Published in final edited form as:

Am J Cardiol. 2011 February 15; 107(4): 545–551. doi:10.1016/j.amjcard.2010.10.013.

Characteristics of Depression Remission and Its Relation with Cardiovascular Outcome among Patients with Chronic Heart Failure (From the SADHART-CHF Study)

Wei Jiang, MD^{a,b}, Ranga Krishnan, MD^b, Maragatha Kuchibhatla, PhD^c, Michael S. Cuffe, MD^a, Carolyn Martsberger, PhD^b, Rebekka M Arias, BS^d, and Christopher M. O'Connor, MD^a for the SADHART-CHF Investigators

^aDepartment of Medicine, Duke University Medical Center, Durham, NC

^bDepartment of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, NC

^cCenter for Aging, Duke University Medical Center, Durham, NC

^dDuke Clinical Research Institute, Durham, NC

Abstract

Depression is prevalent among heart failure (HF) patients, and is associated with a significant increase in hospitalizations and death. Primary results of the SADHART-CHF (Sertraline Against Depression and Heart Disease in Chronic HF) trial revealed that sertraline and placebo had comparable effects on depression and cardiovascular outcomes. In this study, we explore whether remission from depression is associated with better survival and to characterize participants who remitted during the trial. Based on the depression response during the 12-week treatment phase, SADHART-CHF participants were divided into 2 groups: 1) remission, defined as participants whose last measured Hamilton Depression Rating Scale (HDRS) score was <8; 2) non-remission, defined as participants whose last measured HDRS score was ≥8. Patients who dropped out prior to having any repeat HDRS were not included. Baseline characteristics and survival differences up to 5 years were evaluated between the remission and the non-remission groups. Of the 469 SADHART-CHF participants, 208 (44.3%) achieved remission, 194 (41.4%) remained depressed, and 67 (14.3%) dropped out or died without any repeat HDRS assessment. Patients in the remission group had significantly lower cardiovascular events than those in the non-remission group (1.34±1.86 vs. 1.93±2.71; $P_{adjusted}=0.01$). Male patients were more likely to remit than female patients (56.5 vs. 44.8%, $p=0.02$). The remission group had milder depressive symptoms at baseline compared to the non-remission group (HDRS: 17.0±5.4 vs. 19.6±5.5; Beck Depression Inventory scale: 17.9±6.5 vs. 20.3±7.2; $ps<0.001$). In conclusion, this study indicates that remission from depression may improve the cardiovascular outcome of HF patients.

© 2010 Excerpta Medica, Inc. All rights reserved.

Corresponding Author: Wei Jiang, MD, Associate Professor of Psychiatry & Behavioral Sciences, Associate Professor of Medicine, Duke University Medical Center, DUMC Box 3366, Durham, NC 27710, Office: 919-668-0762, Fax: 919-668-5271, jiang001@mc.duke.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Trial Registration: NCT00078286 (clinicaltrials.gov)

Keywords

Depression remission; heart failure; prognosis

INTRODUCTION

Depression is a common and well-documented co-morbidity among patients with heart failure (HF)¹⁻². It is associated with substantial morbidity and mortality, as well as lower quality of life and functional status²⁻⁹. The adverse relationship of depression and HF is independent of HF etiology and other conventional risk factors. Sertraline appeared to be safe in depressed HF patients¹⁰; however, it did not demonstrate any superiority over placebo for depression and HF survival in the SADHART-CHF (Sertraline Against Depression and Heart Disease in Chronic HF) trial¹⁰. Recently, Carney and Glassman et al. each reported that patients with ischemic heart disease whose depression significantly improved during the study periods that was not necessarily related to the trial intervention had better survival than those patients whose depression persisted¹¹⁻¹². Whether this phenomenon applies to HF patients is unknown. This study therefore aimed to explore if remission is associated with better cardiovascular outcome of HF patients with major depressive disorder (MDD) and to examine characteristics that may differentiate patients whose depression remitted from ones whose depression remained during the trial.

METHODS

The SADHART-CHF database was used for this analysis. The detailed methodology of the SADHART-CHF trial has been previously published^{10,13}. SADHART-CHF was a randomized, double-blind study of sertraline versus matching placebo in patients with HF and co-morbid major depression. In addition, all participants received nurse facilitated support (NFS). The primary endpoints of the SADHART-CHF trial were change across time in the severity of depression as measured by the Hamilton Depression Rating Scale (HDRS) total score, and the change in the composite cardiovascular status^{10,13}. The protocol was reviewed and approved by the local institutional review board at each participating center, and all participants provided written, voluntary, informed consent prior to enrollment.

