Depression treatment after myocardial infarction and long-term risk of subsequent cardiovascular events and mortality: A randomized controlled trial

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A B S T R A C T

Objective: Evaluating the effects of implementing an antidepressant treatment strategy in depressed myocardial infarction (MI)-patients on long-term cardiovascular outcomes and all-cause mortality.

Methods: MI-patients were evaluated for the presence of a diagnosis of post-MI depression at 3, 6, 9 and 12 months after hospitalization for MI. A total of 331 depressed MI-patients were randomized to intervention or care-as-usual (CAU). Patients randomized to the intervention were offered several antidepressant treatment options including pharmacological and non-pharmacological therapy. Patients randomized to CAU were not given feedback about their depression status. All patients were free to seek depression treatment outside the study, which was monitored. The primary outcome was a combined endpoint of cardiovascular events and cardiac mortality between randomization and 8 years later. All-cause mortality was evaluated as secondary endpoint.

Results: The intervention did not reduce the risk of the primary outcome (HR: 0.97 (95% CI: 0.67–1.40) n = 330) or all-cause mortality (HR: 0.74 (95% CI: 0.41–1.33) n = 330). Regardless of randomization status, patients who received depression treatment (n = 168) had reduced all-cause mortality rates compared to those who did not receive treatment (n = 143, HR: 0.52 (95% CI: 0.28–0.97)).

Conclusion: Implementing an antidepressant treatment strategy did not reduce the risk of cardiovascular morbidity and mortality compared to usual care. Receiving depression treatment increased survival. It remains unclear whether this represents a direct treatment effect or is due to unmeasured factors that relate to both receiving depression treatment and mortality, such as patients' intrinsic motivation to care for their health.

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Introduction

Depression after myocardial infarction (MI) is associated with worse cardiovascular outcomes [1]. Unfortunately, large-scale randomized controlled trials (RCTs) in depressed cardiac patients found treatment for depression not to affect cardiac prognosis [2–4]. In the Enhancing Recovery in Coronary Heart Disease trial (ENRICHHD), 6 months of cognitive behavioral therapy (CBT) in 2481 MI-patients with depression or low social support had no impact on cardiac morbidity and mortality [2]. In the Sertraline Antidepressant Heart Attack Randomized Trial (SADHART), 6 months of sertraline treatment had no impact on 8-year survival rates in 361 depressed acute coronary syndrome patients [4].

Previously, we reported findings from the Myocardial Infarction and Depression Intervention Trial (MIND-IT) [5]. In this RCT, the implementation of an active antidepressant treatment strategy in depressed MI patients had no effect on depression and cardiovascular outcomes till 18 months post-MI [6]. However, potential beneficial effects on cardiovascular prognosis may only appear after a longer follow-up time. The reason for this is that a substantial part of the prognostic impact of post-MI depression can be explained by mechanisms that act on long-term cardiac prognosis, such as physical inactivity [7], difficulties with smoking cessation [8], and non-adherence to cardiac aftercare regimens [9]. Furthermore, depression has been shown to predict poor health outcomes and mortality even after 10 years of follow-up [10–12]. Therefore, in the present article we evaluated whether MIND-IT’s intervention (i.e. implementing an active antidepressant treatment strategy) is associated with reduced cardiovascular morbidity and mortality rates till 8 years after treatment initiation. After this, we did two secondary analyses, comparing cardiovascular outcomes between (1) patients who responded to antidepressants and those who did not, and (2) patients who actually received treatment for depression and those who did not, regardless of randomization.

Clinical trial registration number: ISRCTN57865866.

