Jason Ricco, MD, MPH; Janice Benson, MD; Shailendra Prasad, MBBS, MPH
University of Minnesota North Memorial Family Medicine Residency Program, Minneapolis (Drs. Ricco and Prasad); Department of Family Medicine, University of Chicago/NorthShore University HealthSystem, Ill (Dr. Benson)

DEPUTY EDITOR
Anne Mounsey, MD
Department of Family Medicine, University of North Carolina, Chapel Hill

SSRIs for depression/heart failure patients? Not so fast

This study should put to rest the practice of starting SSRIs in depressed patients with heart failure in an attempt to affect CVD outcomes.

PRACTICE CHANGER

Do not prescribe selective serotonin reuptake inhibitors to improve depression and reduce cardiovascular risk in patients with congestive heart failure.

STRENGTH OF RECOMMENDATION

B: Based on one large randomized controlled trial.

Angermann CE, Gelbrick G, Störk S, et al, for the MOOD-HF Study Investigators and Committee Members. Effect of escitalopram on all-cause mortality and hospitalization in patients with heart failure and depression. The MOOD-HF randomized clinical trial. *JAMA*. 2016;315:2683-2693.[1]

ILLUSTRATIVE CASE

A 60-year-old man comes to your office for a follow-up visit to talk about his congestive heart failure. He has New York Heart Association Class III heart failure with a left ventricular ejection fraction of 30%. You notice that he is downcast, and after evaluation, including a score of 17 on a self-administered 9-item Patient Health Questionnaire (PHQ-9), you determine that he is having a concomitant major depressive episode. Should you start him on a selective serotonin reuptake inhibitor (SSRI)?

Depression is widely recognized as an independent risk factor for both the development of cardiovascular disease (CVD), as well as adverse outcomes in patients with known CVD.[2-5] Previous studies have identified poor health behaviors as the primary underlying mechanisms linking depression and the risk of CVD.[2,6] Conversely, a recent systematic review suggests that positive constructs—mediated primarily through lifestyle behaviors—may have a protective effect on CVD outcomes.[7]

As a result, researchers have focused on the treatment of depression to improve CVD outcomes in recent years, including in patients with heart failure. While some randomized studies have shown that SSRIs are a safe and effective treatment for depression in patients with coronary disease, they have not demonstrated improvement in CVD outcomes.[8,9] However, a post hoc analysis of the ENRICHD (Enhancing Recovery in Coronary Heart Disease) trial did suggest that SSRI treatment may improve mortality and morbidity post-myocardial infarction.[10]

The prevalence of depression among patients with heart failure ranges from 10% to 40%, depending on disease severity.[11] Depression is associated with worse quality of life, poorer treatment adherence, and higher rates of rehospitalization among patients with heart failure, and is an independent predictor of mortality in this patient population.[1] Until recently, only one randomized controlled trial (RCT), the SADHART-CHF (Sertraline Against Depression and Heart Disease in Chronic Heart Failure) study, looked at treatment with SSRIs in patients with heart failure and depression.[12] In this trial, sertraline, when compared with placebo, did not improve depression or CVD outcomes over 12 weeks, but the study period may have been insufficiently long to capture the impact on long-term outcomes.

STUDY SUMMARY

SADHART-CHF, but better

In the MOOD-HF (The effects of selective serotonin re-uptake inhibition on morbidity, mortality, and mood in depressed heart failure patients) study, investigators sought to determine whether SSRI treatment for depression in patients with heart failure could improve CVD outcomes over a longer study period (up to 24 months).[1] Specifically, this RCT assessed whether treatment with escitalopram vs placebo could reduce the increased morbidity and mortality risk in patients with comorbid chronic systolic heart failure and depression.

This double-blind, placebo-controlled trial was conducted at 16 tertiary medical centers in Germany between 2009 and 2014. Adult patients established at heart failure clinics with New York Heart Association class II to IV heart failure and left ventricular ejection fractions <45% were screened for depression using the PHQ-9. Individuals with PHQ-9 scores ≥12 underwent a structured psychiatric interview with a psychiatrist or psychosomatic specialist. Those who received a diagnosis of major depression were invited to participate in the trial. Patients with recent SSRI use and/or psychotherapy were excluded from participation.