SADHART-CHF trial patient were randomized 1:1 to sertraline 50 mg/day or matched placebo for a 12-week acute treatment phase. Study drug dose was titrated up in 50 mg/day increments every 2 weeks with the maximum dose of 200 mg/day, depending on the severity of depressive symptoms and tolerability of participants to the study drug. Participants who were unable to tolerate the 50 mg daily dose were allowed to remain in the study provided a minimum 25 mg daily dose was tolerated. The study medication was tapered off after the 12-week acute treatment phase. All participants, regardless of acute phase completion, entered into the long-term follow-up phase and were contacted at 6 months, 12 months, and annually thereafter to evaluate clinical events and vital status. The long-term follow-up phase continued until the last enrolled participant completed a 6-month follow-up.

All participants received NFS as a mechanism to ascertain safety and study compliance. The primary goals for the research personnel applying supportive measures were to enhance recruitment and assessment of participants, to ascertain the safety of participants, and to increase participant compliance and retention. Such support was provided by nurses and other study personnel with experience or training in clinical psychiatry, and supervised by the study psychiatrist. Supportive measures included at least 10 hours of active interaction between the research personnel and the study participants during the 12-week acute phase. The interaction consisted of 3 face-to-face visits (1 during the recruitment/baseline

assessment followed by 2 visits conducted primarily in the participants' homes) and 4 follow-up phone contacts. Research personnel aimed to provide psychological support while conducting medical and psychiatric health evaluations. Personnel were instructed to provide active and empathetic listening and validation skills, as well as soothing and other emotional support strategies. Research personnel were asked not to push for dialog with participants who were more reserved, and aimed to establish an individual interpersonal relationship with each participant.

For the present study, SADHART-CHF participants were divided into 2 groups, irrespective of treatment assignment: 1) remission, defined as participants whose last measured Hamilton Depression Rating Scale (HDRS) score was <8 ; 2) non-remission, defined as participants whose last measured HDRS score was ≥ 8 . Patients who dropped out prior to having any repeat HDRS were not included in this study.

The primary endpoint of this analysis was survival or time to death, and rate of recurrent cardiovascular events and/or death until the last follow-up. Cardiovascular events were adjudicated by a blinded clinical events committee as a component of the primary trial¹⁰. Clinical characteristics examined among these groups included effects of randomization, dosing of the study medication, and depressive symptomatology measured by HDRS and the Beck Depression Inventory (BDI) scale. Baseline depressive symptomatology was examined in three ways: 1. Severity of depression based on HDRS scores (mild ≤ 17 , moderate 18–22, and severe ≥ 23); 2. Overall HDRS and BDI score; and 3. Depressive symptom dimension i.e. cognitive/affective (item 2,3,5,6,7,8,9,12,14), somatic/affective (item 1,4,10,11,13,15,16,17,21,22), and appetitive (item 18, 19/20) based on BDI scale¹⁴. Comparative analysis of baseline characteristics was performed upon remission status with respect to the treatment assignment. Change in HDRS by remission status over the 12-week treatment period was analyzed by random coefficient models. The final model included treatment, remission status, time in weeks, and the square of time, as well as the interaction of each of these two time variables with remission status and study site. The model also included the random effects of patient, patient-by-time, and square of patient-by-time. All participants (the remission group and non-remission group) were included in the analysis. Cox-Proportional regression modeling was used to evaluate the survival differences between participants classified in the remission and non-remission groups. Data were censored at the time to death. Logistic regression analysis was used to test the differences of cardiovascular events between groups. Baseline HDRS scores, treatment assignment (sertraline or placebo), age, sex, baseline LVEF, NYHA class, ischemic etiology, and study site were included in the regression model. The assumptions of the model were assessed using standard techniques. Logistic regression was also used to determine which subsets of patients were likely to remit over the 12-week treatment phase. The investigated characteristics were sex, baseline HDRS scores (≤ 17 vs. >17), BDI scores (≤ 16 vs. >16), and somatic/affective scores (S/as) ($< S/as$ mean vs. $\geq S/as$ mean). Statistical analyses were performed by statistical personnel within Duke University Medical Center, using SAS, version 9.1 (SAS Incorporated, Cary, NC).

