ORIGINAL ARTICLE

Onset of Major Depression Associated With Acute Coronary Syndromes

Relationship of Onset, Major Depressive Disorder History, and Episode Severity to Sertraline Benefit

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Context: Depression observed following acute coronary syndrome (ACS) is common and associated with an increased risk of death. The Sertraline Antidepressant Heart Attack Trial (SADHART) tested the safety and efficacy of a selective serotonin reuptake inhibitor in this population. No evidence of harm was seen, and sertraline hydrochloride had an overall beneficial effect on mood that occurred primarily in patients with a history of episodes of major depressive disorder (MDD).

Objectives: To determine how frequently the MDD began before ACS and whether onset of the current MDD episode before or after the ACS event influenced response to sertraline.

Design, Settings, and Participants: A randomized, double-blind, placebo-controlled treatment of 369 patients with ACS and MDD was conducted in 40 outpatient clinics in 10 countries between April 1, 1997, and April 30, 2001.

Main Outcome Measures: Diagnosis of MDD, number of previous episodes of depression, and episode onset before or after hospitalization were established using the Diagnostic Interview Schedule. Treatment response was measured with the Clinical Global Impression–Improvement scale.

Results: Fifty-three percent of MDD episodes began before hospitalization for the index episode of ACS (for 197 of 369 patients), and 94% of the MDD episodes began more than 30 days before the index ACS episode. Episodes of MDD that began prior to ACS responded more frequently to sertraline than to placebo (63% vs 46%, respectively; odds ratio, 2.0; 95% confidence interval, 1.13-3.55) whereas depression with onset beginning after hospitalization showed a high placebo response rate (69% vs 60%, respectively) and low sertraline-placebo response ratio (1.15). Multivariate analysis indicated that time of onset of the current episode, history of MDD, and baseline severity independently predicted the sertraline-placebo response ratio.

Conclusions: Half of the episodes of major depression associated with ACS began long before ACS and therefore were not caused by ACS. Patients whose current episodes of MDD begin before ACS, those with a history of MDD, and those whose episodes are severe should be treated because they will benefit considerably from sertraline. Since these 3 predictors of sertraline response are independent, having more than 1 of them substantially increases the benefit of sertraline while reducing the chance of spontaneous recovery.

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MYOCARDIAL INFARCTION (MI) and unstable angina share pathophysiological abnormalities, and both are referred to as acute coronary syndrome (ACS). Episodes of ACS are comorbid with major depressive disorder (MDD) almost 20% of the time, and that depression is often persistent,[1] impairs health status more than heart disease itself,[2] and substantially increases cardiac morbidity and mortality.[3] The Sertraline Antidepressant Heart Attack Randomized Trial[4] (SADHART) was designed to evaluate the safety and efficacy of sertraline hydrochloride for treatment of MDD in ACS. No adverse cardiovascular effects of sertraline treatment were detected, and there was a modest but statistically significant benefit from sertraline treatment across the entire sample ($P=.02$). Epidemiological studies indicating that MDD increased post-ACS mortality had screened all of the patients after ACS, and the risk seemed to exist even in mild cases.[5] The SADHART, just as in the epidemiological studies, screened all of the patients after ACS. These patients were not seeking treatment, and the expectation was that symptoms would be mild, usually existing only since hospitalization, and that they would have high rates of spontaneous remission or placebo response. Accordingly, patients with more severe MDD symptoms (Hamil-

ton Rating Scale for Depression [HAM-D] score ≥18) and a history of 2 or more episodes of MDD were selected a priori for the primary assessment of efficacy, and randomization was stratified on these criteria. The expectation was that this group with more severe, recurrent MDD was less likely to remit spontaneously and more likely to demonstrate a benefit from sertraline treatment,[6] and this hypothesis was confirmed. The overall greater response rate to sertraline than to placebo was accounted for largely by patients with recurrent and severe depression.

