Published in final edited form as:
J Am Coll Cardiol. 2013 February 12; 61(6): 631–634. doi:10.1016/j.jacc.2012.11.029.

Targeting lifestyle change in patients with depression

James A. Blumenthal, PhD
Department of Psychiatry and Behavioral Sciences, Duke University Medical Center

Depression is widely recognized as being important for both mental and physical health. More than one in five of adults suffer from major depression (MDD) at some point in their lifetimes, and estimates are even higher for patients with coronary heart disease (CHD). Approximately 20% of patients suffer from MDD following a myocardial infarction and an additional 20% may experience elevated depressive symptoms without meeting diagnostic criteria for MDD. Depression is associated with poorer quality of life and increased medical expenditures and healthcare utilization. In addition, depression is one of the leading sources of disability in the United States and is associated with greater absenteeism and missed time at work. According to the World Health Organization, depression is the second leading cause of disability adjusted life years, following only CHD.

There also is a growing literature that has documented the association of depression with adverse health outcomes, particularly in patients with CHD. Numerous studies from multiple research teams have reported that depression is associated with a 2- to 4-fold increase in risk for death and non-fatal CHD events among patients with a variety of cardiac conditions including recent myocardial infarction, coronary disease requiring surgical revascularization, stable and unstable angina, and chronic heart failure[1–3]. As a result of these findings, the American Heart Association commissioned a Scientific Advisory Panel to evaluate the risk with depression in CHD patients[4]. While recognizing that there was no direct evidence that screening for depression leads to improved outcomes, the Panel concluded that because of the overwhelming evidence for the association of depression with worse prognosis, assessment of depression was important with the goal of "targeting those most in need of treatment and support services."

One of the most critical issues now facing clinicians is how to best treat depressed patients. Current recommendations for depression treatment typically involve pharmacotherapy, usually with a selective serotonin reuptake inhibitor (SSRI), although treatments with tricyclic antidepressants, benzodiazepines, and combined therapies are also prescribed. It has been estimated that approximately 50% of patients will have a clinical 'response' to treatment (i.e., a 50% reduction in symptoms), whereas many patients will require augmented treatment with more than one antidepressant agent[5]. However, many patients do not respond to antidepressant medications or experience untoward side effects. Indeed, although data are limited, results from a several randomized controlled trials of antidepressants in cardiac patients have provided negative or equivocal findings. For example, the SADHART trial was a randomized, double-blind, placebo-controlled, 24-week trial of sertraline for MDD among patients hospitalized for acute myocardial infarction[6]. Improvement in depressive symptoms among participants treated with sertraline was observed only in a subset of patients with more severe depression; there was no difference between sertraline and placebo in the full sample. The study was not powered to examine clinical outcomes. A second study (the SADHART-CHF trial) confirmed the safety of

Address for correspondence: Dr. James Blumenthal, Box 3119, Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, NC 27710, telephone: (919) 684-3828, fax: (919) 684-8629; Blume003@mc.duke.edu.

sertraline among patients with chronic heart failure, but sertraline did not reduce depressive symptoms any more than placebo[7]. Moreover, participants treated with sertraline had no better clinical outcomes compared to those receiving placebo. The MIND-IT study failed to demonstrate improvement in either depressive symptoms or cardiac outcomes with antidepressant treatment[8]. In one of the few positive trials, the CREATE study[9] reported that depressive symptoms and remission rates were improved with citalopram compared to placebo, whereas no differences in depressive symptoms were observed between patients receiving interpersonal therapy and clinical management compared to patients receiving clinical management alone. The sample was too small to examine clinical outcomes, however. Meta analyses of randomized, controlled trials of anti-depressant medications in cardiac patients generally have observed no significant differences between antidepressant medication and placebo controls, but the authors encouraged the use of antidepressant drugs because non-randomized trials showed greater benefits with medication[10,11].