RESULTS

A total of 469 participants were enrolled in SADHART-CHF at Duke University Medical Center and three Duke Health System affiliates between 8/13/2003 and 3/3/2008. The primary analysis of SADHART-CHF has been previously reported¹³. Of the 469 SADHART-CHF participants, 208 (44.3%) patients had HDRS scores that improved to < 8 while 194 (41.4%) patients had a HDRS ≥ 8 at the end of 12-week intervention. There were 67 subjects (14.3%) who did not have any repeat HDRS during the 12-week acute phase intervention and were excluded from this study. These participants had greater NYHA class

HF than the other 2 groups (NYHA II 17.9 vs. 29.9, $p < 0.05$). Ten (14.9%) patients deceased prior to any repeat HDRS assessment.

The majority of the baseline characteristics were similar between the remission and the non-remission groups with respect to sertraline or placebo assignment (Table 1). More male participants remitted than female participants (64.4 vs. 53.1%, $p = 0.02$), though the differences among the groups were not statistically significant. Hospitalization due to HF exacerbation within 1 year prior to enrollment was higher among the non-remission group ($p = 0.03$) (Table 1).

The remission group had longer treatment duration time (78 ± 19 days) during the 12-week acute treatment phase than the non-remission group (73 ± 23) ($P < .001$) (Table 2). The interaction of remission by time was significant ($P = .001$) but not remission by square of time ($P = .19$). Change in HDRS total score over the course of the 12-week acute phase (i.e. time) intervention as well as the square of time were significant (time $P = .001$; square of time $P = .001$). The difference in the change of HDRS scores between the remission and the non-remission groups was statistically significant (mean $\pm$ SE -4.8 ± 0.49 ; $P = .001$). Although they remained depressed, symptoms of the non-remission group patients improved notably from baseline (mean $\pm$ SE -4.1 ± 0.33 ; $P < .001$). Of the non-remission group, 40 remained significantly depressed (HDRS total score > 17). There were no differences with these measures between treatment assignments. Doses of sertraline and placebo were significantly different between remission and non-remission groups, but there was no difference within the treatment assignment (Table 2). One hundred and twelve of the 402 participants (27.9%) dropped out during the 12-week treatment phase after providing at least 1 repeat measure of depressive symptoms. Reasons for the acute treatment phase drop out are listed in Table 3.

The average length of follow-up was 798 ± 493 days (ranging from 1–1832) for the entire study population. Patients whose depression remitted had longer survival time than those whose depression remained (866 ± 479 vs. 793 ± 483 days); however, the result of the Cox proportional regression analysis revealed that the difference of survival between the 2 groups was not statistically significant (Hazard ratio for the non-remission vs. remission groups: 1.23, 95% confidence interval: 0.95–1.59). Kaplan-Meier survival curves for the remission and the non-remission groups with respect to treatment assignment are shown in Figure 1.

There were a total of 606 cardiovascular events in the entire study population including deaths, with 230 in the remission group and 323 in the non-remission group. Table 4 summarizes the differences of various cardiovascular events between the 4 groups. Patients whose depression remitted had a smaller number of overall non-fatal cardiovascular events per participant as well as fatal and non-fatal combined cardiovascular events (mean $\pm$ SD 1.11 ± 1.79 and 1.34 ± 1.86) compared to those whose depression remained (mean $\pm$ SD 1.66 ± 2.68 and 1.92 ± 2.71). The differences were statistically significant which remained after a covariate analysis with age, sex, baseline ejection fraction, NYHA classes, ischemic etiology of HF, baseline HDRS scores, and treatment assignment ($ps < .05$). There was no association of baseline depressive symptoms and cardiovascular events (For overall non-fatal cardiovascular events, $p = 0.82$; for fatal and non-fatal combined cardiovascular events, $p = 0.88$).

Baseline HDRS and self-rated BDI scores were lower in the remission group, (HDRS 17.0 ± 5.4 , BDI 17.9 ± 6.5) than the non-remission group (HDRS 19.6 ± 5.5 , BDI 20.3 ± 7.2) ($ps < 0.001$). Further analysis of depressive symptom dimension revealed that it was the dimension of the somatic/affective symptoms measured by BDI at baseline (Table 1) that

separated the patients whose depression remitted from the ones whose depression remained ($p=0.003$). Although non-remission group had higher baseline cognitive/affective symptoms than the remission group, the difference was not statistically significant ($p=0.07$) (Table 1). The odds ratio for the 4 characteristics of remission is summarized in Table 5.

