

Effects of Antidepressant Medication on Morbidity and Mortality in Depressed Patients After Myocardial Infarction

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Background: Depression after myocardial infarction (MI) is associated with higher morbidity and mortality. Although antidepressants are effective in reducing depression, their use in patients with cardiovascular disease remains controversial.

Objective: To undertake a secondary analysis to determine the effects of using antidepressants on morbidity and mortality in post-MI patients who participated in the Enhancing Recovery in Coronary Heart Disease study.

Design: Observational secondary analysis.

Setting: Eight academic sites.

Patients: The Enhancing Recovery in Coronary Heart Disease clinical trial randomized 2481 depressed and/or socially isolated patients from October 1, 1996, to October 31, 1999. Depression was diagnosed using a structured clinical interview. This analysis was conducted on the 1834 patients enrolled with depression (849 women and 985 men).

Intervention: Use of antidepressant medication.

Main Outcome Measures: Event-free survival was defined as the absence of death or recurrent MI. All-cause mortality was also examined. To relate exposure to anti-

depressants to subsequent morbidity and mortality, the data were analyzed using a time-dependent covariate model.

Results: During a mean follow-up of 29 months, 457 fatal and nonfatal cardiovascular events occurred. The risk of death or recurrent MI was significantly lower in patients taking selective serotonin reuptake inhibitors (adjusted hazard ratio [HR], 0.57; 95% confidence interval [CI], 0.38-0.84), as were the risk of all-cause mortality (adjusted HR, 0.59; 95% CI, 0.37-0.96) and recurrent MI (adjusted HR, 0.53; 95% CI, 0.32-0.90), compared with patients who did not use selective serotonin reuptake inhibitor antidepressants, the comparable HRs (95% CIs) were 0.72 (0.44-1.18), 0.64 (0.34-1.22), and 0.73 (0.38-1.38) for risk of death or recurrent MI, all-cause mortality, or recurrent MI, respectively, compared with nonusers.

Conclusions: Use of selective serotonin reuptake inhibitors in depressed patients who experience an acute MI might reduce subsequent cardiovascular morbidity and mortality. A controlled trial is needed to examine this important issue.

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CARDIOVASCULAR DISEASE (CVD) is the leading cause of death, major morbidity, and disability among men and women in the United States, with an estimated 6 million people having symptomatic coronary heart disease.¹ The prevalence of major depression is about 20% in patients with a recent myocardial infarction (MI)^{2,4} and about the same for minor depression.³ In patients who experience an acute MI (AMI), depression is a risk factor for

recurrent nonfatal infarction and cardiac mortality, independent of cardiac disease severity.^{5,6}

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The recently completed Enhancing Recovery in Coronary Heart Disease (ENRICH) study was undertaken to determine whether treatment of depression and low perceived social support with cognitive behavioral therapy (CBT) reduces mortality and recurrent infarction follow-

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Group Information: A list of the members of the ENRICH Investigators appears in *JAMA* (2003;289:3115).

PATIENT ELIGIBILITY AND RECRUITMENT

ing MI.⁷ Patients who met the criteria for either major or minor depression and/or low social support were recruited within 28 days of the index infarction and randomized to a CBT-based psychosocial intervention (PI) or usual medical care (UC). The intervention was a series of individual and group CBT sessions delivered over 6 to 9 months, with adjunctive pharmacotherapy for depression available for patients who had more severe depression or who did not demonstrate a rapid response to CBT. Although a statistically significant improvement in depression and low social support was observed, no significant differences in clinical end points were found between the PI and UC groups after a mean follow-up of 29 months.

Although antidepressants are effective in reducing depression,⁸ their use in patients with CVD remains controversial. Several studies have found that depression and the use of tricyclic antidepressant medications are associated with an increased risk of CVD. For instance, Cohen et al⁹ found an excess risk of MI in patients using tricyclic antidepressant medications and Glassman et al¹⁰ urged caution in the use of tricyclic antidepressants in patients with ventricular arrhythmias and/or ischemic heart disease. Conversely, some studies have found a reduced relative risk for MI in patients using selective serotonin reuptake inhibitors (SSRIs). For instance, in the study by Cohen et al,⁹ the relative risk of MI was 0.8 for users of SSRIs compared with subjects who did not use antidepressants. Meier et al,¹¹ using a population-based case-control analysis of general practice patients in the United Kingdom, found lower, but nonsignificant, adjusted odds ratios for AMI for current use of SSRIs, non-SSRIs, or other antidepressants, compared with the group of nonusers of antidepressants.