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Method

Study design and participants

MIND-IT was a multicenter RCT with the goal to determine the effectiveness of implementing an antidepressant treatment strategy compared to care as usual (CAU). Details of the study have been described before [5,6]. Briefly, patients consecutively admitted for MI to one of eleven hospitals in the Netherlands between September 1999 and November 2002 were assessed for eligibility. Eligible patients met at least two of the following criteria: (1) chest pain for at least 20 min, (2) typical electrocardiographical changes, and (3) a documented increase in cardiac enzyme levels. Patients were excluded if they were unable to communicate, were not available for follow-up, had another somatic disease likely to influence short-term survival, already received treatment for depression or were participating in another clinical trial.

Eligible MI-patients were screened with the Beck Depression Inventory (BDI) [13] at hospitalization, and 3, 6, 9 and 12 months after the MI. Those scoring ≥ 10 were administered the Composite International Diagnostic Interview (CIDI) version 2.1 [14] to assess the presence of an International Classification of Diseases (ICD)-10 diagnosis of a depressive episode after the MI [15]. CIDI interviews were not administered earlier than 3 months after the MI, to allow for natural recovery of depressive symptoms just after the MI. Patients diagnosed with a post-MI depressive episode were randomized.

The institutional review board of each participating hospital approved the protocol and each participant signed informed consent. All participating patients were informed that they were free to seek help for mood problems outside the study protocol.

Intervention

Feedback about the depression status was given only to patients in the intervention arm and not to patients or their practitioners in the CAU arm (i.e. a Zelen design [16]). Patients in the intervention arm were offered several treatment options. The first option was to participate in a double-blind placebo-controlled trial on the efficacy of mirtazapine. In case of no sufficient treatment response after eight weeks, defined as at least 50% reduction in the Hamilton Depression Rating Scale (HDRS [17]) score or an HDRS-score of less than 10 at 8 weeks, patients in both arms were offered open treatment with citalopram. The second option was open treatment with citalopram. The third option was ‘tailored treatment’, which was at the discretion of the psychiatrist. For all patients in the intervention arm, monthly visits to the psychiatrist were scheduled. Treatment duration was six months. More details about the intervention can be found in Van den Brink et al. 2002 [5]. Patients in the CAU arm were free to seek treatment outside the study protocol, which was recorded.

Baseline variables

Demographic and clinical characteristics were assessed during hospitalization for the index-MI and obtained from medical records. Left ventricular ejection fraction (LVEF) was assessed by echocardiography, radionuclide ventriculography, gated single photon emission computed tomography, magnetic resonance imaging or angiography.

Endpoints

Two endpoints were evaluated: (1) a combined endpoint of cardiovascular related hospital readmissions and cardiac mortality, which was the primary endpoint of MIND-IT [5], and (2) all-cause mortality. Date and cause of death and hospital readmissions was obtained from Statistics Netherlands by linkage to the municipal personal records database. Considered as cardiac deaths were causes of death with ICD-10 codes I11 (hypertensive heart disease), I20-I25 (ischemic heart diseases), I42-I50 (cardiomyopathy, conduction disorder, cardiac arrest, cardiac dysrhythmia, heart failure) and R57.0 (cardiogenic shock). Hospital readmissions with the following ICD-9 primary discharge diagnoses were included as cardiovascular readmissions: ischemic heart disease (410, 411, 413, 414), cardiac arrhythmia (427.1, 427.4, 427.5), heart failure (428, 398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93), cerebrovascular disease (433, 434, 435, 437.0, 437.1) and peripheral vascular disease (440, 443.9).

Data on potential endpoints were gathered up to 31 December 2007. The follow-up period started at the date of randomization, ranging between April 2000 and January 2003. Patients who did not have the outcome of interest until 31 December 2007 were censored on 31 December 2007 or date of death as appropriate.

Statistical analyses

The initial study power calculation showed that 190 patients in the intervention arm and 130 patients in the CAU arm were needed to detect a reduction in the incidence of the primary outcome from 38% to 25% [5]. Because the incidence of the primary outcome up to 18 months post-MI was substantially lower than expected (13% instead of 38% over a mean follow-up period of 11 months [6]), the study power was recalculated given this event rate, a sample size of 208 and 122 patients in the intervention and CAU arm respectively, an attrition rate of 0.1% per month, an accrual period of 33 months, and a total follow-up period up to 93 months after the MI. This resulted in a study power of 89% and an expected frequency of 67% in the usual care arm versus 49% in the intervention arm for the primary outcome.