DISCUSSION

This analysis of the SADHART-CHF trial demonstrated an association of depression remission during the 12-week active intervention and significantly reduced fatal and non-fatal cardiovascular events. Such findings support the hypothesis that successful depression treatment may be associated with a cardiac benefit in HF patients. Carney et al. performed a post hoc analysis in ENRICH study to examine whether depression improvement at 6-months from baseline was associated with survival¹¹. They found that patients who were randomized into the intervention arm and remained depressed at the 6-month follow-up had significantly worse survival than those patients whose depression improved, though there was no survival difference between the intervention group and the control group. Furthermore, Glassman et al.¹² examined a 7-year survival difference between the SADHART trial participants whose depression significantly improved and whose depression remained based on Clinical Global Impression-Improvement subscale score (CGI) during the 24-week sertraline or placebo trial intervention. The authors demonstrated that depressed ischemic heart disease patients whose CGI score were reduced to 1 or 2 had significant higher survival than those patients whose CGI score >2 , irrespective of the treatment assignment.

The SADHART-CHF study design followed the traditional phase II–III clinical trial model of randomized and placebo controlled, and it focused primarily on examining differences between active treatment assignments, i.e. drug or psychotherapy, vs. placebo or usual care. Sertraline, compared to placebo, did not result in a statistically significant higher rate of remission in the SADHART-CHF study (54.1% vs. 49.5%, $P = .36$)¹⁰. Several factors may have contributed to this finding, including the placebo effect; the therapeutic impact of the NFS, or the uniqueness of co-morbid depression in HF patients. Therapeutic response to placebo has been recognized in research as well as in clinical practice^{15–16}. Several meta-analyses have demonstrated a placebo response in depression trials exceeding 50%, a finding that was particularly evident among non-published trials^{17–19}. In recent years, an increase in scientific attention to the placebo effect has yielded evidence that the effect may have a neurobiological foundation^{20–21}. However, the potential impact of the NFS on treatment response cannot be overlooked. One of the major predisposing factors for depression is a weak social support network. Persistent and negative life stressors coupled with limited supportive structures are believed to result in reduction of mental function in patients with chronic illnesses. The NFS fostered relationship may have replaced ineffective or insufficient social networks, and established an alliance that contributed to functional improvement^{22–24}. Specific evidence to support the therapeutic impact of the NFS includes the maintenance of remission in these participants after 4–6 weeks when placebo effects tend to diminish²⁵. The majority of the study population was naive to psychological and psychiatric interventions; therefore, these participants may have been innately more responsive to psychosocial supportive measures. Additionally, the fact that a large proportion of study participants had a mild baseline depression in severity (i.e. HDRS total score 8–17) at study entry may have contributed to the high remission rate for those participants. Other studies of this type had failed to demonstrate survival or prognostic benefit of active treatment compared to controls^{11,26–27}. Trials that failed to show treatment benefit of pharmacological agents hypothesized that the lack of a statistically significant difference in outcomes was due to insufficient power^{27–30}.

SADHART-CHF had a similar design to other studies in patients with heart disease and comorbid depression. In SADHART-CHF, the sample size was believed to be adequate to evaluate differences in depression and clinical outcome, however there was no benefit observed with antidepressant treatment over placebo¹⁰. In contrast, in the ENRICH trial, open label treatment of SSRIs showed a statistically significant 40% reduction in death or nonfatal MI, with a crude HR of 0.61 (95% CI, 0.41–0.90) and an adjusted HR of 0.53 (95% CI, 0.38–0.84)²⁸. In this study, because antidepressant prescription was at the discretion of the study physicians and not randomized nor controlled, the impact of the finding is controversial. Whether or not a survival benefit was associated with depression improvement was not reported in the primary analysis. However, in the subgroup analysis for ENRICH, successful treatment of depression appeared to reduce the risk of cardiovascular events¹¹.

The present findings of the SADHART-CHF studies raise several important questions, including the need to determine whose depression is easier to remit versus those who are more resistant to interventions, to examine whether or not subsets of depressed HF patients may be at higher risk for cardiovascular events, and to identify effective antidepressant(s) for this particular population. Our research indicates that male HF patients with mild depression (HDRS ≤ 17) have nearly a 2.5 fold chance to remit compared to the rest of the study population. On the other hand, patients who had greater somatic affective symptoms were less likely to remit. This data suggest that future trials testing therapeutics may need to focus on patients whose depression is more severe and do not respond to general supportive measures. This information may be useful for clinical practice as well. Nevertheless, future studies are needed to confirm the observed association between depression remission and cardiovascular outcomes. NFS appears to be a powerful therapeutic modality that results in depression remission in certain patients with HF. A more sophisticated study design, along with refinement of the support measures, will be needed to fully evaluate the effects of an NFS among patients with HF or other medical conditions. Etiology of depression in patients with cardiac disease or other chronic medical conditions may be more heterogeneous than populations studied in traditional trials that test the antidepressant efficacy. Therefore, outcome studies testing the association between depression treatment and prognosis may need to be aligned with real-world clinical practice techniques, such as employing a naturalistic approach in the acclimatization of individual differences and identifying characteristics of populations who respond differently to various anti-depressive treatments.

