

Sertraline Treatment of Major Depression in Patients With Acute MI or Unstable Angina

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ALTHOUGH A CONNECTION BETWEEN mood and the heart has been a part of language and literature from antiquity, for some time scientific verification was lacking. In the mid 1970s, epidemiologists began to report consistent associations between depression and cardiovascular morbidity and mortality. Initial studies were open to criticism,¹ but in the last decade many large-scale, well-controlled studies, in which initially healthy subjects were followed up prospectively, have identified depression as a significant independent risk factor for both first myocardial infarction (MI) and cardiovascular mortality, with an adjusted relative risk in the range of 1.5 to 2.²⁻⁹ Similarly,

Context Major depressive disorder (MDD) occurs in 15% to 23% of patients with acute coronary syndromes and constitutes an independent risk factor for morbidity and mortality. However, no published evidence exists that antidepressant drugs are safe or efficacious in patients with unstable ischemic heart disease.

Objective To evaluate the safety and efficacy of sertraline treatment of MDD in patients hospitalized for acute myocardial infarction (MI) or unstable angina and free of other life-threatening medical conditions.

Design and Setting Randomized, double-blind, placebo-controlled trial conducted in 40 outpatient cardiology centers and psychiatry clinics in the United States, Europe, Canada, and Australia. Enrollment began in April 1997 and follow-up ended in April 2001.

Patients A total of 369 patients with MDD (64% male; mean age, 57.1 years; mean 17-item Hamilton Depression [HAM-D] score, 19.6; MI, 74%; unstable angina, 26%).

Intervention After a 2-week single-blind placebo run-in, patients were randomly assigned to receive sertraline in flexible dosages of 50 to 200 mg/d (n=186) or placebo (n=183) for 24 weeks.

Main Outcome Measures The primary (safety) outcome measure was change from baseline in left ventricular ejection fraction (LVEF); secondary measures included surrogate cardiac measures and cardiovascular adverse events, as well as scores on the HAM-D scale and Clinical Global Impression Improvement scale (CGI-I) in the total randomized sample, in a group with any prior history of MDD, and in a more severe MDD subgroup defined a priori by a HAM-D score of at least 18 and history of 2 or more prior episodes of MDD.

Results Sertraline had no significant effect on mean (SD) LVEF (sertraline: baseline, 54% [10%]; week 16, 54% [11%]; placebo: baseline, 52% [13%]; week 16, 53% [13%]), treatment-emergent increase in ventricular premature complex (VPC) runs (sertraline: 13.1%; placebo: 12.9%), QTc interval greater than 450 milliseconds at end point (sertraline: 12%; placebo: 13%), or other cardiac measures. All comparisons were statistically nonsignificant ($P \geq .05$). The incidence of severe cardiovascular adverse events was 14.5% with sertraline and 22.4% with placebo. In the total randomized sample, the CGI-I ($P = .049$), but not the HAM-D ($P = .14$), favored sertraline. The CGI-I responder rates for sertraline were significantly higher than for placebo in the total sample (67% vs 53%; $P = .01$), in the group with at least 1 prior episode of depression (72% vs 51%; $P = .003$), and in the more severe MDD group (78% vs 45%; $P = .001$). In the latter 2 groups, both CGI-I and HAM-D measures were significantly better in those assigned to sertraline.

Conclusion Our results suggest that sertraline is a safe and effective treatment for recurrent depression in patients with recent MI or unstable angina and without other life-threatening medical conditions.

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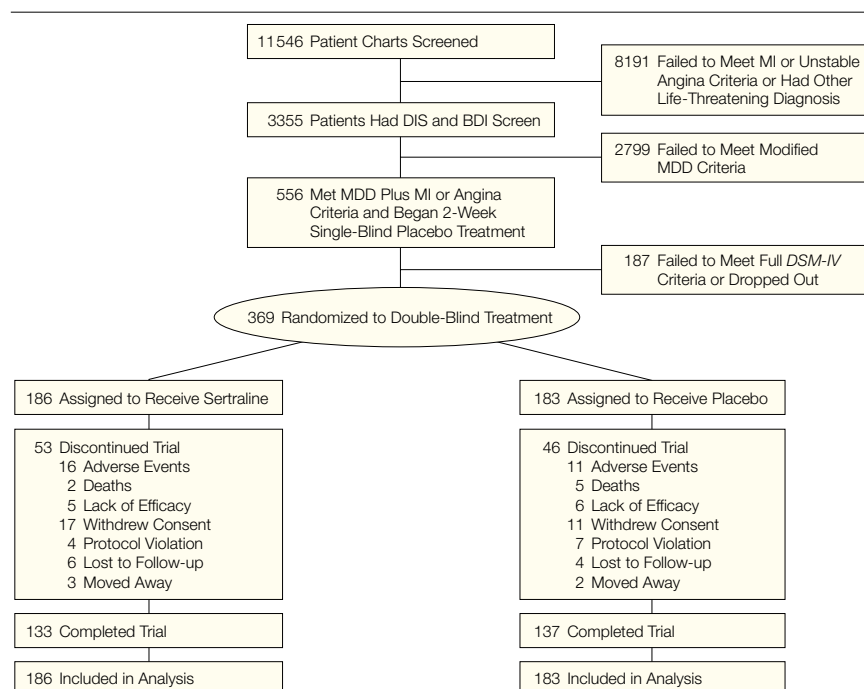
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larly, among individuals with established ischemic heart disease, depression has been found to be associated with an approximately 3- to 4-fold increase in the risk of subsequent cardiovascular morbidity and mortality.¹⁰⁻¹⁶

Author Affiliations, Financial Disclosures, and Members of the SADHART Group are listed at the end of this article.

