Relationship between left ventricular dysfunction and depression following myocardial infarction: data from the MIND-IT

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KEYWORDS
Left ventricular ejection fraction; Myocardial Infarction; Depression; Risk factors

Aims Depression in patients following myocardial infarction (MI) is associated with an increased risk of mortality, but this association may be confounded by cardiac disease severity. We explored the relationship between left ventricular ejection fraction (LVEF) and depression in MI patients.

Methods and results In the Myocardial Infarction and Depression—Intervention Trial (MIND-IT), 1989 MI patients were assessed for depressive symptoms [Beck Depression Inventory (BDI) t = 0, 3, 6, 9, and 12 months post-MI]. Patients with BDI score ≥10 were assessed for the presence of International Classification of Diseases, 10th revision (ICD-10) depressive disorder (t = 3, 6, 9, and 12 months post-MI). Patients were divided into categories according to their LVEF during hospitalization, i.e. LVEF <30%, LVEF 30–45%, LVEF 45–60%, and LVEF ≥60%. During hospitalization, presence of depressive symptoms was higher in patients with LV dysfunction. A relationship was found between LVEF and ICD-10 depressive disorder, i.e. a lower LVEF was associated with a higher rate of depression from 3–12 months post-MI (P < 0.01). Levels of LVEF inversely correlated with the BDI score at 3 months post-MI. Associations persisted after adjustment for demographics, risk factors for coronary artery disease, co-morbidity, Killip class, and baseline BDI score.

Conclusion In MI patients, the rate of depression and the severity of depressive symptoms are significantly related to the severity of LV dysfunction. The association between depression and LV dysfunction must be acknowledged when evaluating the prognostic effects of depression in cardiac patients.

Introduction

A recent meta-analysis concluded that depression following myocardial infarction (MI) should be considered an important risk factor for impaired cardiac prognosis.1 The excess risk was found to be on average 2–2.5 fold for both mortality and morbidity. However, some studies failed to find an association, not even an univariate association,2,3 whereas other studies did report significant univariate associations, but failed to find a significant relationship after adjustment for markers of cardiac disease severity.4,5 Therefore, controversy continues whether depression has an adverse effect on cardiac prognosis independent of cardiac disease severity.6–8

Most studies support the claim that post-MI depression is related to a poor cardiac prognosis, independent of the severity of cardiac disease, because depression continues to be significantly associated with mortality after controlling for left ventricular ejection fraction (LVEF). However, given the association between LVEF and cardiac prognosis in MI patients, a thorough investigation of the prospective relationship between LVEF and depression is crucial. Unfortunately, data on this relationship are limited (Table 1) and therefore we set out to evaluate the relationship between cardiac disease severity, measured by LV function, and depression, breaking down the issue into three questions.

First, it was investigated whether depressive symptoms and LV function, both assessed during hospitalization for MI, are cross-sectionally related to each other. Secondly, it was investigated whether the development of depressive disorder in the first year post-MI is related to the severity of in-hospital LV dysfunction. In other words, do patients with severe LV dysfunction have higher rates of prospective depressive disorder compared with patients with relatively preserved LV function? Finally, it was explored whether the severity of prospective depressive symptoms...
as assessed at 3 months post-MI is related to LV function at hospitalization.

**Methods**

**Setting**

The present study is a pre-defined substudy to a large, multicentre trial in the Netherlands: the Myocardial Infarction and Depression—Intervention Trial (MIND-IT). MIND-IT prospectively investigates the prognostic influence of anti-depressive treatment for a depressive disorder following MI. The MIND-IT data allowed the investigation of the relationship between LV function and depressive disorders in the first year post-MI in a large, representative sample of MI patients.

**Study participants**

Inclusion and exclusion criteria have been described previously. In short, we recruited consecutive patients (September 1999 to November 2002), hospitalized for acute MI, in 10 hospitals (including three tertiary centres) located in different parts of The Netherlands. Patients were enrolled if they met the WHO MONICA criteria for definite MI: increased cardiac enzymes and either electrocardiographic changes and/or chest pain. Exclusion criteria were the occurrence of MI while the patient was hospitalized for another reason (e.g. patients not able to communicate and patients not available for follow-up), any disease likely to influence short-term survival, patients already receiving psychiatric treatment for depression, and participation in another clinical trial. The study complies with the Declaration of Helsinki. The institutional review board at each centre approved the study protocol, and study patients provided written informed consent before enrolment.

