Depression—A Cardiac Risk Factor in Search of a Treatment

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THE ENHANCING RECOVERY IN CORONARY HEART DISease Patients (ENRICHD) trial[1] published in this issue of THE JOURNAL is the largest controlled trial of psychotherapy ever completed. In this study, the first multisite behavioral trial funded by the National Heart, Lung, and Blood Institute (NHLBI), the ENRICHD investigators enrolled 2481 post–myocardial infarction (MI) patients from 73 hospitals in 8 US cities in a 6-month course of weekly cognitive behavior therapy (CBT) vs usual care. Three quarters of the study patients had depression, with the remainder included because of low perceived social support (LPSS). The goal was to determine whether treating depression and LPSS would reduce mortality and recurrent infarction. The intervention produced small, statistically significant decreases in depression symptoms and small, significant increases in perceived support. These differences did not translate into any benefit in event-free survival during a mean follow-up of 29 months, so the study is a negative trial. However, much was learned over the course of the ENRICHD trial, and more will be learned as the investigators and others try to understand why results were not as expected. The study also demonstrates that psychologists, psychiatrists, and cardiologists can successfully collaborate to test complicated intervention protocols with large numbers of patients from multiple sites. For these reasons, the ENRICHD trial will remain a standard of comparison for many years.

Based on the investigators' previous publications,[2-4] as well as the current study, the key assumptions behind the ENRICHD trial were as follows: (1) depression and LPSS are causally related to cardiac mortality and MI recurrence in post-MI patients; (2) these relationships are strong enough to suggest that, with sufficient improvements in depression and LPSS, combined event rates over 36 months can be reduced by at least 30%; (3) these relationships are true regardless of sex, ethnicity, or socioeconomic status; (4) the impact of depression and LPSS is apparent soon after hospital discharge, so intervention needs to be instituted early; (5) it is possible to screen for depression and LPSS during hospitalization, enroll most individuals at apparent risk, and ensure their compliance with weekly therapy sessions beginning soon after discharge; (6) 6 months of individual CBT and group sessions (supplemented by antidepressant treatment for those not responding by 5 weeks) can have a large enough, sustained impact on depression symptoms and LPSS to result in the hypothesized 30% decrease in cardiac events over 36 months; and (7) attending physicians will recognize and treat depression in only a small minority of the usual care group.

Because of the disappointing results of this trial, it is important to reconsider these assumptions. In 1994, when the ENRICHD trial was designed, the number of studies suggesting a link between social support and post-MI prognosis was similar to the number implicating depression. However, the studies of social support differed widely in the ways in which support was conceptualized.[3] Was the important variable marital status, living alone, lack of a confidant, poor perceived support, or a small number of close friends? The fact that the ENRICHD investigators had to develop a new measure to screen for LPSS and to develop a new, untested form of CBT to try to treat it, suggests that it was premature to include LPSS. This is not to refute the importance of social factors in post-MI recovery, but to emphasize that the understanding of their role in cardiac prognosis was, and remains, insufficient to target them in an intervention trial.

When the ENRICHD trial was designed, the reported relative risks associated with post-MI depression were high, the confidence intervals were wide, and the follow-up periods did not exceed 18 months.[5-7] Since then, several studies have confirmed the prognostic importance of depression in patients with established coronary artery disease (CAD).[8-12] A recent review also concluded that depression is a risk factor for incident CAD in previously healthy patients.[13] However, not all studies have been positive,[14,15] suggesting that the long-term risk associated with depression may be lower than originally

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estimated. Dramatic improvements in cardiac care, such as widespread use of statin medications, may also have had an impact on mechanisms linking depression and CAD.

Although the prognostic risk associated with depression is as strong as that of more traditional risk factors, it remains unclear whether depression is causally involved in the processes leading to cardiac events. Several types of relationships could be involved.[16] As assumed in the ENRICHD trial, depression may directly predispose patients to cardiac events through biological mechanisms such as increased sympathetic activity. Alternatively, depression may be a consequence of atherosclerosis of the cerebral arteries.[17] Moreover, both cardiovascular disease and depression may share common causes, such as dysregulation of the serotonin transporter,[18] reduced dietary intake of omega-3 fatty acids,[19] or immune activation.[20] It would have been of great interest to prove that CBT, which influences thoughts and emotions, was sufficient to improve cardiovascular end points, because CBT is not known to have any pleiotropic effects on other factors influencing cardiac prognosis.[21] However, the mechanisms linking the brain and atherosclerotic processes are likely to involve many complex direct and indirect pathways. Future trials concerned with influencing prognosis should use treatments with potentially beneficial effects on the processes involved in both depression and atherosclerosis. Promising candidates include selective serotonin reuptake inhibitors (SSRIs), exercise,[22] and omega-3 supplementation.

The ENRICHD trial was one of the first NHLBI trials carried out after the passage of the National Institutes of Health (NIH) Revitalization Act in 1993 that required appropriate representation of women and minorities in phase 3 clinical trials.[23] The investigators attempted to enroll 50% women and 50% minorities and did very well by including 44% women and 34% minorities in the study sample. However, at the time of its implementation, the NIH policy was highly debated by trialists.[24] Some cautioned that unless there was preliminary evidence that the risk being targeted was likely to be independent of sex or minority status, power could be compromised.[25] To our knowledge, prior to the ENRICHD trial no one had examined the long-term post-MI impact of depression or low social support in women, minority groups, or patients with low socioeconomic status. Thus, it is possible that compliance with the NIH Revitalization Act may have reduced study power. In fact, the subgroup analyses, including the apparent interaction of treatment by sex, point in this direction.