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Figure. Flow of Patients Through the Trial

MI indicates myocardial infarction; DIS, Diagnostic Interview Schedule; BDI, Beck Depression Inventory; MDD, major depressive disorder; and *DSM-IV*, *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*.

The prevalence of major depression (major depressive disorder [MDD]) in individuals with coronary artery disease is estimated to range from 15% to 23%.^{4,10,11,14,17-20} A factor with such a large relative risk and high prevalence impacts a significant number of lives. Therefore, it is important to determine whether treating depression can reduce the associated morbidity and mortality risk. However, there is no published evidence that antidepressant drugs are either safe or efficacious in patients with unstable ischemic heart disease. In fact, there is considerable evidence that tricyclic antidepressants are potentially dangerous.²¹ Most patients with a recent MI or unstable angina and comorbid depression do not receive antidepressant treatment.²²

Accordingly, we conducted an open-label pilot study to evaluate the feasibility of conducting a controlled trial of the selective serotonin reuptake inhibitor (SSRI) sertraline as a treatment for depression in post-MI patients.²³ Because the results were

encouraging, we proceeded with a double-blind, randomized, placebo-controlled trial of the safety and efficacy of sertraline in patients diagnosed as having major depression in the immediate period after hospitalization for acute coronary syndrome (ACS), defined as either MI or unstable angina.

METHODS

Overview

The study was conducted in 40 outpatient cardiology centers and psychiatry clinics in 7 countries. Depressed patients who had been hospitalized for MI or unstable angina were randomized to 24 weeks of double-blind treatment with either sertraline or placebo (FIGURE). Enrollment began in April 1997 and follow-up ended in April 2001. This protocol was approved by each of 50 individual institutional review boards in the United States and ethics boards in Europe, Canada, and Australia.

Hospitalized patients were identified by chart review or physician referral. Those who met preliminary screening

criteria and provided written informed consent were administered the structured Diagnostic Interview Schedule (DIS)²⁴ for major depression by a trained interviewer and completed the self-rated Beck Depression Inventory (BDI).²⁵ The DIS was administered within 30 days of MI or hospitalization for unstable angina. Patients with a BDI score of 10 or greater who also met modified *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) criteria for MDD^{11,26} based on the DIS were asked to provide a second written informed consent after the treatment study was explained and their questions were answered. At screening, the DSM-IV diagnosis²⁶ did not include the requirements for duration or impairment because the interview could have occurred prior to the minimum 2-week symptom duration included in the DSM-IV criteria and because the functional impairment required for MDD is difficult to evaluate during hospitalization.

Inclusion Criteria

To qualify for study entry, male or female adults were required either to have had an acute MI or to have been hospitalized for unstable angina in the past 30 days and to be experiencing a current episode of MDD based on DSM-IV criteria. Enrollment of patients with unstable angina did not begin until July 1998.

For a diagnosis of acute MI, a patient must have met at least 1 criterion from each of the following 2 categories. Category 1 criteria were: (a) creatine kinase isoenzyme MB (CK-MB) level greater than the upper limit of normal; (b) CK or troponin T or troponin I level more than 2 times the upper limit of normal; or (c) a total lactate dehydrogenase (LDH) level more than 1.5 times the upper limit of normal (with LDH 1 greater than LDH 2). Category 2 criteria were: (a) typical ischemic symptoms (chest pain or shortness of breath) lasting for more than 10 minutes; or (b) electrocardiographic (ECG) evidence of ischemic ST-segment depression, ST-segment elevation, or new pathological Q waves.²⁷

Alternatively, patients could enter the study if they met the following criteria for unstable angina: (a) experienced angina or anginal equivalent symptoms at rest, with episodes lasting for at least 10 minutes and leading to hospitalization, and had ECG documentation of transient ST-segment elevation or depression of more than 0.5 mm, or had T-wave inversion of greater than 1 mm within 12 hours of an episode of chest pain; or (b) were hospitalized for symptoms of unstable angina and had known coronary artery disease with a documented history of a prior MI, had undergone a prior revascularization procedure, or had documented coronary artery stenosis greater than 75% in one of the major epicardial vessels.²⁸

Exclusion Criteria

Cardiovascular. Cardiovascular reasons for exclusion were (a) uncontrolled hypertension (systolic blood pressure >180 mm Hg or diastolic blood pressure >100 mm Hg); (b) cardiac surgery anticipated during the next 6 months; (c) index MI or unstable angina developed less than 3 months after coronary artery bypass graft procedure; (d) resting heart rate of less than 40/min (or <50/min if symptomatic or daytime sinus pauses of >3.5 seconds); (e) MI or unstable angina of non-atherosclerotic etiology (eg, anemia, cocaine use, periprocedural); or (f) Killip class III or IV status.

