a trial funded by the Canadian Institutes of Health Research. NFS has received honoraria from Solvay and Tromsdorff. FL has received honoraria from GlaxoSmithKline, Lundbeck, and Wyeth.

We gratefully acknowledge the Régie de l'assurance maladie du Québec and the Ministère de la santé et des services sociaux du Québec for Medicare data, and we thank Ginette Gravel, Elaine Kennedy, Johanne Lalancette, Joanne Lavoignat, Marie-Pierre Leduc, Aline Masson, Isabelle Ménard, and Doris Morisette for their work as research assistants.

Supplementary material cited in this article is available online.

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