One of the problems in developing effective interventions for depression in cardiac patients is that the mechanisms underlying the association between depression and worse outcomes are not fully understood. A number of potentially interrelated of biobehavioral pathways have been studied, albeit often individually. Depressive symptoms have been linked to autonomic nervous system dysregulation, vascular endothelial dysfunction, abnormal inflammatory processes, and maladaptive health behaviors[12]. The Heart and Soul study noted that among a variety of health behaviors, physical inactivity was especially important[13]. Furthermore, there is mounting evidence that patients who exhibit a worsening of depression over time appear to be at especially increased risk for death or other adverse outcomes including non-fatal MI or cardiac-related hospitalizations[14,15]. It remains unclear whether depression is causally related to worse outcomes or whether depression is simply a marker for more severe CHD or some other factor associated with worse outcomes.

In this issue of the *Journal*, Ye and colleagues[16] seek to examine this question by studying prospectively the relationship between depressive symptoms and non-fatal myocardial infarction or all-cause mortality in a subset of participants in the REGARDS (Reasons for the Geographic And Racial Differences in Stroke) study. REGARDS is a population-based, longitudinal study of 30,000 African-American and white men and women ≥ 45 years designed to determine the reasons for the higher incidence of stroke mortality in the southeastern “stroke belt” region of the United States and among African Americans[17]. Individuals were identified from commercially available lists of residents and were recruited using an initial mailing followed by telephone screening calls. The present study was limited to 4,676 participants with a history of CHD at baseline and complete data. Over a median follow up period of 3.8 years, 125 of 638 (19.6%) participants with elevated depressive symptoms experienced a clinical event compared to 657 of 4038 (16.3%) participants without elevated depressive symptoms. After adjustment for medical comorbidities, medications, and lifestyle factors, the association of depression and worse clinical outcomes was no longer statistically significant, and the authors emphasized the importance of lifestyle factors in explaining the prognostic value of depression and CHD, and in guiding intervention efforts to reduce the elevated risk of depression in cardiac patients.

The authors are to be congratulated for their contribution to the literature with this interesting analysis of a large and important dataset. Several important limitations of the study should be acknowledged, however. As with many substudies in which the variables under investigation are of secondary importance to the parent study, the assessment measures were not optimal and only a limited number of potential mediators were examined. Depression was assessed by a seldom used, 4-item self-report measure of depressive symptoms that may not accurately classify depression in all patients, while the four behavioral factors relied on brief measures of self-reported alcohol use, medication

adherence, smoking, and physical activity. This lack of precision may help to explain the lower-than-expected rates of depression in this CHD population and also some unexpected results, such as trends for better outcomes in patients with high alcohol consumption and poor medication adherence. Smoking and physical activity explained a substantial proportion of the association of depression and the combined endpoint of MI and death, leading the authors to recommend smoking cessation and increasing physical activity in this population.

These lifestyle recommendations should come as little surprise to readers of the *Journal*. Cigarette smoking is not uncommon in patients with MDD[18], and patients who continue to smoke, despite having CHD, may be engaged in a highly maladaptive effort to treat their depression. Similarly, a number of cross sectional and observational studies have shown that physical inactivity is associated with depression. For example, in the Alameda County Study, Camacho and colleagues[19] measured subjects' activity level and depressive symptoms in 1965, 1974, and 1983. Compared to men and women who reported higher activity levels, those who were inactive at baseline were at greater risk for higher depression scores at the first follow-up. Participants who increased their physical activity level between 1965 and 1974, however, were at no greater risk for depression in 1983 than those who were active throughout the period. Conversely, those who became more inactive by 1974 were more likely to have higher depression scores in 1983 than those maintaining a high level of physical activity.

The effect of exercise on depression now has been examined in over two dozen randomized trials, and has been the topic of several meta-analyses and systematic reviews[20,21]. Existing studies vary substantially in size, type of control group, methodological rigor, length of follow-up, and even the type of exercise modality. In a recent Cochrane review[20], the primary analyses were limited to those trials comparing exercise treatment with no treatment or a control intervention (n = 25). There were large, clinically meaningful improvements in depressive symptoms associated with exercise in comparison with controls (standardized mean difference [SMD] = −0.82 (95% CI −1.12 to −0.51), which was somewhat diminished when the analyses were further limited to those trials using intention-to-treat analyses and blinded outcome assessments. In addition, when analyses were conducted among the five trials that collected long-term follow-up data, the effects of treatment were again slightly weaker, consistent with a moderate clinical improvement (SMD −0.44, 95% CI −0.71 to −0.18). However, in three randomized trials[22–24], including a recent trial of 101 CHD patients[24], exercise training resulted in significant reductions in depressive symptoms that were greater than placebo and comparable, or even superior, to antidepressant medications. A recent substudy from the HF-ACTION trial[25] also found exercise to be superior to guideline-based, usual care in reducing depressive symptoms in over 2,300 HF patients.