Other Medical. Other medical reasons for exclusion were (a) persistent clinically significant laboratory abnormalities; (b) significant renal dysfunction, hepatic dysfunction, or other significant noncardiac disease; or (c) women of childbearing potential not using adequate contraception.

Concomitant Treatment Exclusions. Concomitant treatment reasons for exclusion were (a) current use of class I antiarrhythmic medications; (b) use of reserpine, guanethidine, clonidine, or methyldopa; anticonvulsants or neuroleptics; antidepressants; or regular benzodiazepine; or (c) initiation of psychotherapy in the 3 months prior to study entry.

Psychiatric Exclusions. Psychiatric reasons for exclusion were (a) alcohol or substance abuse or dependence in past 6 months; (b) psychotic symptoms, history of psychosis, bipolar disorder, organic brain syndrome, dementia (or a Mini-Mental State Examination²⁹ score <23); or (c) significant suicide risk.

Study Design

Patients who met the study criteria enumerated above started receiving single-blind placebo for 14 days to permit time to complete pretreatment cardiovascular assessments (multiple gated acquisition [MUGA] scans and Holter recording) and to ensure that the symptoms of depression had been present for a minimum of 2 weeks (Figure). Prior to randomization, a psychiatrist repeated the DIS to verify that the patient met full criteria for MDD including 2-week duration and impairment. Some patients no longer met MDD criteria and were excluded.

Randomization was stratified by percentage of left ventricular ejection fraction (LVEF) (<30% or ≥30%) and by the presence of 2 depression severity criteria (≥2 prior episodes of depression and a current Hamilton Depression [HAM-D] scale³⁰ score ≥18). Although all patients met full *DSM-IV* criteria for MDD at randomization, the severity was frequently mild and the duration was often just over 2 weeks. Clinical experience suggests that the course of many post-MI depressions resembles that of an adjustment disorder, with high spontaneous recovery and placebo response rates. Such patients provide little information about the true efficacy of a treatment for depression. Consequently, individuals meeting the higher depression severity (HAM-D score ≥18) and 2 previous episodes of MDD were defined a priori as the group in whom efficacy would be evaluated. Epidemiologic studies have consistently shown that recurrent depression is associated with persistent depression in the year following MI.^{18,31-34} Therefore, we also examined treatment efficacy in the subset of patients having at least 1 prior episode of major depression regardless of their baseline HAM-D score.

Patients received 50 mg/d of sertraline or matching placebo for the first 6 weeks of treatment. Based on clinical response and tolerability, the dosage could be increased to 2 tablets (100 mg/d or matching placebo) at the end of week 6, to 3 tablets (150 mg/d or matching placebo) at week 10, and to the maximum dosage of 4 tablets (200 mg/d or matching placebo) at week 12. If adverse events occurred, the dosage could be reduced by 50 mg (1 tablet) at a time, as long as a minimum daily dose of 50 mg was maintained. Compliance was checked using pill counts.

Concomitant medications with clinically relevant psychotropic properties were not permitted, with the exception of chloral hydrate, which could be used intermittently for sleep at a maximum dose of 1 g if required. Patients could be removed from the study at the psychiatrist's discretion because of failure to improve despite escalating doses of medication, worsening of depression, or increasing suicidal ideation.

At the end of 24 weeks of double-blind treatment, the study was completed and patients were tapered off study medication at a rate of 50 mg/wk. If the clinician determined that there was a need for further treatment, provision was made for an appropriate referral. Some sites also made arrangements for follow-up contact at the patient's initiative and by the study team at 6 and 12 months. To ensure patient safety, an independent data and safety monitoring board (DSMB) provided study oversight.

Outcome Variables, Sample Size, and Schedule of Assessments

The protocol-defined primary outcome variable was LVEF. Based on assumptions that an LVEF change of 5% or more is clinically significant, an SD of 13.7% (as observed in previous studies), and a 25% dropout rate, 450 patients would be needed to detect a difference of 4.2% between treatments with 90% power. However, an interim blinded DSMB safety analysis found the

SD to be 9.5%, which indicated that 225 paired assessments (baseline and with medication) were needed to achieve 90% power. Baseline MUGA scans using a standardized protocol were performed prior to randomization and at the end of week 16 of treatment. Scans were read by the core laboratory at the Duke Clinical Research Institute (DCRI). Secondary safety variables consisted of heart rate, blood pressure, standard ECG, runs of ventricular premature complexes and

heart rate variability, and the occurrence of cardiovascular events, MI, stroke, severe angina, congestive heart failure, and death.

Left ventricular ejection fraction was used as the primary safety end point for several reasons. No surrogate end points have been validated in the post-MI setting. However, clinical experience with several other end points has been disappointing. In particular, ventricular arrhythmias as used in the Cardiac Ar-

rhythmia Suppression Trial (CAST)³⁵ proved to be a poor surrogate end point following MI. In contrast, left ventricular function was used in many of the early thrombolytic trials (eg, Thrombolysis in Myocardial Infarction [TIMI] trials³⁶) and has been a major component of the TIMI composite end point score. Using LVEF as an end point is appealing because LVEF is a strong predictor of clinical outcome in the post-ACS setting; drugs that reduce LVEF and left ventricular volumes over time have been associated with increased mortality; LVEF is an accepted measure of safety; although there are no data suggesting that the SSRIs suppress LVEF, the tricyclic antidepressants can suppress left ventricular function; and because it was thought that using LVEF as a primary end point would require a sample in the range of 200 to 400 patients. We believed this trial size was appropriate in going from the small pilot study that we conducted to a large morbidity/mortality trial requiring screening of thousands of patients.

