Depression and mortality following myocardial infarction: the issue of disease severity

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Symptoms of depression are particularly prevalent and persistent following myocardial infarction (MI)(Lane *et al.*, 2002) and have been reported to predict subsequent short-term (≤18 months) cardiac and/or all-cause mortality (Frasure-Smith *et al.*, 1995; Irvine *et al.*, 1999). Such findings have helped inspire a large scale, multi-site intervention trial in the United States, aimed at reducing mortality in MI patients by enhancing their psychological status through cognitive-behavioural therapy (ENRICHD Investigators, 2001). However, at least two recent prospective observational studies have failed to detect an association between in-hospital symptoms of depression and short-term cardiac and/or all-cause mortality in such patients (Lane *et al.*, 2000; Mayou *et al.*, 2000).

How do these two studies differ from those reporting positive associations? While they vary in a number of respects, there is at least one obvious difference. In neither of them were symptoms of depression linked to measures of disease severity. For example in our own study (Lane *et al.*, 2000; 2001), symptoms of depression were not related to our main indices of disease severity (Killip class and Peel Index score) and, with the exception of diabetes, neither were they associated with conventional cardiac disease risk factors (such as blood pressure status, hypercholesterolaemia, and cigarette smoking). In the other study (Mayou *et al.*, 2000), distressed and non-distressed patients did not differ in the terms of the sorts of cardiological variables (previous MI history, and relevant surgical procedures) often connected to prognosis.

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In contrast, positive association between depression and mortality after MI would seem to arise either in studies that have not adjusted for disease severity (Denollet & Brutsaert, 1998) or in studies in which measures of disease severity correlate significantly with symptoms of depression (Frasure-Smith *et al.*, 1995; 1999; Kaufmann *et al.*, 1999; Irvine *et al.*, 1999). A recent editorial in the journal *Psychosomatic Medicine* indicated that disease severity remained a major potential source of confounding in such studies (Mendes de Leon, 1999): "One of the main issues regarding the role of depression is the potential confounding with severity of disease (p. 738)". In the majority of studies in which symptoms of depression were associated with disease severity, statistical adjustment for disease severity rendered non-significant the relationship between depression and mortality (Kaufmann *et al.*, 1999; Irvine *et al.*, 1999). However, in one very influential study (Frasure-Smith *et al.*, 1993; 1995), the significant association between in-hospital symptoms of depression and mortality survived adjustment for indices of disease severity. Nevertheless, caution is still warranted.

The inference that some variable constitutes an independent risk factor for some outcome is usually based on multivariate analysis in which the statistically significant bivariate relationship between the variable and the outcome remains following adjustment for potential confounders. However, it has been argued that declarations of independence on this basis may be premature (Davey Smith & Phillips, 1992a; Phillips & Davey Smith, 1992; Phillips & Davey, 1991). The ability of multivariate statistical models to determine independence depends on the accuracy of measurement of potentially confounding variables; any inaccuracy in the measurement of the potential confounder will inevitably lead to underestimation of its true impact. In other words, as Davey Smith & Phillips (1992b) pointed out, "it can appear that a risk factor

is related to disease after the adjustment for confounding factors, but this residual relationship only exists because of underadjustment for these confounding factors" (p.257).

The indices of disease status employed in these studies have been various and all are imperfect. For example, some studies have relied on very indirect measures, such as self-evaluations of fatigue and dyspnea (Irvine *et al.*, 1999) and the patients' cardiological histories prior to the target MI (Mayou *et al.*, 2000). Another group has added to these measures, ECG abnormalities (Ladwig *et al.*, 1991; 1992). Our own study (Lane *et al.*, 2000; 2001) used Killip class and Peel Index scores, as well as post-discharge medical regimen. Killip class (Killip & Kimball, 1967) is a widely used measure of the degree of left ventricular dysfunction; it is 4-point clinical assessment based on a chest X-ray, heart and lung sounds, and signs of cardiac shock. The Peel Index (Peel *et al.*, 1962) is a prognostic device, and includes, in arriving at a score, consideration of: age, sex, previous cardiological history, degree of severity of shock, presence and severity of heart failure, cardiac rhythm, and the nature and extent of ECG abnormalities.

In our study (Lane *et al.*, 2000; 2001), both Killip class (OR = 8.06, 95%CI = 2.35-27.61) and Peel Index score (OR = 6.05, 95%CI 2.46-14.89) were strongly predictive of 12-month cardiac mortality; both were unrelated to symptoms of depression, as measured by the *Beck Depression Inventory* (Beck *et al.*, 1961). In contrast, in the study by Frasure-Smith *et al.* (1993; 1995), *Beck Depression Inventory* scores, although not major depression as determined by a diagnostic interview schedule, correlated significantly with Killip class; Killip class was once again strongly predictive of cardiac mortality. Additionally, in the Frasure-Smith study, the prescription of warfarin at discharge, which was strongly predictive of subsequent mortality, was also associated with depression. In our study, warfarin prescription was also significantly related to 12-month cardiac mortality (OR = 9.12, 95%CI = 3.14-26.45), but unrelated to symptoms of depression (OR = 1.21, 95%CI = 0.47-3.12); these latter statistics are from previously unreported analyses. Thus, in two reasonably similar studies with very different outcomes regarding the prognostic significance of depressive symptoms post-MI, one noticeable difference concerns the degree of the association between depression and clinical predictors of mortality.