This article describes a new and unexpected observation from the SADHART that contradicts our assumption that most episodes of post-ACS MDD begin in the hospital shortly after the onset of the coronary episode. A large percentage of MDD episodes observed after hospitalization in the SADHART began long before ACS onset, indicating that in these instances, MDD was not caused by the coronary event. Therefore, we now examine in detail when MDD episodes began, and we explore the individual and joint contributions of onset before or after ACS, previous episodes of MDD, and MDD symptom severity in determining the rate of response to sertraline. Such an analysis could be useful in understanding and guiding decisions about antidepressant therapy in depression associated with ACS.

METHODS

The SADHART is a 40-center trial that was conducted with patients with MDD who were hospitalized for ACS. Detailed methods have been published previously.[4,7] Eligible patients who signed consent were randomized to 24 weeks of double-blind treatment with either sertraline or placebo. Enrollment began April 1, 1997, and follow-up ended April 30, 2001. The protocol was approved by institutional review boards at all of the participating centers.

INCLUSION CRITERIA

To qualify for the SADHART, patients were required to be hospitalized for ACS within 30 days of screening.[8] They were also required to meet criteria for MDD[9] and have a Beck Depression Inventory (BDI) score of 10 or higher.

EXCLUSION CRITERIA

Patients were excluded from the trial for the following cardiovascular reasons: (1) poor hypertension control (systolic blood pressure >180 mm Hg or diastolic blood pressure >100 mm Hg); (2) cardiac surgery anticipated during the next 6 months; (3) index event developed less than 3 months after coronary artery bypass graft surgery; (4) resting heart rate of less than 40 beats/min or daytime sinus pauses longer than 3.5 seconds; (5) MI or unstable angina of nonatherosclerotic causes (eg, anemia, cocaine, periprocedural); or (6) Killip class III or IV heart failure.

Other medical reasons for exclusion included the following: (1) persistent, clinically significant laboratory abnormalities; (2) other significant noncardiac disease; or (3) women of childbearing potential not using adequate contraception.

Concomitant treatment exclusion reasons included the following: (1) current use of class I antiarrhythmic agents, reserpine, guanethidine monosulfate, clonidine hydrochloride, or methyldopa; (2) use of anticonvulsants or neuroleptics; or (3) antidepressant use or regular benzodiazepine use.

Psychiatric exclusions included the following: (1) alcohol or substance abuse or dependence in past 6 months; (2) psychotic symptoms, history of psychosis, bipolar disorder, organic brain syndrome, or dementia (or a Mini-Mental State Examination score <23)[10]; (3) significant suicide risk; or (4) initiation of psychotherapy in the 3 months before screening.

STUDY DESIGN

Patients who met the screening criteria for MDD and gave consent began receiving single-blind placebo therapy for 14 days to permit pretreatment cardiovascular assessments to be completed. After 2 weeks, a psychiatrist repeated the Diagnostic Interview Schedule[11] to verify that the patient met all of the criteria for MDD. Patients who met the criteria were stratified by ejection fraction as well as depression severity or recurrence criteria (HAM-D score ≥18 as well as ≥2 previous episodes) and were randomized to sertraline or matching placebo. They received 50 mg/d for 6 weeks, and based on clinical response and tolerability, the dose could be increased in increments to a maximum dose of 4 tablets (200 mg/d or matching placebo) by week 12.

OUTCOME VARIABLES, SAMPLE SIZE, AND SCHEDULE OF ASSESSMENTS

The protocol-defined primary cardiovascular safety variable was left ventricular ejection fraction. Measures of depression severity included the BDI[12] score obtained during screening and the 17-item HAM-D[13] score obtained at baseline and at weeks 6, 10, and 16; the primary outcome measures were the Clinical Global Impression–Severity and Clinical Global Impression–Improvement scale[14] scores obtained at baseline and at weeks 2, 6, 10, 16, and 24. Inferences regarding efficacy based on the Clinical Global Impression–Improvement scale scores extended to week 24 whereas those based on the HAM-D scores extended only to week 16. Finally, a patient was considered a responder if a Clinical Global Impression–Improvement scale score of 2 or lower (much or very much improved) was achieved by week 24. Both the duration of the current episode and the number of previous episodes were established from a series of questions during the Diagnostic Interview Schedule that was administered by a psychiatrist at the end of the 2-week, single-blind placebo period.