Twenty-four-hour outpatient Holter ECG recordings were performed at baseline and at the end of week 16. Tapes were analyzed at the Holter Core Laboratory at Columbia University. In addition, a 12-lead ECG was performed at the screening and baseline visits and at weeks 6, 16, and 24. These were analyzed by the ECG Core Laboratory at DCRI. Interpretation of MUGA scans, Holter monitoring, and ECG records was performed by clinicians blinded to treatment assignment. Complete blood cell count, platelet count, and a full blood chemistry profile were performed at the initial screening visit and at the week 16 visit. Blood pressure, pulse rate, and adverse events were recorded at each assessment visit.

Measures of depression severity included the BDI,²⁵ obtained at screening; the 17-item HAM-D,³⁰ obtained at baseline and weeks 6, 10, and 16; and the Clinical Global Impression, Severity (CGI-S) and Improvement (CGI-I) scales,³⁷ obtained at baseline and at weeks 2, 6, 10, 16, and 24. For patients who discontinued the study prematurely (but after the first random-

Table 1. Baseline Characteristics of Patients*

	Sertraline (n = 186)	Placebo (n = 183)
Demographic Characteristics		
Age, mean (SD), y	56.8 (11.1)	57.6 (10.4)
Women, No. (%)	69 (37)	66 (36)
Race, No. (%)		
White	138 (74)	145 (79)
Black	22 (12)	26 (14)
Hispanic	26 (14)	13 (7)
Cardiac Factors		
Coronary risk factors, No. (%)		
Current smoking	50 (27)	51 (28)
Hypertension	113 (61)	126 (69)
Diabetes mellitus	58 (31)	55 (30)
Hyperlipidemia	130 (70)	122 (67)
Obesity	67 (36)	55 (30)
Body mass index, mean (SD), kg/m ²		
Men	29.8 (6.8)	28.8 (6.5)
Women	29.7 (6.6)	30.5 (6.9)
Cardiac event leading to current hospitalization, No. (%)		
MI	151 (81)	143 (78)
Unstable angina	35 (19)	40 (22)
LVEF, mean (SD), %	54 (10)	52 (13)
Killip class II or higher, No. (%)	13 (7.1)	13 (7.1)
Documented runs of ventricular premature depolarizations, No. (%)	28 (15)	37 (20)
Cardiovascular history, No. (%)		
Congestive heart failure	22 (12)	29 (16)
Prior coronary artery revascularization (CABG, PTCA)	79 (43)	77 (42)
Prior MI (excluding index MI)	80 (43)	75 (41)
Depression Characteristics		
HAM-D total score (17 items), mean (SD) [No.]		
Total randomized sample (N = 369)	19.6 (5.3) [186]	19.6 (5.4) [183]
Any recurrent depression (n = 186)	20.6 (5.1) [96]	20.8 (5.6) [90]
2 Prior episodes, plus HAM-D score ≥ 18 (n = 90)	22.9 (3.6) [50]	24.5 (4.4) [40]
Prior episodes of major depression, No. (%)		
None	89 (48)	93 (51)
1	37 (20)	38 (21)
≥ 2	60 (32)	53 (29)
Prior psychotropic treatment, No. (%)		
Total randomized sample (N = 369)	65 (35)	62 (34)
2 Prior episodes, plus HAM-D score ≥ 18	126 (68)	101 (55)

*MI indicates myocardial infarction; LVEF, left ventricular ejection fraction; CABG, coronary artery bypass graft; PTCA, percutaneous transluminal coronary angioplasty; and HAM-D, Hamilton Depression Scale.

ization visit), primary and secondary outcome assessments performed at the last visit were carried forward. Inferences regarding efficacy based on CGI-I scores extend to week 24 while inferences based on HAM-D scores extend only to week 16. Finally, a patient was considered a "responder" if a CGI-I score of 1 or 2 (very much or much improved) was achieved by study end.

Statistical Analysis

Comparability of the treatment groups at baseline was assessed using 2-way analyses of variance including effects for treatment group, study center, and treatment-by-center interaction for continuous measures and Cochran-Mantel-Haenszel tests for categorical measures. A mixed-model repeated-measures analysis of covariance was used to assess the changes in the CGI-I score and the Hamilton Total Score over the treatment period. The model used the baseline measure as a covariate, and treatment group, visit, and visit-by-treatment-group interaction as fixed effects. Cochran-Mantel-Haenszel methods were used to compare treatments with respect to responder and remitter rates. All statistical tests were 2-tailed, with statistical significance set at a .05 level. No adjustments were made for the multiplicity of tests. Statistical analyses were performed using SAS v6.12 (SAS Institute Inc, Cary, NC).