So what is the take home message? The term "cardiovascular vulnerable patient" has been used to describe patients susceptible to acute coronary events based upon plaque, blood, or myocardial characteristics.[26,27] It has become clear that depression is one of those characteristics that also increases the vulnerability of CHD patients to adverse events. In their report, Ye and colleagues[16] provide support for the prognostic importance of elevated depressive symptoms in CHD patients. Moreover, by identifying smoking and physical inactivity as mediators of this relationship, they remind us of the importance of promoting healthy lifestyle changes, and specifically smoking cessation and exercise training, to improve clinical outcomes in this vulnerable population.

Acknowledgments

Supported by a grant HL080664 from the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD. Thanks are also extended to Drs. Andrew Sherwood and Alan Hinderliter for their comments on an earlier draft of this manuscript.

REFERENCES

1. Barth J, Schumacher M, Herrmann-Lingen C. Depression as a risk factor for mortality in patients with coronary heart disease: a meta-analysis. Psychosomatic medicine. 2004; 66(6):802–813. [PubMed: 15564343]
2. Lett HS, Blumenthal JA, Babyak MA, et al. Depression as a risk factor for coronary artery disease: evidence, mechanisms, and treatment. Psychosomatic medicine. 2004; 66:304–315.
3. van Melle JP, de Jonge P, Spijkerman TA, et al. Prognostic association of depression following myocardial infarction with mortality and cardiovascular events: a meta-analysis. Psychosomatic medicine. 2004 Nov-Dec;66(6):814–822. [PubMed: 15564344]
4. Lichtman JH, Bigger JT Jr, Blumenthal JA, et al. AHA science advisory. Depression and coronary heart disease. Recommendations for screening, referral, and treatment. A science advisory from the American Heart Association Prevention Committee to the Council on Cardiovascular Nursing, Council on Clinical Cardiology, Council on Epidemiology and Prevention, and Interdisciplinary Council on Quality of Care Outcomes Research. Endorsed by the American Psychiatric Association. Prog Cardiovasc Nurs. 2009 Mar; 24(1):19–26. [PubMed: 19261139]
5. Olfson M, Marcus SC, Druss B, Elinson L, Tanielian T, Pincus HA. National trends in the outpatient treatment of depression. JAMA : the journal of the American Medical Association. 2002 Jan 9; 287(2):203–209. [PubMed: 11779262]
6. Glassman AH, O'Connor CM, Califf RM, et al. Sertraline treatment of major depression in patients with acute MI or unstable angina. JAMA : the journal of the American Medical Association. 2002 Aug 14; 288(6):701–709. [PubMed: 12169073]
7. O'Connor CM, Jiang W, Kuchibhatla M, et al. Safety and efficacy of sertraline for depression in patients with heart failure: results of the SADHART-CHF (Sertraline Against Depression and Heart Disease in Chronic Heart Failure) trial. J Am Coll Cardiol. 2010 Aug 24; 56(9):692–699. [PubMed: 20723799]
8. van Melle JP, de Jonge P, Honig A, et al. Effects of antidepressant treatment following myocardial infarction. Br J Psychiatry. 2007 Jun.190:460–466. [PubMed: 17541103]
9. Lesperance F, Frasure-Smith N, Koszycki D, et al. Effects of citalopram and interpersonal psychotherapy on depression in patients with coronary artery disease: the Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy (CREATE) trial. JAMA : the journal of the American Medical Association. 2007 Jan 24; 297(4):367–379. [PubMed: 17244833]
10. Pizzi C, Rutjes AW, Costa GM, Fontana F, Mezzetti A, Manzoli L. Meta-analysis of selective serotonin reuptake inhibitors in patients with depression and coronary heart disease. Am J Cardiol. 2011 Apr 1; 107(7):972–979. [PubMed: 21256471]
11. Mazza M, Lotrionte M, Biondi-Zoccai G, Abbate A, Sheiban I, Romagnoli E. Selective serotonin reuptake inhibitors provide significant lower re-hospitalization rates in patients recovering from acute coronary syndromes: evidence from a meta-analysis. J Psychopharmacol. 2010 Dec; 24(12): 1785–1792. [PubMed: 19965939]
12. de Jonge P, Rosmalen JG, Kema IP, et al. Psychophysiological biomarkers explaining the association between depression and prognosis in coronary artery patients: a critical review of the literature. Neurosci Biobehav Rev. 2010 Sep; 35(1):84–90. [PubMed: 19962401]
13. Whooley MA, de Jonge P, Vittinghoff E, et al. Depressive symptoms, health behaviors, and risk of cardiovascular events in patients with coronary heart disease. JAMA : the journal of the American Medical Association. 2008 Nov 26; 300(20):2379–2388. [PubMed: 19033588]
14. Carney RM, Blumenthal JA, Freedland KE, et al. Depression and late mortality after myocardial infarction in the Enhancing Recovery in Coronary Heart Disease (ENRICHD) study. Psychosomatic medicine. 2004 Jul-Aug;66(4):466–474. [PubMed: 15272090]