In sum, the possibility remains that depression is a marker of disease severity in some studies and that it is disease severity, not depression, which is the underlying cause of death. This evaluation obviously implies a different sort of causal pathway from that envisaged by others (Frasure-Smith *et al.*, 1993; 1995). It suggests that depression may be an epi-phenomenon or, indeed, an effect of rather than the cause of illness in this context. There are two ways of trying to decipher whether the positive relationship between in-hospital symptoms of depression and short-term mortality in MI patients represents an independent or a confounded association. One is to conduct a randomised controlled trial in such a population of an intervention whose primary target is alleviating symptoms of depression. The results from the large-scale trial in the United States (ENRICHD Investigators, 2001) are thus of critical importance. Another way is to study a group of patients in which the potential confounding variable is unrelated to the putative predictive variable, that is, in this context, a group of MI patients in which symptoms of depression are not related to measures of disease severity. That is precisely what our study (Lane *et al.*, 2001; 2001) and the other null study (Mayou *et al.*, 2000) have done, although in neither case was this the intention.

These variations among studies still leave a host of further unanswered questions. Most obvious among them is why are symptoms of depression associated with cardiac disease severity in some studies but not others? Either there is something different about the design of the study, the patients enrolled, or the circumstances of their in-hospital treatment. Since positive and null studies generally have had similar levels of power to detect effects and have used similar or highly correlated measures of depressive symptomatology, gross features of design would not seen to hold the key. Explanations in terms of patient characteristics are for the most part similarly problematic. Nevertheless, it should be conceded that relatively more of our patients were allocated to Killip classes II – IV than patients in the other study that used Killip class as a measure of disease severity (Frasure-Smith *et al.*, 1993; 1995). Thus, it is possible that depression predicts mortality mainly in MI patient groups unencumbered by high levels of cardiac morbidity, and this relatively high frequency of Killip classes II-IV somehow proscribes a positive correlation between Killip class and symptoms of depression. However, our recorded death rates are not dissimilar to those reported in other studies, which would tend to argue against this sort explanation.

This leaves the in-hospital context. It is worth noting that both of the null studies were conducted in England in large state hospitals. If symptoms of depression are an effect rather than a cause in MI patients, it is interesting to speculate that the accuracy of patients' perceptions about the severity of their condition might explain whether or not depression and disease severity are linked statistically. By an effect we mean that depression would be regarded

as a consequence of the patient's encounter with a life threatening medical event. As a corollary of this view, the extent of depressive symptoms would, among other things, reflect patients' perceptions of just how serious that event was and the likely prognosis. Where physicians provide only scant and general prognostic information or, at least, patients perceive this to be the case, then one would expect depression to be largely independent of objective disease severity and likely prognosis. On the other hand, if physicians' communications make explicit just how ill patients are, the extent of depression might be presumed to follow from the patient's reasonably accurate appreciation of the severity of their condition and the prognosis. We acknowledge that this is highly speculative, but, at the very least, it does generate a testable hypothesis: that a positive association between depression and disease severity will appear where there are positive associations between objective measures of disease severity and the patients' perceptions of how ill they are.

Finally, although mortality will necessarily remain a key consideration in managing cardiac disease, we should not lose sight of other outcomes, in particular quality of life. In the two null mortality studies (Lane *et al.*, 2000; Mayou *et al.*, 2000), in-hospital symptoms of depression were powerfully related to subsequent quality of life among survivors. This result and the finding that over a third of MI patients experience mild to severe symptoms of depression, which in many cases persists up to at least a year following discharge from hospital (Lane *et al.*, 2002), emphasise the need to both assess mood and develop appropriate intervention strategies. In an editorial in *Psychosomatic Medicine*, that may or may not prove prescient with respect to the findings of the current large-scale intervention trial of cognitive-behavioural therapy for MI patients, Lesperance & Frasure-Smith (1999) commented that "We should not lose sight of the fact that an intervention that improves well-being, but fails to change survival, is still a very valuable treatment" (p. 20). We would thoroughly endorse this sentiment. We would also argue strongly that addressing the high prevalence of distress in MI patients is an abiding imperative. It will remain, even if the association between symptoms of depression and short-term mortality following MI, reported by others, turns out to be largely spurious, driven by their mutual relationship with disease severity.

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