The clinical events committee (CEC), based at the DCRI, provided adjudication of all serious adverse events by physicians who were blinded to treatment assignment. The CEC-adjudicated composite end points were death or urgent rehospitalization for MI, congestive heart failure, stroke, or angina. Revascularization was not included as an end point because of the known large site-to-site and country-to-country threshold differences.

RESULTS

Baseline Clinical and Demographic Characteristics

More than 11 500 patient charts were screened to identify patients with MI or unstable angina who met eligibility cri-

teria. The Figure summarizes the disposition of patients from screening to the end of the study. After preliminary chart review, 3355 remained eligible and signed an informed consent to undergo diagnostic screening. Seventeen percent (556 individuals) met criteria for MDD and were not taking antidepressant drugs. After the 2-week placebo run-in period, 369 patients remained eligible and were randomized to study treatment. This is the intent-to-treat sample, of which 186 received sertraline and 183 received placebo.

The baseline demographic, medical, and depression characteristics of patients in the 2 treatment groups are summarized in TABLE 1. There were no significant between-group differences in any baseline demographic or clinical variables. Most patients were in their 50s or 60s and had at least 2 cardiovascular risk factors. Approximately 40% of the patients had experienced a previous MI and about half had experienced at least 1 previous major depression. For the total sample, depression severity was in the mild to moderate range. Twenty-four percent of the sample fell into the more severe subgroup defined by higher depression severity (HAM-D score ≥ 18) and multiple prior episodes of depression (in antidepressant trials, the term "severe" is frequently used to describe patients with HAM-D scores of ≥ 25 ; these patients were in that sense not severe).

Study Treatment, Concomitant Medications, and Discontinuations

TABLE 2 summarizes the proportion of patients who were treated with various classes of medication during the course of the study. All patients received concomitant cardiovascular medication. In both treatment groups, the mean number of concomitant medications was 11.

The mean (SD) time from MI or hospitalization for unstable angina to the start of active medication was 33.7 (9.9) days. The mean (SD) duration of treatment was 149.5 (51.2) days for sertraline and 153.8 (56.7) days for placebo. The mean (SD) final daily dose

Table 2. Concomitant Cardiovascular Medications

Medication	No. (%)	
	Sertraline (n = 186)	Placebo (n = 183)
Calcium channel blockers	61 (33)	66 (36)
Nitrates	122 (66)	117 (64)
Digoxin	23 (12)	25 (14)
β -Blockers	145 (78)	155 (85)
Angiotensin-converting enzyme inhibitors	99 (53)	101 (56)
Statins	158 (85)	157 (86)
Aspirin	170 (91)	158 (86)
Antiplatelet drugs (eg, ticlopidine, clopidogrel)	35 (19)	26 (14)
Anticoagulants	55 (30)	51 (28)
Diuretics	59 (32)	83 (45)

of sertraline was 68.8 (40.1) mg for sertraline and 70.5 (38.9) mg-equivalent for placebo.

Primary Outcome: Cardiovascular Safety

There was no statistically significant difference in LVEF between patients receiving sertraline or placebo (TABLE 3). There was also no difference among patients in the high-risk strata, defined as having a baseline ejection fraction of less than 30%. Nor were between-group differences observed in secondary ECG parameters (Table 3), including heart rate, blood pressure, PR interval, QRS duration, QTc interval, and SDNN (standard deviation of all normal R-R intervals in a 24-hour ECG recording), a measure of autonomic balance.³⁸ Serial Holter recordings did not reveal any significant treatment-emergent between-group difference in the number of runs of ventricular tachycardia. There were also no between-group differences in laboratory indices such as electrolytes, creatinine, or blood cell counts.

Both nausea and diarrhea were significantly more common in patients taking sertraline (TABLE 4). Cardiovascular events were not significantly different although severe cardiovascular events were numerically less frequent with sertraline (14.5% vs 22.4%). The incidence of major adverse cardiovascular events involving death or requiring hospitalization any time during the 24-

week course of study treatment is shown in TABLE 5. All together, 73 of the 369 individuals (20%) in the study had such events (44% allocated to sertraline vs 56% allocated to placebo). There were 2 additional cerebrovascular events (1 stroke and 1 transient ischemic attack) that were not CEC-adjudicated be-

cause they occurred during a rehospitalization but were not the initial reason for hospitalization. Both occurred in patients allocated to placebo, but neither is reflected in the relative risk for stroke. They would influence the risk for stroke, but because both individuals were already hospitalized for angina they would not change the composite risk.