The results of this analysis should be interpreted in the context of limitations. This was a secondary analysis of a trial, which was originally designed to assess treatment response to sertraline vs. placebo, examining subgroups that are defined by changes in measures over the course of the trial. Therefore, any changes in depression and cardiovascular outcomes between the remission group and non-remission group may be considered to be due to pre-existing baseline characteristic differences between those who do and do not respond to sertraline or other interventional measures. Whether these participants received depression treatment after the 12-week acute phase of trial were not further evaluated, similar to the studies of Carney and Glassman^{11–12}. Although the analysis was adjusted for differences in baseline variables and baseline depression severity was not associated with the prognosis, the fact that participants who remitted had a baseline lower depressive score, especially by the self-administered test, might have reflected a sub-population who had perceived their illness milder and/or were more receptive to psycho-supportive intervention. In addition, this study had limited statistical power to evaluate survival.

Acknowledgments

The SADHART-CHF study was funded by the NIMH. The Pfizer Inc. supplied the study drug. NIMH and Pfizer Inc. did not participate in the study development, data collection, analysis, or interpretation. Dr. Wei Jiang had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Pelle AJM, Gidron YY, Szabo BM, Denollet J. Psychological predictors of prognosis in chronic heart failure. *J Card Fail.* 2008; 14:341–350. [PubMed: 18474348]
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. Jiang W, Kuchibhatla M, Clary GL, Cuffe MS, Christopher EJ, Alexander JD, Califf RM, Krishnan RR, O'Connor CM. Congestive heart failure - Relationship between depressive symptoms and long-term mortality in patients with heart failure. *Am Heart J.* 2007; 154:102–108. [PubMed: 17584561]
4. Johansson P, Dahlstrom U, Alehagen U. Depressive symptoms and six-year cardiovascular mortality in elderly patients with and without heart failure. *Scand Cardiovasc J.* 2007; 41:299–307. [PubMed: 17852786]
5. Muller-Tasch T, Peters-Klimm F, Schellberg D, Holzapfel N, Barth A, Junger J, Szecsenyi J, Herzog W. Depression is a major determinant of quality of life in patients with chronic systolic heart failure in general practice. *J Card Fail.* 2007; 13:818–824. [PubMed: 18068614]
6. Penninx B, Beekman ATF, Honig A, Deeg DJH, Schoevers RA, van Eijk JTM, van Tilburg W. Depression and cardiac mortality - Results from a community-based longitudinal study. *Arch Gen Psychiat.* 2001; 58:221–227. [PubMed: 11231827]
7. Rozzini R, Sabatini T, Frisoni GB, Trabucchi M. Depression and major outcomes in older patients with heart failure. *Arch Intern Med.* 2002; 162:362–363. [PubMed: 11822939]
8. Rumsfeld JS, Havranek E, Masoudi FA, Peterson ED, Jones P, Tooley JF, Krumholz HM, Spertus JA. Cardiovascular Outcomes Res C. Depressive symptoms are the strongest predictors of short-term declines in health status in patients with heart failure. *J Am Coll Cardiol.* 2003; 42:1811–1817. [PubMed: 14642693]
9. Vaccarino V, Kasl SV, Abramson J, Krumholz HR. Depressive symptoms and risk of functional decline and death in patients with heart failure. *J Am Coll Cardiol.* 2001; 38:199–205. [PubMed: 11451275]
10. O'Connor CM, Jiang W, Kuchibhatla M, Silva S, Cuffe M, Callwood D, Zakhary B, Stough W, Arias R, Rivelli S, Krishnan R. for the SADHART-CHF Investigators. Safety and efficacy of sertraline for depression in patients with heart failure: results of the SADHART-CHF trial. *J Am Coll Cardiol.* 2010; 56:692–699. [PubMed: 20723799]
11. Carney RM, Blumenthal JA, Freedland KE, Youngblood M, Veith RC, Burg MM, Cornell C, Saab PG, Kaufmann PG, Czajkowski SM, Jaffe AS. for the ENRICHD Investigators. Depression and late mortality after myocardial infarction in the Enhancing Recovery in Coronary Heart Disease (ENRICHD) study. *Psychosom Med.* 2004; 66:466–474. [PubMed: 15272090]
12. Glassman AH, Bigger JT, Gaffney M. Psychiatric Characteristics Associated With Long-term Mortality Among 361 Patients Having an Acute Coronary Syndrome and Major Depression Seven-Year Follow-up of SADHART Participants. *Arch Gen Psychiat.* 2009; 66:1022–1029. [PubMed: 19736359]
13. Jiang W, O'Connor C, Silva SG, Kuchibhatla M, Cuffe MS, Callwood DD, Zakhary B, Henke E, Arias RM, Krishnan R. for the SADHART-CHF Investigators. 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]
14. Linke SE, Rutledge T, Johnson BD, Vaccarino V, Bittner V, Cornell CE, Eteiba W, Sheps DS, Krantz DS, Parashar S, Merz CNB. Depressive Symptom Dimensions and Cardiovascular Prognosis Among Women With Suspected Myocardial Ischemia A Report From the National