STATISTICAL ANALYSIS

The statistical methods used to evaluate treatment outcome have been described previously.[4] In this article, the Cochran–Mantel-Haenszel method was used to test for differences in response ratios among treatment groups within the 4 groups defined by onset of MDD relative to ACS and a history of depression. Logistic regression was used to test for differences in the response ratios among the groups. The predictor model was then expanded to include symptom severity measured by the HAM-D or BDI. The categorical model procedure was used to adjust each predictor (eg, onset of MDD before or after ACS) for all of the other predictors (eg, history of depression, severity of depressive symptoms).

RESULTS

After preliminary record review, 3355 patients with MI or unstable angina appeared to be eligible and provided informed consent for a psychiatric diagnostic interview. There were 556 patients (17%) who met modified criteria (2-week duration omitted) for MDD. After a 2-week placebo run-in, 369 patients met full MDD diagnosis criteria, remained eligible, and agreed to be randomized; 186 pa-

tients were assigned to sertraline and 183 to placebo. As described previously, there were no significant between-group differences in any baseline demographic or clinical variables. Most patients were aged 50 to 69 years, and 42% had a previous MI. For the total sample, depression severity was mild to moderate as measured on the HAM-D, and 51% had at least 1 previous MDD episode.

The expectation that most MDD episodes observed during hospitalization for ACS began in the hospital after the onset of ACS influenced the SADHART protocol design. We expected that because of the brief duration and frequently mild nature of their current episodes, these patients would have a high placebo response rate and a small sertraline-placebo response ratio. Therefore, patients with 2 or more previous episodes and a HAM-D score of 18 or higher were selected a priori to evaluate the efficacy of sertraline. Contrary to expectation, half of the episodes of MDD associated with ACS began before rather than after the onset of ACS, indicating that MDD in those instances could not be a reaction to the coronary event. Of the 369 cases of major depression, 197 (53%) began before hospitalization for the index episode of ACS. Of these 197 patients, 185 (94%) had been depressed more than 1 month before hospitalization and 120 (61%) had been depressed more than 6 months before. We tested whether the onset of depression before or after hospitalization for the index episode of ACS influenced the clinical response. For patients whose episodes began after hospitalization, all of the response rates were high, as expected (69% for sertraline and 60% for placebo; response ratio, 1.15; $P=.22$). For patients whose episodes of MDD began before their episodes of ACS, response rates were 63% for sertraline and 46% for placebo (response ratio, 1.38; $P=.02$). Because onset of MDD before or after ACS was not a stratum for randomization, we examined whether patients with depression onset after ACS differed from those with onset before ACS with respect to baseline characteristics (**Table 1**). There were no significant differences (all $P>.24$).

We previously reported that patients with ACS for whom the present MDD episodes were their first episodes of depression did not have a significantly greater rate of response to sertraline than to placebo ($P=.58$) whereas patients who had previous episodes of MDD were more likely to respond to sertraline than to placebo (72% vs 51%, respectively; response ratio, 1.41; $P<.003$).[4] Here we examined whether onset of the current episode of depression before or after entering the hospital for ACS influenced the likelihood of a better response to sertraline than to placebo. **Table 2** shows the distribution of patients cross-tabulated by previous episodes of MDD, onset of the current MDD episode before or after ACS, and response of these groups to sertraline and placebo. Each of the 4 cells (onset of MDD before or after ACS and with or without previous episodes of depression) contains approximately one quarter of the total sample. Patients whose MDD began before ACS or who had prior episodes of MDD had almost a 40% greater response to sertraline than to placebo (response ratios, 1.38 and 1.41,