**Design of the study**

Demographics, medical history, clinical variables, and information about medication at discharge were collected in a prospective manner. Data management was performed by the Trial Coordination Centre in Groningen, The Netherlands. Severity of index MI was assessed by maximum values of serum aspartate transaminase during hospitalization (ASAT max) and LVEF after MI, as measured by either echocardiography or radio-nuclide ventriculography. Before study participation, study sites had to agree to perform echocardiographic assessments in accordance with the recommendations of the American Society of Echocardiography. An echocardiographic core lab checked the quality of randomly selected echocardiographic assessments. The presence of heart failure at admission was assessed by the Killip class. During hospitalization, the cumulative burden of medical co-morbidity was assessed with a modified version of the Charlson co-morbidity index. Higher scores on this scale indicate more co-morbidity (i.e. rheumatological disease, chronic pulmonary disease, congestive heart failure (CHF), peripheral vascular disease, cerebrovascular disease, diabetes, renal disease, malignancies, liver disease).

All study patients were screened for depressive symptoms during hospitalization and at 3, 6, 9, and 12 months post-MI with the Beck Depression Inventory (BDI). The BDI is a self-report instrument consisting of 21 questions (total score ranging from 0 to 63), higher BDI scores indicating more severe depressive symptoms. It is the most commonly used measure of depression, and its reliability and validity has been assessed in a variety of patients. MI patients with depressive symptoms (i.e. BDI score ≥10, at any time point; and in case of more than one successive positive BDI: only if the BDI score was higher than the previous one) underwent an additional psychiatric evaluation with a standardized psychiatric interview by trained interviewers (Composite International Diagnostic Interview (CIDI); auto version 2.1). This interview provides diagnoses according to criteria of the International Classification of Diseases, 10th revision (ICD-10). In the present study, ‘diagnosis of depression’ refers to a positive CIDI interview according to these criteria. The first interviews were performed not earlier than 3 months post-MI to allow natural recovery of depressive symptoms following a major life event. Of note, only patients who screened positive based on the BDI underwent a CIDI interview. Therefore, the term ‘depressive disorder’ denotes a positive CIDI interview in those patients who already scored positive on their BDI.

**Statistical analysis**

The aim of the study was to assess the relationship between the severity of LV dysfunction (as assessed shortly after MI) and (i) the severity of in-hospital depressive symptoms (ii) the rate of prospective depressive disorder (3–12 months post-MI), and (iii) the severity of prospective depressive symptoms (3 months post-MI). We used LVEF as a measure of LV (dys)function. We categorized the study sample into four groups: MI patients with LVEF <30%, LVEF 30–45%, LVEF 45–60%, and LVEF ≥60%. In principle, dividing LVEF into categories is arbitrary. Because we investigated a graded response between LVEF and depression, cut-off values were chosen resulting in comparable increases in LVEF without having too many categories. This categorization may have resulted in an overestimation of the association between LVEF and depression. However, it was not possible to implement an uniform procedure for assessing LVEF as a continuous variable across the centres that participated in MIND-IT.

First, the BDI scores during hospitalization were used. Secondly, the interview data as obtained from the CIDI (3–12 months post-MI) were used. The bivariate association between LVEF and ICD-10 depressive disorder was assessed by means of logistic regression analysis using a hierarchical approach with pre-specified potential confounders of the relationship between LVEF and depression. All multiple regression models included LVEF as a categorical independent variable and depression as the dependent variable. The first model also included demographic factors (age, sex), the second model added risk factors of coronary artery disease (CAD) (smoking, hypertension, family history of CAD, and dyslipidaemia), and the third model added co-morbidity (modified Charlson co-morbidity index). Although adjustment for the Charlson co-morbidity index implies that diabetes and CHF are controlled, it is a rather diffuse measure to adjust because co-morbidities other than diabetes and CHF may also contribute to the co-morbidity score. Given the

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**Table 1** Studies presenting the prevalence of depression in post-MI patients according to LVEF

