Depression has been associated with worse cardiovascular prognosis in individuals with heart disease, particularly among patients with established coronary heart disease but also among patients with heart failure.\(^1\)\(^2\) 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 Atrial Fibrillation and Congestive Heart Failure (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 \(\leq 0.35\) 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.\(^6\)\(^–\)\(^9\)

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Frasure-Smith and colleagues found that 32% 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 nondepressed groups had an ischemic cause for their cardiomyopathy. Of note, several differences at baseline 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 2 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 a higher risk of cardiac mortality (hazard ratio, 1.57; 95% confidence interval, 1.20 to 2.07) during an average follow-up of 37 months. It is striking that multivariable adjustment did not significantly attenuate the hazard ratio estimates compared with the unadjusted analyses, indicating in this new patient population the independent risk imparted by depressive symptoms.

Depressive symptoms were associated with arrhythmic death (hazard ratio, 1.69; 95% confidence interval, 1.13 to 2.53) in multivariable analyses, and arrhythmic death made up approximately half of the cardiac deaths in the depressed group. In addition, 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. Growing evidence implicates ventricular arrhythmia contributory to death in individuals with depression and heart disease. Depression has been associated with shock for ventricular arrhythmia in patients with implantable cardioverter-defibrillators\(^11\) and with ventricular arrhythmia among patients with coronary artery disease.\(^12\) In addition, a prior study from Frasure-Smith et al\(^13\) 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.

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 with no overt cardiac disease. That is, individuals with worse heart failure may have a greater tendency to develop depression and a worse prognosis primarily because of their heart failure. Another limitation that the authors acknowledge is a lack of information about antidepressant medication use, which could be important if confounding by indication has occurred.

This unique study raises a number of questions. About 8% of the patients in this study had an implantable cardioverter-defibrillator; a future study could test whether the association between depression and arrhythmic death holds in implantable cardioverter-defibrillator patients. Prior antiarrhythmic therapy had been prescribed more frequently in the depressed group, indicating a possible higher arrhythmia burden among the patients with depressive symptoms, so yet another follow-up study could test whether depression confers an 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. A wealth of evidence characterizes depression as a risk factor for cardiac mortality, with a relative risk that is arguably comparable to that associated with more physiological 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.\textsuperscript{14,15} We suggest that active consideration of the approach to depressed patients with heart failure be undertaken as well because depression often remains unrecognized and untreated in these patients.\textsuperscript{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. We suspect that this challenge requires further investigation into defining the depressive phenotype\textsuperscript{17} and into the different potential mechanisms by which cardiovascular risk is conferred.\textsuperscript{18} Randomized trials of therapy such as Safety and Efficacy of Sertraline for Depression in Patients With CHF (SADHART-CHF),\textsuperscript{19} the final results of which are forthcoming, will point us in a direction, but many more trials will likely be required 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.

**Disclosures**

None.

**References**


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Is It Time to Treat Depression in Patients With Cardiovascular Disease?
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