

Correspondence

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Depression post-myocardial infarction

Van Melle *et al* (2007) reported that cardiac prognosis post-myocardial infarction was not improved by antidepressant treatment (MIND-IT trial). The SADHART and ENRICH trials reported similar findings and Carney & Freedland (2007), in their commentary in the same issue, suggest these negative findings are a result of insufficient statistical power in the trials. These results are disappointing but perhaps they might have been anticipated.

There is strong evidence that individuals with depression show increased morbidity and mortality from coronary heart disease (Rugulies, 2002) but the mechanisms involved remain unclear. Individuals with a history of recurrent depression, who are otherwise healthy, show increased inflammation, platelet activation, endothelial dysfunction, and reduced heart rate variability and baroreceptor sensitivity. However, with the exception of platelet function, which improves with selective serotonin reuptake inhibitors, these anomalies are not corrected by antidepressant treatment. Furthermore, endothelial function and baroreceptor sensitivity, which can lead respectively to progression of the atherosclerotic process and to sudden cardiac death, do not improve when depressive symptoms are in remission (Broadley *et al*, 2006). Thus there is no evidence that treatment of depressive symptoms post-myocardial infarction corrects these underlying pathological processes and, if it does not, cardiac outcomes disclosed by clinical trials are unlikely to show improvement irrespective of their statistical power. By analogy, although hyperglycaemia characterises diabetes, tight glucose control alone has only a modest impact on cardiovascular events. Similarly, depressive illness is characterised by acute episodes of depression, but other systemic abnormalities are present and persist between acute depressive

episodes. Accordingly, it may be unreasonable to believe that treatments assessed by their influence on the affective state alone will reduce cardiovascular events.

Although it is important to alleviate the suffering associated with developing depression post-myocardial infarction and improve prognosis by addressing the secondary effects of depression (e.g. reduced adherence to treatment and poor health behaviours), treatment needs to be aimed at earlier stages of the disorder. Atherosclerosis begins in childhood and becomes manifest much later in life, with myocardial infarction as a very late presentation. Similarly, depression is a lifelong disorder with onset in early adulthood. It should be noted that currently depression is not even included in cardiovascular risk tables and that individuals with depression might benefit from introduction of statins, or other preventative measures.

We agree with Carney & Freedland (2007) that treatments for depression might alter the risk of cardiac events via pathways that are unrelated to their effects on depression. However, if the focus of research were shifted to the study of earlier stages of coronary heart disease in people with depression, this could be clarified by monitoring earlier indices of heart disease in relation to treatment of depression. It is also recognised that mechanisms for associations between depression and onset of heart disease may differ from those between depression and progression of coronary heart disease post-myocardial infarction. These pathways need to be better understood and present evidence suggests that survival times following myocardial infarction could be improved by developing treatments for depression that also target the underlying cardiovascular abnormalities and by augmenting these by preventative programmes for coronary heart disease in individuals with mood disorders.

Coronary heart disease and depression are two major public health problems and

it is of concern that reports of treatments for depression failing to enhance survival post-myocardial infarction may result in less interest in studying the links between them.

Broadley, A. J., Korszun, A., Abdelaal, E., et al (2006) Metyrapone improves endothelial dysfunction in patients with treated depression. *Journal of the American College of Cardiology*, **48**, 170–175.

Carney, R. M. & Freedland, K. E. (2007) Does treating depression improve survival after acute coronary syndrome? *British Journal of Psychiatry*, **190**, 467–468.

Rugulies, R. (2002) Depression as a predictor for coronary heart disease: a review and meta-analysis. *American Journal of Preventive Medicine*, **23**, 51–61.

Van Melle, J. P., de Jonge, P., Honig, A., et al (2007) Effects of antidepressant treatment following myocardial infarction. *British Journal of Psychiatry*, **190**, 460–466.

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Van Melle *et al* (2007) present findings from their randomised controlled trial examining the effects of antidepressant treatment for depression following myocardial infarction. I would like to comment on the design of the study. Patients were allocated to two arms: antidepressant treatment and care as usual. Patients in the care-as-usual arm were not told about their research diagnosis of depression. The authors quote Zelen (1979), thus implying that they are following the research design he proposed. However, Zelen's method seems best suited to trials where there is a 'gold standard' control treatment available and the trial is attempting to evaluate a new experimental treatment (Zelen, 1979). In this design, the ethical concerns are mainly about randomising before consent is sought. It must be pointed out that after randomisation, consent is sought from patients in the experimental arm. If they decline, they are moved to the 'gold standard' arm (Torgerson, 2001). I am not sure whether the trial of van Melle *et al* fits into this category.

Furthermore, there are ethical issues about not informing patients about their diagnosis of depression. I am disappointed that the paper did not discuss these in further detail. Their information pack stated

that all patients were free to seek help for their mood problems. Patients may feel tired and low in mood but may not recognise this as depression, for which there are effective interventions available. Is it ethical to withhold information regarding the diagnosis from such patients? Will patients seek help if they are not told they have depression?

Performing research can raise difficult ethical issues and I hope this letter will encourage some debate on this.

Torgerson, D. J. (2001) Contamination in trials: is cluster randomisation the answer? *BMJ*, **322**, 355–357.

Zelen, M. (1979) A new design for randomized clinical trials. *New England Journal of Medicine*, **300**, 1242–1245.