Less is known about the effects of antidepressants in patients with CVD and especially in patients with CVD and depression. In a small controlled study, Roose et al¹² found that paroxetine and nortriptyline hydrochloride are effective treatments for depressed patients with ischemic heart disease. However, nortriptyline treatment was associated with a significantly higher rate of serious adverse cardiac events compared with paroxetine. Glassman et al¹³ recently reported that sertraline hydrochloride, an SSRI, was a safe and an effective treatment for recurrent depression in patients with recent MI or unstable angina and without other life-threatening medical conditions. Sauer et al¹⁴ compared post-MI rates in smokers aged 30 to 65 years reporting antidepressant use with those of smokers not reporting antidepressant use. The odds ratio for MI among SSRI users compared with nonusers was 0.35 (95% confidence interval [CI], 0.18-0.68). Non-SSRI antidepressant users had a nonsignificant reduction in MI risk with wide CIs (adjusted odds ratio, 0.48; 95% CI, 0.17-1.32; $P = .15$). Hence, overall, the evidence suggests that SSRIs are safe in patients with CVD and may even reduce post-MI morbidity and mortality.

The post hoc secondary analyses reported herein were undertaken to determine the effects of using antidepressants on morbidity and mortality in patients who participated in the ENRICHD trial.

Details of the ENRICHD study design, screening measures, and number of patients who met specific enrollment criteria are described elsewhere.^{7,15,16} In brief, the study recruited 2481 individuals from 8 sites around the United States from October 1, 1996, to October 31, 1999. All patients admitted to the participating hospitals with AMI were considered for possible enrollment into the study. The diagnosis of AMI required a characteristic increase in 1 or more of the biomarkers of myocardial injury to twice the upper limit of normal established within the institution from which the patient was being recruited, except for creatine kinase-MB, for which any elevation with an increasing and decreasing pattern deemed indicative of AMI by the attending physician was considered diagnostic. The patient then also had to manifest at least 1 of the following: (a) symptoms compatible with AMI or (b) characteristic evolutionary electrocardiographic ST-T changes or new Q waves. Patients could be included even if the marker criteria were not met if they underwent an immediate artery-opening intervention for ST elevation on presentation. Patients with postprocedure (eg, angioplasty or coronary artery bypass grafting) AMI were excluded. Patients were also excluded if they had a major psychiatric comorbidity, such as schizophrenia or bipolar disorder, severe dementia, or active substance abuse; they had other major psychological conditions precluding participation in the trial; they were deemed to be at imminent risk for suicide; they refused to participate or were disallowed from participating by their attending physician; or they could not be enrolled within 28 days of the event.

Patients who were not excluded were screened for the presence of depression and/or low social support. They were administered the Depression Interview and Structured Hamilton (DISH) questionnaire, a semistructured diagnostic interview developed for the ENRICHD study to diagnose current depressive episodes in cardiac patients according to the *DSM-IV* criteria, to provide a severity measure based on the Hamilton Depression Rating Scale (HRSD), and to screen for other psychiatric disorders. The DISH includes all items from the 17-item HRSD and all depression questions necessary to make a *DSM-IV* diagnosis. Some of the HRSD depression questions were rewritten slightly to facilitate integration with the *DSM-IV* probes. In a validity study, the DISH and the Structured Clinical Interview for *DSM-IV* were administered in randomized order to 57 patients. Trained interviewers administered the DISH, and clinicians administered the Structured Clinical Interview for *DSM-IV*. The Structured Clinical Interview for *DSM-IV* diagnosis agreed with the DISH diagnosis on 88% of the interviews (weighted $\kappa = 0.86$).¹⁷ Patients were classified as depressed if they met the ENRICHD-modified *DSM-IV* diagnostic criteria for major or minor depression or dysthymia.

