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EDITORIAL COMMENT

Anxiety, Depression, and Prognosis After Myocardial Infarction

Is There a Causal Association?*

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It is commonly thought that traditional risk factors, namely, hypertension, high cholesterol, cigarette smoking, and physical inactivity, can at best explain only 50% of the variation in mortality in coronary heart disease (1), although this has recently been called into question (2). This apparent explanatory *lacuna* has prompted many investigators to seek additional, particularly behavioral, risk factors. Early inquiry focused on type A behavior and hostility, but more recently attention has shifted to mood states, such as depression and anxiety.

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Symptoms of depression and anxiety are prevalent among patients after myocardial infarction (MI), with rates ranging from 17% to 37% (3–9) and 24% to 31% (3,4,6,9–12), respectively. In addition, such symptoms often persist over the ensuing months (13,14), adversely affecting a patient's quality of life (6,9) and increasing their cardiac morbidity (3,5,15). Furthermore, symptoms of depression after MI have been associated with an increased risk of recurrent cardiac events (3,8,10,11) and an increase in short-term cardiac and/or all-cause mortality (≤18 months) (3–5,7,10,12).

The apparently independent association reported between mortality and depression has helped inspire three randomized controlled trials, two pharmacologic (Myocardial INfarction and Depression-Intervention Trial, or MIND-IT [16], and Setraline Antidepressant Heart Attack Randomized Trial, or SADHART [17]) and one cognitive-behavioral, supplemented where necessary with antidepressant medication (ENhancing Recovery In Coronary Heart Disease, or ENRICHD [18]). These trials were designed to afford an experimental test of the proposition that depression after MI was causally linked to clinical prognosis (recurrent events and death). In MIND-IT (16), an ongoing trial, patients with a post-MI depressive episode were randomized to receive antidepressant medication or usual care. Unfortunately, the results of this trial are not yet available. In ENRICHD (18), substantial numbers of MI patients with evidence of current depression and/or a history of depression were allocated to either cognitive-behavioral therapy or usual care. Whereas the intervention reduced depression at six months, it had no effect on re-infarction or mortality (19). A not-insignificant number of the intervention patients, 249 (27%), received adjunctive antidepressant medication. It is perhaps hardly surprising, then, that analogous outcomes emerged from a much smaller study, that is, SADHART (17), of pharmacotherapy in this context. Although treatment with antidepressants reduced depression, it did not effect left ventricular ejection fraction (LVEF), ventricular arrhythmias, or electrocardiogram profile (19). It is worth noting that since the launch of these trials, a number of observational studies have failed to find an independent association between symptoms of depression (6,9,15,20,21) and/or anxiety (6,9) and short-term mortality after MI.

Compared with the extensive literature on depression and MI, relatively little research has been conducted investigating the effects of anxiety post-MI. This is surprising given that anxiety and depression are highly comorbid disorders (22). To date, only five prospective studies had examined anxiety in this context, and their results are far from consistent (3,6,9,10,12). One reported a positive association (10) between symptoms of anxiety and increased risk of mortality post-MI, whereas three found no association (6,9,12), and the other presented mixed findings, with anxiety predicting cardiac events but not mortality (3). Given the relative paucity of research on anxiety and prognosis after MI, the observational study by Strik et al. (15) reported in this issue of the *Journal* is particularly welcome.

Why are there differences in study outcomes exploring the link(s) between MI and depression/anxiety? The inconsistency in previous findings may be due, in part, to the dissimilar MI populations studied and methodologic differences. The sample populations varied markedly, with highly selected MI populations, namely patients with arrhythmias (12) and those with significant left ventricular dysfunction (10), which may have heightened their mortality risk. Studies also vary markedly in the time delay between the occurrence of MI and measurement of anxiety symptoms. The variety of diagnostic instruments and standardized questionnaires used may also have contributed to the variations in the outcomes of studies. Furthermore, small samples sizes and the failure to report multivariate analyses controlling for other risk factors cast doubts on the outcomes of some studies (10). With such variations in population measurement, design, and statistical control, it might

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be expected that results would vary considerably. Because the studies measuring anxiety in this context also measured depression, the same can be and has been said about variations in the results regarding depression and clinical outcome (23).

