ORIGINAL ARTICLE

Psychiatric Characteristics Associated With Long-term Mortality Among 361 Patients Having an Acute Coronary Syndrome and Major Depression

Seven-Year Follow-up of SADHART Participants

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Context: Major depressive disorder (MDD) after acute coronary syndrome (ACS) is associated with an increased mortality rate. We observed the participants of the Sertraline Antidepressant Heart Attack Randomized Trial (SADHART) to establish features of MDD associated with long-term mortality.

Objectives: To determine whether the following variables were associated with long-term mortality: baseline depression severity, previous MDD episodes, onset of MDD before or after the ACS event, 6 months of sertraline hydrochloride therapy, and mood improvement independent of treatment.

Design: SADHART was a double-blind, placebo-controlled, randomized trial comparing the safety and antidepressant efficacy of sertraline vs placebo in 369 patients with ACS who met criteria for MDD. The trial was completed in June 2000, and follow-up for vital status was completed in September 2007.

Setting: Academic research.

Participants: SADHART participants.

Main Outcome Measures: Vital status was determined in 361 participants (97.8%) during a median follow-up of 6.7 years.

Results: During the study, 75 participants (20.9%) died. Neither previous episodes of MDD, nor onset before or after the index ACS, nor an initial 6 months of sertraline treatment was associated with long-term mortality. Cox proportional hazards regression models showed that baseline MDD severity (hazard ratio, 2.30; 95% confidence interval, 1.28-4.14; $P<.006$) and failure of MDD to improve substantially during treatment with either sertraline or placebo (hazard ratio, 2.39; 95% confidence interval, 1.39-2.44; $P<.001$) were strongly and independently associated with long-term mortality. Marked improvement in depression (Clinical Global Impression–Improvement subscale score of 1) was associated with improved adherence to study medication.

Conclusions: Severity of MDD measured within a few weeks of hospitalization for ACS or failure of MDD to improve during the 6 months following ACS predicted more than a doubling of mortality over 6.7 years of follow-up. Because persistent depression increases mortality and decreases medication adherence, physicians need to aggressively treat depression and be diligent in promoting adherence to guideline cardiovascular drug therapy.

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A 1993 STUDY BY FRASURE-Smith et al[1] reporting that major depressive disorder (MDD) increased 6-month mortality 3.5-fold in patients following an acute myocardial infarction (MI) raised the question whether antidepressant treatment would reduce that risk. At the time, it was unclear whether antidepressant drugs were safe soon after an MI. The Sertraline Antidepressant Heart Attack Randomized Trial (SADHART) tested the safety and antidepressant efficacy of sertraline hydrochloride, a selective serotonin reuptake inhibitor (SSRI), for the treatment of MDD after acute coronary syndrome (ACS).[2] Sertraline gave no evidence of harm and trended toward a reduction in recurrent MI, rehospitalization for angina or heart failure, stroke, or deaths.[2] Although the study did not specifically test safety, patients in the Enhancing Recovery in Coronary Heart Disease Patients (ENRICHD) trial treated with an open-label SSRI had significantly fewer deaths or recurrent MI.[3] Although neither study was definitive, both suggested that serious adverse cardiac events were decreased during SSRI treatment. Surprisingly, a small (n=104) blinded placebo-controlled stroke study[4] showed a persistent beneficial effect on mortality 9 years after 3 months of an-

tidepressant treatment. This was the basis for our hypothesis that 6 months of sertraline treatment might show a long-term reduction in mortality rates.