The ENRICHD trial proved that, although labor intensive, systematic screening can result in the randomization of the majority of eligible patients. This is crucial for subsequent trials. While hospitalization is the easiest time to screen for psychological risk, the early postdischarge period may not be the best time to begin treatment. The ENRICHD investigators assumed that because the risk associated with depression becomes apparent in the first few weeks after MI, intervention should begin early. This likely resulted in the inclusion of some patients with rapidly remitting depression or adjustment disorder. Even when screened patients are experiencing symptoms, it is difficult enough to convince those who never perceived themselves as depressed to participate in treatment. This is especially problematic for interventions like CBT that require increasing awareness of the thought processes regulating mood. Thus, a drug treatment, while not without problems, might be easier to administer to those who prefer to avoid psychological issues. However, the timing of such a treatment, like that of CBT, remains debatable.

One of the most important aspects of trial design has to do with the effect size (standardized difference between group means), ie, how much of a difference in outcomes is reasonable to expect. Depression is a heterogeneous condition and can be difficult to treat, even in patients who seek intervention and who do not have a comorbid physical illness. For example, a recent review[26] found an average effect size of 0.40 in 19 placebo-controlled trials of SSRIs. However, most antidepressant trials have excluded patients with physical illness, and the effect size of 0.2 to 0.3 reported in the ENRICHD trial may represent a realistic expectation in post-MI patients when the comparison group involves current usual care. The ENRICHD investigators assumed that patients in the usual care group would not receive treatment. However, more of these patients improved than expected. With better education of patients and physicians, decreased stigmatization of depression, and extensive marketing by pharmaceutical companies, antidepressant use is increasing.[27] A recent British study also suggested that much of the research on family physicians' recognition of depression has only considered a single visit.[28] When longitudinal evaluation is carried out, many persistently depressed patients do receive treatment.[28] In fact, by 36 months, 20.6% of the usual care patients in the ENRICHD trial had been prescribed an antidepressant in contrast to 28% of the treatment patients.

The ENRICHD trial's impact on depression scores, although statistically significant ($P<.001$), was only between 1.5 and 2.8 points depending on the scale used. These results need to be considered in light of another recent study of depression in acute coronary syndromes, the Sertraline Antidepressant Heart Attack Randomized Trial (SADHART).[29] The SADHART trial enrolled 369 depressed post-MI or unstable angina patients in a 6-month comparison of an SSRI (sertraline) vs placebo. Overall, the difference between the groups amounted to about 1 point on the Hamilton Depression Rating Scale and was not significant ($P=.14$). However, within a preplanned subgroup of patients with recurrent depression, the difference in favor of sertraline was 2.2 points ($P=.009$). As in the ENRICHD trial, the results involved a statistically significant difference with a small effect size, making them of unclear clinical importance.[30] To achieve higher effect sizes, a more aggressive, stepwise treatment approach may be warranted.

Last year in THE JOURNAL, Unützer et al[31] reported results of a trial of collaborative management of depression vs usual care in primary care patients aged 60 years and older, a group

that is very difficult to treat. Interventions were individually tailored, took into account patient preferences for psychotherapy vs antidepressants, and included follow-up over 12 months by a depression case manager and a series of stepped-care protocols. Although the sample was planned to be able to detect a small effect size (0.2) between depression management and usual care, at 6 months the observed effect size was greater than 0.4 and at 12 months was greater than 0.6. It may even be possible to improve on this outcome. The ongoing Sequenced Treatment of Alternatives to Relieve Depression (STAR*D) Trial,[32] which compares various switching and augmentation strategies for major depression and takes into account patient and physician choices, will certainly provide additional knowledge for building appropriate stepped-care protocols for future assessment in cardiac patients.

Even with a bigger impact on depression symptoms, would the ENRICHD trial have influenced cardiac prognosis? Designed in the mid 1990s, it was powered to detect a 30% group difference in cardiac mortality and MI recurrences. Even 10 years earlier, cardiologists were not expecting to be able to achieve that great an impact. For example, the Studies of Left Ventricular Dysfunction (SOLVD) trial,[33] which involved patients with reduced ejection fractions, was designed in 1984-1985 and was powered to detect a moderate mortality reduction of only about 20%. Recently, a reduction of 15% in recurrent events has become the standard for clinical significance.[34] With the sobering benefit of hindsight, a 30% reduction in combined all-cause mortality and MI recurrences was overly optimistic.

The ENRICHD investigators have demonstrated that depressed CAD patients can be identified, randomized, properly treated with complex interventions, and followed up for long periods. This is a major accomplishment. However, depression remains a CAD risk factor in search of a successful intervention. Future trials should evaluate treatments with probable impacts on multiple cardiovascular and behavioral mechanisms. If reasonable sample sizes are to be envisaged, trials should also combine flexible interventions that respect patients' individual treatment preferences with aggressive stepwise protocols. Although such multifaceted protocols will not permit the identification of active components, single-treatment studies with the goal of achieving realistic effect sizes on cardiac prognosis would need to be much larger.

The ENRICHD trial has provided important, clinically meaningful knowledge, and future studies will surely benefit from this milestone study. Regardless of whether rigorous studies will convincingly show that treating depression can influence cardiac prognosis, more trials are needed to find the best ways to improve care for patients with depression and CAD.

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