<table>
<thead>
<tr>
<th>First author</th>
<th>Sample size</th>
<th>LVEF cut-off value (%)</th>
<th>Prevalence of depression (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frasure-Smith⁷</td>
<td>222</td>
<td>35</td>
<td>29</td>
</tr>
<tr>
<td>Frasure-Smith⁹</td>
<td>896</td>
<td>35</td>
<td>39</td>
</tr>
<tr>
<td>Bush¹¹</td>
<td>285⁸</td>
<td>35</td>
<td>34</td>
</tr>
<tr>
<td>Strik¹²</td>
<td>318²</td>
<td>50</td>
<td>48</td>
</tr>
<tr>
<td>Strik¹³</td>
<td>206²</td>
<td>50</td>
<td>39</td>
</tr>
<tr>
<td>Carney¹⁴</td>
<td>766²</td>
<td>40</td>
<td>49</td>
</tr>
</tbody>
</table>

⁷MI patients ≥65 years.
⁸Male patients with first MI.
⁹Patients with first MI.
¹⁰Computed from data as presented in article (χ² test).
¹¹Controls free of depression and social isolation.

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*References*
strong relationship between LV function and CHF as well as diabetes, we made an additional adjustment for the presence of heart failure at admission (Killip class) and diabetes in the fourth model. In the fifth model, we adjusted for baseline BDI score ≥ 10.

Finally, mean BDI scores were compared between groups with different LV EF using a one-way analysis of variance (ANOVA). To study whether there is a gradual increase in depressive symptoms and decrease in LV EF levels, we added a polynomial contrast that mimics a linear relationship between LV EF levels and BDI scores. Of note, we used the data as obtained from the 3 months BDI, because we were interested in discharged, stable MI patients. To adjust for potential confounders, we entered the variables from model 5 into a multiple regression model and obtained the unstandardized beta for the change in BDI score across LV EF categories. All tests are two-sided.

MIND-IT investigates the effects of anti-depressive treatment for post-MI depression on cardiac prognosis. However, any study treatment was started after a positive CIDI diagnosis of depression.

Results

In MIND-IT, 4780 MI patients were assessed for eligibility, of whom 1403 (29%) met the exclusion criteria. Of the 3377 remaining patients, 2177 (64%) were included (mean age 61.2 years, SD 11.9). From the 2177 included patients, 1989 patients (91.4%) had an evaluation of LV EF. These patients did not differ on any of the baseline variables from those patients of whom no LV EF assessment was available, except for the administration of thrombolysis during hospitalization (35.9 vs. 45.4% for patients with and without LV EF assessment, respectively; P = 0.01). In addition, the occurrence of depressive disorder (3–12 months post-MI) was not significantly different in both samples (17.1 vs. 18.6%, respectively; P = 0.60). We therefore confined analyses to the 1989 patients with LV EF assessment. Table 2 shows the baseline characteristics of the participants according to their LV EF. Differences between patients with different levels of LV function were found with respect to BDI scores at hospitalization (P < 0.01). In addition, age, diabetes mellitus, hypertension, family history of CAD, smoking, previous MI, ASAT max, Killip class, Charlson score, Q-wave infarction, thrombolysis, and prescribed post-MI cardiac medication were related to levels of LV function (P ≤ 0.05).

Severity of depressive symptoms during hospitalization

In regression analysis, when compared with individuals with preserved LV function (>60%), patients with an LV function...
of 45–60% had the same mean BDI score during admission (95% CI 0.64–0.60; \(P = 0.96\)), patients with an LV function of 30–45% had 0.99 points higher BDI scores (95% CI 0.19–1.79; \(P = 0.02\)), and patients with an LV function <30% had 3.00 points higher BDI scores (95% CI 1.83–4.17; \(P < 0.01\)). After controlling for demographics, risk factors of CAD, co-morbidity, diabetes, and Killip class, these results were 0.14 (−0.49–0.77; \(P = 0.66\)) for LV function 45–60%, 1.13 (0.32–1.94; \(P < 0.01\)) for LV function 30–45%, and 2.96 (1.73–4.18; \(P < 0.01\)) for LV function <30%.