- Heart, Lung, and Blood Institute-Sponsored Women's Ischemia Syndrome Evaluation. *Arch Gen Psychiat.* 2009; 66:499–507. [PubMed: 19414709]
15. Katz, J. *The Silent World of Doctor and Patient.* New York, New York: The Free Press; 1984.
 16. Shapiro, A.; Shapiro, E. The placebo: is it much ado about nothing?. In: Harrington, A., editor. *The placebo effect: an interdisciplinary exploration.* 1st ed.. Cambridge, MA: Harvard University Press; 1997. p. 12-36.
 17. I Kirsch GS. Listening to prozac but hearing placebo: a meta-analysis of antidepressant medication. *Prev Treat.* 1998; 1:0002a.
 18. I Kirsch TM, Scoboria A, Nicholls S. The emperor's new drugs: an analysis of antidepressant medication data submitted to the U.S. Food and Drug Administration. *Prev Treat.* 2002; 5 article ID 23 article ID 23.
 19. Khan A, Detke M, Khan SRF, Mallinckrodt C. Placebo response and antidepressant clinical trial outcome. *J Nerv Ment Dis.* 2003; 191:211–218. [PubMed: 12695731]
 20. Leuchter AF, Cook IA, Witte EA, Morgan M, Abrams M. Changes in brain function of depressed subjects during treatment with placebo. *Am J Psychiat.* 2002; 159:122–129. [PubMed: 11772700]
 21. Mayberg HS, Silva JA, Brannan SK, Tekell JL, Mahurin RK, McGinnis S, Jerabek PA. The functional neuroanatomy of the placebo effect. *Am J Psychiat.* 2002; 159:728–737. [PubMed: 11986125]
 22. Ong LML, Dehaes J, Hoos AM, Lammes FB. Doctor-Patient Communication - A Review Of The Literature. *Social Science & Medicine Soc Sci Med.* 1995; 40:903–918.
 23. Stewart MA. Effective Physician-Patient Communication And Health Outcomes - A Review. *Can Med Assoc J.* 1995; 152:1423–1433. [PubMed: 7728691]
 24. Wolfaardt UB, Reddon JR, Joyce AS. Assessing the efficacy of antidepressants: The transactional paradigm. *Med Hypotheses.* 2005; 64:1229–1236. [PubMed: 15823724]
 25. Walsh BT, Seidman SN, Sysko R, Gould M. Placebo response in studies of major depression - Variable, substantial, and growing. *Jama-J Am Med Assoc.* 2002; 287:1840–1847.
 26. Frasere-Smith N. The Montreal Heart Attack Readjustment Trial. *J Cardiopulm Rehabil.* 1995; 15:103–106. [PubMed: 8542512]
 27. Glassman AH, O'Connor CM, Califf RM, Swedberg K, Schwartz P, Bigger JT, Krishnan KRR, van Zyl LT, Swenson JR, Finkel MS, Landau C, Shapiro PA, Pepine CJ, Mardekian J, Harrison WM, Grp S. Sertraline treatment of major depression in patients with acute MI or unstable angina. *Jama-J Am Med Assoc.* 2002; 288:701–709.
 28. Berkman LF, Blumenthal J, Burg M, Carney RM, Catellier D, Cowan MJ, Czajkowski SM, DeBusk R, Hosking J, Jaffe A, Kaufmann PG, Mitchell P, Norman J, Powell LH, Raczynski JM, Schneiderman N. 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-J Am Med Assoc.* 2003; 289:3106–3116.
 29. Taylor CB, Youngblood ME, Catellier D, Veith RC, Carney RM, Burg MM, Kaufmann PG, Shuster J, Mellman T, Blumenthal JA, Krishnan R, Jaffe AS. Investigators E. Effects of antidepressant medication of morbidity and mortality in depressed patients after myocardial infarction. *Arch Gen Psychiat.* 2005; 62:792–798. [PubMed: 15997021]
 30. Van Melle JP, De Jonge P, Honig A, Schene AH, Kuyper AMG, Crijns H, Schins A, Tulner D, Van den Berg MP, Ormel J. Investigators M-I. Effects of antidepressant treatment following myocardial infarction. *Brit J Psychiat.* 2007; 190:460–466.