However, aside from these methodologic variations, there is one other fairly consistent distinction between prospective observational studies failing to find and those reporting an association between anxiety and/or depression on the one hand and cardiac events and mortality after the index MI on the other. This has to do with the issue of disease severity and its relationship with anxiety and depression. For example, in the two most recent studies to report null findings, symptoms of anxiety and depression measured in-hospital were not significantly associated with indices of disease severity and mortality (6,9). In our own study (6), symptoms of depression and anxiety were not related to our main indices of disease severity (Peel Index score and Killip class) and, with the exception of diabetes, neither were they associated with conventional cardiac disease risk factors. In the other study (9), distressed and non-distressed patients did not differ in terms of the sorts of cardiologic variables (previous history of MI and relevant surgical procedures) often connected to prognosis. Although indices of disease severity predicted clinical prognosis in these studies, anxiety and depression, as indicated, did not.

Anxiety and depression would appear to predict clinical prognosis after MI mainly in studies that have either not controlled for cardiac disease severity (10) or in which disease severity is significantly correlated with depression or anxiety (3–5,7,8). Others have noted that one of the main obstacles to attributing a causal role to mood status in clinical prognosis after MI is the potential confounding of mood after MI with disease severity (24). In many of the studies that have reported a positive association between mood and mortality, the relationship between mood state and mortality was no longer statistically significant after adjustment for disease severity (7,8,20,21). However, in one very influential study (3–5), the association between depression and mortality survived correction for indices of disease severity, such as Killip class, even though mood status and Killip class were related. Furthermore, in the study reported by Strik et al. (15), symptoms of anxiety and depression were not significantly related to traditional coronary heart disease risk factors in univariate analyses, with the exception of smoking, nor with LVEF. However, both depression and anxiety predicted subsequent cardiac events, although only the latter survived in a multivariate analysis that tested both depression and anxiety.

Let us consider these two apparent exceptions in turn (3–5,15). First, let us examine the most apparently compelling evidence available that the association between mood and mortality survives adjustment for disease severity (3–5). The inference that some exposure or characteristic constitutes an independent risk factor for some health outcome is usually based on multivariate analysis in which a statistically significant bivariate association between the exposure or characteristic and the health outcome remains after adjustment for potential confounding variables. However, declarations of independence on this basis may be premature (25–27). The ability of multivariate statistical models to determine independence depends on the accuracy of measurement of the potentially confounding variables; any inaccuracy will inevitably lead to underestimation of their true impact (25–27). In other words, as Davey Smith and Phillips (28) 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 under-adjustment for these confounding factors." The indices of disease severity used in observational studies in this area have been various and all are imperfect. Accordingly, characteristics such as mood can appear to have an independent association with mortality, but this could arise as a consequence of the confounding of mood with disease severity and the imprecise measurement of disease severity. Let us now examine the result reported in Strik et al. (15). Here, the association between anxiety and depression and subsequent cardiac events also survived correction for disease severity, indexed in this case by LVEF. This is hardly surprising, given that LVEF did not correlate with mood. However, LVEF per se is an imprecise index of *overall* disease severity because a great many other factors (including blood pressure, renal function, the presence of arrhythmias and heart failure) are all relevant in defining how "sick" a patient is. It remains possible that controlling for some of these other indices of severity may have abolished the association between mood and subsequent cardiac events.

The balance of evidence and argument suggests that it is right for one to be skeptical about a causal link between mood, whether anxiety or depression, after MI and subsequent cardiac events and mortality. Nevertheless, the high prevalence and persistence of symptoms of anxiety and depression over the first 12 months after MI (13) provides a sufficiently strong argument per se that much more attention needs to be directed to the emotional status of recovering MI patients. Although "hard" clinical end points will necessarily remain a key consideration in managing cardiac disease, cardiology is beginning to embrace other outcomes, such as quality of life. Research has shown that depression and anxiety measured at the time of MI are predictive of quality of life 12 months later (6,9). A poor emotional state in MI patients may also comprise compliance with medical advice (29) and participation in cardiac rehabilitation (30,31), as well as increasing health care consumption (15). It is for these reasons that we have argued recently (23) that treating symptoms of anxiety and depression in MI patients is an abiding imperative. It will remain so even if there is no causal link between such symptoms and subsequent cardiac events and mortality.

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