BASELINE MEASUREMENTS

At baseline, demographic information, a standardized medical history (including risk factor profiles and possible comorbid conditions), and current medical status, including left ventricular ejection fraction, were collected, and a physical examination was completed. An electrocardiogram was obtained at enrollment into the study. The Beck Depression Inventory (BDI),¹⁶ a 21-item measure of the self-reported severity of depression symptoms, was also obtained at baseline. The BDI scores can range from 0 to 64; the standard BDI cutoff indicating clinical depression is a score of 10 or higher.¹⁶

TREATMENT

The protocol was designed to enroll and treat patients as soon as possible after the index AMI, with the belief that the optimal time for the intervention would be during the period of highest risk for recurrent infarction and death (ie, the initial 6 months following the index event).¹⁵ All patients received the American Heart Association Active Partnership Program risk factor reduction pamphlet. Patients receiving UC were provided no further information after discharge and received the care provided by their physicians. Those randomized to the intervention received CBT, which was selected to be the ENRICH intervention based on its effectiveness in earlier studies. The details of the PIs are presented elsewhere.¹⁶ The protocol required intervention group patients with scores of 25 or higher on the HRSD, or who showed less than 50% reduction in BDI scores after 5 weeks of treatment, to be referred to study psychiatrists for consideration of pharmacotherapy. Study psychiatrists met individually with these patients as needed to monitor medication use. Unless contraindicated, sertraline was initiated at 50 mg/d and adjusted to a maximum of 200 mg/d if deemed necessary by the treating psychiatrist. Sertraline was chosen because of its efficacy and minimal effects on cardiac physiological features.¹⁸ Alternative antidepressants were considered for patients unable to tolerate sertraline or judged unresponsive. The maximum duration of the behavioral intervention was 6 months. Group therapy could extend an additional 12 weeks, and adjunctive pharmacotherapy for up to 12 months, at which time the patient was reexamined by the ENRICH psychiatrist. If antidepressants were deemed still to be needed, the patient was referred to his or her physician for subsequent antidepressant medication.

FOLLOW-UP EVALUATIONS

Follow-up evaluations occurred 6 months after randomization and annually thereafter. Evaluations were done independent of treatment sessions by evaluators blinded to the participant's randomization status. At the time of evaluation, patients from both groups were asked if they had used antidepressants. If so, the name of the antidepressant was recorded and the antidepressant was categorized as an SSRI, tricyclic, or other. Individuals prescribed combinations of antidepressants were categorized as other.

END POINTS

Potential end points were identified through patient interview, hospital records, and/or the patients' physicians. Records of every identified hospitalization were obtained for review. The primary end point (recurrent MI or death from any cause) was classified using standardized criteria by a member of the treatment-masked Endpoints Committee, which adjudicated ambiguous cases. An electrocardiographic core laboratory classified electrocardiograms by Minnesota code serial change rules. Criteria for recurrent MI were as defined for study eligibility, except that periprocedural MI was diagnosed if biomarkers of cardiac injury were 3-fold above baseline after a percutaneous coronary intervention or if new Q waves developed in 2 or more leads after coronary artery bypass grafting. Secondary end points, including revascularization procedures and cardiovascular-related hospitalizations, were also determined.

STATISTICAL ANALYSIS

Baseline demographic and clinical characteristics were compared for differences according to antidepressant medication use of SSRIs, non-SSRIs, a combination of SSRI and non-SSRI

antidepressants, or neither during the entire follow-up using the Mantel-Haenszel χ^2 test for categorical data and the *t* test for continuous data.

Cox proportional hazards regression models, with antidepressant drug use (yes vs no) treated as a binary time-dependent covariate, were used to obtain hazard ratios (HRs) of death or recurrent MI, death only, or recurrent MI only.¹⁹ The status of antidepressant use was evaluated at baseline, 6-month follow-up, and every year thereafter. To incorporate antidepressant drug use in a time-dependent fashion, the medication use variable was coded as 1 beginning on the visit date on which the antidepressant was prescribed until the midpoint of the subsequent interval or beginning at the midpoint of the previous interval up to the visit date if a patient reported having taken antidepressants since the last visit, and was coded as 0 for all other days. For example, a report of current antidepressant use at the 18-month visit, but no reported use at the 6-month visit and no indication that antidepressants were prescribed after the 18-month visit, would have time-dependent covariate values of 0 up to 12 months, 1 from 12 to 24 months, and 0 thereafter. Separate models examined the predictive value of any antidepressant use and SSRI antidepressant use (after excluding patients who received other antidepressants). Adjustment was made for baseline patient characteristics, including continuous age and baseline BDI score, and variables that reflect the severity of medical illness: Killip class (continuous); ejection fraction categorized as normal ($\geq 50\%$), mild (40%-49%), moderate (30%-39%), or severe ($< 30\%$) left ventricular dysfunction; serum creatinine value dichotomized at the 75th percentile (≥ 1.3 mg/dL [≥ 115 $\mu\text{mol/L}$]); previous MI; and prior diagnosis of congestive heart failure, stroke or transient ischemic attack, pulmonary disease, or diabetes mellitus. SAS statistical software, version 8.2 (SAS Institute Inc, Cary, NC), was used for all analyses, and the level of significance was set at $P \leq .05$.