Table 1. Baseline Characteristics for Patients With Episodes of Major Depressive Disorder Starting Before or After the Index Acute Coronary Syndrome Event

Characteristic	Onset Before ACS (n = 197)	Onset After ACS (n = 172)
Age, mean (SD), y	57.6 (10.9)	56.8 (10.7)
Women, No. (%)	74 (38)	60 (35)
Left ventricular ejection fraction, %	53.5	51.8
Index MI event, No. (%)	137 (70)	124 (72)
History of hypertension, No. (%)	133 (68)	106 (62)
History of diabetes mellitus, No. (%)	58 (29)	55 (32)
Previous MI, No. (%)	84 (43)	70 (41)
Prior revascularization, No. (%)	81 (41)	75 (44)
Hyperlipidemia, No. (%)	134 (68)	118 (69)
Current smoker, No. (%)	57 (29)	46 (27)
10 most common cardiac drugs used, No.*	5.1	4.8

Abbreviations: ACS, acute coronary syndrome; MI, myocardial infarction.
*The 10 most common cardiac drugs were aspirin, statins, β-blockers, nitrates, angiotensin-converting enzyme inhibitors, calcium channel blockers, diuretics, anticoagulants, antiplatelet drugs, and digoxin.

Table 2. Effect of History of Depression and Onset of Current Episode of Major Depressive Disorder on Rate of Response to Treatment*

	0 Previous Episodes of MDD		≥1 Previous Episode of MDD		Total	
Onset of Current MDD Episode	No. (Response Rate, %)	Response Ratio (95% CI)	No. (Response Rate, %)	Response Ratio (95% CI)	No. (Response Rate, %)	Response Ratio (95% CI)
Before ACS						
Sertraline	51 (53)	1.06 (0.71-1.59)	55 (73)	1.69 (1.21-2.35)†	106 (63)	1.38 (1.06-1.78)‡
Placebo	40 (50)		51 (43)		91 (46)	
After ACS						
Sertraline	39 (67)	1.14 (0.83-1.58)	41 (71)	1.15 (0.84-1.58)	80 (69)	1.15 (0.92-1.44)
Placebo	53 (58)		39 (62)		92 (60)	
Total						
Sertraline	90 (59)	1.10 (0.86-1.42)	96 (72)	1.41 (1.12-1.77)†	186 (66)	1.25 (1.06-1.49)‡
Placebo	93 (55)		90 (51)		183 (53)	

Abbreviations: ACS, acute coronary syndrome; CI, confidence interval; MDD, major depressive disorder.
*Response is indicated by a Clinical Global Impression Scale score of 2 or less at week 24. The response ratio is the sertraline response rate divided by the placebo response rate. Combined response ratios (95% CIs) for onset are obtained by the Cochran–Mantel-Haenszel method adjusted for onset. Combined response ratios (95% CIs) for history of MDD are obtained by the Cochran–Mantel-Haenszel method adjusted for onset.
†$P<.01$.
‡$P<.05$.

