Five-Year Risk of Cardiac Mortality in Relation to Initial Severity and One-Year Changes in Depression Symptoms After Myocardial Infarction

François Lespérance, MD; Nancy Frasure-Smith, PhD; Mario Talajic, MD; Martial G. Bourassa, MD

Background—Although previous research demonstrated an independent link between depression symptoms and cardiac mortality after myocardial infarction (MI), depression was assessed only once, and a dose-response relationship was not evaluated.

Methods and Results—We administered the Beck Depression Inventory to 896 post-MI patients during admission and at 1 year. Five-year survival was ascertained using Medicare data. We observed a significant long-term dose-response relationship between depression symptoms during hospitalization and cardiac mortality. Results remained significant after control for multiple measures of cardiac disease severity. Although 1-year scores were also linked to cardiac mortality, most of that impact was explained by baseline scores. Improvement in depression symptoms was associated with less cardiac mortality only for patients with mild depression. Patients with higher initial scores had worse long-term prognosis regardless of symptom changes.

Conclusions—The level of depression symptoms during admission for MI is more closely linked to long-term survival than the level at 1 year, particularly in patients with moderate to severe levels of depression, suggesting that the presumed cardiovascular mechanisms linking depression to cardiac mortality may be more or less permanent for them. (Circulation. 2002;105:1049-1053.)

Key Words: myocardial infarction ■ depression ■ prognosis

Although there is increasing evidence that depression is related to cardiac prognosis in patients with acute coronary syndrome,1-3 no studies have examined the importance of repeated depression assessments. Furthermore, although demonstration of a biological gradient between exposure and subsequent risk is a major criterion for causality,6 the evidence of a dose-response relationship between depression and prognosis is limited. Barefoot et al5 observed an increasing risk of 15-year cardiac mortality associated with increasing baseline depression symptoms in a sample of 1250 cardiac catheterization patients assessed during the 1970s. Although Penninx et al8 documented a dose-response relationship between depression symptoms and 4-year cardiac mortality among 450 older community residents who reported a history of cardiac disease at baseline, the lack of objective baseline cardiac measurement limits study validity. Bush et al9 recently found evidence of a dose-response relationship between in-hospital depression symptoms and 4-month post–myocardial infarction (MI) mortality in 144 patients 65 years of age and older. However, the number of deaths was small and the follow-up period was limited.

We carried out a 5-year follow-up of post-MI patients assessed for depression during admission and 1 year later to evaluate a dose relationship between depression symptoms and long-term cardiac mortality, confirm that any impact of depression symptoms remains significant after control for measures of cardiac disease severity, compare the impact of depression measurement during hospitalization and at 1 year, and evaluate the prognostic importance of changes in depression symptoms over the first post-MI year.

Methods

The sample included 896 acute MI patients who completed the 21-item self-report Beck Depression Inventory (BDI)10 during hospitalization. Patients included participants in a study of psychosocial risks in usual care patients (n=218) and the control group from a randomized trial of a psychosocial intervention (n=678). Details of the methodologies of both studies have been described previously.1,2,11-13

Consecutive patients admitted for an acute MI and meeting study eligibility criteria were recruited between January 1991 and October 1994. Protocols were approved by institutional review boards, and participants provided informed consent for interviews and long-term follow-up. Interviews included questions about sociodemographics, medical history, and cardiac risk factors and a self-report measure of social support.14 Additional data were abstracted from hospital charts. Home interviews were completed 1 year after discharge with 767 (89.9%) of the 853 1-year survivors. No measures of disease severity were associated with follow-up interview completion.

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Provincial government agencies that administer the Canadian universal health care system keep centralized computer records of all hospitalizations and outpatient medical services. These records provide an efficient means for determining patients’ survival status and cardiac outcomes. We classified patients with any physician contact after 1825 days as living at the 5-year point. Additional information was obtained from hospital charts and death certificates. Causes of death were independently and blindly classified as cardiac and noncardiac by a cardiologist and trained research assistant. In addition to cause of death, we examined readmissions for nonfatal MIs, angioplasty procedures, and bypass surgeries.

Data analysis was carried out using SPSS for Windows (version 10.07). Analyzes were based on continuous BDI scores, and scores were divided into 4 categories: <5, 5 to 9, 10 to 18, and ≥19. Although these categories are based on those suggested by Beck et al., because of the large number of scores <10, we included a subdivision for scores <5.

Visual inspection of log cumulative hazards plots for the 5-year survival times for the BDI categories supported the proportional hazards assumption. We used Cox proportional hazards regression analysis to assess the impact of BDI scores and other measures. Multiple linear regression analyses were used to assess the baseline characteristics associated with continuous BDI scores, and χ² statistics were calculated for comparisons of categoric scores. To select covariates for statistical control, all baseline variables other than depression were entered together into a Cox proportional hazards regression analysis. Variables with any evidence of an independent impact (P<0.50) were retained as covariates. Because of the high correlation between living alone and being unmarried, only marital status was included.