Figure 1. Survival by Remission and Treatment Groups

The blue line represents the patients in the remission group assigned to placebo; The red line indicates the patients who remitted assigned to sertraline; the green line represents the patients in the non-remission group who were assigned to placebo; and black line represents the patients in the non-remission group assigned to sertraline.

The non-remission group vs. the remission group unadjusted HR = 1.23 (95% CI = 0.95–1.59).

Table 1

Baseline Characteristics

Characteristics	Remission Group		Non-Remission Group		P value [*]
	Sertraline (n = 106)	Placebo (n = 102)	Sertraline (n = 90)	Placebo (n = 104)	
Age, mean (SD) (years)	63.0±9.9	61.2±9.8	61.9±10.5	62.0±11.3	.52
Male	62.3 %	66.7 %	50.0 %	55.8 %	.09
Race					.71
White	52.8 %	55.9 %	56.7 %	60.6 %	
Black	40.6 %	35.3 %	40.0 %	34.6 %	
Other	6.6 %	8.9 %	3.3 %	4.8 %	
LVEF ^a mean (SD)	31.5±8.9	29.7±10.2	32.2±9.7	29.8±10.1	.20
NYHA ^b class, No.					.56
II	32.8 %	27.5 %	32.2 %	27.9 %	
III	51.9 %	51.1 %	43.3 %	45.2 %	
IV	16.0 %	21.6 %	24.4 %	26.9 %	
Ischemic etiology	68.9 %	67.7 %	68.9 %	69.2 %	.99
≥ 1 heart failure hospitalizations in previous 12 months	57.6 %	62.4 %	52.2 %	72.1 %	.03
Prior myocardial infarction	52.8 %	44.1 %	51.1 %	43.3 %	.41
History of hypertension	93.4 %	83.3 %	87.8 %	83.7 %	.10
Hypertlipidemia	83.0 %	73.5 %	71.1 %	82.7 %	0.09
Diabetes mellitus	55.7 %	45.1 %	51.1 %	47.1 %	.43
Current smoking	32.1 %	24.5 %	24.4 %	28.9 %	.82
Prior Coronary Bypass	36.8 %	31.4 %	28.9 %	32.7 %	.69
Pacemaker	7.6 %	3.9 %	8.9 %	5.8 %	.52
Implantable Cardioverter Defibrillator	14.2 %	13.7 %	22.2 %	22.1 %	.20
Inpatient at enrollment Baseline medications	70.8 %	79.4 %	72.2 %	79.8 %	.29
Angiotensin Converting Enzyme Inhibitor	68.9 %	76.5 %	72.2 %	68.3 %	.54
Angiotensin Receptor Blocker	9.4 %	9.8 %	10.0 %	5.7 %	.67
Beta Blocker	84.9 %	84.3 %	91.1 %	83.7 %	.43
Aspirin	86.8 %	80.4 %	81.1 %	84.6 %	.57

Characteristics	Remission Group		Non-Remission Group		P value [*]
	Sertraline (n = 106)	Placebo (n = 102)	Sertraline (n = 90)	Placebo (n = 104)	
Digoxin	14.2 %	18.6 %	15.6 %	18.3 %	.79
Statin	72.6 %	65.7 %	71.1 %	69.2 %	.73
Loop diuretic	60.4 %	59.8 %	61.1 %	61.5 %	.99
Calcium channel blocker	8.5 %	4.9 %	13.3 %	10.6 %	.22
Baseline HDRS ^c , mean ± SD (range)	16.9±5.6 (6–30)	17.1±5.2 (7–30)	19.6±5.8 (5–35)	19.5±5.2 (7–33)	.0002
Depression severity (HDRS)					<.0001 [‡]
HDRS ≤17	31.6 %	30.5 %	16.4 %	21.5 %	.96 [‡]
HDRS 18–22	24.8 %	24.1 %	25.6 %	25.6 %	
HDRS ≥23	18.5 %	17.4 %	29.4 %	34.8 %	
Baseline BDI ^d , mean ± SD (range)	18.3±6.9 (9–40)	17.6±6.2 (8–34)	21.3±7.2 (9–41)	19.5±5.3 (7–40)	.0009
Depressive symptom dimension (BDI)					
Cognitive/Affective	4.4±3.7 (0–19)	4.0±3.4 (0–21)	5.5±4.0 (0–16)	4.6±4.1 (0–19)	0.7
Somatic/Affective	11.8±3.9 (5–26)	11.5±3.7 (3–21)	13.7±4.5 (4–28)	12.4±4.0 (4–24)	.003
Appetitive	2.1±1.7 (0–7)	2.0±1.8 (0–6)	2.1±1.6 (0–6)	2.4±1.9 (0–7)	.28
Antidepressant use prior to enrollment	6.6 %	4.9 %	8.9 %	8.0 %	.73
History of major depressive disorder	15.1 %	8.8 %	22.2 %	16.4 %	.08

