Depression and coronary artery disease: time to move from observation to trials

François Lespérance, Nancy Frasure-Smith

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Over the past decade, evidence has accumulated to suggest that depression may be a risk factor for cardiac mortality in patients with established coronary artery disease (CAD), as well as in previously healthy individuals. The authors of several excellent review papers have concluded that the evidence supporting the impact of depression is strong.[1–3] Most published, prospective studies have documented a marked association between different measures of depression and objective cardiac outcomes in patients with different clinical presentations of CAD, and usually this link has been demonstrated to be independent of traditional cardiac risk factors. Some recent studies have reported a dose–response relation between severity of depression symptoms and prognosis.[4–6] Also, there are plausible biological mechanisms that could account for the association.[7] Further investigation is needed to evaluate the possibility that depression may be caused by vascular disease of the brain (the vascular depression hypothesis[8]) or that both depression and CAD share common biological pathways such as subchronic inflammation[9] or reduced levels of omega-3–free fatty acids.[10]

Despite the weight of accumulated evidence, it is premature to say that depression is causally related to cardiac mortality. Indeed, in contrast to earlier evidence, 3 recent studies,[11,12] including the one by Claude Lauzon and colleagues reported in this issue (page 547),[13] have not found an association between depression and mortality. However, the sample sizes for all 3 of these studies were insufficient to draw conclusions about the absence of risk. Recent improvements in survival rates for patients with CAD due to the more widespread use of early revascularization procedures, statins and angiotensin-converting-enzyme (ACE) inhibitors have had consequences not only for the sample sizes needed in clinical trials (we are now in the era of megatrials), but also for epidemiological studies designed to evaluate risk factors. For example, in the research by Lauzon and colleagues, although the sample was large, the 1-year postdischarge mortality rate was only 3.8%. (Causes of death are not described, and in-hospital mortality is included in the 1-year results.) Based on our calculations, this means that the study's observed power of 80% was sufficient to detect only a relative risk greater than 3 for overall mortality. Thus, despite the high prevalence of depression, this study cannot exclude the possibility that depression may be associated with a more than doubling in risk of postdischarge cardiac mortality.

We also have to consider that, in addition to the recent decrease in mortality rates for patients with CAD, the link between depression and cardiac mortality may be diminished with current treatments, particularly the use of statins. If we compare the rates of prescription of statins, β-blockers, ACE inhibitors, ASA and revascularization procedures between 1991–1994 (when our data were collected[4]) and 1996–1998 (when the study by Lauzon and colleagues was carried out), we find a major shift in the use of statins in secondary prevention after myocardial infarction. There are reasons to believe that depression may both contribute to, and be a consequence of, the inflammatory process in CAD. Statins are known to have anti-inflammatory properties.[14] Therefore, if the inflammation hypothesis of depression is true, statins might be particularly effective in blocking any relation between depression and CAD.

In addition to the fact that it is premature to state that depression is causally related to cardiac mortality, we also cannot assert that a reduction in depression (the risk) lowers cardiac mortality (the disease). Only clinical trials can determine whether or not this is the case, and only 1 controlled trial has been designed so far to target the treatment of depression as a means of improving prognosis, namely, the ENRICHD trial. The results, presented at the 2001 American Heart Association Annual Meeting,[15] showed that cognitive–behavioral psychotherapy was ineffective in reducing mortality from all causes and recurrence of nonfatal myocardial infarctions. There are other treatments for depression that should be properly evaluated, particularly those selective serotonin reuptake inhibitors (SSRIs) with a low risk of drug interactions.

Given the success of currently available treatments for acute coronary syndromes, how big an increase in risk is needed to justify conducting large trials to try to further improve cardiac prognosis? Are risks between 1.5 and 2.5 important enough? Do they justify launching a megatrial with an SSRI? We believe that they do. The independent risk associated with depression in patients with CAD appears to be at least as important as smoking, hypertension or diabetes[4] and, for this reason, may be of enough clinical significance to constitute a target for improving prognosis, particularly given the number of patients with CAD affected by depression.

Many studies in the last 10 years have documented a high prevalence of major depression and elevated depres-

sive symptoms in patients with CAD, and the study by Lauzon and colleagues confirms these results. We can safely say that about 1 in 3 patients admitted to hospital for CAD shows some degree of depression and that this is true for patients after myocardial infarction,[16,17] with unstable angina[18] or congestive heart failure,[19] and after catheterization[20] or coronary artery bypass surgery.[21] This level of depression is far above that seen in random community samples, where over a 1-year period at most 1 in 10 people is affected with major depression and a smaller number have more minor forms of the illness.[22] Moreover, Lauzon and colleagues confirm that it is not a transitory phenomenon. At least following myocardial infarction, rates remain high as long as 1 year after discharge.[17] It is undeniable that depression is painful and that it should be treated to improve quality of life. However, even here, the paucity of efficacy trials in depressed patients with CAD puts clinicians in a difficult situation. Only 1 large trial, SADHART,[23] has been published so far, and the reported efficacy of sertraline is not impressive.

Until better designed and powered clinical trials of treatments for depression in patients with CAD are completed, clinicians are left with a probable risk (depression) and a definite correlate (poor quality of life), but no evidence-based guidelines to modify either. This leads us to conclude that in the last 10 years, although epidemiological studies of depression and related risks have continued to accumulate, there has not been any major progress in our field. Lauzon and collagues believe that we need yet another large observational study to assess more accurately the risks associated with depression. We already know that depression is highly prevalent in patients with CAD, and there is evidence that it is likely to increase risk of mortality, but we do not know what to do about it. Guidance will come only from experimental trials.

Our lack of information about effective treatments is due in part to the fact that pharmaceutical companies have been reluctant to risk billions of dollars in sales on the possibility of proving that antidepressants can also reduce cardiac events, when such studies would also involve the possibility of finding an increase in cardiac events or cardiac side effects. The financial and logistic challenges of conducting a properly designed and powered randomized controlled trial of depression treatment with the goal of improving prognosis in patients with CAD are considerable: such a trial would probably require more than 6000 depressed patients with CAD and would almost certainly require the cooperation of industry, government and academic and community medicine. We believe it is time to concentrate on this goal.

Dr. Lespérance is with the Department of Psychiatry, Centre Hospitalier de l'Université de Montréal, and Dr. Frasure-Smith is with the Department of Psychiatry, McGill University, and the Montreal Heart Institute Research Center, Montréal, Que.

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Correspondence to: *Dr. François Lespérance, Department of Psychiatry, Centre hospitalier de l'Université de Montréal, 3840 Saint-Urbain St., Montréal QC H2W 1T8; fax 514 412-7196; francois.lesperance@umontreal.ca*