Because mortality rates increase monotonically as the severity of post-MI depression increases from nondepressed, to depressive symptoms less than MDD, to a diagnosis of MDD[5-7] and because it was previously observed that severity of depression during hospitalization for ACS was associated with treatment outcome,[8] we tested whether, among SADHART participants, the severity of depression was associated with mortality during follow-up. Although not as extensively studied as severity, the literature at the time the SADHART follow-up was designed suggested that recurrent depression[9] and failure of MDD to improve with antidepressant treatment[10] were associated with increased mortality. In addition, it was reported that severity, prior episodes of MDD, and onset before or after the ACS event predicted improvement with sertraline therapy.[8]

To determine whether the same baseline characteristics that predict antidepressant success were associated with lower mortality rates, we determined the vital status of SADHART participants during almost 7 years of follow-up. Our principal objectives were to determine the long-term mortality effect of (1) baseline depression severity, (2) previous episodes of MDD, (3) onset of MDD before or after the index ACS, (4) six months of placebo-controlled sertraline treatment, and (5) mood improvement during 6 months of treatment with either sertraline or placebo.

METHODS

ORIGINAL SADHART DESIGN

Details of the original trial have been published previously.[2,8] All patients gave written informed consent for participation, and institutional review or ethics boards at each participating center approved the study. In brief, the study recruited patients who were hospitalized for ACS and found to have MDD by screening. The study tested the safety and antidepressant efficacy of sertraline in a 6-month randomized double-blind placebo-controlled trial. Randomization was stratified on left ventricular ejection fraction (<0.30 vs ≥ 0.30), depression severity using a Hamilton Depression Rating Scale (HAM-D) score of less than 18 vs 18 or higher, and the presence or absence of at least 2 previous episodes of depression. Change in MDD during treatment was quantified using the Clinical Global Impression–Improvement subscale (CGI-I).[11] Remission refers to complete recovery, defined as a CGI-I score of 1 (very much improved) and is similar to a Ham-D score of 7 or less. Enrollment began in April 1997, and the last patient was randomized in December 1999.

SUBJECT SELECTION

Patients 18 years or older hospitalized for ACS were screened for MDD (exclusion criteria were previously published[2]). At the end of a 2-week single-blind placebo period, a psychiatrist administered the Depression Interview Schedule.[12] Only patients satisfying *DSM-IV* criteria for MDD were randomized to 6 months of blinded treatment with placebo or sertraline.

FOLLOW-UP VITAL STATUS ASCERTAINMENT

The mortality follow-up protocol was approved by the Columbia University Institutional Review Board and by the Advisory Board of the National Death Index, Division of Vital Statistics, National Center for Health Statistics, US Department of Health and Human Services. The original safety and efficacy study was conducted at 44 outpatient centers in 7 countries; 81.0% of participants were recruited in the United States. Five years after the final patient completed the trial, researchers began to collect the vital status of SADHART participants. Site personnel were asked to provide evidence (office visit, laboratory testing, or documented telephone calls) of the last date on which each participant was known to be alive or the date of death if they knew the patient had died. If evidence that the patient was alive in the previous 18 months was unavailable, US sites were asked to send names and Social Security numbers to Columbia University College of Physicians and Surgeons, where they were combined with sex and birth date to create a database for submission to the National Death Index, Division of Vital Statistics, National Center for Health Statistics, US Department of Health and Human Services. The National Death Index sensitivity ranged from 87.0% to 97.9%, whereas the sensitivity of Social Security Administration files ranged from 83.0% to 83.6%.[13]

MEDICATION ADHERENCE

SADHART was conducted under Pfizer Inc's new drug application. Accordingly, the use of trial drugs was under strict supervision by protocol, sponsor monitoring, and auditing by the Food and Drug Administration. Drug use data were complete in 98.1% of participants. At each of 5 visits during treatment, SADHART supplied sufficient drug or placebo tablets to last until the patient's next scheduled visit plus 1 additional week's supply. Patients were instructed to return all unused medication at the next visit. The returned tablets were counted and subtracted from the number of tablets originally dispensed to obtain the nominal number of tablets ingested. Adherence was measured as the number of tablets presumed to be ingested divided by the number of tablets prescribed for the treatment interval.