Data on the combined endpoint were present for 295 of the 330 randomized patients. To be as inclusive as possible, we included previously obtained data on the combined endpoint during the first 18 months after MI [6] for the 35 patients with missing data on long-term cardiac outcomes. With Cox regression, endpoints were compared between the intervention and the CAU arm. After this, two subgroup analyses were done. The first subgroup analysis compared endpoints between responders (i.e. ≥ 50% reduction in the HDRS score or an HDRS-score of < 10 after 24 weeks of treatment) and non-responders to antidepressants. This was done as a long-term follow-up of our previous publication, in which we reported better 18-month cardiovascular outcomes for responders to antidepressants, compared to non-responders [23]. This analysis included patients who received antidepressants only (n = 70). Some patients in the intervention arm received no treatment for depression, and some patients in the CAU arm did. Therefore, the second subgroup analysis compared endpoints between patients who received treatment for depression and patients who did not, regardless of randomization status. This analysis included all patients with information on treatment status (n = 311) and was done twice: once including patients from the nested trial receiving placebo only in the group that received treatment, and once in the group that did not receive treatment. This is because of the ambiguity of their treatment status, i.e. they were randomized to the intervention, but received placebo. In case of a statistically significant effect on long-term cardiac outcomes, Chi-square and t-tests were used to determine whether subgroups differed on characteristics known to influence cardiac outcomes. These a priori determined characteristics were age, sex, smoking, hypertension, hypercholesterolemia, diabetes, Killip Class, LVEF, and depression severity [1,18,19]. Then, the Cox regression was repeated after adjustment for those characteristics that differed substantially (p < 0.10) between the groups to evaluate whether these may explain the differential risk.
Results

Sample

Of 2176 eligible patients, 375 had a post-MI depressive episode, of whom 331 were randomized. Forty-four patients were not randomized due to risk of suicide (n = 28) and end of the study (n = 16, see Fig. 1). Patients in the intervention arm did not differ from those in the CAU arm in terms of demographics, depressive symptom severity, cardiovascular disease severity and cardiovascular risk factors [6]. One patient who died before the start of the intervention, was excluded from further analysis, leaving 330 patients. The combined endpoint occurred in 121 (36.7%) of the patients during a mean follow-up of 4.0 years (standard deviation (SD) 2.5 years; range 2 days–7.7 years, total follow-up time 1332.3 person-years). The crude event rate was 90.8 events per 1000 person-years. All-cause mortality occurred in 46 (13.9%) of patients with a mean follow-up of 5.2 years (SD 2.1 years, range 19 days–7.7 years, total follow-up time 1730.8 person-years). The crude death rate was 26.6 deaths per 1000 person-years.

Effects of the intervention

Seventy-six (36.5%) of 208 patients in the intervention arm and 45 (36.9%) of 122 patients in the CAU arm had the combined endpoint of cardiovascular related hospital readmissions and cardiac mortality (HR: 0.97 (95% CI: 0.67–1.40; p = 0.850) see Fig. 2). All-cause mortality occurred in twenty-six (12.5%) of 147 patients receiving antidepressants. Of these, there were 27 responders and 43 non-responders. The combined endpoint occurred in 9 (33.3%) of 27 responders and in 16 (37.2%) of 43 non-responders (HR (95% CI) for non-responders: 1.15 (0.51–2.61) p = 0.731). Three (11.1%) of the 27 responders died versus 5 (11.6%) of the 43 non-responders (HR (95% CI) for responders: 0.98 (0.23–4.12) p = 0.976).