Table 3. Cardiac Safety Results at Baseline and at Week 16 or Final Treatment Observation*

	Sertraline		Placebo	
	Baseline	Week 16	Baseline	Week 16
LVEF by MUGA, Mean (SD)				
	n = 135		n = 125	
Total sample, %	54 (10)	54 (11)	52 (13)	53 (13)
Baseline LVEF <30%	20 (2) [n = 2]	20 (2) [n = 2]	24 (5) [n = 7]	24 (7) [n = 7]
Patients showing >5-point decrease in LVEF, No. (%)	...	6 (4.4)	...	5 (4.0)
Secondary Parameters				
	n = 159		n = 157	
Blood pressure, mean (SD), mm Hg				
Systolic	124 (17)	127 (18)	126 (20)	130 (21)
Diastolic	74 (10)	76 (10)	74 (10)	77 (11)
12-Lead ECG, mean (SD)				
Heart rate, beats/min	65 (13)	64 (12)	65 (14)	66 (12)
PR interval, ms	167 (27)	167 (27)	172 (26)	173 (26)
QRS duration, ms	97 (19)	98 (20)	98 (21)	98 (22)
QT _c , ms	420 (45)	418 (27)	424 (35)	419 (31)
QT _c >450 ms at end point, No. (%)	30 (19)	19 (12)	30 (19)	21 (13)
24-Hour (Holter) ECG				
	n = 145		n = 147	
Premature complexes per hour, %				
Ventricular				
<3	57	57	52	57
3-<10	17	12	20	14
≥10	27	31	28	29
Supraventricular				
<3	65	63	63	59
3-<10	16	17	22	22
≥10	19	21	16	19
Runs of VPCs, No. (%)†				
Patients with runs of VPCs	23 (15.9)	23 (15.9)	35 (23.8)	27 (18.4)
Patients with ≥1 run faster than 100 beats/min	20 (13.8)	14 (9.7)	21 (14.3)	23 (15.6)
Patients with an increase in runs on treatment	NA	19 (13.1)	NA	19 (12.9)
R-R Interval Variability, Mean (SD)				
	n = 125		n = 133	
SDNN, ms	100 (33)	104 (36)	109 (39)	103 (34)
RMSSD, ms	26 (19)	25 (17)	27 (18)	27 (15)
PNN50	8.4 (10.1)	7.5 (9.4)	8.8 (10.2)	9.7 (9.6)
LnLF power, ms ²	5.47 (1.15)	5.35 (1.13)	5.51 (1.15)	5.46 (1.26)
LnHF power, ms ²	4.57 (1.02)	4.47 (1.02)	4.65 (1.12)	4.68 (1.08)
LnLF/HF ratio	0.90 (0.66)	0.88 (0.68)	0.87 (0.75)	0.78 (0.72)

*No significant between-group differences exist for any parameter. LVEF indicates left ventricular ejection fraction; MUGA, multiple gated acquisition scan; ECG, electrocardiogram; VPC, ventricular premature complex; NA, not applicable; SDNN, standard deviation of all normal R-R intervals in a 24-hour ECG recording; RMSSD, root mean square successive difference; PNN50, percent of normal R-R intervals >50 milliseconds; Ln, natural logarithm; LF, low-frequency power; and HF, high-frequency power.

†Run indicates ≥3 consecutive VPCs.

Efficacy Outcome: Depression

Between-treatment differences in depression were assessed for the total population (sertraline, n=186; placebo, n=183), for the a priori–defined more severe subset (sertraline, n=50; placebo, n=40), and for the subset of patients with any prior history of MDD regardless of their severity at entry to the study (sertraline, n=96; placebo, n=90). Among all patients (TABLE 6), a repeated-measures analysis found sertraline to be significantly superior to placebo on the CGI-I scale measured over 24 weeks, but not on the HAM-D scale, which was obtained over 16 weeks. In the 2 recurrent depression groups, sertraline was significantly superior to placebo on both the CGI and HAM-D measures. In all 3 groups, responder status using the standard criteria of CGI-I score of 1 or 2 (very much or much improved) was achieved at end point by significantly more patients treated with sertraline than with placebo. Responder rates for placebo-treated patients decreased as criteria for severity of the subgroup increased.

COMMENT

Our study was designed primarily to evaluate the cardiovascular safety of sertraline in patients with MDD after hospitalization for MI or unstable angina. We found no evidence of harm: sertraline was indistinguishable from placebo across all surrogate measures of cardiovascular safety. Treatment was not associated with any change in LVEF, blood pressure, heart rate, arrhythmias, or SDNN on 24-hour ambulatory ECGs, with QTc prolongation, or with any other ECG parameters (Table 3). Furthermore, though not statistically significant, the incidence of severe cardiac

events, the gold standard for cardiac safety, was numerically lower among patients receiving sertraline than among those receiving placebo (Table 5).

As a secondary outcome, sertraline's antidepressant efficacy was measured in the same population. Although SSRIs have been widely used for many years and their antidepressant activity is well established,³⁹⁻⁴⁵ their efficacy in the setting of ACS has not been demonstrated. Depression in patients in this situation might be viewed as a normal reaction to stress and, as with adjustment reaction, be expected to remit spontaneously. In fact, spontaneous remission occurs in about half of cases of post-MI depression, while the other half will either persist or remit only to relapse within a year.^{18,31-34}

In this population, demonstrating antidepressant efficacy could be problematic. Antidepressant efficacy trials typically enroll patients who seek treatment, have a minimum HAM-D severity score of 18, and have for the most part been depressed for many months. Patients in this trial did not seek treatment but were approached in the cardiac care unit days after their hospitalization and were screened for depression. Their symptoms were not only less severe than the usual patient in an antidepressant trial, but more importantly many were depressed for just 2 or 3 weeks prior to randomization. For these reasons a much higher placebo response rate would be expected.⁴⁶ Anticipating this possibility, we defined an a priori "more severe sample" as the target group for the primary efficacy analysis. By requiring a minimum HAM-D score of 18, the subgroup more closely resembled the severity level of a more typical antidepressant trial. To compensate for the very short episode duration in this post-MI sample, 2 prior episodes of depression were required. Despite the limited number of these "more severe" patients, sertraline was found to be robustly superior to placebo using either CGI-I or HAM-D measures (Table 6). As expected, for the total sample sertraline demonstrated a less consistent advantage over placebo.