STATISTICAL ANALYSIS

Differences in baseline characteristics between patients who responded and those who did not were evaluated by *t* test (continuous variables) or χ^2 test (categorical variables). Cox proportional hazards regression models were used to analyze univariate and multivariate effects of risk factors on the time to death.[14] The risk factors are (1) baseline severity (HAM-D score <18 vs ≥ 18), (2) a previous episode of major depression, (3) onset of depression before or after the index event, (4) treatment assignment at randomization (sertraline vs placebo), and (5) response to 6 months of therapy (judged by the CGI-I score). The effects of the risk factors are described by their Cox regression hazard ratios (HRs) and 95% confidence intervals (CIs). All Cox regression models included age and sex as covariates. Cumulative mortality curves were computed by the Kaplan-Meier method.

RESULTS

Collection of vital status information began in the spring of 2005, which was 5 years after the last patient completed treatment, and was finished in the summer of 2007. Vital status was obtained on 361 of the SADHART's 369 participants (97.8%); 75 (20.9%) died during a median follow-up of 6.7 years.

We first tested whether, among SADHART participants, the severity of depression was associated with the mortality rate during follow-up. Because the SADHART

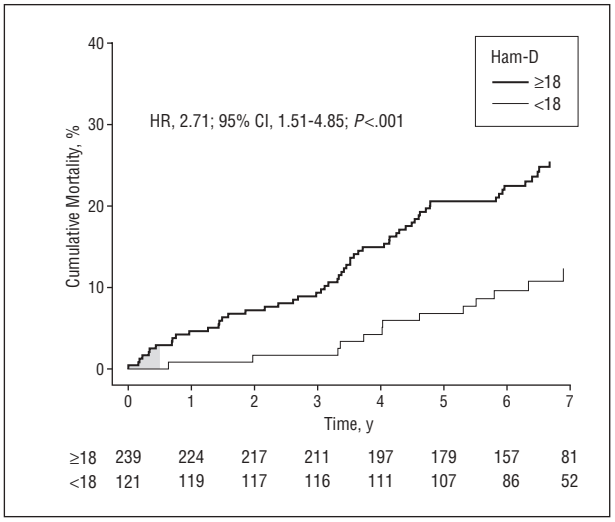

Figure 1. Cumulative mortality among 360 participants with an acute coronary syndrome and major depressive disorder. The severity of depression at baseline was stratified by Hamilton Depression Rating Scale (HAM-D) score and was adjusted for age and sex. The thicker line represents participants with a baseline HAM-D score of 18 or higher (severe depression), and the thinner line represents participants with a baseline HAM-D score of less than 18. The numbers of participants who are at risk at the beginning of each year after randomization are listed under the x-axis. The shaded area between curves represents the 6-month period when participants were treated with blinded Sertraline Antidepressant Heart Attack Randomized Trial medication. CI indicates confidence interval; HR, hazard ratio.

Table 1. Time of Depression Onset, History of MDD, and Mortality Rate

Present Episode, Onset Prior to ACS Event	Previous Episode of MDD, No. of Deaths/Total No. (%)		Overall No. of Deaths/ Total No. (%)
	No	Yes	
No	16/90 (17.8)	14/80 (17.5)	**30/170** (17.6)
Yes	20/86 (23.3)	25/103 (24.3)	**45/189** (23.8)
Total	**36/176** (20.5)	**39/183** (21.3)	**75/359** (20.9)

Abbreviations: ACS, acute coronary syndrome; MDD, major depressive disorder.

sample was stratified by severity of MDD at randomization using a HAM-D score of less than 18 or 18 or higher, this same dichotomy was used to evaluate the association of MDD severity with mortality during follow-up. We found that severity of depression during hospitalization for ACS was strongly and significantly associated with mortality during 6.7 years of follow-up (**Figure 1**).

Next, we determined the association of recurrent vs first-episode MDD with long-term mortality. Previous episodes of depression were not associated with increased mortality. Mortality was also not influenced by whether a first episode of MDD began before or after hospitalization (**Table 1**).