RESULTS

BASELINE CHARACTERISTICS AND TREATMENT GROUP COMPARABILITY

A detailed description of the study population has been previously reported.^{7,15} To summarize, 2481 patients were randomized from 73 participating hospitals in the United States. Of the participants, 39.4% had depression only, 26.1% had low social support only, and 34.5% had both depression and low social support. The analyses reported herein focus on the 73.9% of patients ($n = 1834$; 985 men and 849 women) who had depression, with or without low social support. Of patients who were enrolled for low social support, 13.8% (89/647) reported antidepressant use at any point during the trial. Patients taking antidepressants for at least 14 days at baseline were enrolled in the study if they met all other study criteria.

Among patients who were depressed at enrollment, the cumulative rates of any antidepressant use in the UC and PI arms were 4.8% and 9.1% at baseline, 13.4% and 20.5% at the 6-month visit, and 20.6% and 28.0% by the end of follow-up, respectively. Selective serotonin reuptake inhibitors were the most often prescribed antidepressant, with use rates in the UC and PI arms of 3.8% and 6.9% at baseline, 9.4% and 15.3% at the 6-month visit, and 14.6% and 21.0% by the end of follow-up, respectively. Based on self-report, the median duration of anti-

Table 1. Baseline Characteristics by Antidepressant Medication Use Assessed During the Entire Follow-up*

Characteristic	No Antidepressant Use (n = 1388)	SSRI Antidepressant Use (n = 301)	Other Antidepressant Use (n = 145)†	P Value‡
Demographics				
Age, mean (SD), y	61 (12.6)	59 (12.6)	58 (11.2)	.02
Female sex	45	54	43	.02
Minority race	35	28	22	<.001
Married or living with a partner	54	53	53	.77
College education	44	46	43	.65
Medical history and cardiac risk factors				
Diabetes mellitus	34	38	37	.31
Hypertension	60	57	70	.03
Ever smoker	63	69	77	<.001
Renal insufficiency	10	10	10	.97
Pulmonary disease	19	23	16	.18
Previous myocardial infarction	27	26	28	.88
Prior stroke or TIA	9	12	21	.06
Previous CABG	13	14	10	.57
Previous PTCA	15	16	17	.87
History of heart failure	14	16	17	.44

Abbreviations: CABG, coronary artery bypass grafting; PTCA, percutaneous transluminal coronary angioplasty; SSRI, selective serotonin reuptake inhibitor; TIA, transient ischemic attack.

*Data are given as percentage of each group unless otherwise indicated.

†Includes non-SSRIs or use of a combination of SSRI and non-SSRI antidepressants during the follow-up.

‡Based on the Mantel-Haenszel χ^2 test or the *t* test.

depressant treatment was approximately 12 months for both groups. Individuals in the PI arm with an HRSD score of 25 or higher after 5 weeks of CBT were to be examined for pharmacologic treatment with sertraline according to protocol-specified procedures. In the PI group, 35.3% (49/139) of patients with an HRSD score of 25 or higher were given antidepressants. While this is significantly ($P=.002$ by χ^2 test) higher than the rate among patients in the UC arm with an HRSD score of 25 or higher (19.2%), the data suggest that antidepressants were underused in the PI group.

As seen in **Table 1**, individuals prescribed antidepressants at any point during follow-up were younger and more likely to be white. In addition, women were more likely to be prescribed SSRIs than men. There were no significant differences in SSRI or other antidepressant use associated with level of education or household income.

At baseline, patients prescribed antidepressants other than SSRIs were more likely to be hypertensive, to be hypercholesterolemic, to be tobacco users, and to have peripheral vascular disease, compared with the other groups (**Table 1**). Patients using SSRIs were less likely to be using antiarrhythmic drugs and β -blockers.

