Mind Your Heart

Clinicians as far back as the father of internal medicine, Sir William Osler, have noted characteristic behavioral patterns in patients with heart disease. In 1897, Osler observed that “the typical heart disease patient is a keen and ambitious man...whose engine is always at full speed ahead” (1). Almost a century later, cardiologists Friedman and Rosenman picked up on this theme by linking the type A behavior pattern, a combination of time urgency and hostility, with coronary heart disease (CHD) (2). In 1986, they published a randomized, controlled trial of type A behavioral therapy in 862 patients after myocardial infarction and found that, during 4.5 years of follow-up, patients who received type A behavioral therapy plus group cardiac counseling were less likely to develop CHD events (myocardial infarction or cardiac death) than those who received group cardiac counseling alone (3). Subsequent work by Barefoot and colleagues (4) and others demonstrated that hostility was the component of type A personality primarily responsible for its association with CHD events.

During the past 20 years, several other psychological factors, such as anger, anxiety, and depression, have also been associated with an increased risk for CHD events and with adverse outcomes among patients with established CHD (5, 6). A recent study of more than 25,000 patients from 52 countries found that psychological factors were stronger risk factors for incident myocardial infarction than diabetes, smoking, hypertension, and obesity (7). Despite the strong evidence supporting this relationship, however, we do not know whether or how psychological factors actually cause CHD events.

In this issue, Diez Roux and colleagues (8) report the results of an elegant cross-sectional study examining the relationship between psychological factors and coronary artery calcium in a multiethnic, community-based sample of 6814 Americans age 45 to 85 years with no history of clinical cardiovascular disease. Coronary calcium is a marker of atherosclerosis that predicts incident CHD events in asymptomatic individuals, independent of traditional risk factors (9). Diez Roux and colleagues found no association between any of 4 psychological factors (depressive symptoms, anxiety, anger, and chronic burden) and coronary calcium as measured by computed tomography. Given the substantial body of evidence supporting an association between psychological factors and CHD events, are these negative findings surprising? Do they contradict more than a century of epidemiologic observations? How do they improve our understanding of the link between psychological factors and CHD events?

There are 3 possible explanations for this association: 1) Psychological disorders may lead to atherogenesis or to CHD events (causation), 2) psychological disorders may result from atherosclerosis or from CHD events (reverse causation), and 3) psychological disorders may be associated with other variables that lead to CHD events (confounding). The lack of relationship between psychological factors and coronary calcium observed by Diez Roux and colleagues makes it unlikely that psychological factors lead to atherogenesis, but it does not rule out the causal hypothesis because psychological factors may trigger CHD events without necessarily causing atherosclerosis. Combining the coronary calcium score with traditional risk factors and C-reactive protein improves prediction of CHD events, increasing the area under the receiver-operating characteristic curve from 0.69 to 0.79 (9). However, at least 20% of the variance in risk for CHD events remains unexplained, and the factors that trigger CHD events are unclear (10). Thus, it is possible that psychological factors may account for some of the variance in risk for CHD events that is not explained by coronary calcium or traditional risk factors.

Indeed, several plausible biological and behavioral factors have been identified as candidate mechanisms by which psychological factors may lead to CHD events without necessarily causing atherosclerosis (11). Potential biological mechanisms include mental stress–induced ischemia, alterations in cardiac autonomic tone, enhanced activity of the hypothalamic–pituitary axis, increased catecholamine levels, and greater platelet activation. Potential behavioral mediators include dietary indiscretion, lack of exercise, and medication nonadherence. Genetic factors may predispose patients to both depression and CHD events (12). However, further studies are needed to determine which—or what combination—of these potential mechanisms explain the increased risk for CHD events in patients with psychological disorders.

