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 al7 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.1,2,3,11-13

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.
Long-Term Prognosis

Baseline Depression Symptoms and Long-Term Prognosis

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 to 9), followed by 30.2% with scores at the high normal level (10 to 19), and only 8.8% who could be considered moderately to severely depressed (≥20). Their prognostic impact was assessed using Cox proportional hazards regression analysis.
nosophogenesis that began below the cutoff point of \( \geq 10 \) suggested by Beck et al\(^{10} \) for defining at least mild symptoms (Figure 1).

As reported previously,\(^{18} \) we observed significantly higher baseline depression symptoms in women, patients with less education, and patients with lower social support (unmarried, living alone, no close friends, or low perceived support) as well as in patients with several known prognostic factors (history of treatment for hypertension, diabetes, advanced Killip Class, and left ventricular ejection fraction \( \leq 35\% \)).

Lack of \( \beta \) 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\(^{16} \) 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.
TABLE 3. Multivariate Model for 5-Year Cardiac Mortality (n=879)

<table>
<thead>
<tr>
<th></th>
<th>Hazards Ratio Adjusted for Other Variables in Model (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per year increase)</td>
<td>1.04 (1.02 - 1.07)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female sex</td>
<td>0.63 (0.39 - 1.02)</td>
<td>0.062</td>
</tr>
<tr>
<td>≤8 Years education</td>
<td>1.20 (0.80 - 1.81)</td>
<td>0.38</td>
</tr>
<tr>
<td>Unmarried</td>
<td>1.17 (0.75 - 1.82)</td>
<td>0.48</td>
</tr>
<tr>
<td>Daily smoking</td>
<td>1.45 (0.93 - 2.25)</td>
<td>0.11</td>
</tr>
<tr>
<td>History of treatment for hypertension</td>
<td>1.19 (0.77 - 1.86)</td>
<td>0.43</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.06 (1.34 - 3.24)</td>
<td>0.001</td>
</tr>
<tr>
<td>Previous MI</td>
<td>1.97 (1.28 - 3.05)</td>
<td>0.002</td>
</tr>
<tr>
<td>Thrombolysis</td>
<td>0.56 (0.34 - 0.91)</td>
<td>0.019</td>
</tr>
<tr>
<td>Killip class &gt;1</td>
<td>1.22 (0.77 - 1.93)</td>
<td>0.40</td>
</tr>
<tr>
<td>Q-wave MI</td>
<td>1.26 (0.84 - 1.89)</td>
<td>0.27</td>
</tr>
<tr>
<td>Left ventricular ejection fraction</td>
<td>2.25 (1.42 - 3.57)</td>
<td>0.001</td>
</tr>
<tr>
<td>Revascularization during admission</td>
<td>0.48 (0.27 - 0.85)</td>
<td>0.012</td>
</tr>
<tr>
<td>β-Blockers at discharge</td>
<td>0.78 (0.51 - 1.18)</td>
<td>0.24</td>
</tr>
<tr>
<td>Beck Depression Inventory*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 to 9 vs &lt;5</td>
<td>1.76 (0.98 - 3.17)</td>
<td>0.059</td>
</tr>
<tr>
<td>10 to 18 vs &lt;5</td>
<td>3.17 (1.79 - 5.60)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥19 vs &lt;5</td>
<td>3.13 (1.56 - 6.27)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*Adjusted hazards ratio per SD increase in BDI = 1.24 (1.06 - 1.44); P = 0.007.

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 reduced the impact of 1-year scores to nonsignificant (P = 0.83), whereas the baseline 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.17 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,\textsuperscript{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 thrombotic. Despite their greater disease severity, patients with 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 thrombotic. However, we did not measure depression after 1 year, it is also possible that the in-hospital BDI scores captured some aspect of depression at baseline.

Although we included a baseline diagnostic measure of depression in our smaller epidemiological study,\textsuperscript{11} for reasons of feasibility, patients in our larger interventional study\textsuperscript{12} 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, 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 survivors\textsuperscript{21,25} 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.

Acknowledgments

This work was supported by the Medical Research Council of Canada, National Heart, Lung and Blood Institute, Health Canada, Fonds de la recherche en santé du Québec, Quebec Council of Social Research, Montreal Heart Institute Research Fund, and salary support (to Dr Lespérance) from the Pierre David Fund. The authors are indebted to the Régie de l’assurance maladie and the Ministère de la santé du Québec for medicare data and Ginette Gravel, MSc, and Aline Masson, MSc, for preparing the database.

References

Five-Year Risk of Cardiac Mortality in Relation to Initial Severity and One-Year Changes in Depression Symptoms After Myocardial Infarction
François Lespérance, Nancy Frasure-Smith, Mario Talajic and Martial G. Bourassa

_Circulation_. 2002;105:1049-1053; originally published online February 4, 2002;
doi: 10.1161/hc0902.104707
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2002 American Heart Association, Inc. All rights reserved.
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/105/9/1049

**Permissions:** Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

**Reprints:** Information about reprints can be found online at:
http://www.lww.com/reprints

**Subscriptions:** Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org//subscriptions/