Depression as a Risk Factor for Post-MI Mortality

In a recent editorial, Lane et al. (1) conclude that depression is probably not a risk factor for cardiac mortality. They assert that the SADHART and ENRICHD trials were designed to determine whether depression after myocardial infarction (MI) is causally linked to clinical prognosis and that both trials failed to do so. In fact, SADHART investigated the safety and efficacy of sertraline in patients with recent MI or unstable angina (2). It was not intended or powered to study the effects of depression treatment on medical outcomes. The ENRICHD trial found no effect of depression treatment on survival, but Lane et al. failed to mention that there was only a small between-group difference in depression outcomes (3). If a clinical trial of a cholesterol-lowering drug produced little difference in cholesterol levels between the treatment and control groups and no between-group difference in survival, this finding would not justify demotion of cholesterol from the ranks of major coronary risk factors. Similarly, the ENRICHD findings do not negate the importance of depression as a risk factor for post-MI mortality.

Lane et al. (1) claim that depression has predicted mortality almost exclusively in studies in which it correlated with coronary heart disease (CHD) severity at baseline. However, one of the studies they cite to support this claim actually found that a diagnosis of major depression was *not* related to CHD severity, but *was* associated with an increased risk for six-month mortality (4). Furthermore, in an ENRICHD ancillary study that included a nondepressed comparison group, depression was *not* related to left ventricular ejection fraction (LVEF), prior MI, or to Killip class (4). The unadjusted hazard ratio (HR) was 2.8 ($p < 0.001$) for all-cause mortality. After adjusting for diabetes, smoking, LVEF, prior MI, and other medical, demographic, and treatment variables associated with mortality, the HR dropped only slightly to 2.4 ($p < 0.02$). Thus, depression was indeed a risk factor in the ENRICHD trial. In studies in which depression has not predicted survival, or has not remained an independent predictor after covariate adjustment, inadequate statistical power has usually been responsible. For example, one of the studies cited in the editorial yielded a covariate-adjusted odds ratio of 4.9 for moderate to severe depression that nevertheless was not statistically significant; its sample included 560 patients but there were only 12 deaths (5).

It is not possible to measure or adjust for all possible risk factors in any study. Furthermore, the measurement of any risk factor is imperfect. Consequently, it can always be argued that an association between nearly any risk factor and survival is due to "inadequate" covariate adjustment. However, researchers in this area have adhered to the same rules of evidence as those investigating other cardiovascular risk factors. The totality of evidence supports a significant, independent influence of depression on cardiac mortality.

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REFERENCES

1. Lane D, Carroll D, Lip GYH. Anxiety, depression, and prognosis after myocardial infarction: is there a causal association? J Am Coll Cardial 2003;42:1801–10.
2. Glassman AH, O'Connor CM, Califf RM, et al., for the Sertraline Antidepressant Heart Attack Randomized Trial (SADHART). Sertaline treatment of major depression in patients with acute MI or unstable angina. JAMA 2002;288:701–9.
3. The ENRICHD investigators. Effects of treating depression and low perceived social support on clinical events after a myocardial infarction: the Enhancing Recovery in Coronary Heart Disease Patients (ENRICHD) randomized trial. JAMA 2003;289:3106–16.
4. Frasure-Smith N, Lespérance F, Talajic M. Depression following myocardial infarction: impact on 6-month survival. JAMA 1993;270:1819–25.
5. Carney, RM, Blumenthal JA, Catellier D, et al. Depression as a risk factor for mortality following acute myocardial infarction. Am J Cardiol 2003;92:1277–81.
6. Ladwig KH, Kieser M, Konig J, Breithardt G, Borggrefe M. Affective disorders and survival after acute myocardial infarction. Eur Heart J 1991;12:959–64.

Is Depression a Risk Factor for Coronary Heart Disease?

The editorial by Lane et al. (1), which cast doubt on the relationship between depression and myocardial infarction (MI), was inappropriately pessimistic and looked only at part of the evidence. Their argument appears to be that in post-MI patients any apparent relationship between depression and outcome is an epiphenomenon and that the only causal relationship is between disease severity and outcome. Certainly, if all we had were post-MI data on which to base the "depression–heart disease" hypothesis, our case would be weak because the potentially confounding effect of an MI causing or exacerbating depression is hard to dismiss.

The strongest support for the hypothesis comes from a diverse series of prospective studies showing that depression in asymptomatic and apparently healthy subjects is a strong and independent predictor of MI. A recent meta-analysis identified 10 prospective studies (2), where the overall relative risk for depression as an independent risk factor for coronary events was 1.64, a risk between that of passive smoking (n = 1.25) and active smoking (n = 2.5). Nine of the 10 studies obtained positive results. Considering that depression is much harder to quantify than smoking behavior (nine different measures of depression were used), that depression was evaluated only once, and that the average follow-up between the evaluation of depression and the outcome was on average 13.6 years (up to 40 years in one case), this is a truly impressive result.

