

Does treating depression improve survival after acute coronary syndrome?

Invited commentary on . . . Effects of antidepressant treatment following myocardial infarction[†]

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Summary Both the MIND–IT and the ENRICHD studies failed to show that medical outcomes of acute myocardial infarction can be improved by treating depression. However, neither study had sufficient statistical power to convincingly test this hypothesis. More effective treatments for depression will have to be developed if this hypothesis is to be tested with sufficient power in attainable samples.

Declaration of interest None.

Six years ago, the Enhancing Recovery in Coronary Heart Disease (ENRICHD) investigators sat in a small room near Washington, D.C. and listened quietly as the results of their trial were revealed. It was the first clinical trial ever to test whether treatment of depression improves survival after an acute myocardial infarction (Berkman *et al*, 2003). After spending over 6 years designing and conducting this challenging study, they learned that there was no difference in reinfarction-free survival between the intervention and control groups. After recovering from the initial shock and disappointment, they began to consider a variety of possible reasons why ENRICHD did not succeed. They also began to think about the need for additional trials.

The current issue of the *Journal* presents the long-awaited results of the second major trial of treatment for depression post-myocardial infarction and survival, the Myocardial Infarction and Depression Intervention Trial (MIND–IT; van Melle *et al*, 2007). This was a much smaller study than ENRICHD with a greater use of antidepressants and less of psychotherapy than its predecessor. Despite these differences,

the primary outcomes of these two trials are very similar. There is no difference in the primary medical end-point between the intervention and ‘usual care’ arms of MIND–IT.

APPRAISAL OF STUDIES

Should we conclude from these two trials that treating depression simply does not improve survival following an acute coronary syndrome? Before we do, and before abandoning plans for additional trials, we should first consider whether either of these studies was large enough to provide an adequate test of the hypothesis.

Based on what they now know to be optimistic assumptions, the MIND–IT investigators enrolled only 331 patients. The ENRICHD trial, based on different assumptions, enrolled 2481 patients, 1839 of whom had depression (Berkman *et al*, 2003). Although it was much larger than MIND–IT, even the ENRICHD trial may have been too small. This possibility rests, in part, on two considerations that were not fully appreciated when these trials were planned.

The first is that even the best available treatments have only modest effects on depression. In the Sertraline Antidepressant Heart Attack Randomized Trial (SAD-HART), for example, there was less than a 1-point difference between groups on the Hamilton Rating Scale for Depression (HRSD; Hamilton, 1960) after 24 weeks of treatment with a widely used antidepressant or a placebo (Glassman *et al*, 2002). Similarly, after 6 months of treatment in the ENRICHD trial, there was less than a 2-point difference on the HRSD between the intervention and usual care arms. The MIND–IT investigators found no difference in depression between the intervention and usual care arms at 18 months. In each of these trials, depression declined substantially in patients in the intervention arm but almost

as much in the control group. Antidepressant trials with medically well patients tend to produce similar results. A review of the efficacy data for some of the most widely prescribed antidepressants found that the average HRSD difference between drug and placebo groups is just 2 points (range 0.89–3.21; Kirsch *et al*, 2002).

Because these differences are so small, it is difficult to demonstrate that effective treatment of depression improves survival. As an analogy, suppose that the first cholesterol-lowering trial ever conducted failed to improve cardiac outcomes. Further, suppose that total cholesterol declined from 300 to 200 mg/dl in the experimental drug arm and from 300 to 210 mg/dl in the placebo arm. It is very unlikely that the investigators would have concluded that cholesterol is not a causal risk factor for heart disease. It is also unlikely that they would have abandoned further efforts to determine whether cardiac outcomes could be improved by decreasing total cholesterol. They would have tried to discover more efficacious treatments for cholesterol. When they found them, they would have conducted the next round of large treatment trials assessing cardiac outcomes. Of course, cholesterol levels, unlike depression, generally do not improve without intervention. In that sense, depression is a much more difficult cardiac risk factor to study than cholesterol.