### Rate of depressive disorder

During the follow-up period from 3 to 12 months post-MI, 17% (340/1989) of all patients met the criteria of depressive disorder according to ICD-10 criteria. The distribution of the positive CIDI interviews during the post-MI year was skewed, with the majority identified at 3 months (72.4%) and a minority identified at 6 (15.0%), 9 (7.4%), and 12 months (5.3%). The unadjusted logistic regression analysis indicated that MI cases with severe LV dysfunction (LV EF <30%) had 4.46 times the odds (95% CI 2.91–6.83) of being depressed compared with individuals with preserved LV function (LV EF >60%) (Table 3). The relationship between LV EF and depression remained significant and did not diminish when adjusting for demographic factors (model 1), risk factors of CAD (model 2), co-morbidity (model 3), diabetes and Killip class (model 4), and baseline BDI score ≥10 (model 5). To take into account the higher percentage of patients receiving thrombolysis in those patients with LV EF assessment, we conducted a sensitivity analysis and forced the administration of thrombolysis into multiple regression analysis. Adjustment for thrombolysis did not alter the association between LV EF and depression (LV EF 45–60%: OR 1.81, 95% CI 1.31–2.52; LV EF 30–45%: OR 2.91, 95% CI 2.01–4.21; LV EF <30%: OR 2.96, 95% CI 2.01–4.21; LV EF 45–60%, LV EF 30–45%, and LV EF <30%), respectively, (\(P < 0.01\)). After controlling for demographics, risk factors of CAD, co-morbidity, diabetes, and Killip class, these results were 0.43 (−0.20–1.06; \(P = 0.18\)) for LV EF 45–60%, 1.03 (0.22–1.85; \(P = 0.04\)), and patients with an LV EF >30% had 4.46 times the odds (95% CI 2.91–6.83) of being depressed compared with individuals with preserved LV function (≥60%), patients with an LV EF 45–60% had 0.2 points higher mean BDI score during admission (95% CI −0.39–0.85; \(P = 0.47\)), patients with an LV EF 30–45% had 1.0 point higher BDI scores (95% CI 0.20–1.80; \(P = 0.01\)), and patients with an LV EF <30% had 2.66 points higher BDI scores (95% CI 1.52–3.81; \(P < 0.01\)). After controlling for demographics, risk factors of CAD, co-morbidity, diabetes, and Killip class, these results were 0.43 (−0.20–1.06; \(P = 0.18\)) for LV EF 45–60%, 1.03 (0.22–1.85; \(P = 0.04\)).

### Severity of depressive symptoms at 3 months post-MI

The mean (standard error of mean) BDI scores, assessed at 3 months post-MI, in the four LV EF categories (LV EF ≥60%, LV EF 45–60%, LV EF 30–45%, and LV EF <30%) were 6.1 (0.3), 6.3 (0.2), 7.3 (0.3), and 9.4 (0.6), respectively. Significant differences in the mean BDI score were found across different levels of LV function, with higher scores reported in patients with lower LV EF (F 32.6; \(P < 0.01\)). In regression analysis, when compared with individuals with preserved LV function (>60%), patients with an LV EF 45–60% had 0.2 points higher mean BDI scores during admission (95% CI −0.39–0.85; \(P = 0.47\)), patients with an LV EF 30–45% had 1.0 point higher BDI scores (95% CI 0.20–1.80; \(P = 0.01\)), and patients with an LV EF <30% had 2.66 points higher BDI scores (95% CI 1.52–3.81; \(P < 0.01\)). After controlling for demographics, risk factors of CAD, co-morbidity, diabetes, and Killip class, these results were 0.43 (−0.20–1.06; \(P = 0.18\)) for LV EF 45–60%, 1.03 (0.22–1.85; \(P = 0.04\)).

### Table 3 Unadjusted and adjusted logistic regression analysis of the relationship between LVEF and ICD-10 depressive disorder

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF (%)</td>
<td></td>
</tr>
<tr>
<td>≥60</td>
<td>1.0</td>
</tr>
<tr>
<td>45–60</td>
<td>1.69 (1.23–2.31)</td>
</tr>
<tr>
<td>30–45</td>
<td>2.67 (1.88–3.79)</td>
</tr>
<tr>
<td>&lt;30</td>
<td>4.46 (2.91–6.83)</td>
</tr>
<tr>
<td>Demographics</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.97 (0.96–0.98)</td>
</tr>
<tr>
<td>Sex (female)</td>
<td>1.21 (0.93–1.56)</td>
</tr>
<tr>
<td>Risk factors of CAD</td>
<td></td>
</tr>
<tr>
<td>Smoking†</td>
<td>1.36 (1.08–1.69)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.02 (0.86–1.29)</td>
</tr>
<tr>
<td>Family history</td>
<td>1.25 (1.00–1.57)</td>
</tr>
<tr>
<td>CAD</td>
<td>1.63 (1.22–2.18)</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td>1.47 (1.06–2.02)</td>
</tr>
<tr>
<td>Co-morbidity</td>
<td></td>
</tr>
<tr>
<td>Charlson</td>
<td>1.08 (1.00–1.17)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.04 (0.88–1.22)</td>
</tr>
<tr>
<td>Killip class</td>
<td>1.22 (1.00–1.49)</td>
</tr>
<tr>
<td>BDI score ≥10</td>
<td>7.02 (5.47–9.00)</td>
</tr>
</tbody>
</table>

