Effects of antidepressant treatment following myocardial infarction†

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Background Depression following myocardial infarction is associated with poor cardiac prognosis. It is unclear whether antidepressant treatment improves long-term depression status and cardiac prognosis.

Aims To evaluate the effects of antidepressant treatment compared with usual care in an effectiveness study.

Method In a multicentre randomised controlled trial, 2177 myocardial infarction patients were evaluated for ICD–10 depression and randomised to intervention (n=209) or care as usual (n=122). Both arms were evaluated at 18 months post-myocardial infarction for long-term depression status and new cardiac events.

Results No differences were observed between intervention and control groups in mean scores on the Beck Depression Inventory (11.0, s.d.=7.5 v 10.2, s.d.=5.1, P=0.45) or presence of ICD–10 depression (30.5 v 32.1%, P=0.68). The cardiac event rate was 14% among the intervention group and 13% among controls (OR=1.07, 95% CI 0.57–2.00).

Conclusions Antidepressant treatment did not alter long-term depression post-myocardial infarction status or improve cardiac prognosis.

Declaration of interest None. Funding detailed in Acknowledgements.

†See invited commentary, pp. 467–468, this issue.
**Design of the study**

Patients admitted with an acute myocardial infarction were screened for depressive symptoms during hospitalisation and at 3, 6, 9 and 12 months post-myocardial infarction, using the Beck Depression Inventory (BDI; Beck, 1979). Those with depressive symptoms (i.e. BDI score $\geq 10$) underwent a psychiatric evaluation using the WHO Composite International Diagnostic Interview (CIDI auto version 2.1; World Health Organization, 1990). The first CIDI interviews were performed at least 3 months post-myocardial infarction to allow natural recovery of depressive symptoms following a major life event. Both screening tools are widely used and their feasibility and reliability have been described elsewhere (Robins et al., 1988; Strik, 1988; Strik et al., 2001). Patients with a research diagnosis of ‘current depressive episode’ (World Health Organization, 1993) according to ICD–10 (further: ‘depression’) were randomised (1:1) to antidepressant treatment or care as usual. The assignment was carried out at the Trial Coordination Centre in Groningen with the use of computer-generated permuted blocks of four, stratified according to clinical site and time of onset of depression (within 6 months, 6–12 months, or more post-myocardial infarction). Because the number of patients actually treated with antidepressants was lower than expected, the randomisation ratio was changed to 2:1 on 14 March 2001. Patients with a significant risk of suicide were excluded from randomisation and referred for treatment outside the study. To compare both strategies, we used the Zelen design (Zelen, 1979): patients allocated to the ‘care as usual’ arm were not informed about their research diagnosis of depression to avoid influencing usual care. Data management was independently performed at the Trial Coordination Centre, Groningen, The Netherlands.

**Baseline variables**

Data were collected on demographics, medical history, clinical variables and medication use during hospitalisation for the index myocardial infarction. The cumulative burden of medical comorbidity was assessed with a modified version of the Charlson Comorbidity Index (Watkins et al., 2003). Higher scores on this scale indicate more comorbidity. To account for a possible relationship between depression post-myocardial infarction and cardiac disease severity, the following parameters of risk stratification were assessed: Killip class at admission, maximum values of serum aspartate transaminase during hospitalisation, left ventricular ejection fraction (as measured by either echocardiography or radionuclide ventriculography) and wall motion score index (WMSI) according to the recommendations of the American Society of Echocardiography (Schiller et al., 1989). Independent analysis was performed at the core echocardiography laboratory by technicians who were unaware of the patients’ randomisation status.