Response to treatment with antidepressants

In the nested trial, 47 patients received mirtazapine and 44 placebo. After 8 weeks, 23 patients in the placebo group switched to citalopram, resulting in a total of 70 patients receiving antidepressants. Of these, there were 27 responders and 43 non-responders. The combined endpoint occurred in 9 (33.3%) of 27 responders and in 16 (37.2%) of 43 non-responders (HR (95% CI) for non-responders: 1.15 (0.51–2.61) p = 0.731). Three (11.1%) of the 27 responders died versus 5 (11.6%) of the 43 non-responders (HR (95% CI) for responders: 0.98 (0.23–4.12) p = 0.976).

Treatment versus no treatment for depression

Treatment status was known for 311 patients, of whom 21 received placebo only, 147 received treatment for depression (27 mirtazapine only, 20 initially mirtazapine and later citalopram, 23 initially placebo and later citalopram, 17 open pharmacological treatment, 40 nonpharmacological treatment, 20 of the CAU arm receiving treatment) and 143 did not (45 from the intervention arm and 98 from the CAU arm, see Fig. 1).

The combined endpoint occurred in 50 (34.0%) of 147 patients who received treatment, in 55 (38.5%) of 143 patients who did not, and in 10 (47.6%) of 21 patients who received placebo. When patients on placebo were included in the group that received treatment, the HR (95% CI) for the combined endpoint was 0.94 (0.65–1.35; p = 0.728) for those who received treatment. When including the patients who received placebo in the group who received no treatment this was 0.84 (0.58–1.21; p = 0.340).

Fourteen (9.5%) of 147 patients who received treatment, 26 (18.2%) of 143 patients who did not, and 2 (9.5%) of 21 patients who received placebo died. When patients on placebo were included in the group that received treatment, the HR (95% CI) for all-cause mortality for the group that received treatment was 0.52 (0.28–0.97; p = 0.041). When including the patients on placebo in the group who received no treatment this was 0.56 (0.29–1.05; p = 0.072).

Patients who received treatment (when including patients on placebo in this group) were significantly more likely to be men (p = 0.008), and had higher

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Fig. 1. Flow-chart of patients in MIND-IT. 1 Of 94 patients randomized in the nested trial, 3 did not show up, 47 received mirtazapine of whom 27 (57%) responded at week 8, and 44 received placebo of whom 18 (41%) responded. Non-responders (20 + 26) were offered open pharmacological treatment (citalopram first choice).
BDI-scores ($p=0.054$; see Table 1). Adjusting for these characteristics essentially did not change the association between treatment status and all-cause mortality, although after adjustment for sex alone the association lost its significance (see Table 2).

**Discussion**

The present paper reports the effectiveness of implementing an antidepressant treatment strategy on cardiovascular outcomes for depressed MI patients enrolled in MIND-IT. Previously, we showed in antidepressant treatment strategy on cardiovascular outcomes for depressed patients who received treatment for depression versus 143 who did not.

### Table 1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Received treatment (n=168)</th>
<th>Received no treatment (n=143)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age mean (SD)</td>
<td>57.2 (10.5)</td>
<td>59.0 (11.5)</td>
</tr>
<tr>
<td>Male n (%) (n=311)</td>
<td>135 (80.4)</td>
<td>96 (67.1)</td>
</tr>
<tr>
<td>Smoking n (%) (n=311)</td>
<td>92 (53.6)</td>
<td>74 (51.7)</td>
</tr>
<tr>
<td>Hypertension n (%) (n=311)</td>
<td>56 (33.3)</td>
<td>52 (36.4)</td>
</tr>
<tr>
<td>Hypercholesterolaemia n (%) (n=310)</td>
<td>141 (84.4)</td>
<td>120 (83.9)</td>
</tr>
<tr>
<td>Diabetes mellitus n (%) (n=311)</td>
<td>22 (13.1)</td>
<td>19 (13.3)</td>
</tr>
<tr>
<td>LVEF&lt;45% n (%) (n=286)</td>
<td>65 (42.5)</td>
<td>58 (43.6)</td>
</tr>
<tr>
<td>Killip class 3+ n (%) (n=310)</td>
<td>18 (10.7)</td>
<td>21 (14.8)</td>
</tr>
<tr>
<td>BDI 3 months post-MI mean (SD) (n=299)</td>
<td>13.4 (6.4)</td>
<td>12.0 (5.4)</td>
</tr>
<tr>
<td>Depression severity during year following MI (n=311)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild n (%)</td>
<td>48 (28.6)</td>
<td>47 (32.9)</td>
</tr>
<tr>
<td>Moderate n (%)</td>
<td>77 (45.8)</td>
<td>69 (48.3)</td>
</tr>
<tr>
<td>Severe n (%)</td>
<td>43 (25.6)</td>
<td>27 (18.9)</td>
</tr>
</tbody>
</table>