The argument by Lane et al. that the reason why some of the

studies in post-MI patients were positive is that the studies did not adequately control for confounding variables is also open to criticism. The fact that controlling for one variable eliminates the significance of a second one does not necessarily mean that the second factor is unimportant, because it may operate through the first one. Thus, it is conceivable that if we had very good measures of the extent of atherosclerotic plaque, the role of blood cholesterol in causing MI would be "controlled for" by the plaque burden. Would this lead us to conclude that cholesterol is not a risk factor? Clearly, the issue here is which comes first; that is why the prospective studies of disease-free subjects are so important.

What the depression–heart disease hypothesis sorely needs in order to become established or refuted are more observational and interventional studies. In addition to coronary artery disease severity, variations in patient populations and differences in when and how depression was assessed have been other explanations for why some depression–heart disease studies have been negative. We should not forget that many of the early intervention studies attempting to test the lipid–heart disease hypothesis were negative. To date, ENRICHD is the only published study that attempted to reduce recurrence rates by treating depression, and its negative results may well be due to an inadequate treatment effect, as was observed with the lipid-lowering arm of ALLHAT (3).

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REFERENCES

1. Lane D, Carroll D, Lip GYH. Anxiety, depression, and prognosis after myocardial infarction: is there a causal association? J Am Coll Cardiol 2003;42:1808–10.
2. Wulsin LR, Singal BM. Do depressive symptoms increase the risk for the onset of coronary disease? A systematic quantitative review. Psychosom Med 2003;65:201–10.
3. Major outcomes in moderately hypercholesterolemic hypertensive patients randomized to pravastatin vs usual care: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). JAMA 2002;288:2998–3007.

REPLY

We welcome rejoinders to our editorial (1) by Carney et al. and Pickering et al. The precise nature of the association between depression and cardiac mortality in myocardial infarction (MI) patients and, in particular, whether it is a causal association, is an important public health matter; thus, we are grateful that our arguments have sparked debate. However, there appear to be a number of misconceptions in these responses as to our purpose in writing the editorial and, indeed, in what we were trying to say.

Pickering and colleagues accuse us of being "inappropriately pessimistic." This they ascribe to our failure to consider prospective observational studies of depression in participants initially free of cardiac disease, focusing instead solely on studies of depression (and anxiety) in MI patients. The results from the latter, they readily concede, afford a "weak" case for a causal association between depression and cardiac mortality. Studies in initially disease-free populations were simply beyond the scope of our editorial and the brief given us. We would agree with Pickering et al. that the data from such studies are somewhat more persuasive (2). We would, however, make two points here. First, there are sufficient instances where risk factors for mortality vary between disease-free and diseased populations to suggest that caution is warranted in generalizing from one to the other. Second, confounding cannot be summarily dismissed as a possible explanation of the association between depression and cardiac mortality in studies of initially disease-free participants; confounding always has to be considered as a potential explanation in observational epidemiological research (3). We also appreciate that it can be difficult on occasion to distinguish between confounders and mediators. This is one of the reasons why experimental evidence is so critical (4). What we are arguing is that the data to date do not preclude the possibility that depression after MI may not be a cause, however mediated, of cardiac mortality, and for the reasons articulated above, it is not at all clear to us how prospective observational studies in initially disease-free populations will help resolve this issue.

Furthermore, we were not asserting, as Carney et al. seem to suggest, that depression is not an identified risk factor for cardiac mortality after MI. What we are questioning, as we had hoped that we had made plain, is whether depression is an *independent* risk factor (i.e., a fundamental cause of cardiac mortality) so that successful intervention for depression would improve survival after MI. Based on the available evidence at this juncture, particularly the results of the ENRICHD study, the one substantial published randomized controlled trial (RCT) (5), it seems to us that the parsimonious conclusion is that the independence of depression still remains to be established. Moreover, we would submit these null results from ENRICHD should cause us to pause and consider alternative explanations for the pattern of results that have emerged from observational epidemiological studies.

Carney et al. argue that the equivalence of outcome in the ENRICHD trial between the intervention and usual care groups most likely reflected the modest, albeit statistically significant, between-group differences in depression post-intervention, and they chide us as to whether we would dismiss cholesterol as a risk factor on the basis of an ineffectual cholesterol-lowering drug. Clearly we would not: but this is because there is now strong experimental evidence from elsewhere implicating cholesterol (e.g., 6). However, there was a time earlier in the history of cholesterol research when the risk status of cholesterol was controversial and it was perfectly appropriate to be skeptical (7). Likewise, we would be among the first to shift our position on the nature of depression as a risk for mortality after MI were positive experimental data to become available. We have addressed the interpretation by Carney et al. of the results of the ENRICHD ancillary study elsewhere (8). Here we would simply make the point that correlational and experimental data are not evidentially equivalent.

Because both Carney et al. and Pickering et al. use cholesterol research as a metaphor, we should point out that other, possibly more apposite, analogies could be drawn. For example, consider the cautionary tale of hormone replacement therapy (HRT). That HRT was apparently protective against cardiac disease was demonstrated in numerous prospective observational studies. Indeed, the authors of a meta-analysis of these