In retrospect, 2 prior episodes and the severity requirement were excessive for demonstrating an antidepressant effect. Therefore, we examined drug efficacy in

individuals with any prior history of MDD regardless of the severity. This is the group in which post-MI depression is likely to persist,^{12,18,31-34} and the drug

Table 4. Emergent Adverse Events During 24 Weeks of Study Treatment*

Adverse Event	Total, No. (%)		Severe, No. (%)†	
	Sertraline	Placebo	Sertraline	Placebo
Total cardiovascular‡	98 (52.7)	108 (59.0)	27 (14.5)	41 (22.4)
Nausea	37 (19.9)	20 (10.9)	3 (1.6)	1 (0.5)
Diarrhea	35 (18.8)	14 (7.7)	3 (1.6)	1 (0.5)
Insomnia	35 (18.8)	34 (18.8)	5 (2.7)	6 (3.3)
Dyspnea	25 (13.4)	36 (19.7)	3 (1.6)	4 (2.2)
Fatigue	27 (14.5)	25 (13.7)	2 (1.1)	2 (1.1)
Pain	19 (10.2)	21 (11.5)	2 (1.1)	3 (1.6)
Headache	38 (20.4)	30 (16.4)	5 (2.7)	4 (2.2)
Dizziness	29 (15.6)	22 (12.0)	4 (2.2)	0 (0)

*Ten percent or more in either group.

†Severe indicates the higher-severity subgroup (Hamilton Depression scale score of 18 or higher and 2 previous episodes of major depressive disorder).

‡Includes angina, chest pain, edema, palpitations, syncope, postural dizziness, congestive heart failure, myocardial infarction, tachycardia, bradycardia, and changes in blood pressure.

Table 5. Relative Risk of Death and Urgent Cardiovascular Rehospitalizations*

End Point	No. of Patients		RR (95% CI)
	Sertraline	Placebo	
Death	2	5	0.39 (0.08-1.39)
Myocardial infarction	5	7	0.70 (0.23-2.16)
Congestive heart failure	5	7	0.70 (0.23-2.16)
Stroke	2	2	0.98 (0.14-6.93)
Angina	26	30	0.85 (0.53-1.38)
Composite end point	32	41	0.77 (0.51-1.16)

*If a patient is hospitalized more than once for the same end point, the patient is counted only once. A patient may be included for more than 1 end point. In the composite end point a patient is counted only once. RR indicates relative risk; CI, confidence interval.

Table 6. Antidepressant Efficacy Results*

	Sertraline	Placebo	P Value
All randomized patients			
No.	186	183	
CGI-I score, mean (SD)†	2.57 (0.06)	2.75 (0.07)	.049
HAM-D change score, mean (SD)‡	-8.4 (0.41)	-7.6 (0.41)	.14
CGI-I responder, No. (%)	125 (67)	97 (53)	.01
Any recurrent MDD			
No.	96	90	
CGI-I score, mean (SD)†	2.49 (0.09)	2.80 (0.09)	.02
HAM-D change score, mean (SD)‡	-9.8 (0.59)	-7.6 (0.61)	.009
CGI-I responder, No. (%)	69 (72)	46 (51)	.003
More severe (2 prior episodes plus HAM-D score ≥18)			
No.	50	40	
CGI-I score, mean (SD)†	2.41 (0.13)	2.98 (0.12)	.002
HAM-D change score, mean (SD)‡	-12.3 (0.88)	-8.9 (0.98)	.01
CGI-I responder, No. (%)	39 (78)	18 (45)	.001

*Patients with no follow-up data are included in the analysis by imputing no change. CGI-I indicates Clinical Global Impression Improvement Scale; MDD, major depressive disorder; and HAM-D, Hamilton Depression Scale.

†For repeated measures of analysis of CGI-I, weeks 2, 6, 10, 16, and 24 are used. CGI-I at week 0 is used as a covariate in the model. Responders have CGI-I scores of ≤2 (much or very much improved) at end point.

‡For repeated-measures analysis of HAM-D, weeks 6, 10, and 16 are used.

was found to be highly efficacious. Interestingly, patients with no prior history of depression before their present post-MI episode showed no evidence of a drug-placebo difference. As expected, the placebo response rate was considerably higher than rates typically seen in antidepressant trials³⁹⁻⁴¹ across all 3 subsets.