Eligible participants were randomized to receive either escitalopram (10-20 mg/d) or placebo for up to 24 months in addition to standard heart failure care. The starting dose of 5 mg was increased to 10 to 20 mg as tolerated until week 12 of the study; the dose at 12 weeks was considered the maintenance dose. Psychiatric and medical assessments were performed every 6 months during the study period. Depression severity was assessed using the 10-item Montgomery-Åsberg Depression Rating Scale (MADRS).

Outcomes. The primary study outcome was time to a first event of the composite of all-cause death or hospitalization. Secondary outcomes included MADRS score at 12 weeks, anxiety as assessed by the Generalized Anxiety Disorder 7-item scale (GAD-7), and health-related quality of life (QoL) as assessed by the Kansas City Cardiomyopathy Questionnaire (KCCQ). The sample size was calculated to achieve 80% power for the primary outcome. Baseline characteristics between the intervention and placebo groups were balanced after randomization, and the modified intention-to-treat study population included participants who took at least one dose of the study medication.[1]

Results. Ultimately, 372 participants were included in the analysis (185 in the escitalopram group and 187 in the placebo group). A primary endpoint event occurred in 116 participants (63%) in the escitalopram group and in 119 participants (64%) in the placebo group (hazard ratio [HR]=0.99; 95% confidence interval [CI], 0.76 to 1.27]; *P*=.92).[1] No differences were found between treatment groups for the primary endpoints in either adjusted or unadjusted analyses.

The mean (SD) MADRS score changed from 20.2 (8.6) at baseline to 11.2 (8.1) at 12 weeks with escitalopram and from 21.4 (8.8) to 12.5 (7.6) in the placebo group (between-group difference = -0.9; 95% CI, -2.6 to 0.7; *P* =.26).[10] Overall, participants in the 2 treatment groups had comparable daily doses of study medications, as well as mean treatment duration (18 months), and both groups demonstrated partial remission of depression symptoms over the study period, as well as improved health status and QoL as measured by KCCQ.

Interestingly, QoL as assessed by the KCCQ symptom score was significantly improved in the placebo group at 12 months.[1] There were no between-group differences in adverse events or safety measures.[1] The trial was discontinued prematurely on February 28, 2014, based on futility after a recommendation from the data and safety monitoring committee.

Using SSRIs for depression treatment to affect chronic disease outcomes that are likely lifestyle-related may not be cost-effective or patient-centered.

WHAT'S NEW

Longer study period/different SSRI doesn't change earlier finding

The MOOD-HF trial directly addresses the major criticism of the SADHART-CHF trial by looking at SSRI treatment of patients with heart failure and depression over a much longer study duration (up to 24 months vs 12 weeks). Also, in contrast to SADHART-CHF, this trial studied escitalopram, rather than sertraline, because some evidence indi-

cates that escitalopram is superior at treating primary depression.[13] Despite these differences, the results of MOOD-HF are consistent with the findings of SADHART-CHF: treating patients with both heart failure and depression with an SSRI did not improve the elevated morbidity and mortality risk seen with these comorbid conditions.

Also consistent with SADHART-CHF findings, participants in both groups in the MOOD-HF trial had partial remission of depressive symptoms over the study period, with no significant difference between those treated with escitalopram vs placebo. Given that this high-quality trial, with a much longer treatment period and a possibly more effective SSRI, replicated the findings of SADHART-CHF, the results of MOOD-HF should put to rest the practice of initiating SSRI treatment in depressed patients with heart failure in an attempt to affect CVD outcomes.

Although there are other SSRIs besides escitalopram and sertraline, it is likely that this is a class effect.

CAVEATS

There are other SSRI fish in the sea

There are other SSRIs, besides escitalopram and sertraline, available for use. However, it is likely that this is a class effect.

Additionally, none of the patients in this trial had severe depression, as their PHQ-9 scores were all below 19. Therefore, it remains to be determined if treating patients with severe depression has an impact on cardiovascular outcomes.

Lastly, and most importantly, this study only looked at screening patients for depression and initiating SSRIs in the setting of heart failure. The trial did not include patients already taking SSRIs for pre-existing depression. Thus, the results do not imply evidence for discontinuing SSRIs in patients with heart failure.