The second possible explanation for the relationship between psychological factors and CHD events is that psychological symptoms may result from atherosclerosis. Although previous studies of the association between psychological factors and coronary calcium have yielded mixed results, the study by Diez Roux and colleagues included more than twice the number of participants as all of these studies combined. The lack of association observed between psychological factors and coronary calcium essentially rules out the possibility that greater atherosclerosis causes psychological symptoms. Coronary heart disease events (as opposed to atherosclerosis) can of course cause psychological symptoms (13), and the association of psychological factors with CHD events may well be bidirectional. However, the findings of Diez Roux and colleagues make it unlikely that greater underlying atherosclerosis explains the increased risk for future CHD events in patients with psychological disorders.

The third possible explanation for the relationship between psychological factors and CHD events is that psychological factors may be associated with confounding variables that lead to CHD events. Most, although not all,
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Editorial

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studies have demonstrated that the increased risk for CHD events associated with psychological disorders is independent of age, diabetes, smoking, lipids, obesity, physical activity, and measures of baseline CHD (5, 6). Thus, it seems unlikely that traditional risk factors explain the association of psychological factors with CHD events. However, patients with psychological disorders may have a higher frequency of unmeasured characteristics that predispose them to CHD events. To exclude confounding, a randomized trial would need to demonstrate that treatment of psychological disorders decreases the incidence of CHD events without affecting traditional risk factors. Showing that changes in psychological factors precede a decreased incidence of CHD events would eliminate residual confounding and strengthen the causal hypothesis.

Despite the initially encouraging findings of Friedman and coworkers (3), subsequent randomized trials have failed to show that psychotherapy for mental health disorders reduces CHD events (14), and no trial has examined whether pharmacotherapy for mental health disorders reduces CHD events. In the Sertraline Anti-Depressant Heart Attack Randomized Trial (SADHART), researchers examined the safety of the selective serotonin reuptake inhibitor sertraline in 369 patients with depression and CHD and concluded that this drug is safe in patients with CHD (15). Although a trend was observed toward fewer CHD events in the sertraline group, SADHART was not designed or powered to detect a reduction in CHD events. A recent observational study found that use of antidepressant medication after myocardial infarction was associated with reductions in future CHD events, independent of CHD severity and traditional risk factors (16). However, the effect of antidepressant medication on CHD events has not been evaluated in a large randomized trial, and a trial would be necessary to rule out confounding as the explanation for increased CHD events in patients with psychological disorders.

Of the 3 possible explanations for the association of psychological factors with CHD events (causation, reverse causation, and confounding), Diez Roux and colleagues have virtually eliminated the possibility of reverse causation by demonstrating that psychological factors are not associated with atherosclerosis, at least in patients without symptoms of CHD. Whether confounding explains the association of psychological factors with CHD events cannot be determined by the currently available evidence. A randomized trial testing the effect of antidepressant medication on CHD events would be the cleanest way to examine this question. However, since patients with depression cannot be assigned to placebo, ethical considerations make designing such a trial challenging.

Regardless of whether psychological disorders are associated with CHD events, they must be recognized and treated. Depression is second only to ischemic heart disease as the leading cause of worldwide disability as the leading cause of worldwide disability (17), and it is a stronger predictor of health status than ejection fraction or inducible ischemia (18). Depression is present in approximately 10% of primary care patients and in 20% of outpatients with CHD (13). Treatment of depression improves mood, employment, functional status, and quality of life (19), and brief, validated depression screening tools are readily available and easy to use (13). Both cognitive behavioral therapy and selective serotonin reuptake inhibitors are safe and effective treatments for depression in patients with CHD (15, 20).

In summary, the preponderance of evidence indicates that psychological factors are associated with an increased risk for CHD events, but the reasons for this association are not well understood. By demonstrating a lack of relation between psychological factors and coronary calcium, Diez Roux and colleagues have ruled out the possibility that greater underlying atherosclerosis is responsible for the link between psychological factors and future CHD events. It is less clear whether the association between psychological factors and CHD events is causal. In the case of depression, only a randomized trial testing the effect of antidepressant medication on incidence of CHD events can answer this question.

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