BDI: Beck Depression Inventory; LVEF: Left Ventricular Ejection Fraction; MI: Myocardial Infarction; SD: Standard Deviation.

1 21 patients in the intervention arm receiving placebo only were included in the group who received treatment.

2 $p=0.008$ (Chi-square).

3 $p=0.054$ (independent sample t-test).

Results from other large-scale RCTs on depression treatment in depressed cardiac patients do not give support for a beneficial effect of depression treatment on cardiovascular outcomes [2–4,20]. The results of the present study do not change this view.

One potential reason why depression treatment did not affect cardiovascular outcomes is that a more severe underlying cardiovascular disease is driving the increased risk of new cardiovascular events in some of the depressed patients. In the present sample, depression severity was associated with cardiovascular disease severity [21], and cardiovascular disease severity explains up to 40% of the long-term cardiac morbidity and mortality associated with depression [22]. Therefore, the depression treatment may not have affected cardiovascular outcomes because it was not the depression itself, but the more readmissions during the 8 month treatment period, despite a modest effect on depression scores [20].

Lack of power may be a reason why MIND-IT’s intervention did not affect cardiovascular outcomes and mortality. The prevalence of the primary outcome (37% in both arms) was lower than expected based on the power calculation (49% in the intervention arm and 67% in the CAU arm). Therefore, the study power was less than the anticipated 89% for the combined endpoint, which could explain the null findings of the present study. After all, the HR of 0.74 for all-cause mortality may have been statistically significant in the presence of more power (note that the study was not powered for all-cause mortality). Therefore, it remains unclear whether an active antidepressant treatment strategy, such as that used in MIND-IT, would increase survival rates in depressed MI patients. This needs further evaluation in future studies. On the other hand, the primary endpoint of cardiovascular readmissions and cardiac mortality occurred similarly in both groups (HR 0.97). This gives not much reason to believe that the intervention would have had a beneficial effect on the primary endpoint in the presence of more power. In addition, results from other large-scale RCTs on depression treatment in depressed cardiac patients do not give support for a beneficial effect of depression treatment on cardiovascular outcomes [2–4,20]. The results of the present study do not change this view.

### Table 2

All-cause mortality risk for 168 MI-patients who received treatment for depression versus 143 who did not.

<table>
<thead>
<tr>
<th>Adjusted for</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td>0.52 (0.28–0.97); $p=0.041$</td>
</tr>
<tr>
<td>Sex</td>
<td>0.54 (0.29–1.01); $p=0.055$</td>
</tr>
<tr>
<td>BDI 3 at months post-MI</td>
<td>0.49 (0.26–0.93); $p=0.029$</td>
</tr>
<tr>
<td>Sex and BDI at 3 months post-MI</td>
<td>0.50 (0.26–0.96); $p=0.036$</td>
</tr>
</tbody>
</table>

BDI: Beck Depression Inventory; CI: Confidence Interval; HR: Hazard Ratio; MI: Myocardial Infarction.