Multiple linear regression analysis was used to predict 1-year BDI scores as a linear function of baseline scores. Differences between the predicted and observed scores constituted residual change scores. Their prognostic impact was assessed using Cox proportional hazards regression analysis.

**Results**

**Baseline Variables and Long-Term Prognosis**

Only 2.9% of patients (n=26) were lost to 5-year follow-up. Among the 870 patients whose 5-year status was known, there were 155 deaths, including 121 cardiac and 34 noncardiac deaths. Some 121 of these patients survived a MI, including 40 who later died of cardiac causes and 3 with noncardiac deaths. Finally, 178 patients were revascularized after discharge, and for 123, revascularization was the only event. Table 1 shows the baseline characteristics as well as their univariate relationships with 5-year cardiac mortality.

**Baseline Depression Symptoms and Long-Term Prognosis**

Some 47.4% of patients had BDI scores in the low normal range (<5), followed by 30.2% with scores at the high normal level (5 to 9), 23.5% with scores indicative of mild depression (10 to 18), and only 8.8% who could be considered moderately to severely depressed (≥19). As Table 2 shows, baseline BDI scores were significantly related to both 5-year cardiac and all-cause mortality as well as the combination of survived MIs and cardiac deaths. However, separate analyses for survived MIs, angioplasty procedures, and bypass surgeries revealed no impact of baseline BDI scores. Results based on continuous BDI scores also showed that the long-term impact of in-hospital depression was concentrated in fatal events. Furthermore, there was evidence of a dose-response relationship between depression symptoms and long-term prog-
Lespérance et al. Post-MI Changes in Depression and Long-Term Mortality

TABLE 2. Cardiac Events Over 5 Years in Relation to Level of Depression Symptoms in Hospital and at 1 Year

<table>
<thead>
<tr>
<th>Assessment Time and Event Type</th>
<th>BDI &lt;5 (n=335)</th>
<th>BDI 5–9 (n=271)</th>
<th>BDI 10–18 (n=211)</th>
<th>BDI ≥19 (n=79)</th>
<th>Percent of Patients With Event (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beck Depression Inventory in hospital*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All deaths</td>
<td>10.7 (36)</td>
<td>16.2 (44)</td>
<td>23.2 (49)</td>
<td>32.9 (26)</td>
<td>1.54 (0.99–2.40), P=0.054</td>
</tr>
<tr>
<td>Noncardiac deaths</td>
<td>3.6 (12)</td>
<td>2.6 (7)</td>
<td>4.7 (10)</td>
<td>6.3 (5)</td>
<td>0.75 (0.29–1.87), P=0.52</td>
</tr>
<tr>
<td>Cardiac deaths</td>
<td>7.2 (24)</td>
<td>13.7 (37)</td>
<td>18.5 (39)</td>
<td>26.6 (21)</td>
<td>1.94 (1.16–3.25), P=0.011</td>
</tr>
<tr>
<td>Cardiac deaths or survived MIs</td>
<td>17.0 (57)</td>
<td>23.2 (63)</td>
<td>26.1 (55)</td>
<td>34.2 (27)</td>
<td>1.40 (0.98–2.00), P=0.066</td>
</tr>
<tr>
<td>Survived MIs</td>
<td>12.5 (42)</td>
<td>14.4 (39)</td>
<td>13.3 (28)</td>
<td>15.2 (12)</td>
<td>1.18 (0.76–1.82), P=0.47</td>
</tr>
<tr>
<td>Revascularizations</td>
<td>19.4 (65)</td>
<td>22.9 (62)</td>
<td>19.0 (40)</td>
<td>13.9 (11)</td>
<td>1.28 (0.91–1.82), P=0.16</td>
</tr>
<tr>
<td>PTCA</td>
<td>13.1 (44)</td>
<td>12.5 (34)</td>
<td>12.3 (26)</td>
<td>10.1 (8)</td>
<td>0.98 (0.62–1.53), P=0.92</td>
</tr>
<tr>
<td>CABG</td>
<td>8.1 (27)</td>
<td>11.4 (31)</td>
<td>10.4 (22)</td>
<td>5.1 (4)</td>
<td>1.49 (0.89–2.50), P=0.13</td>
</tr>
<tr>
<td>Lost to follow-up by 5 years</td>
<td>4.5 (15)</td>
<td>2.2 (6)</td>
<td>1.9 (4)</td>
<td>1.3 (1)</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Beck Depression Inventory at 1 year†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All deaths</td>
<td>8.1% (29)</td>
<td>13.8% (29)</td>
<td>15.7% (21)</td>
<td>15.9% (10)</td>
<td>1.77 (1.06–2.96), P=0.030</td>
</tr>
<tr>
<td>Noncardiac deaths</td>
<td>1.4% (5)</td>
<td>3.8% (8)</td>
<td>3.7% (5)</td>
<td>1.6% (1)</td>
<td>2.82 (0.92–8.62), P=0.069</td>
</tr>
<tr>
<td>Cardiac deaths</td>
<td>6.7% (24)</td>
<td>10.1% (21)</td>
<td>11.9% (16)</td>
<td>14.3% (9)</td>
<td>1.55 (0.86–2.78), P=0.14</td>
</tr>
<tr>
<td>Cardiac deaths or survived MIs</td>
<td>13.4% (48)</td>
<td>16.3% (34)</td>
<td>20.9% (28)</td>
<td>22.2% (14)</td>
<td>1.24 (0.80–1.93), P=0.33</td>
</tr>
<tr>
<td>Survived MIs</td>
<td>6.7% (24)</td>
<td>6.3% (13)</td>
<td>9.0% (12)</td>
<td>7.9% (5)</td>
<td>1.22 (0.72–2.08), P=0.47</td>
</tr>
<tr>
<td>Lost to follow-up by 5 years</td>
<td>3.2% (12)</td>
<td>2.9% (6)</td>
<td>3.7% (5)</td>
<td>0.0% (0)</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>