**Antidepressant intervention**

The MIND-IT study was designed as an effectiveness study comparing active antidepressant treatment with usual care. In the intervention arm, the research diagnosis provided by the CIDI interview was confirmed by a psychiatrist prior to the patient starting antidepressant treatment. Several treatment modalities were possible. Flexibility in treatment was permitted because the main research question was whether implementing any active depression treatment strategy would be associated with better outcomes than usual care in which antidepressant treatment is almost negligible (Frasure-Smith et al., 1993). However, allocation to these modalities was strictly defined in the protocol. First-choice treatment was double-blind placebo-controlled treatment with the selective noradrenaline reuptake inhibitor mirtazapine (a non-tricyclic, presynaptic $\alpha_2$-antagonist which enhances both noradrenergic and serotonergic neurotransmission; De Boer, 1996). In case of refusal or insufficient treatment response after 8 weeks, open treatment with the selective serotonin reuptake inhibitor (SSRI) citalopram was offered (Montgomery & Djarv, 1996). Sufficient treatment response was defined as at least 50% reduction on the Hamilton Depression Rating Scale (HDRS; Hamilton, 1960) compared with baseline score or a HDRS score at 8 weeks of $\leq 9$. Thus, patients who were initially treated with placebo and who did not improve within 8 weeks were subsequently treated with an SSRI. The third option was ‘tailored treatment’ which was at the discretion of the clinical psychiatrist (e.g. SSRI, psychotherapy, etc.). Patients were scheduled to visit the psychiatrist on average once a month during the treatment period of 6 months. In the care as usual arm, psychiatric treatment outside the study was recorded but no treatment was offered by the MIND-IT investigators. Whether the patient was referred for cardiac rehabilitation was left to the discretion of the patient’s cardiologist (who was masked to the psychiatric screening results).

**Long-term depression status and quality of life**

At approximately 18 months post-myocardial infarction, the course and outcome of the depressive episode was assessed in a CIDI interview. The BDI was administered to evaluate the severity of depressive symptoms. In addition, health-related quality of life was assessed with the RAND 36-item Health Survey, which consists of 36 items organised into eight scales (Ware et al., 1993; Essink-Bot et al., 1997). Somatic health complaints were assessed with the Health Complaints Scale (HCS), a self-report measure to assess common health complaints in patients with coronary heart disease (Denollet, 1994). Disability was assessed according to Broadhead et al. (1990). Patients were asked to indicate with a time frame of the past month: ‘how many days were you not able to do your daily activities (for example your work, housework, studies, leisure activities) owing to physical or emotional problems? and ‘apart from the above, on how many days were you able to do your daily activities for less than half of the time owing to physical or emotional problems?’ Both complete and partial disability were categorised as having been present for either less than 1 week or for 1 week or more during the previous month.

**Cardiac events**

The occurrence of any significant cardiac event served as the primary end-point for the study. Cardiac events included cardiac death or hospital admission for documented non-fatal myocardial infarction, myocardial ischaemia, coronary revascularisation (coronary angioplasty or bypass surgery), heart failure or ventricular tachycardia occurring in the time between randomisation and 18 months post-myocardial infarction. Time to follow-up (6–15 months) depended on the time of randomisation (range 3 months to 12 months post-myocardial infarction). Other cardiac-related hospital admissions (defined as admissions with an initial evaluation by a cardiologist or hospitalisations at the
cardiology ward) were considered as secondary end-points. Potential end-points were recorded at 12 months and 18 months post-myocardial infarction, and were reviewed and classified according to pre-specified, established criteria (Cannon et al, 2001) by an independent end-point committee that was unaware of patients’ treatment assignments. Discrepancies were discussed until agreement was reached.

**Statistical analysis**

Study power was calculated for long-term depression outcomes and cardiac events. With respect to the long-term depression status, a sample of 320 randomised patients would result in a study power of 80%, assuming a drop-out rate of 20% and a small-to-medium effect size (0.35). With respect to cardiac events, we expected a 12-month incidence of 38% for patients with depression and 19% for patients without depression (Frasure-Smith et al, 1995). If psychiatric treatment could reduce the risk for patients with depression from 38 to 25% (i.e. reduction of the attributable risk by two-thirds), 190 patients in the intervention arm and 130 in the care as usual arm would give a statistical power of 0.84 to detect this effect with a log-rank test (α=0.05).

$t$-tests were used to compare normally distributed continuous variables and the $\chi^2$-test was used to compare categorical data. Time-to-event data were analysed with the Kaplan–Meier method and differences between care as usual and intervention groups in the incidence of cardiac events were assessed with the log-rank test. Outcome data were considered at 18 months post-myocardial infarction, the time of last contact, withdrawal from the study, or at the time of a primary end-point. All $P$ values were two-tailed.