1 21 patients in the intervention arm receiving placebo only were included in the group who received treatment.

2 In this model the HR (95% CI) for mortality for men was 1.33 (0.70–2.55; $p=0.383$).
severe cardiovascular disease in the depressed patients that predicted the new events.

Although we previously reported better cardiac outcomes till 18 months after the index-MI for responders [23], treatment-response was not associated with better long-term cardiac outcomes. A potential reason why treatment-response was associated with short-term but not long-term cardiac prognosis is that during the follow-up period differences between responders and non-responders on depressive symptom severity, cardiac disease severity and cardiac risk factors have become less apparent. A potential reason why we could not replicate findings from ENRICHD and SADHART [4,24] showing that improvements in depression are associated with better long-term cardiac outcomes, is that the size of our subgroup was smaller (27 responders and 43 non-responders).

Better survival was found for patients who received depression treatment compared to those who did not, which is comparable to findings from two other studies. In ENRICHD, some patients in both arms received (additional) treatment with antidepressants when it was deemed necessary. While the intervention (CBT) did not reduce the risk of poor cardiac outcomes, antidepressant use was significantly associated with a reduced risk of death or nonfatal recurrent MI [25]. Another study found in 93,653 depressed veterans a reduced risk of incident MI and all-cause mortality for those who received antidepressant treatment [26]. The increased survival rates for patients receiving depression treatment may reflect a direct treatment response. However, since these findings are all based on non-randomized comparisons, the association may be confounded by factors associated with receiving treatment as well as increased survival. In MIND-IT, the association lost its statistical significance after adjustment for sex (i.e. men were more likely to receive treatment and had somewhat better survival). Surprisingly, age, cardiovascular disease severity and risk factors known to influence cardiac prognosis were not associated with receiving depression treatment, suggesting that whether or not a patient received depression treatment was not depending on his age or cardiovascular risk profile. Still, one other reason why patients who received antidepressant treatment have better survival may be the intrinsic motivation of patients to care for their health. Patients more likely to seek treatment for depression may be more adherent to cardiac aftercare and have a healthier lifestyle. For instance, depression is found to be associated with non-adherence to medical treatment recommendations [27], not completing and adhering to cardiac rehabilitation procedures [9], and recommendations for risk factor reduction after MI [28]. Non-adherence to both depression treatment and cardiac aftercare procedures may explain why cardiac patients with treatment resistant depression have the highest risk of cardiovascular morbidity and mortality [29,30].

Some limitations should be considered when interpreting the results of the present study. First, recruitment took place 10 years ago, while in the meantime the medical management of MI and recognition of depression has changed, potentially affecting the generalizability of our findings to the current MI population. Second, the lower prevalence of the primary outcome expected resulted in a study power less than the anticipated 89%. A third limitation is that we had no sufficient information concerning the depression after the treatment period for the complete sample of 330 patients. Although depression was evaluated at 18 months post-MI, data were present for only 218 (66%) patients and there may have been selective loss to follow-up (i.e. depression data may have been missing for those with most severe depression). This is why we could not evaluate whether patients who did not receive depression treatment have persisting depression, or whether persisting or treatment-resistant depression was associated with cardiovascular morbidity and mortality in the complete sample of 330 patients. Fourth, it should be considered that MIND-IT’s intervention was complex. Patients received different types and intensities of treatment, and for some patients the type and intensity of the depression treatment were not known (i.e. those in the intervention arm who received tailored treatment and those in the CAU arm who received treatment from their own physicians). Therefore, it is difficult to judge the adequacy of treatment in many patients.

Taken together, our results suggest that the implementation of an antidepressant treatment strategy in depressed MI-patients does not affect long-term cardiovascular outcomes. Although patients receiving treatment for depression had better survival rates, it remains unclear whether this is due to the treatment itself or is due to unmeasured factors that relate to both receiving depression treatment and mortality.

Competing interest statement

The authors have no competing interests to report.

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