*P values for continuous BDI scores in hospital are: all deaths, P=0.001; noncardiac deaths, P=0.060; cardiac deaths, P<0.001; cardiac deaths or survived MIs, P<0.001; survived MIs, P=0.20; revascularizations, P=0.51; PTCA, P=0.44; and CABG, P=0.50.
† P values for continuous BDI scores at 1 year are: all deaths, P=0.042; noncardiac deaths, P=0.68; cardiac deaths, P=0.038; cardiac deaths or survived MIs, P=0.039; and survived MIs, P=0.50.

Lack of β blockade and prescription of ACE inhibitors were also significantly linked to BDI scores. There was no relationship with age, smoking, previous MI, thrombolysis, presence of new Q waves, and revascularization at index. With the exception of left ventricular ejection fraction, which was not related to BDI scores at 1 year, the baseline variables linked to 1-year scores were identical.

Depending on the interrelationships among variables, stepwise procedures can lead to the exclusion of true predictors. Therefore, we used an approach for small data sets suggested by Steyerberg et al to assess the independent impact of baseline depression symptoms on cardiac prognosis. All baseline variables were entered together in a Cox proportional hazards regression analysis. Those not independently associated with prognosis (P>0.50) were eliminated, and all others were retained for covariate adjustment. As shown in Table 3, baseline depression remained significantly associated with 5-year cardiac mortality after covariate control and had an independent impact at least as great as left ventricular ejection fraction or diabetes. The independent impact of baseline depression symptoms continued when the analyses were restricted to 1-year (70 cardiac deaths, P=0.009) and 2-year survivors (49 cardiac deaths, P=0.015). Although the same trend persisted with the 3-year survivors, the subsequent number of cardiac deaths was too small (n=28) to analyze.

Long-term survival after MI in relation to Beck Depression Inventory Score during hospitalization.
One-Year Depression Symptoms and Long-Term Prognosis

One-year BDI scores were also significantly related to long-term cardiac and all-cause mortality and the combination of survived MIs and cardiac deaths (Table 2). The dose-response relationship was less evident than with baseline scores, partially a function of the smaller sample. Adjustment for the baseline BDI scores continued to have a close to significant impact after adjustment for the 1-year measures (P=0.052). Thus, the impact of the 1-year measures was largely a function of the initial severity of depression, suggesting that changes between the assessments had little prognostic impact.

Although the correlation between baseline and 1-year BDI scores was 0.62 (P<0.001), the average patient experienced a slight decrease of 0.9 points over the year, and there was some variation in the change (SD, 6.6). We evaluated the prognostic importance of change by calculating residual change scores between baseline and 1 year. Cox proportional hazards regression revealed that although residual change scores were not related to long-term cardiac mortality overall (P=0.75) and categorized baseline BDI scores continued to have a significant impact after control for change scores (P=0.006), there was an interaction between patients’ initial level of depression and their symptom changes (P=0.040). Changes only had a significant impact on prognosis in patients with BDI scores from 10 to 18 (mild depression symptoms). Among them, the greater the decline in symptoms, the better the long-term prognosis (P=0.016). However, for both groups of the nondepressed (BDI <5, P=0.18; BDI 5 to 9, P=0.93) and the more severely depressed (BDI ≥19; P=0.35) patients, change was unrelated to long-term prognosis. For these groups, it was the baseline measure that predicted prognosis.