*Current smoker or stopped smoking <3 months.
higher rates of depression in patients with low LVEF is discernable in most studies. Hence, the statistical non-significance may be due to a type II error resulting from the relatively small sample size when compared with our study. In addition, we included consecutive MI patients without excluding female MI patients, patients ≤65 years, and MI patients with previous MI. Only in one study, LVEF was analysed as a continuous variable, which resulted in no difference in LVEF in those with and without depression (45.8 vs. 46.8%; P = 0.39). Taken together, the available data, including our study, point to a possible relationship between LV dysfunction and depression during hospitalization for MI, although further research is warranted.

The present study shows, for the first time, that LVEF, as assessed shortly after MI, is also prospectively associated with the development of depression in the year post-MI. It was shown that the lower the LVEF, the higher the rate of post-MI depressive disorder. This association remained significant, even after adjustment for important correlates of depression. The presence of depressive symptoms during hospitalization did not alter this association. The association tended to be stronger for men when compared with women.

As far as we know, our study is the first to show the relationship between LVEF and the severity of depressive symptoms in post-MI patients. Previous studies have shown that patients with a clinical diagnosis of CHF have higher depression scores than their counterparts without CHF. One may argue that our results merely reproduce these findings in CHF patients; however, we observed that the relationship between LVEF and depression remained significant after adjustment for CHF at admission (i.e. Killip class). Moreover, it must be taken into account that we included only MI patients, making the comparison with CHF patients at least speculative. In this connection, it is of relevance that, in CHF patients, a substantial part is free from CAD. As evidence is growing that depression is more prevalent in the context of clinical manifestations of vascular disease (‘vascular depression’ hypothesis), the absence of clinically overt vascular disease in some CHF patients might be important.

As to the mechanism underlying the strong link between LV function and both rate and severity of depression, two pathways could be involved, i.e. a psychological and a biological pathway. First, extrapolating from the comprehensive literature on CHF, the association might be due to poor quality of life as a result of worse overall health status, more co-morbidity, higher rehospitalization rate, worse social functioning, and more non-employment. All of these factors may result in higher rates of depression as they represent or lead to increased depressogenic stress. Alternatively, the association between LV dysfunction and depression might be the result of biological adaptations that accompany LV dysfunction. It was surmised that the increased cytokine levels in CHF, such as interleukin-1, interleukin-6, and tumour necrosis factor-alpha, play a mediating role in the genesis of depression. A similar mechanism may be operative in patients with severe LV dysfunction. Because the associations we have found do not elucidate causal mechanisms, it is also possible that depression leads to LV dysfunction. In this connection, a study by Williams et al. is of interest in which depression was an independent risk factor for CHF among elderly patients.
women. The observed relationship between LV dysfunction and depression would support both possibilities, but further research is warranted before causal inferences can be made.

Several limitations of our study deserve comment. First, we have no data on two potential confounders, namely, pre-MI psychiatric morbidity and alcohol abuse. Secondly, only MI patients with BDI scores ≥ 10 had a psychiatric interview. Therefore, we cannot exclude that MI patients with low BDI scores had a depressive disorder if they would have been interviewed. However, the probability of false-negatives is low, because of the high specificity of the BDI. Finally, to feed the debate on depression and cardiac disease severity, we focused on the relationship between depression and LVEF. Another important determinant of cardiac disease severity in the post-MI setting is the extent of CAD. Although a substantial part of the study population underwent coronary angiography, our data set lacks systematical information on the extent of CAD.

This study provides evidence for a strong relationship between LVEF and depression in MI patients. These findings add to the ongoing discussion whether depression and cardiac disease severity are related. If anything, our data clearly show that the relationship between depression and LVEF must be taken into account, when evaluating the effect of depression on cardiac prognosis.

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Conflict of interest: we have no conflict of interest to state.

Appendix

The following investigators en institutions in The Netherlands participated in the MIND-IT study. 


Study coordination: P. de Jonge, J.P. van Melle.

Data management: Trial Coordination Centre (TCC), Groningen, The Netherlands.


References