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Van Melle *et al* (2007) found no difference in efficacy and cardiac prognosis between treatment with antidepressive medication and care as usual in patients with depression after myocardial infarction. Carney & Freedland (2007) commented that the lack of difference in efficacy prohibits the demonstration that effective treatment of depression improves survival. They emphasised the need for developing highly efficacious treatments for depression following myocardial infarction. Such a treatment, however, already exists, as electroconvulsive therapy (ECT), and has been shown to have superior efficacy compared with antidepressive medication (ECT UK Review Group, 2003).

A trial using ECT as an intervention will more likely find a superior efficacy compared with treatment as usual and may demonstrate that effective depression treatment improves survival. Because of concerns about the cardiac risks some textbooks do not recommend the use of ECT within 3 months of myocardial infarction. Zielinski *et al* (1993) found a higher rate of cardiac complications during ECT in patients with a pre-existing cardiac abnormality compared with patients with no pre-existing abnormality. Most complications, however, were transitory and did not prevent the completion of the ECT course. Rice *et al* (1994) found that ECT increased the risk of minor but not severe complications. They pointed to the advances in ECT techniques which have resulted in improved safety in cardiac patients. The risk of ECT has to be weighed against the risk of an inadequate treatment of depression, which

is known to increase mortality (van Melle *et al*, 2007). Considering the high risk of cardiac events of 13% in the 18 months following myocardial infarction (van Melle *et al*, 2007), which may partly be attributable to the inadequate treatment of depression, treatment with ECT could be safer because of its superior efficacy as an antidepressant.

Carney, R. M. & Freedland, K. E. (2007) Does treating depression improve survival after acute coronary syndrome? *British Journal of Psychiatry*, **190**, 467–468.

ECT UK Review Group (2003) Efficacy and safety of electroconvulsive therapy in depressive disorder: a systematic review and meta-analysis. *Lancet*, **361**, 799–808.

Rice, E. H., Sombrotto, L. B., Markowitz, J. C., et al (1994) Cardiovascular morbidity in high-risk patients during ECT. *American Journal of Psychiatry*, **151**, 1637–1641.

Zielinski, R. J., Roose, S. P., Devanand, D. P., et al (1993) Cardiovascular complications of ECT in depressed patients with cardiac disease. *American Journal of Psychiatry*, **150**, 904–909.

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Authors' reply: To explain why antidepressant treatment with selective serotonin reuptake inhibitors (SSRIs) does not improve cardiac prognosis, Korszun *et al* suggest that SSRIs may not alter the mechanisms through which depression leads to increased cardiovascular morbidity and mortality. However, two other explanations may be more plausible. First, the effects of antidepressant treatment on depression itself are not strong enough. In both the ENRICH and SADHART trials, the response rates of patients in the active treatment arm hardly exceeded those of patients receiving usual care or placebo. Second, the cardiotoxic effects of depression are limited to patients for whom antidepressant treatment is not effective (Grace *et al*, 2005; de Jonge *et al*, 2006a). We have shown that the cardiotoxic effects of depression are concentrated in incident post-myocardial infarction depression, whereas results from the SADHART study have indicated that sertraline is only effective in non-incident depression (of interest, Korszun *et al* mention mechanisms related to recurrent depression, which appears not to be cardiotoxic). If antidepressant treatment is only effective in non-cardiotoxic depression, no effects on cardiovascular prognosis can be expected.

Shetty raises ethical concerns about our study, because we used Zelen's method of randomisation. Controls were not told about their diagnosis of depression and, as argued by Shetty, therefore may have 'missed' an offer of adequate treatment. However, we feel that in 1999, when the study started, Zelen's method was both scientifically useful and ethical because no controlled comparative studies had yet investigated the clinical efficacy and safety of antidepressant drugs in depression post-myocardial infarction. At that time, the proportion of myocardial infarction patients with depression who were treated for their post-myocardial infarction depression was negligible. In addition, serious concerns existed about the safety of antidepressant drugs in cardiac patients. Moreover, in our study patients with a significant risk of suicide or severe depression were excluded from randomisation and referred for psychiatric treatment outside the study. Finally, all patients received usual care, i.e. had cost-free access to all usual treatment facilities such as normal cardiac rehabilitation programmes and healthcare from family physicians. We therefore feel it was ethical to use Zelen's method in our study and scientifically useful as our control patients were truly representative of patients receiving usual care.

We agree with Dr Kho that we need to develop new treatments for depression post-myocardial infarction, but believe it is premature to consider electroconvulsive therapy (ECT) as an effective alternative. In our experience those types of depression that are least similar to those seen in general psychiatry (i.e. incident depression occurring for the first time after myocardial infarction; de Jonge *et al*, 2006b) and those that are dominated by feelings of exhaustion rather than negative self-esteem or suicidality (de Jonge *et al*, 2006a) are the most cardiotoxic. To our knowledge the mechanism(s) explaining this remain unclear. Similarly, it is not known whether ECT is effective in these subtypes (although it appears that antidepressive medication is not). In fact, the studies mentioned by Dr Kho suggest increased rather than decreased cardiovascular events.

New, effective treatments for depression post-myocardial infarction will improve quality of life but perhaps also survival, as rightfully argued by Dr Kho. Carney *et al* (2004) showed that responders to antidepressive medication had a better cardiovascular prognosis than non-responders,