Published in final edited form as:
Circulation. 2009 July 14; 120(2): 99–100. doi:10.1161/CIRCULATIONAHA.109.881987.

Is it time to treat Depression in cardiovascular disease?

William Whang, MD, MS and **Karina W. Davidson, PhD**
Department of Medicine, Columbia University College of Physicians and Surgeons (Drs Whang and Davidson)

Depression has been associated with worse cardiovascular prognosis in individuals with heart disease, particularly among patients with established coronary heart disease,[1] but also among patients with heart failure.[2,3] We can now add to this list those patients with the confluence of heart failure and atrial fibrillation. In this issue of Circulation, Frasure-Smith and colleagues[4] evaluate the relationship between depression and cardiovascular mortality among individuals with both heart failure and atrial fibrillation in an analysis from the AF-CHF Trial.[5] In the main trial, which was a multicenter randomized study conducted across 4 continents, a strategy of rhythm control in patients with atrial fibrillation and heart failure with left ventricular ejection fraction ≤0.35 was comparable to a rate control strategy. The group of patients studied was at particularly high risk given the presence of atrial fibrillation, which is independently associated with mortality in patients with heart failure.[6–9]

Frasure-Smith and colleagues found that 32 percent of the 974 patients who completed the Beck Depression Inventory II reported at least mild to moderate symptoms of depression, which is comparable to the proportion of patients with depressive symptoms in other studies of patients with heart failure.[2,3,10] Slightly fewer than half of the patients in both the depressed and non-depressed groups had an ischemic cause for their cardiomyopathy. Of note, there were several differences at baseline that indicated worse cardiac disease severity among those with depressive symptoms. Depressed patients were more likely to have heart failure symptoms more severe than New York Heart Association functional class 2, to have been hospitalized for heart failure, and to be taking aldosterone antagonists. Although the authors point out that left ventricular ejection fraction was similar between the two groups, it nonetheless seems likely that heart failure was more severe among the depressed patients. Despite adjustment for these differences and numerous other possible confounders, the presence of depressive symptoms was associated with higher risk of cardiac mortality (hazard ratio 1.57, 95% CI 1.20 – 2.07) during average follow-up of 37 months. It is noteworthy that multivariable adjustment did not significantly attenuate the hazard ratio estimates when compared with the unadjusted analyses, indicating in this new patient population, the independent risk imparted by depressive symptoms.

Interestingly, depressive symptoms were associated with arrhythmic death (hazard ratio 1.69, 95% CI 1.13 – 2.53) in multivariable analyses, and arrhythmic death comprised approximately half of the cardiac deaths in the depressed group. Also, there was no detectable interaction between depression symptoms and treatment assignment to rate or rhythm control, implying that amiodarone therapy did not significantly affect the risk of arrhythmic death for the depressed patients. There is growing evidence to implicate ventricular arrhythmia as an important mode of death in individuals with depression and

Corresponding Author: Karina W. Davidson, PhD, Department of Medicine, Columbia University College of Physicians and Surgeons, 622 W 168th St, PH9 Center, Room 948, New York, NY 10032 (kd2124@columbia.edu); phone: 212-342-4493; fax: 212-342-3431.

Disclosures: None

heart disease. Depression has been associated with shock for ventricular arrhythmia in patients with implantable cardioverter-defibrillators (ICDs),[11] and with ventricular arrhythmia among patients with coronary artery disease.[12] In addition, a prior study from Frasure-Smith, et al., demonstrated a particularly high risk of death among post-myocardial infarction patients with depression and ventricular arrhythmia defined by frequent ventricular premature complexes according to 24-hour continuous ambulatory ECG monitoring.[13]

In a group of patients with this degree of disease severity, it is more difficult to contend with the issue of reverse causality than in a group in whom there is no overt cardiac disease. That is, individuals with worse heart failure may have greater tendency to develop depression as well as worse prognosis primarily due to their heart failure. The authors performed multiple adjustments for many possible confounders, including left ventricular ejection fraction and heart failure class, but the possibility of unmeasured confounders exists. Another limitation that the authors acknowledge is lack of information about antidepressant medication use, which could be important if confounding by indication has occurred.

