Depression and Coronary Heart Disease: More Pieces of the Puzzle

It has been nearly 20 years since major depression was identified as a risk factor for cardiac events in patients with stable coronary heart disease (1) and nearly 15 years since it was found to increase the risk of mortality after acute myocardial infarction (2). Because depression is treatable, and therefore a modifiable risk factor, these discoveries raised the hope that treating major depression would improve medical outcomes in the estimated 20% of patients with coronary heart disease who have this comorbid psychiatric disorder. However, things are often more complicated than they first appear. Although many subsequent studies have supported the initial findings, some have not (3). This has led to the conclusion that some but not all depressed patients are at high risk for cardiac events and that the high-risk subset has not yet been identified.

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Despite inconsistencies across studies, recent meta-analyses support the status of depression as a risk factor for cardiovascular morbidity and mortality in patients with coronary heart disease (4, 5). So far, however, only two clinical trials have been conducted to determine whether treating depression reduces the risk for cardiac events following a recent acute myocardial infarction: the Enhancing Recovery in Coronary Heart Disease (ENRICHD) study (6) and the Myocardial Infarction and Depression Intervention Trial (MIND-IT) (7). In the primary analyses, both the ENRICHD and MIND-IT interventions had only modest effects on depression, and neither of them improved survival.

These studies have been discussed at length (6–9), and a detailed review is beyond the scope of this commentary. However, most of these discussions have concluded that more effective treatments for depression in post-myocardial infarction patients are needed and that more work is needed to identify the subset of depressed patients who are at the highest risk for cardiac events. Two reports in this issue of the *Journal* have brought us closer to reaching these goals and therefore closer to readiness for the next major clinical trial in this area.

The report by de Jonge et al. is a secondary analysis of data from the MIND-IT clinical trial. The authors investigated whether there was a relationship between response to depression treatment and subsequent cardiac events. The 18-month incidence of cardiac events was 7.4% in treatment responders (≥50% reduction in Hamilton Depression Rating Scale score or score <9 at 24 weeks) and 25.6% in nonresponders. The incidence of cardiac events in the untreated comparison subjects, who unfortunately were not assessed for change in depression, was 11.2%. Thus, patients who responded to a standard treatment for depression after an acute myocardial infarction were at low risk for subsequent cardiac events. Those who did not respond to first-line depression treatment, or in some cases even second-line depression treatment, were at high risk for cardiac events during the follow-up. These findings are very similar to those recently reported in a secondary analysis of data from ENRICHD (8). Moreover, de Jonge et al. found that nearly 60% of the nonresponders were depressed 18 months after the index event, compared

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with less than 10% of the treatment responders. This suggests that patients who have persistent depression, despite treatment, may be at increased cardiac risk.

Does this mean that patients who did not respond to the depression treatments in the ENRICHD and MIND-IT studies were at high risk for cardiac events *only* because they remained depressed? Another possibility is that there may have been preexisting differences between the responders and nonresponders that placed them at risk both for chronic depression and for cardiac events. However, there were few significant pretreatment differences between responders and nonresponders in either trial. They did not differ in the severity of their medical illness, and there was no evidence of a relationship between treatment nonresponse and cardiac risk factors associated with vascular depression (8). In short, these studies have left few clues as to why the patients who remained depressed despite receiving standard treatments for depression are at high risk for future cardiac events, except that they remain depressed.

However, the second study of depression and coronary heart disease in this issue of the *Journal* may suggest another line of research for identifying high-risk patients and perhaps even identifying more effective treatments for them. Otte et al. found that patients with stable coronary heart disease who had the short (S) allele of the serotonin transporter (5-HTTLPR) polymorphism were more likely to be depressed, to report higher stress levels, and to have higher urinary epinephrine excretion than those patients who were homozygous for the long allele (LL). This study adds to the growing evidence that the S allele may interact with stressful events, including the stresses associated with chronic medical illness, to increase the risk for becoming depressed. In an earlier study, Nakatani et al. found that the S allele not only predicted depression symptoms following an acute myocardial infarction, but depression and the S allele also predicted subsequent cardiac events (10).

The Nakatani et al. finding seems to be at variance with earlier studies that found the L allele to be a risk factor for incident myocardial infarction. However, the risk factors for incident myocardial infarction and those for cardiac events following a myocardial infarction are not identical. The risk for depression and for cardiac events following an acute coronary syndrome may share a common genetic pathway.

There is also some evidence that patients with the S allele may be less responsive to selective serotonin reuptake inhibitor (SSRI) antidepressants and/or have more adverse events when receiving these agents (11, 12) than those with the L allele. This response to SSRIs in patients with the S allele has been well documented in older adults (11), but a recent meta-analysis of available studies concluded that there is a highly significant association of the S variant of the 5-HTTLPR with remission and response rates across all ages (13). The effect is also quite robust to ethnic differences, although there was a significant heterogeneity among the Asian cohorts. Patients who did not respond adequately to either mirtazapine or to a placebo in MIND-IT and those who did not respond to cognitive behavior therapy in ENRICHD were given an SSRI. Thus, many of the patients in both studies were classified according to their response to SSRIs following failure to respond to the initial treatment.

Whether the presence of the S allele of the serotonin transporter (5-HTTLPR) polymorphism identifies the depressed postmyocardial infarction patients who will not respond well to SSRIs—and who are also at high risk for cardiac events—remains for future studies to determine. However, further investigation of genetic factors, including the S allele, may prove to be a fruitful approach for identifying the subset of depressed patients who are at high risk for cardiac events and for selecting the most effective depression treatments for these patients. This information would be of great value to the investigators who will design the next major clinical trial to determine whether treating depression will improve survival in patients with heart disease.

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