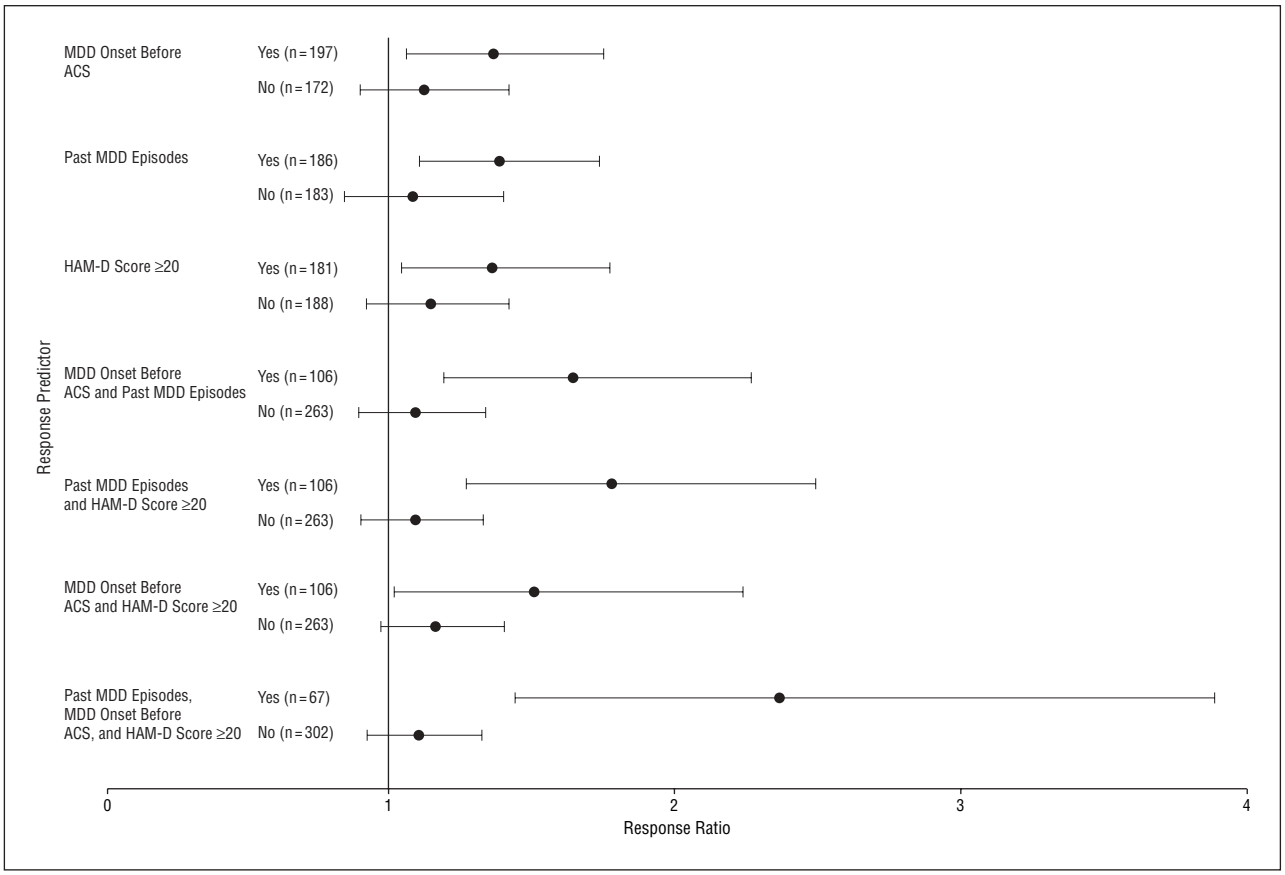

Figure. Response ratio by response predictors. Response ratio is the probability of responding to sertraline hydrochloride divided by the probability of responding to placebo. Predictor characteristic(s) present (yes) controlled for the characteristic(s) not present (no) by use of logistic regression, except for the final case in which onset, history, and severity are all used as predictors. Error bars indicate 95% confidence intervals; MDD, major depressive disorder; ACS, acute coronary syndrome; and HAM-D, Hamilton Rating Scale for Depression.

respectively) whereas patients both with episodes of MDD that began before ACS and with a history of previous MDD were almost 70% more likely to respond to sertraline than to placebo (response ratio, 1.69) (Table 2).