**RESULTS**

A total of 4780 myocardial infarction patients were assessed for eligibility (Fig. 1). Of these, 1403 (29%) met one or more of the eligibility criteria.
more exclusion criteria, and of the excluded patients, 104 were receiving treatment for depression (see Table 1 for reasons for exclusion). Of the 3377 remaining patients, 1200 refused to participate and 2177 were included (64%). During the screening period from 3 to 12 months post-myocardial infarction, 375 patients (17.2%) met the ICD–10 criteria for depression. After exclusion of potentially suicidal patients (n=28) and patients who were diagnosed with depression after randomisation was closed (n=16), 331 patients were available for randomisation. The intervention (n=209) and care as usual (n=122) arms did not differ with respect to demographics, depressive symptoms during hospitalisation (BDI score), risk factors for coronary artery disease and important prognostic variables such as WMSI and comorbidity (Table 2). In addition, there were no differences with respect to ICD–10 depression characteristics (Table 3). Seventeen patients (5%) were lost to follow-up.

**Antidepressant intervention**

Of the 196 patients assigned to the intervention and not lost to follow-up, 45 (23%) did not receive antidepressant treatment, either because they refused to accept the proposed therapy or because the psychiatrist did not confirm the diagnosis of depression at the time of the visit. The median length of time from the randomisation date to the first visit to the psychiatrist was 13 days (interquartile range 7–21 days). The majority of patients in the intervention arm received clinical management of depression and 94 (45%) were enrolled in the double-blind placebo-controlled medication treatment sub-study. Of these patients, 47 initially received mirtazapine and 44 initially received placebo. Three patients received no treatment because they failed to keep their appointment. Twenty patients originally treated with mirtazapine and 26 who received placebo subsequently received 16 weeks of open-label treatment with citalopram because of an insufficient response after 8 weeks of the initial treatment. The remaining patients continued to receive their original treatment. Seventeen (8%) received immediate open-label antidepressant treatment with citalopram and 40 (19%) received non-pharmacological antidepressant treatment (i.e. psychotherapy, counselling, etc.). Patients in the intervention arm who received these different treatments...
VAN MELLE ET AL

Table 3 Characteristics of depression in the intervention and care as usual groups

<table>
<thead>
<tr>
<th></th>
<th>Intervention group</th>
<th>Care as usual group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=209)</td>
<td>(n=122)</td>
</tr>
<tr>
<td>Early-onset depression¹</td>
<td>167 (80)</td>
<td>96 (80)</td>
</tr>
<tr>
<td>Recurrent depression</td>
<td>45 (22)</td>
<td>28 (23)</td>
</tr>
<tr>
<td>Severity according to ICD–10 criteria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>65 (31)</td>
<td>36 (30)</td>
</tr>
<tr>
<td>Moderate</td>
<td>98 (47)</td>
<td>58 (48)</td>
</tr>
<tr>
<td>Severe</td>
<td>46 (22)</td>
<td>28 (23)</td>
</tr>
</tbody>
</table>

¹. Within 3 months of myocardial infarction.

Table 4 Depression status and quality of life at 18 months post-myocardial infarction

<table>
<thead>
<tr>
<th></th>
<th>Intervention group</th>
<th>Care as usual group</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICD–10 depressive disorder, %</td>
<td>30.5</td>
<td>32.1</td>
</tr>
<tr>
<td>BDI score: mean (s.d.)</td>
<td>11.0 (7.5)</td>
<td>10.2 (5.1)</td>
</tr>
<tr>
<td>Complete disability (≥7 days during past month), %</td>
<td>30.5</td>
<td>33.3</td>
</tr>
<tr>
<td>Partial disability (≥7 days during past month), %</td>
<td>28.2</td>
<td>26.7</td>
</tr>
<tr>
<td>HCS score: mean (s.d.)</td>
<td>13.4 (9.1)</td>
<td>14.6 (9.8)</td>
</tr>
<tr>
<td>Physical health (RAND–36) score: mean (s.d.)</td>
<td>39.5 (6.0)</td>
<td>39.5 (5.7)</td>
</tr>
<tr>
<td>Mental health (RAND–36) score: mean (s.d.)</td>
<td>44.5 (8.1)</td>
<td>43.4 (8.0)</td>
</tr>
</tbody>
</table>

BDI, Beck Depression Inventory; HCS, Health Complaints Scale.