There are also a number of questions that are raised by this unique study. About 8 percent of the patients in this study had an ICD; a future study could test if the association between depression and arrhythmic death holds in ICD patients. Prior anti-arrhythmic therapy had been more frequently prescribed in the depressed group, indicating a possible higher arrhythmia burden among the patients with depressive symptoms; so yet another follow-up study could test if depression confers increased risk of incident atrial fibrillation, or of more persistent forms of atrial fibrillation. In this group of patients with excellent rates of optimal medical therapy, including beta blockers, angiotensin converting-enzyme inhibitors, and anticoagulation, what therapies can be implemented to reduce the high cardiac mortality risk associated with depression?

This analysis adds a high-risk group to the diverse set of populations in whom depression has been shown to predict poor cardiac prognosis. There is a wealth of evidence to characterize depression as a risk factor for cardiac mortality, with relative risk that is arguably comparable to that associated with more physiologic measures such as heart failure symptomatology. The American Heart Association has published an advisory recommending screening for depression among individuals with coronary heart disease with a 2 question screening instrument,[14,15] and we would suggest that active consideration of the approach to patients with heart failure be enacted as well, as depression often remains unrecognized and untreated in these patients.[16]

The study by Frasure-Smith et al. is a valuable addition to the literature and highlights the challenge of developing treatment strategies that can reduce the cardiac mortality risk attributable to depression. This is a challenge that we suspect will require further investigation into defining the depressive phenotype,[17] as well as into the different potential mechanisms by which cardiovascular risk is conferred.[18] Randomized trials of therapy such as SADHART-CHF,[19] whose final results we await, will point us in a direction but we likely require many more trials before clinical guidelines can be developed for treating these comorbid conditions. Successfully treating depression is difficult; successfully treating depression in the context of heart failure and atrial fibrillation presents challenges for all of us; patient, clinician, and scientist.

References

1. Frasure-Smith N, Lesperance F. Recent evidence linking coronary heart disease and depression. Can J Psychiatry. 2006; 51:730–737. [PubMed: 17168247]