Baseline severity measures (HAM-D and BDI) were weakly associated with both onset time and history of depression. Because severity is frequently the primary characteristic used by clinicians to determine when a patient needs treatment, the predictive value of MDD onset and history of depression were examined, taking severity into account (**Figure**). Onset and history of MDD continued to predict a higher sertraline-placebo response ratio after adjusting for severity of the current episode of MDD using either the HAM-D or BDI dichotomized at their median values (response ratios, 1.37 and 1.39, respectively). However, greater symptom severity also predicted a similar increase in response ratio (response ratio, 1.36). All of the 3 characteristics of depression had statistically significant univariate associations with the response ratio (sertraline response rate divided by placebo response rate) (onset of MDD before ACS, $P=.02$; MDD history, $P<.001$; HAM-D score, $P=.03$), each remained significant when they were entered into the logistic regression model, and each variable produced essentially equal increases in the response ratio. Patients with all of the 3 characteristics had a 70% response to sertraline compared with a 29% response to placebo (response ratio, 2.37); however, fewer than 20% of the SADHART cohort had all of the 3 characteristics.

Table 1 shows that neither age nor sex confounds the effect of episode onset before or after ACS hospitalization. However, because history of MDD and the severity of the present episode are also independently associated with drug benefit and since both age and sex could influence drug benefit, the associations of age and sex with severity and history were examined. Age was not associated with severity ($P=.46$) or prior episodes ($P=.54$). Sex did not differ by severity ($P=.25$). However, the number of prior episodes was associated with sex, as women were more likely to have had prior episodes than men ($P=.04$).

COMMENT

Acute coronary syndrome is both psychologically and physiologically stressful, and it is common to attribute depression observed following ACS to that stress. However, to our knowledge, this is the first systematically collected data addressing how often MDD observed following ACS actually began in the hospital after the ACS event. Contrary to expectation, more than half of the SADHART's 369 MDD cases of depression identified during hospitalization had onset of the current MDD long before the

coronary events. The 53% of MDD episodes observed to begin before hospitalization are probably an underestimate because patients receiving antidepressants at hospitalization were excluded from the study. It is important for psychiatrists to realize that most patients with ACS are hospitalized less than 24 hours after the onset of symptoms. The MDD episodes beginning before the ACS episodes could not result from the stress of the coronary events; however, they could have contributed to the ACS events. Thus, studies of mechanisms that might link depression and cardiac risk, such as platelet activity, inflammation, or autonomic dysfunction, could benefit by subgrouping ACS-associated depression by onset before or after the coronary event. The inconsistencies that have been characteristic of such data to date may come from subgroup differences among post-ACS depression. It would be important to test whether increased mortality itself is associated with onset before the ACS event and/or prior episodes of MDD.

We began the SADHART with the assumption that MDD episodes beginning in the hospital were likely to be reactive. Most were expected to be mild and to barely satisfy the 2-week duration criterion of *DSM-IV*. Such episodes frequently remit spontaneously, and finding no drug-placebo difference was a concern.[15] As a result a priori, patients in the SADHART with a HAM-D score of 18 or higher and 2 or more previous episodes of MDD were identified to evaluate efficacy. It was expected that recurrent MDD would increase the odds of identifying more persistent depression and finding higher sertraline and lower placebo response rates. As expected, patients with previous MDD episodes did have greater sertraline response rates. However, it was not expected that half of the MDD cases would have their onset long before the ACS events, and no thought was given to their response ratios. In fact, there was a 36% increase in benefit from sertraline compared with placebo among those cases beginning before hospitalization whereas there was no significant benefit among MDD cases beginning in the hospital. This difference in benefit resulted primarily from a lower placebo response rate between cases beginning before hospitalization compared with those beginning in the hospital. That most episodes of MDD began in the hospital was an a priori hypothesis that proved incorrect; the observation that MDD beginning before vs after ACS influences drug benefit was a post hoc hypothesis and requires replication. If confirmed, our findings have significant implications for treatment of MDD associated with episodes of ACS.