Because patients following stroke who received 12 weeks of antidepressant treatment had significantly decreased mortality rates during 9 years of follow-up,[4] we tested the hypothesis that 24 weeks of sertraline treatment in patients having ACS with MDD would show a similar persistent benefit on mortality. However, we found no evidence to support this hypothesis. A Kaplan-Meier

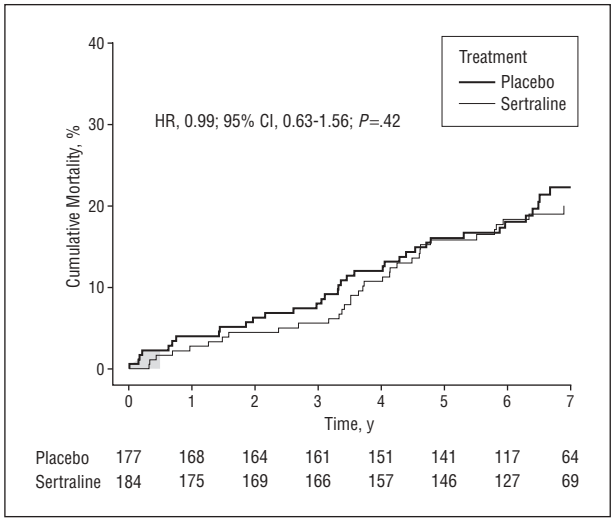

Figure 2. Cumulative mortality by treatment assignment to sertraline hydrochloride (thinner line) or placebo (thicker line) among 361 participants with an acute coronary syndrome and major depressive disorder, adjusted for age and sex. See the legend to Figure 1 for additional information.

plot (**Figure 2**) revealed no long-term mortality difference by treatment assignment (HR, 0.99; 95% CI, 0.63-1.56; $P=.42$). Therefore, the data supported only 1 of our first 4 hypotheses.

Our final objective was to test the hypothesis that mood improvement in MDD after ACS, independent of treatment, was associated with a long-term decrease in mortality. The post hoc subgroup analysis from the ENRICHD trial suggested that patients after an MI with MDD who improved while receiving treatment had lower 30-month mortality than patients whose depression persisted.[10] However, this result was puzzling because it was seen only in the group randomized to cognitive behavioral therapy and not in the usual care group.

SADHART participants whose depression improved substantially (CGI-I score 1-2 at 6 months) regardless of randomized treatment assignment (placebo or sertraline) had significantly lower mortality during 6.7 years of follow-up (**Figure 3**); 15.6% (33 of 211) of participants who were judged very much or much improved died compared with 28.4% (42 of 148) of patients whose depression showed little or no improvement (age- and sex-adjusted Cox regression model HR, 2.39; 95% CI, 1.50-3.81; $P<.001$). Because patients who improved substantially and those who did not might differ at baseline in characteristics that are associated with mortality, we compared baseline characteristics for these 2 groups (**Table 2**). The left ventricular ejection fraction (LVEF) and a history of hypertension differed significantly between patients who improved substantially and those who did not. Patients whose depression did not improve had a lower LVEF and were more likely to have a history of hypertension, both of which are risk factors for mortality. Controlling for hypertension in a multivariate Cox regression analysis reduced the HR for response from 2.39 to 2.27 (95% CI, 1.42-3.65), while controlling for the LVEF reduced the HR to 1.92 (95% CI, 1.15-3.20; $P=.01$). Controlling for both hypertension and LVEF, the HR was 1.76 (95% CI, 1.04-2.97; $P=.04$).

To determine whether the degree of improvement in depression was associated with lower mortality, CGI-I score categories were tabulated (**Table 3**). A Cox regression model showed that lower CGI-I scores were associated with decreased mortality ($P<.001$) during a median follow-up of 6.7 years and that the reduction in mortality was primarily associated with complete remission (CGI-I score of 1). In the ENRICHD trial, failure of depression to improve was associated with increased mortality but only in the active treatment arm[10]; we found that lack of improvement in depression was associated with increased mortality in both the sertraline and placebo arms of SADHART (**Table 4**).