15. Sherwood A, Blumenthal JA, Trivedi R, et al. Relationship of depression to death or hospitalization in patients with heart failure. Archives of Internal Medicine. 2007; 167(4):367–373. [PubMed: 17325298]

16. Ye S, Muntner P, Shimbo D, et al. Behavioral mechanisms, elevated depressive symptoms, and the risk for myocardial infraction or death in indidviduals with coronary heart disease (A reason for geographic and racial differences in stroke [REGARDS] study. JACC. 2012 in press.

17. Howard VJ, Cushman M, Pulley L, et al. The reasons for geographic and racial differences in stroke study: objectives and design. Neuroepidemiology. 2005; 25(3):135–143. [PubMed: 15990444]

18. Glassman AH, Helzer JE, Covey LS, et al. Smoking, smoking cessation, and major depression. JAMA : the journal of the American Medical Association. 1990 Sep 26; 264(12):1546–1549. [PubMed: 2395194]

19. Camacho TC, Roberts RE, Lazarus NB, Kaplan GA, Cohen RD. Physical activity and depression: evidence from the Alameda County Study. Am J Epidemiol. 1991 Jul 15; 134(2):220–231. [PubMed: 1862805]

20. Mead GE, Morley W, Campbell P, Greig CA, McMurdo M, Lawlor DA. Exercise for depression. Cochrane Database Syst Rev. 2009; (3):CD004366. [PubMed: 19588354]

21. Lawlor DA, Hopker SW. The effectiveness of exercise as an intervention in the management of depression: systematic review and meta-regression analysis of randomised controlled trials. BMJ. 2001 Mar 31; 322(7289):763–767. [PubMed: 11282860]

22. Blumenthal JA, Babyak MA, Moore KA, et al. Effects of exercise training on older patients with major depression. Archives of Internal Medicine. 1999; 159(19):2349–2356. [PubMed: 10547175]

23. Blumenthal JA, Babyak MA, Doraiswamy PM, et al. Exercise and pharmacotherapy in the treatment of major depressive disorder. Psychosomatic medicine. 2007; 69:587–596. [PubMed: 17846259]

24. Blumenthal JA, Sherwood A, Babyak MA, et al. Exercise and Pharmacological Treatment of Depressive Symptoms in Patients With Coronary Heart Disease: Results From the UPBEAT (Understanding the Prognostic Benefits of Exercise and Antidepressant Therapy) Study. J Am Coll Cardiol. 2012 Sep 18; 60(12):1053–1063. [PubMed: 22858387]

25. Blumenthal JA, Babyak MA, O'Connor C, et al. Effects of exercise training on depressive symptoms in patients with chronic heart failure: the HF-ACTION randomized trial. JAMA : the journal of the American Medical Association. 2012 Aug 1; 308(5):465–474. [PubMed: 22851113]

26. Naghavi M, Libby P, Falk E, et al. From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment strategies: Part I. Circulation. 2003; 108(14):1664–1672. [PubMed: 14530185]

27. Naghavi M, Libby P, Falk E, et al. From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment strategies: Part II. Circulation. 2003; 108(15):1772–1778. [PubMed: 14557340]