Several limitations of this study should be noted. The sample size was well short of the numbers needed to identify rare adverse events or drug-drug interactions. Also, because of the safety focus of the study, which required completion of MUGA scans and Holter recording prior to randomization, treatment was initiated an average of 34 days following MI. As a result, the effect of time-to-treatment onset requires further study. In addition, a large number of patients were excluded from this trial either because they had a second medical condition that might jeopardize their survival over the next year or because they had alcoholism, drug abuse, or schizophrenia. The results cannot be generalized beyond the populations that were actually examined. Finally, although there was no evidence of efficacy among those patients without a prior history of depression, because of the emphasis on safety, patients in this study received much more "medical attention" than do the usual post-MI patients. It is unclear if that level of support influenced response rates, and it is possible that in the usual care setting lower spontaneous remission rates would result and higher drug-placebo treatment differences would emerge.

Based on the 369 patients in our study, sertraline appears to be a safe and, in patients with any recurrent major depression, an effective treatment in the setting of ACS. More than a million individuals in the United States experience ACS each year and approximately 20% of these persons will also experience major depression, which imparts a 3-fold increase in the risk of morbidity and mortality.^{11,14-16} Even a modest reduction in risk, given the prevalence of these 2 conditions, would have significant public health consequences.

Clopidogrel, which is considered an important advance in ACS care, reduced risk by slightly less than 20%.⁴⁷ Though not statistically significant, in this study there were about 20% fewer serious adverse cardiovascular events for patients allocated to sertraline compared with those allocated to placebo. Power calculations indicate that to confirm a 20% reduction in risk a randomized trial would require a sample size of at least 4000 depressed patients with ACS.

Depression in untreated populations has repeatedly been demonstrated to increase cardiovascular morbidity and mortality.¹ If SSRIs reduced that risk, an epidemiologic study would be likely to find no difference in cardiovascular risk between SSRI-treated depressed patients and nontreated, nondepressed controls; indeed, that has been reported twice.^{48,49} Recently, Sauer et al⁵⁰ have also observed a statistically significant reduction of cardiovascular risk of MI in SSRI-treated smokers. Although such epidemiologic data are difficult to interpret, taken together with the present study, these observations underscore the public health need for a properly powered, prospective trial to determine whether SSRIs can alter cardiovascular outcomes. In any case, it should be emphasized that, even without definitive evidence of risk reduction, depression that recurs or persists in ACS should be identified and treated because it is a serious illness that is both painful to patients and impedes their medical care.^{51,52}

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Author Contributions: Dr Glassman had full access to all study data and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Glassman, O'Connor, Califf, Swedberg, Schwartz, Bigger, Krishnan, Pepine, Finkel, Shapiro, Harrison.

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Comment. We found persistent decreases in mortality over a 30-year period among Americans aged 20 through 44 years, and little change for women aged 45 through 64 years. These mortality trends reflect declining rates of melanoma case fatality. Moreover, incidence rates in the youngest age groups have not continued to increase as they have for older Americans. Mortality trends are also consistent with earlier birth-cohort analyses suggesting an anticipated leveling off and decline in melanoma death rates.² Mortality data also reflect recent studies in which melanoma incidence rates declined more for distant-stage tumors among women than among men and rates for thick tumors (>4 mm) increased significantly only in men aged 60 years and older.³

Mortality reductions for this strongly sun exposure-associated malignancy⁴ in younger Americans suggests positive effects of public education during the past 30 years. However, as incidence rates among middle-aged and older men continue to increase and the proportion of thick melanoma remains high, concerted efforts must be made for outreach and early detection for this at-risk group now characterized by decades of excessive sun exposure.

Thus, the Third United States Preventive Services Task Force (2001) and the Institute of Medicine (2000) have both recognized the heightened melanoma risk among middle-aged and older white men,^{5,6} a concern reinforced by our analysis.

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CORRECTIONS

Factual Error and Incorrect Units: In the Scientific Review and Clinical Applications article entitled "Vitamins for Chronic Disease Prevention in Adults: Scientific Review," published in the June 19, 2002, issue of THE JOURNAL (2002;287:3116-3126), the units for vitamins A, D, K, and B₁₂ and folate in Table 3 should have been micrograms, not micrograms per liter. On page 3119, under the heading "Vitamin E," "α-Tocopherol is the most abundant form in foods and is generally the form used in supplements" should have read "γ-Tocopherol is the most abundant form and α-tocopherol is the form used for most supplements." On page 3123, under the heading "Vitamin A," "vitamin A is 1500 μg/L" should have read 1500 μg. On page 3124, under the heading "Vitamin K," "vitamin K is 80 μg/L" should have read 80 μg.

Incorrect Data and Table Footnote, and Omitted Investigators: In the Original Contribution entitled "Sertraline Treatment of Major Depression in Patients With Acute MI or Unstable Angina" published in the August 14, 2002, issue of THE JOURNAL (2002;288:701-709), incorrect data were presented in Table 1. In the row "2 Prior episodes, plus HAM-D score ≥18," the numbers of patients who had received prior psychotropic treatment should have been 34 (rather than 126) for the sertraline group and 22 (rather than 101) for the placebo group. In Table 4, the footnote indicated by the dagger should have read "Treatment-emergent adverse events are rated by the treating physician as mild, moderate, or severe." In addition, the following persons were inadvertently omitted from the list of SADHART Investigators: David Barton, MD, and Michael McIvor, MD.

CME ANNOUNCEMENT

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