Because previous work showed that the interaction between perceived social support and dichotomized baseline BDI scores was significantly related to residual change scores over the year (P=0.026),13 we explored the interaction using the 4 BDI categories. Social support was not linked to change in patients with more severe symptoms of depression (P=0.23) but was linked to improvement in the mildly depressed (P=0.042), the group for whom changes in depression predicted long-term survival.

Discussion

Results confirm a dose-dependent association between the level of depression symptoms during MI admissions and long-term cardiac mortality independent of established prognostic factors. Similar to the recent study by Bush et al,9 we began to observe an increase in risk of cardiac mortality at BDI scores below the usual cutoff for identifying mild depression. This suggests that, like low-density lipoprotein cholesterol levels, depression symptoms within the normal range for a healthy population may constitute a risk in patients with coronary artery disease.

Although there was also an association between the severity of depression symptoms at 1 year and long-term cardiac mortality, it was not independent of the baseline depression level. Although reassessment of depression symptoms at 1 year might not be useful for identifying additional patients at risk, it could be useful for those not evaluated during admission. Hospitalization seems to be the best time to screen for depression-related increases in risk. The value of repeated screening closer to discharge remains untested. We hypothesize that BDI scores during admission tap a personality factor influencing the degree to which patients’ psychological resources are strained by the acute coronary event and may provide a good estimate of emotional states in response to other stresses even years later. The 1-year scores were obtained at home in a more relaxed environment and may not reflect this trait as clearly. However, as Ketterer et al19 have suggested, it is also possible that the stress of hospitalization acted to unmask pre-existing depression that was previously minimized or denied.

Residualized change score analyses revealed that patients with moderate to severe baseline BDI scores (those most likely to have had major depression) had little improvement in prognosis associated with reductions in depression symptoms, whereas improvements were associated with better prognosis in patients with milder depression. This suggests that high levels of depression symptoms during a MI admission may also identify patients with more or less permanent disturbances in some of the mechanisms postulated to link depression and cardiac mortality.20 However, as we previously speculated,21 it is also possible that both depression and coronary disease are expressions of the same underlying pathophysiology. These results also reflect that depression is a chronic disease, with a high risk of relapse among those who show remission in symptoms.22 In contrast, for patients with mild baseline scores (BDI 10 to 18), we found that improvement in depression symptoms was associated with lower risk of cardiac mortality, suggesting less permanent pathophysiological disturbances. Thus, in addition to previous results showing that patients with high social support, lack of...
diabetes, and normal Killip class were most likely to show improvements in depressive symptoms over the first post-MI year,13 these results suggest that those with milder levels of baseline symptoms also have a better chance of improvement. Although we did not measure depression after 1 year, it is also possible that these patients had a better chance of sustaining their reduction in depression symptoms than those with higher initial scores. Interestingly, in the group with mild depression, depression symptoms were more likely to improve if patients perceived positive support from other people. This was not true for patients with more severe depression. This suggests that interventions to improve interpersonal relationships may be more appropriate for patients with mild depression. However, the small number of individuals with more severe depression at baseline prevents drawing firm conclusions.

We did not observe relationships between baseline depression and survived MIs, bypass surgery, or angioplasty. The prognostic impact of depression seems to be mostly limited to fatal events, suggesting that its mechanism is more likely arrhythmic than thrombogenic or linked to the progression of atherosclerosis. However, despite their greater disease severity, patients with depression were not more likely than patients without depression to undergo revascularization during hospitalization and after discharge. This suggests that, as one recent study showed,23 some potentially eligible patients with depression may not have been revascularized.

Although we included a baseline diagnostic measure of depression in our smaller epidemiological study,11 for reasons of feasibility, patients in our larger interventional study12 did not undergo diagnostic interviews. Thus, the present combined analyses were limited to the self-report BDI. Intriguingly, we found risks at lower levels of depressive symptoms than would likely have been evident with a diagnostic measure. Future research should assess the full spectrum of depression. With a relatively small data set and number of events, there are limitations in our ability to adjust for multiple baseline variables and their potential interrelationships. It remains possible that the in-hospital BDI scores captured some aspect of cardiac disease severity or medical comorbidity that was not tapped by our measures. Our results for nonfatal MI recurrences are also limited to events that led to hospital admissions. We have no information about silent MIs, nor do we have data on use of medications over the follow-up period. Finally, 1-year death rates were lower than in most earlier research. As previously reported,18 women and older patients were more likely to refuse participation, possibly resulting in a low-risk sample. However, our mortality level parallels those of other recent studies of hospital survivors22,25 and may also reflect a time trend in mortality.

Although these results provide additional support for the prognostic importance of depression, they do not establish that depression causes fatal cardiac events. We do not know if patients who were depressed in hospital were still depressed at the time of their deaths up to 5 years later. To establish a causal relationship, we need longitudinal research combining repeated measurement of depression and its presumed pathophysiological mechanisms, followed by adequately powered, randomized trials targeting the implicated mechanisms.

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References
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