The second consideration is that treatments for depression may alter the risk of cardiac events via pathways that are unrelated to their effects on depression. For example, tricyclic antidepressants affect cardiac conduction in ways that may increase the risk of cardiac events in a subset of patients with depression and coronary heart disease (Glassman *et al*, 1993). Selective serotonin reuptake inhibitors, on the other hand, may reduce the risk for cardiac events by inhibiting platelet activation (Serbruany *et al*, 2001; Taylor *et al*, 2005). Psychotherapy may also affect cardiac outcomes via pathways that are independent of its effects on depression (Frasure-Smith *et al*, 1997). Thus, both pharmacological and non-pharmacological treatments for depression have pleomorphic effects, some of which may improve, and others of which may worsen, cardiac outcomes (Frasure-Smith, 2005).

Because of these effects, trials such as MIND–IT and ENRICHD can have two closely related yet distinct aims. One is to determine whether a particular treatment

[†]See pp. 460–466, this issue.

improves cardiac outcomes and the other is to test the mediation hypothesis that the intervention improves cardiac outcomes via its effects on depression. Whereas the former addresses a clinically relevant question, the latter tests a scientific hypothesis concerning whether depression plays a causal role in cardiac outcomes. Recent developments in mediation modelling and sample size estimation procedures for trials with mediated outcomes (Freedman & Schatzkin, 1992; Hansen & McNeal, 1996) suggest that both aims will require considerably larger samples than those in the ENRICHD and MIND-IT trials. Our initial estimates suggest that an adequately powered test of the clinical hypothesis may require a sample between two and four times larger than the subgroup with depression in the ENRICHD trial. Furthermore, an even larger sample will be required to test the mediation hypothesis.

FUTURE DIRECTIONS

The sample size requirements for both aims depend, in part, on the efficacy of the intervention with respect to depression outcomes, and on the strength of the relationship between depression and cardiac morbidity and mortality. This suggests that there are at least two ways to make the sample size requirements of future trials less onerous. One is to develop more efficacious treatments for depression. There have not been any dramatic breakthroughs in this area in years, so the success of the next large clinical trial for depression post-acute coronary syndrome will probably depend on the incremental progress in depression therapy. The other way is to strengthen the association between depression and cardiac outcomes. It may be possible to achieve this by refining the measurement of depression, pinpointing the aspects of depression that have harmful cardiac effects, specifying the harmful cardiac effects with greater precision and identifying the mechanistic pathways that link depression to worse cardiac outcomes.

Even if these steps are taken, the next large trial for depression post-acute coronary syndrome may still require a larger sample than the ENRICHD or MIND-IT trials. The question this raises is whether there is sufficient interest within the

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(First received 8 January 2007, accepted 16 February 2007)

scientific community, and within industry, non-profit and government funding sources to undertake a trial of this magnitude. We think that there should be, given the high prevalence and prognostic importance of depression in patients with heart disease (Barth *et al*, 2004; van Melle *et al*, 2004). The ENRICHD and MIND-IT trials yielded many important new findings but they were both 'failed' trials in the sense that they did not show the hypothesised effects. Both, however, were considerably underpowered, if our rough estimates are even remotely accurate. It will undoubtedly be challenging to secure funding for the next major trial in this area, especially if the sample size requirements turn out to be as large as we are suggesting. However, if highly efficacious treatments for depression are eventually developed, and if we continue to refine our understanding of the role of depression in heart disease, then smaller samples will probably be needed to study these treatments in relation to cardiac outcomes. That would be very good news for researchers in this area, and even better news for patients with depression following myocardial infarction.

RECOMMENDATIONS

The MIND-IT investigators recommend that more effort should be devoted to finding more effective treatments for depression post-acute coronary syndrome, to determining which patients with depression are at the highest risk for cardiac events, and to identifying patients who are most likely to require treatment for depression following an acute myocardial infarction (van Melle *et al*, 2007). We wholeheartedly agree with their recommendations.

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patients with coronary heart disease: a meta-analysis. *Psychosomatic Medicine*, **66**, 802–813.

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