Because severity of MDD also was associated with mortality, we tested whether the association of baseline severity (HAM-D score ≥18) with long-term mortality was independent of the association of failure of MDD to improve (CGI-I score ≥3) with long-term mortality. In a multivariate Cox regression model, baseline depression severity and failure to improve were significantly associated with long-term mortality (**Table 5**). A CGI-I score of 1 (very much improved) had a stronger association with long-term mortality, and like patients with a CGI-I score of 2 or lower, the association with mortality among 130 participants who had a CGI-I score of 1 remained independent of baseline depression severity compared with 228 participants who had a CGI-I score of 3 or higher, adjusting for the HAM-D score (<18 vs ≥18). In a Cox regression model for participants with a CGI-I score of

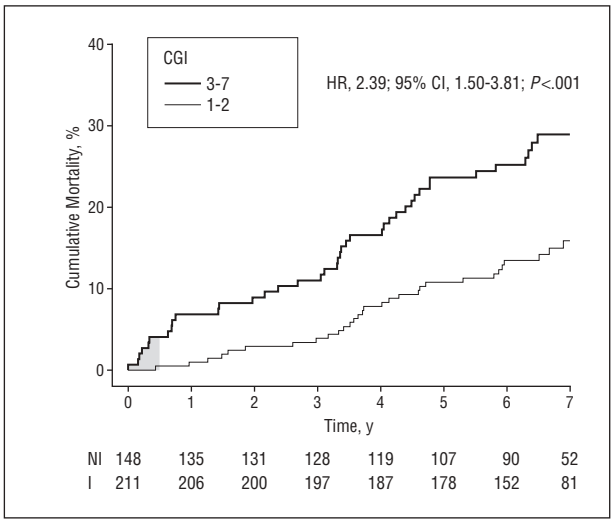

Figure 3. Cumulative mortality by response of depression (improved or not improved) to blinded therapy with sertraline hydrochloride or placebo, adjusted for age and sex. The thinner line represents participants who were very much or much improved (Clinical Global Impression–Improvement subscale [CGI-I] score 1-2), and the thicker line represents participants who were not improved (CGI-I score 3-7). I (improved) and NI (not improved) represent the numbers of participants who are at risk at the beginning of each year after randomization. See the legend to Figure 1 for additional information.

Table 3. Clinical Global Impression–Improvement Subscale (CGI-I) Score Categories, Proportions, and Mortality Rates[a]

CGI-I Score	Definition	No. (%)	No. of Deaths (%)
1	Very much improved	131 (36.5)	15 (11.5)
2	Much improved	80 (22.3)	18 (22.5)
3	Minimally improved	65 (18.1)	20 (30.8)
4	No change	45 (12.5)	13 (28.9)
5	Minimally worse	26 (7.3)	8 (30.8)
6	Much worse	12 (3.3)	1 (8.3)
7	Very much worse	0	0
Total	. . .	**359** (100.0)	**75** (20.9)

Abbreviation: ellipsis, not applicable.
[a] There were 361 Sertraline Antidepressant Heart Attack Randomized Trial participants for whom baseline and follow-up all-cause mortality information was available but only 359 participants with CGI-I scores and mortality information.