^{*} P-values apply to differences among the four groups.

[‡] P-values here demonstrate that depression severity was significantly associated with remission status (p=<.0001), but not with treatment assignment (p=.96).

^a LVEF = left ventricular ejection fraction;

^b NYHA = New York Heart Association;

^c HDRS = Hamilton-D rating scale;

Table 2

Performance of Each Group during 12-week Acute Treatment Phase

Characteristics	Remission Group (N=208)		Non-Remission Group (N=194)		P value
	Sertraline	Placebo	Sertraline	Placebo	
Treatment Assignment	26.4%	26.4%	22.4%	25.9%	
	77.4±19.5	78.8±18.9	73.5±21.8	71.8±24.1	0.061
Days in 12-week intervention	(19–119)	(1–110)	(13–104)	(11–108)	
Dosing	64.1±30.7	65.8±29.1	112.2±57.2	108.7±55.5	<.0001
	(50–150)	(50–200)	(50–200)	(50–200)	
Last HDRS, mean (SD)	3.8±2.1	3.5±2.1	13.9±5.4	13.5±4.7	.0002
	(0–7)	(0–7)	(8–31)	(8–27)	
Last BDI, mean (SD)	4.8±3.2	4.9±3.6	13.6±7.8	12.5±7.2	.0009
	(0–16)	(0–19)	(3–41)	(2–36)	

Table 3

Reasons of Termination during the 12-Week Treatment Phase

Reasons for Termination During Acute Phase	Remission Group (n = 208 [22.5%])	Non-Remission Group (n = 194 [33.5%])	P-value
Patient withdrew	1 (0.5%)	4 (2.1%)	0.15
Patient lost to follow-up	4 (1.9%)	7 (3.6%)	.30
Side Effect	13 (6.3%)	16 (8.3%)	.44
Withdraw by study physician	5 (2.4%)	14 (7.2%)	<.02
Noncompliance	19 (9.1%)	13 (6.7%)	<.37
Death	3 (1.44%)	5 (2.58%)	0.42
Other	2 (0.9%)	6 (3.1%)	.13

Table 4

Number of Cardiovascular Events per Participant among the Groups

CV Events	Remission Group (N=208)		Non-Remission Group (N=194)	
	Sertraline	Placebo	Sertraline	Placebo
Any non-fatal cardiovascular event ^a	1.04±1.73	1.18±1.86	1.82±3.08	1.52±2.28
Acute Myocardial Infarction	0.04±0.19	0.07±0.29	0.07±0.29	0.02±0.14
Exacerbation of Heart Failure	0.42±1.05	0.57±1.40	0.88±2.02	0.70±1.34
Unstable Angina Pectoris	0.11±0.48	0.07±0.39	0.20±0.62	0.18±0.63
Arrhythmia	0.05±0.25	0.11±0.37	0.20±0.71	0.14±0.53
Syncope	0.04±0.19	0±	0.01±0.11	0.05±0.21
Stroke	0.05±0.25	0.03±0.22	0.06±0.23	0.04±0.21
Transient Ischemic Attack	0±	0±	0.02±0.15	0±
Other	0.36±0.81	0.32±0.64	0.40±0.96	0.42±0.83
Any cardiovascular event and/or death ^b	1.27±1.81	1.40±1.90	2.1±3.13	1.79±2.3

^a Adjusted *p*-value = .02;^b Adjusted *p*-value = .01 for comparisons between the remission and the non-remission groups.

Table 5

Logistic analysis assessing the baseline characteristics that best predict remission

Characteristics	Odds Ratio	95% CI
Male	1.57	1.055–2.345
Male+HDRS≤17	2.48	1.544–3.973
Male+BDI≤16	2.27	1.441–3.554
Male+Somatic/affective score≤ mean (S/as)	2.01	1.324–3.042
Male+HDRS ≤17+Somatic/affective score(S/as)≤ mean (S/as)	2.68	1.583–4.524