2. Rutledge T, Reis VA, Linke SE, Greenberg BH, Mills PJ. Depression in heart failure a meta-analytic review of prevalence, intervention effects, and associations with clinical outcomes. J Am Coll Cardiol. 2006; 48:1527–1537. [PubMed: 17045884]
3. Rumsfeld JS, Jones PG, Whooley MA, Sullivan MD, Pitt B, Weintraub WS, Spertus JA. Depression predicts mortality and hospitalization in patients with myocardial infarction complicated by heart failure. Am Heart J. 2005; 150:961–967. [PubMed: 16290972]
4. Frasure-Smith N, Lesperance F, Habra M, Talajic M, Khairy P, Dorian P, Roy D. Elevated Depression Symptoms Predict Long-term Cardiac Events in Patients with Atrial Fibrillation and Heart Failure. Circulation. In press.
5. Roy D, Talajic M, Nattel S, Wyse DG, Dorian P, Lee KL, Bourassa MG, Arnold JM, Buxton AE, Camm AJ, Connolly SJ, Dubuc M, Ducharme A, Guerra PG, Hohnloser SH, Lambert J, Le Heuzey JY, O'Hara G, Pedersen OD, Rouleau JL, Singh BN, Stevenson LW, Stevenson WG, Thibault B, Waldo AL. Rhythm control versus rate control for atrial fibrillation and heart failure. N Engl J Med. 2008; 358:2667–2677. [PubMed: 18565859]
6. Wang TJ, Larson MG, Levy D, Vasan RS, Leip EP, Wolf PA, D'Agostino RB, Murabito JM, Kannel WB, Benjamin EJ. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: the Framingham Heart Study. Circulation. 2003; 107:2920–2925. [PubMed: 12771006]
7. Olsson LG, Swedberg K, Ducharme A, Granger CB, Michelson EL, McMurray JJ, Puu M, Yusuf S, Pfeffer MA. Atrial fibrillation and risk of clinical events in chronic heart failure with and without left ventricular systolic dysfunction: results from the Candesartan in Heart failure-Assessment of Reduction in Mortality and morbidity (CHARM) program. J Am Coll Cardiol. 2006; 47:1997–2004. [PubMed: 16697316]
8. Lehto M, Snapinn S, Dickstein K, Swedberg K, Nieminen MS. Prognostic risk of atrial fibrillation in acute myocardial infarction complicated by left ventricular dysfunction: the OPTIMAAL experience. Eur Heart J. 2005; 26:350–356. [PubMed: 15618041]
9. Zareba W, Steinberg JS, McNitt S, Daubert JP, Piotrowicz K, Moss AJ. Implantable cardioverter-defibrillator therapy and risk of congestive heart failure or death in MADIT II patients with atrial fibrillation. Heart Rhythm. 2006; 3:631–637. [PubMed: 16731460]
10. Jiang W, Kuchibhatla M, Clary GL, Cuffe MS, Christopher EJ, Alexander JD, Califf RM, Krishnan RR, O'Connor CM. Relationship between depressive symptoms and long-term mortality in patients with heart failure. Am Heart J. 2007; 154:102–108. [PubMed: 17584561]
11. Whang W, Albert CM, Sears SF Jr, Lampert R, Conti JB, Wang PJ, Singh JP, Ruskin JN, Muller JE, Mittleman MA, Investigators TS. Depression as a predictor for appropriate shocks among patients with implantable cardioverter-defibrillators: results from the Triggers of Ventricular Arrhythmias (TOVA) study. J Am Coll Cardiol. 2005; 45:1090–1095. [PubMed: 15808769]
12. Watkins LL, Blumenthal JA, Davidson JR, Babyak MA, McCants CB Jr, Sketch MH Jr. Phobic anxiety, depression, and risk of ventricular arrhythmias in patients with coronary heart disease. Psychosom Med. 2006; 68:651–656. [PubMed: 17012517]
13. Frasure-Smith N, Lesperance F, Talajic M. Depression and 18-month prognosis after myocardial infarction. Circulation. 1995; 91:999–1005. [PubMed: 7531624]
14. Lichtman JH, Bigger JT Jr, Blumenthal JA, Frasure-Smith N, Kaufmann PG, Lesperance F, Mark DB, Sheps DS, Taylor CB, Froelicher ES. Depression and coronary heart disease: recommendations for screening, referral, and treatment: a science advisory from the American Heart Association Prevention Committee of the Council on Cardiovascular Nursing, Council on Clinical Cardiology, Council on Epidemiology and Prevention, and Interdisciplinary Council on Quality of Care and Outcomes Research: endorsed by the American Psychiatric Association. Circulation. 2008; 118:1768–1775. [PubMed: 18824640]
15. Whooley MA, Simon GE. Managing depression in medical outpatients. N Engl J Med. 2000; 343:1942–1950. [PubMed: 11136266]
16. Koenig HG. Recognition of depression in medical patients with heart failure. Psychosomatics. 2007; 48:338–347. [PubMed: 17600171]
17. Goodman J, Shimbo D, Haas DC, Davidson KW, Rieckmann N. Incident and recurrent major depressive disorder and coronary artery disease severity in acute coronary syndrome patients. J Psychiatr Res. 2008; 42:670–675. [PubMed: 17709116]

18. Carney RM, Freedland KE, Miller GE, Jaffe AS. Depression as a risk factor for cardiac mortality and morbidity: a review of potential mechanisms. J Psychosom Res. 2002; 53:897–902. [PubMed: 12377300]

19. Jiang W, O'Connor C, Silva SG, Kuchibhatla M, Cuffe MS, Callwood DD, Zakhary B, Henke E, Arias RM, Krishnan R. Safety and efficacy of sertraline for depression in patients with CHF (SADHART-CHF): a randomized, double-blind, placebo-controlled trial of sertraline for major depression with congestive heart failure. Am Heart J. 2008; 156:437–444. [PubMed: 18760123]