At present, if a physician decides to treat depression in the setting of ACS, that decision is almost always based on the severity of symptoms in the present episode. The SADHART did find that baseline severity (measured with either the BDI or HAM-D) predicted almost a 36% increase in sertraline-placebo response ratios. However, MDD onset before the ACS episode and a history of episodes of depression are independently associated with an additional 35% to 40% increase in the sertraline-placebo response ratio. In the SADHART, less than 20% of MDD cases have all of the 3 characteristics, but this group experienced a 70% response to sertraline compared with a 29% response to placebo (ratio of sertraline response to placebo response, 2.37).

Previous episodes of depression are not diagnostic criteria for MDD, but they are predictors of the seriousness and long-term impact of the illness.[16,17] It is not surprising that classic recurrent MDD identifies cases that are more persistent and less likely to remit spontaneously. Although it was not anticipated that onset of MDD before or after ACS would predict a sertraline-placebo response difference, in retrospect, it seems likely that the onset of MDD immediately following ACS onset is also often reactive and is more likely to remit spontaneously whereas onset before the ACS episode, like recurrent MDD, identifies cases that are more persistent and less likely to remit spontaneously.

A limitation of these results is the unique population from which they are drawn, ie, a screened rather than clinical sample of patients hospitalized for ACS. Almost half of these patients experienced the onset of their present episodes of MDD following a very acute and serious stress. Whether a history of depression and MDD onset predict drug-placebo differences in more usual clinical settings or when the stressful event is the loss of a job or breakup of a relationship needs to be explored. In addition, the influence of episodes beginning before or after hospitalization is a post hoc finding and should be considered exploratory. If correct, the observation could be conceptualized as the more chronic the MDD episode, the smaller the placebo response and the larger the drug-placebo difference. In that case, episode duration should be important. If response difference between onset before and after hospitalization is conceptualized as a means of separating more classic MDD from the development of an MDD-like depressive reaction in response to the coronary event, then the important distinction is only onset before or after the stressful event. It is also possible that both issues are relevant. The data were not sufficient to support this kind of analysis. Another limitation that should be noted is that the SADHART was primarily a safety trial. Both patients receiving the drug and patients receiving placebo received multiple extra clinic visits and numerous extra tests, including electrocardiographic analysis, repeated multiple gated acquisition scans, Holter electrocardiographic recordings, and platelet studies. This added attention might itself be therapeutic and improve remission rates with both drug and placebo.

Although involving fewer than 400 patients, the SADHART found a 23% reduction in life-threatening events for patients treated with sertraline, which strongly suggests that sertraline treatment does not increase cardiac morbidity or mortality.[4] This observation is concordant with the National Heart Institute trial[18] comparing psychotherapy with usual care in which 353 patients with depression after MI also received a selective serotonin reuptake inhibitor (SSRI) (usually sertraline). Although SSRI treatment was not randomized or controlled, there was a highly significant 42% reduction in mortality and recurrent MI among the patients treated with an SSRI. While the 2 studies are not definitive evidence of a cardiac benefit of SSRI treatment and cannot rule out the risk of infrequent adverse events, they are certainly reassuring about the safety of SSRI use by most patients with ACS.

Clinicians often view MDD associated with ACS as an understandable reaction to a frightening medical ill-

ness, and they expect that depression will remit spontaneously over a few weeks. The SADHART did find that MDD observed after ACS remits on placebo more than half of the time. However, previous episodes of depression, onset of the current episode of MDD before ACS, or a severe episode of MDD each independently predicted between a 35% and 40% better response to sertraline than to placebo, but previous MDD episodes or onset of the current episode before the coronary event are seldom, if ever, used by clinicians for treatment decisions. Given the low risk of sertraline treatment, treatment based on any of these 3 characteristics seems appropriate. Depression is a painful state, and it should be treated aggressively when indicators of benefit are present. We do not know whether the mortality associated with ACS depression is predicted by the same clinical characteristics as those that predict treatment response. A large, definitive clinical trial to establish whether SSRI treatment of post-ACS depression reduces mortality and whether the type of depression influences mortality rates is needed.

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