Table 5 Cardiac events at 18 months post-myocardial infarction

<table>
<thead>
<tr>
<th></th>
<th>Intervention group</th>
<th>Care as usual group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=196)</td>
<td>(n=118)</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>1 (1)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Recurrent myocardial infarction</td>
<td>6 (3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Revascularisation (PTCA/CABG)</td>
<td>11 (6)</td>
<td>8 (7)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>7 (4)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Myocardial ischaemia</td>
<td>1 (1)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Ventricular arrhythmia</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Total</td>
<td>27 (14)</td>
<td>15 (13)</td>
</tr>
</tbody>
</table>

PTCA, percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass grafting.

did not significantly differ on severity of depressive symptoms during hospitalisation (mean BDI score for those receiving double-blind treatment 11.6, s.d.=6.9; open label treatment 13.8, s.d.=8.7); other treatment 11.6, s.d.=6.6; no treatment 11.0, s.d.=6.7; F=0.66; P=0.58). Moreover, these patient groups did not differ significantly on ICD–10 depression characteristics.

In contrast, only 8 patients (7%) in the care as usual arm received antidepressant medication and 12 (10%) received non-pharmacological treatment for their depression (Fig. 1).

Effects on long-term depression status

Of the 307 patients who were alive at 18 months and available for follow-up, depression assessments were obtained for 218 patients (71%), which was comparable for patients in the intervention (69%) and care as usual arm (74%). The prevalence of ICD–10 depression was 30.5% in the patients assigned to the intervention and 32.1% in the care as usual arm (P=0.68; Table 4). No significant differences were observed between patients assigned to intervention or care as usual with respect to depressive symptoms, health complaints, disability and quality of life.

Treatment effect on cardiac outcome

The total event rate between randomisation and 18 months post-myocardial infarction was 42 out of 314 (13%, Table 5). The incidence of events did not differ among the two treatment strategies (13% in the care as usual and 14% in the intervention arm, log-rank test 0.09, P=0.76). Similarly, no differences were observed in Kaplan–Meier curves (Fig. 2). The Cox regression analyses also revealed no differences between the treatment arms (OR=1.07, 95% CI 0.57–2.00). In addition, there were no differences in the incidence of cardiac events between patients in the intervention arm who received antidepressant medication (mirtazapine n=47; open pharmacological treatment n=17) and non-responders to placebo who received citalopram (n=26) (total n=90) compared with those patients in the care as usual arm who received no antidepressant treatment (n=98; OR=0.84, 95% CI 0.38–1.84; 14% vs. 12% event rate). Within the intervention arm, the event rate for patients receiving pharmacological treatment was 13%, whereas this was 15% for patients who did not receive pharmacological treatment in the intervention arm (OR=0.80, 95%
antidepressant treatment following myocardial infarction


It could also be argued that perhaps these findings are the result of a large rate of spontaneous recovery from depression which has been observed previously in both ENRICHD and SADHART clinical trials. Although this is plausible, our study was not designed to evaluate this possibility in detail since we used a Zelen design in which the care as usual patients were not informed about their depression and randomisation status. The advantage of this design is that usual care was truly representative but the disadvantage is that we cannot evaluate the (short-term) spontaneous recovery. However, the fact that both arms were comparable in depression outcomes at 18 months does support this possibility. This stresses the need to improve the identification of patients with persistent depression post-myocardial infarction in future clinical trials.

An important limitation is the power of the study. When the trial was initiated the results of the ENRICHD and SADHART trials had not been published and we had to rely on data that in retrospect may have been too optimistic (e.g. Frasure-Smith et al., 1995). First, the expected incidence of cardiac events was substantially higher than the observed incidence. Second, the association between depression and cardiac outcomes might have been overestimated and third, the anticipated effects of treatment on depression were overly optimistic. As a result, we believe that our study had sufficient power to detect differences in long-term depression outcomes (standardised effect size >0.35) but was underpowered to detect differences in cardiac outcomes. However, the nearly identical long-term depression status in the two arms and the similar rates of cardiac events offer little evidence that a significant difference would have emerged if more patients had been included. Thus, although we believe that our trial was underpowered, the observation that there were no consistent differences suggests that more study power would very likely not have yielded different conclusions.

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