OUTCOMES

During an average of 29 months of follow-up, 26.0% (361/1388) of the patients who did not receive antidepressants died or had a recurrent MI vs 21.5% (96/446) of the patients who did take antidepressants during follow-up (**Table 2**). Some of the events in the antidepressant drug use group occurred during a period in which the participant had not yet been prescribed antidepressants, or had discontinued pharmacotherapy. With a time-dependent approach, events are classified according to concurrent drug

use. For this reason, the morbidity and mortality rates for any antidepressant use may differ from the rates determined when people are taking antidepressants. For instance, **Table 2** shows that there were 73 events in individuals in the group that had used an antidepressant at any time, but only 58 events were attributed to antidepressant drug use in determining a hazard rate ratio and level of significance (hazard rate ratio, 0.66; $P=.008$). By using a time-dependent multivariable Cox proportional hazards regression model to adjust for baseline depression score and cardiac risk factors, SSRI use was associated with 43% lower risk of death or nonfatal MI and 43% lower risk of all-cause mortality. The use of other antidepressants was associated with lower HRs, but the results were not significant. The HRs for the rate of revascularization procedures, adjusted for age, previous coronary artery bypass grafting, previous percutaneous transluminal coronary angioplasty, location of MI, diabetes mellitus, and use of angiotensin-converting enzyme inhibitors (the best predictive variables for revascularization), were not significantly different between antidepressant use and non-use (HR, 0.93; 95% CI, 0.67-1.30).

Because a previous diagnosis of depression is associated with a worse prognosis, and consistent with the findings of Glassman et al,¹³ we also examined the relationship of a history of major depressive disorder and its potential influence on cardiovascular (recurrent MI or death) and all-cause mortality events. The event rates in the groups with a history of depression given antidepressants compared with patients with a history of depression not given antidepressants were lower than for death or recurrent MI (adjusted HR, 0.62; 95% CI, 0.39-0.97), and, although of similar magnitude, did not reach statistical significance for all-cause mortality (adjusted HR, 0.63; 95% CI, 0.34-1.16; $P=.14$).

Table 2. Effect of Antidepressant Drug Use on Clinical Events

Variable	No Antidepressant Use (n = 1388)	Any Antidepressant Use (n = 446)	Type of Antidepressant Use	
			SSRI (n = 301)	Other (n = 145)
Death or Recurrent MI				
Patients, No. (%)	361 (26.0)	96 (21.5)	59 (19.6)	37 (25.5)
HR (95% CI)				
Unadjusted	1.00	0.66 (0.48-0.91)	0.61 (0.41-0.90)	0.79 (0.48-1.28)
Adjusted*	1.00	0.61 (0.45-0.84)	0.57 (0.38-0.84)	0.72 (0.44-1.18)
All-Cause Mortality				
Patients, No. (%)	222 (16.0)	35 (7.8)	21 (7.0)	14 (9.7)
HR (95% CI)				
Unadjusted	1.00	0.72 (0.48-1.06)	0.69 (0.43-1.10)	0.72 (0.38-1.35)
Adjusted*	1.00	0.63 (0.43-0.93)	0.59 (0.37-0.96)	0.64 (0.34-1.22)
Recurrent MI				
Patients, No. (%)	205 (14.8)	73 (16.4)	45 (15.0)	28 (19.3)
HR (95% CI)				
Unadjusted	1.00	0.63 (0.41-0.95)	0.58 (0.34-0.97)	0.80 (0.42-1.50)
Adjusted*	1.00	0.57 (0.38-0.87)	0.53 (0.32-0.90)	0.73 (0.38-1.38)

Abbreviations: CI, confidence interval; HR, hazard ratio; MI, myocardial infarction; SSRI, selective serotonin reuptake inhibitor.

*Multivariable model incorporating baseline age, baseline Beck Depression Inventory score, Killip class, ejection fraction, creatinine value, previous MI, and prior diagnosis of congestive heart failure, stroke or transient ischemic attack, pulmonary disease, or diabetes mellitus.

COMMENT

The main finding of this study is that antidepressant use post-AMI by depressed patients in the ENRICH clinical trial was associated with significantly lower rates of the study primary end points, death and reinfarction. Depressed patients reporting SSRI use post-AMI had a relative risk of death or recurrent MI of 0.57 (95% CI, 0.38-0.84), adjusted for disease severity and other factors, compared with nonusers. These analyses reflect the effects on morbidity and mortality when individuals are using antidepressants and do not address the effects of antidepressants when they are discontinued.