Table 2. Baseline Characteristics by CGI-I Scores

Baseline Characteristic	CGI-I Score 1-2 (n=211)	CGI-I Score 3-7 (n=148)	*P* Value
Age, mean (SD), y	58 (11.0)	57 (11.0)	.43
Female sex, No. (%)	82 (38.9)	46 (31.1)	.13
MI at enrollment, No. (%)	176 (83.4)	112 (75.7)	.07
Current smoker, No. (%)	59 (28.0)	42 (28.4)	.93
History of hypertension, No. (%)	126 (59.7)	107 (72.3)	.01
History of diabetes mellitus, No. (%)	63 (29.9)	47 (31.8)	.70
Hyperlipidemia, No. (%)	148 (70.1)	95 (64.2)	.24
Previous MI, No. (%)	83 (39.3)	68 (45.9)	.21
History of vascular procedure, No. (%)	127 (60.2)	80 (54.1)	.25
Obesity, No. (%)	69 (32.7)	48 (32.4)	.96
Body mass index, mean (SD)[a]	29 (7.0)	31 (7.0)	.08
Killip class 1, No. (%)	194 (91.9)	136 (91.9)	.63
Left ventricular ejection fraction, mean (SD), %	54 (11.0)[b]	50 (13.0)[c]	.003
Heart failure, No. (%)	27 (12.8)	23 (15.5)	.46
New York Heart Association class II-IV, No. (%)	15 (7.1)[d]	12 (8.1)	.72

Abbreviations: CGI-I, Clinical Global Impression–Improvement Subscale; MI, myocardial infarction.
[a] Calculated as weight in kilograms divided by height in meters squared.
[b] Information missing for 26 participants.
[c] Information missing for 27 participants.
[d] Information missing for 3 participants.

Table 4. Association of Depression Improvement With Mortality by Treatment Assignment

CGI-I Score	No. of Deaths/Total No. (%)		
	Placebo	Sertraline	Total
1-2	12/92 (13.0)	21/119 (17.6)	**33/211** (15.6)
3-7	25/84 (29.8)	17/64 (26.6)	**42/148** (28.4)
Total	**37/176** (21.0)	**38/183** (20.8)	**75/359** (20.9)
Hazard ratio (95% confidence interval)[a]	2.94 (1.46-5.91)	1.98 (1.02-3.84)	. . .

Abbreviations: CGI-I, Clinical Global Impression–Improvement subscale; ellipsis, not applicable.

[a] P=.42, test for interaction (ie, 2.94 is not significantly different from 1.98).

Table 5. Relationships of Baseline Depression Severity (HAM-D Score), CGI-I Score, and Crude Mortality Rate During a Median Follow-up of 6.7 Years

HAM-D Score	CGI-I Score, No. (Crude Mortality %)			
	1	2	3-7	Total
<18	58 (5.2)	20 (15.0)	43 (18.6)	**121** (11.6)
≥18	72 (16.7)	60 (25.0)	105 (32.4)	**237** (25.7)
Total	**130** (11.5)[a]	**80** (22.5)	**148** (28.4)	**358** (20.9)[a]

Abbreviations: CGI-I, Clinical Global Impression–Improvement subscale; HAM-D, Hamilton Depression Rating Scale.

[a] The discrepancy between the 130 participants in CGI-I score category 1 in this table and the 131 participants in Table 3 results from a single participant who had CGI-I score data but no baseline HAM-D score.

3 or higher, the adjusted HR was 2.92 (95% CI, 1.63-5.22; $P<.001$), and the HR was 2.30 (95% CI, 1.28-4.14; $P<.006$) for a HAM-D score of 18 or higher.

A recent study[15] documents that improvement in depressive symptoms improves adherence to aspirin therapy after ACS. Adherence to cardiovascular medications after ACS reduces mortality[16] and could mediate the relationship between failure of MDD to improve substantially and long-term mortality. SADHART did not measure adherence to cardiovascular medications but performed pill counts for sertraline and placebo, which could be a surrogate for adherence to cardiovascular medications. Participants whose depression improved had significantly greater medication adherence. The mean (SD) percentage of prescribed tablets taken by 187 patients whose depression improved substantially (CGI-I score 1-2) after they attained a clinical response was 77.4% (22.1%). For 146 patients with a CGI-I score of 3 to 7, the mean (SD) percentage over the entire treatment period was 68.6% (22.6%). This 8.8% higher adherence is statistically significant (P=.002) but could result from adherent patients' being more likely to respond rather than responding patients' becoming more adherent. To determine this, we compared responders' medication adherence before and after improvement in MDD. Medication adherence increased among 128 of 187 participants (68.4%) who remitted (CGI-I score of 1) following remission. This is significantly greater than would be expected by chance ($P<.001$).

