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CLINICAL RESEARCH | Clinical Trial

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

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Objectives The objective was to test the hypothesis that heart failure (HF) patients treated with sertraline will have lower depression scores and fewer cardiovascular events compared with placebo.

Background Depression is common among HF patients. It is associated with increased hospitalization and mortality.

Methods The SADHART-CHF (Sertraline Against Depression and Heart Disease in Chronic Heart Failure) trial was a randomized, double-blind, placebo-controlled trial of sertraline 50 to 200 mg/day versus matching placebo for 12 weeks. All participants also received nurse-facilitated support. Eligible patients were age 45 years or older with HF (left ventricular ejection fraction ≤45%, New York Heart Association functional class II to IV) and clinical depression (Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition criteria for current major depressive disorder). Those with significant cognitive impairment, psychosis, recent alcohol or drug dependence, bipolar or severe personality disorder, active suicidal ideation, and current antipsychotic or antidepressant medications were excluded. Primary end points were change in depression severity (Hamilton Depression Rating Scale total score) and composite cardiovascular status at 12 weeks.

Results A total of 469 patients were randomized (n = 234 sertraline, n = 235 placebo). The mean ± SE change from baseline to 12 weeks in the Hamilton Depression Rating Scale total score was −7.1 ± 0.5 (sertraline) and −6.8 ± 0.5 (placebo) ($p < 0.001$ from baseline, $p = 0.89$ between groups, mean change between groups −0.4; 95% confidence interval: −1.7 to 0.92). The proportions whose composite cardiovascular score worsened, improved, or was unchanged were 29.9%, 40.6%, and 29.5%, respectively, in the sertraline group and 31.1%, 43.8%, and 25.1%, respectively, in the placebo group ($p = 0.78$).

Conclusions Sertraline was safe in patients with significant HF. However, treatment with sertraline compared with placebo did not provide greater reduction in depression or improved cardiovascular status among patients with HF and depression. (Antidepressant Medication Treatment for Depression in Individuals With Chronic Heart Failure [SADHART-CHF]; NCT00078286) (J Am Coll Cardiol 2010;56:692–9) © 2010 by the American College of Cardiology Foundation

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Heart failure (HF) is prevalent in both the U.S. and Europe. An estimated 5.7 million Americans have HF (1), and there are at least 15 million patients with HF in the 51 countries represented by the European Society of Cardiology (2). HF is a major cause of death and disability. Despite extensive therapeutic advances in pharmacologic and device therapies for HF, morbidity and mortality remain high in this population (3).

Depression is common in HF, with a reported prevalence of 21.5% (4), and it is one of many factors that contribute to poor outcome in HF patients (5–8). Depression has been independently associated with a poor quality of life, limited functional status, and an increased risk of morbidity and mortality in this population (4,9–13).

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Small studies have demonstrated improvements in depressive symptoms and quality of life and decreases in heart rate and plasma norepinephrine in HF patients treated with antidepressants (14,15). Selective serotonin reuptake inhibitors (SSRIs) have been shown to inhibit platelet function, promote endothelial stabilization, and possess anti-inflammatory properties, although the clinical relevance of these properties has yet to be established (16–24). These pharmacologic properties have led to the hypothesis that SSRIs may be associated with cardiovascular benefits beyond their antidepressant effects. SSRIs have been shown to improve depression scores without adverse cardiovascular effects in several studies conducted in patients with acute myocardial infarction, unstable angina, or stable coronary artery disease (25,26). These data suggested that the safety profile of sertraline was adequate to permit testing in the HF population. The objective of the SADHART-CHF (Sertraline Against Depression and Heart Disease in Chronic Heart Failure) trial was to evaluate the safety and efficacy of sertraline in patients with depression and HF.

Methods

The SADHART-CHF trial was a randomized, double-blind trial of sertraline or placebo in 469 participants with HF and clinical depression. The study was conducted at 3 centers in the United States between August 13, 2003, and March 3, 2008. The protocol was reviewed and approved by the appropriate institutional review board for each center. All participants provided written, voluntary informed consent.

Eligibility criteria. A complete description of the trial methodology was published (27). Briefly, patients 45 years of age or older with a left ventricular ejection fraction ≤45% (within the previous 6 months), New York Heart Association (NYHA) functional class II to IV HF symptoms, and major depressive disorder (as determined by Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition criteria) were eligible to participate. HF was confirmed at the time of presentation by clinical HF specialist cardiologists. The main exclusion criteria included significant cognitive impairment, alcohol or drug dependence within the previous year, psychoses, bipolar disorder, severe personality disorder, active suicidal ideation, life-threatening comorbidity (estimated 50% mortality within 1 year), and current use of antipsychotic or antidepressant medications.

Abbreviations and Acronyms

HDRS = Hamilton Depression Rating Scale

HF = heart failure

NYHA = New York Heart Association

SSRI = selective serotonin reuptake inhibitor

Study design. The SADHART-CHF trial tested the hypothesis that sertraline would improve symptoms of depression and reduce cardiac events and morbidity/mortality in HF patients with clinical depression to a greater extent than placebo. Eligible participants were randomized 1:1 to sertraline or matching placebo for the 12-week treatment period. The initial dose was 50 mg/day and was increased in 50-mg/day increments based on the results of the Beck Depression Inventory total score and the clinical opinion of the examining investigator to a maximum of 200 mg/day. For patients who were unable to tolerate higher doses, the dose could be decreased. The minimum dose was 50 mg/day. Participants were categorized as completers if they completed 12 weeks of study drug and assessment at the end of the 12-week intervention, and noncompleters if they discontinued study drug before 12 weeks. All participants, regardless of whether they completed the 12-week treatment period, were included in all analyses as described in the statistical analysis section.

All participants also received nurse-facilitated support, designed to build rapport and trust with the study participants, ascertain compliance with the study protocol, re-evaluate depression status, monitor suicidal ideation, and consult with study physicians on appropriate patient management. Support was provided by nurses and other study personnel with previous experience or training in clinical psychiatry, and they conducted interviews with the study participants by telephone at 2, 4, 8, and 10 weeks and during in-clinic or home visits at 6 and 12 weeks. Participants were also screened for suicidal ideation. The 17-item Hamilton Depression Rating Scale (HDRS) was completed at baseline and at 2-week intervals during the 12-week treatment phase.

All participants were referred to their primary care physician or a psychiatrist for follow-up as indicated after the initial 12-week period. All participants were followed via phone or mail to ascertain clinical events and vital status every 2 weeks during the 12-week treatment phase and at 6 months, 1 year, and annually thereafter until the last participant completed at least 6 months of follow-up. The national death index was used to ascertain vital status of participants who could not be reached via phone or mail.

Primary end points. The primary end points of the study were change across time in the severity of depression