Because post-MI depression is likely to persist in patients with a history of depression,²⁰⁻²² in a preplanned secondary analysis, Glassman et al¹³ examined the effects of sertraline in groups of patients as defined by high depression severity (HRSD score, ≥ 18) and multiple prior episodes of depression or simply having had a history of depression. There was a significantly greater reduction in the HRSD score in both of these groups compared with the placebo group; mortality data for these subgroups were not presented. In our sample, although the unadjusted rates for all-cause or recurrent events were lower in the groups with a history of depression given antidepressants compared with patients with a history of major depression not given antidepressants, the number of events was small and the adjusted all-cause mortality hazard rate was not significant, suggesting that there was not a differential effect based on having had a previous depressive episode on all-cause mortality.

Patients in this trial generally received early and aggressive cardiologic care. During the past several years, the evolution of this aggressive approach has lowered reinfarction rates, thereby diminishing the ability to discern potential beneficial effects of additional therapies,

whether behavioral or medical. For example, in the present study, thrombolytic agents were administered to 37% of patients and revascularization interventions (a percutaneous coronary intervention or coronary artery bypass grafting) to 39% of patients within 12 weeks after the AMI. Many patients received aspirin (84%), β -blockers (72%), and/or angiotensin-converting enzyme inhibitors (45%) during the later phases of recovery.⁷ The fact that our patients received aggressive state-of-the-art care confirms the applicability of our data to contemporary MI patients.

The findings related to SSRIs are consistent with those of other studies that have found them to be safe for post-MI patients and possibly associated with a reduced risk for cardiovascular morbidity and mortality. However, some limitations of the study need to be kept in mind in considering these findings. First, the study was not designed to evaluate the use of antidepressants. As such, the findings are observational and represent post hoc analyses. Second, the data on actual drug exposure (length and dose) were estimated from patients' reports of drug use at a particular point. Third, half of the patients also received an intensive cognitive behavioral intervention. While the cognitive behavioral intervention did not reduce morbidity and mortality in the randomized trial, there may have been effects of such variables as compliance to medication that could have affected these results.⁷ On the other hand, the findings are robust, the sample is large and diverse, and the patients were followed up for a relatively long time. The use of a time-dependent series analysis also reduces the probability that the findings only reflect individuals who survived long enough to be prescribed antidepressants. While our findings suggest that SSRIs confer benefit, they do not provide information on the relative safety or benefit of the various SSRIs. The antidepressants by SSRI type were ser-

traline (49.5%), paroxetine (28.9%), fluoxetine hydrochloride (13.0%), citalopram (7.6%), and others (1.0%). The higher use of sertraline is likely related to the study protocol that used it as the first-choice antidepressant and prescribing habits from the patients' nonstudy physicians at the time the study was conducted.

The mechanisms by which depression might affect morbidity and mortality remain unclear. Depression may have some adverse effects on the autonomic control of the cardiovascular system. For instance, there is some evidence suggesting parasympathetic nervous system dysregulation in those with major depression. Heart rate variability reflects altered cardiac autonomic tone, with a higher variability observed in healthy hearts with good cardiac function. The relative risk of sudden death after AMI is significantly higher in patients with a decreased heart rate variability,²³ and recent studies have found a reduced heart rate variability in depressed post-MI and coronary heart disease patients.²⁴⁻²⁷ Moreover, there is at least some evidence that antidepressant treatment may improve heart rate variability.^{25,28}

Major depression is also associated with increased sympathetic nervous system activity.²⁹ Increased sympathetic nervous system activity may also lead to increased risk for CVD-related death in post-MI patients. Preclinical data suggest that serotonin inhibition can reduce sympathetic nervous system outflow. Short-term (2-day) administration of sertraline has also been shown to reduce the plasma norepinephrine appearance rate, which reflects total body sympathetic nervous system activity, in healthy volunteers at least.³⁰ There is also evidence that depressed cardiac patients have increased platelet activation,^{27,31-33} a risk factor for cardiac events. Selective serotonin reuptake inhibitors have been shown to improve platelet function.^{34,35} It is also possible that antidepressants may have effects on mechanisms related to increased risk of recurrent events but not related to depression (eg, the potential effects of sertraline on reducing platelet activation).

The results of this study, combined with the epidemiologic and other data, clearly demonstrate the need for a properly powered, prospective, randomized trial to determine whether SSRIs can alter cardiovascular outcomes post-MI.

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