Treating comorbid depression and CVD to improve the elevated risk for adverse clinical outcomes remains nuanced and elusive. In fact, the same can be said of non-CVD chronic conditions—such as diabetes—based on recent systematic reviews.[13] The summation of these studies suggests that a traditional screen-and-treat approach utilizing SSRIs for depression treatment to affect chronic disease outcomes (that are likely lifestyle-related) may not be cost-effective or patient-centered.

The publication of a recent study showing that cognitive behavioral therapy did improve depression—but not heart failure—among patients with both conditions[14] reaffirms that teasing out the impact of depression on lifestyle behaviors and chronic disease outcomes among multimorbid patients is more complex than previously thought. Nevertheless, this is an area of research that should continue to be explored, given the obvious increased risk for poorer chronic disease outcomes in the presence of depression.

CHALLENGES TO IMPLEMENTATION

Changing the tide can be difficult

As with any behavior change among providers, we expect that it will be a challenge to convince providers to stop screening for depression and initiating treatment with an SSRI to affect CV outcomes in patients with heart failure. This is especially so given the body of evidence for depression as a risk factor for increased morbidity and mortality in this population. **JFP**

ACKNOWLEDGEMENT

The PURLs Surveillance System was supported in part by Grant Number UL1RR024999 from the National Center For Research Resources, a Clinical Translational Science Award to the University of Chicago. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Center For Research Resources or the National Institutes of Health.

References

1. Angermann CE, Gelbrich G, Störk S, et al, for the MOOD-HF Study Investigators and Committee Members. Effect of escitalopram on all-cause mortality and hospitalization in patients with heart failure and depression. The MOOD-HF randomized clinical trial. *JAMA*. 2016;315:2683-2693.
2. Sin NL, Kumar AD, Gehi AK, et al. Direction of association between depression and lifestyle behaviors in patients with coronary heart disease: the heart and soul study. *Ann Behav Med*. 2016;50:523-532.
3. Lett HS, Blumenthal JA, Babyak MA, et al. Depression as a risk factor for coronary artery disease: evidence, mechanisms, and treatment. *Psychosom Med*. 2004;66:305-315.
4. Whooley MA, Wong JM. Depression and cardiovascular disorders. *Annu Rev Clin Psychol*. 2013;9:327-354.
5. Barth J, Schumacher M, Herrmann-Lingen C. Depression as a risk factor for mortality in patients with coronary heart disease: a meta-analysis. *Psychosom Med*. 2004;66:802-813.
6. 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*. 2008;300:2379-2388.

7. DuBois CM, Lopez OV, Beale EE, et al. Relationships between positive psychological constructs and health outcomes in patients with cardiovascular disease: a systematic review. *Int J Cardiol*. 2015;195:265-280.
8. Glassman AH, O'Connor CM, Califf RM, et al, for the Sertraline Antidepressant Heart Attack Randomized Trial (SADHART) Group. Sertraline treatment of major depression in patients with acute MI or unstable angina. *JAMA*. 2002;288:701-709.
9. Writing Committee for the ENRICHD Investigators. Effects of treating depression and low perceived social support on clinical events after myocardial infarction: the Enhancing Recovery in Coronary Heart Disease Patients (ENRICHD) randomized trial. *JAMA*. 2003;289:3106-3116.
10. Taylor CB, Youngblood ME, Catellier D, et al, for the ENRICHD Investigators. Effects of antidepressant medication on morbidity and mortality in depressed patients after myocardial infarction. *Arch Gen Psychiatry*. 2005;62:792-798.
11. Rutledge T, Reis VA, Linke SE, et al. 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.
12. O'Connor CM, Jiang W, Kuchibhatla M, et al, SADHART-CHF Investigators. 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;56:692-699.
13. Health Quality Ontario. Screening and management of depression for adults with chronic diseases: an evidence-based analysis. *Ont Health Technol Assess Ser*. 2013;13:1-45.
14. Freedland KE, Carney RM, Rich MW, et al. Cognitive behavior therapy for depression and self-care in heart failure patients: a randomized clinical trial. *JAMA Intern Med*. 2015;175:1773-1782.