COMMENT

The literature indicates that depression is associated with increased mortality and that the risk increases from nondepressed, to depressive symptoms less than MDD, to a diagnosis of MDD.[5-7] Even in this truncated sample in which all patients met criteria for MDD, severity strongly predicts long-term mortality. When this study was designed, a published study[9] supported (and we expected) that patients with previous MDD episodes would also have greater mortality. Our rationale was that previous episodes reflected chronic depression and would be associated with higher mortality, while a first MDD episode during a coronary event was more likely to be a reaction to ACS and to be associated with less mortality. Contrary to our expectation and the early data by Lesperance et al,[9] SADHART participants with no previous episodes, those with only 1 previous episode, and those with 2 or more previous episodes had similar long-term mortality. Onset of MDD before or after the index coronary event also had no significant association with long-term mortality. These issues have recently become a point of controversy in the literature.[17] Our evidence indicates that a first episode of post-MI MDD carries at least as much risk for long-term mortality as recurrent MDD.

Similar to the suggestion by Carney et al,[10] failure of depression to improve substantially during 6 months of treatment (sertraline or placebo) was associated herein with increased long-term mortality rates. Two recent studies[18,19] also indicate that cardiovascular events are associated with depression response. Although it remains uncertain whether treating MDD reduces mortality rates, patients whose post-ACS depression does not improve have twice the risk of dying as those who improve. When patients with MDD after ACS do not respond to antidepressant treatment, a special effort should be made to promote lifestyle improvements and cardiovascular medication adherence. Lack of adherence to guideline cardiovascular drug therapy increases mortality after an MI,[16,20,21] and depression reduces medication adherence.[22-24] Recently, improvement in depression was shown to improve aspirin adherence,[15] and the SADHART pill counts support this observation and suggest that medication adherence improves primarily with complete remission.

A striking observation in SADHART is that 2 psychological characteristics, severity of MDD soon after admission for ACS and failure of depression to improve substantially when treated for 6 months with sertraline or placebo, are independently associated with more than a doubling of the 7-year mortality rate. The association of recovery from depression with lower mortality rates could be partially explained by medication adherence, but this does not explain the effect of severity. Adherence improves when depression remits, while baseline severity is associated with mortality independent of the 6-month outcome. Among consecutive patients with an MI, the risk of dying increases with greater depressive severity, and this association is independent of the usual post-MI risk factors.[5,7,25] Depres-

sion[26,27] and cardiovascular disease[28] are associated with increased serum levels of inflammatory markers, and these markers are not usually included when examining post-ACS risk factors. Traditionally, the inflammatory state associated with depression is thought to accelerate atherosclerosis and to increase the risk of cardiac death.[29-31] However, inflammatory activity may also be a risk factor for depression.[32] Interferon alfa increases inflammation and is associated with augmented onset of MDD,[33] while treatment with drugs that decrease inflammatory markers have been noted to decrease depression.[34,35]

If an inflammatory state associated with ACS provokes depression, it could explain the extraordinary frequency of depression after acute coronary events. The rate of MDD observed in the first few weeks after an infarction is regularly reported to approach 20%.[3,36,37] In the US general population, the 1-year MDD prevalence is 7%, and the lifetime prevalence is 16%.[38] Thus, the rate of MDD during the first few weeks after a coronary event is more than the lifetime prevalence in the general population, even though MDD occurs primarily among women while patients with ACS are predominantly men. The rate of MDD associated with ACS is often attributed to the stress of the acute cardiac event, but recent studies[8,39] show that most MDD episodes observed during ACS begin before the coronary event. However, if inflammatory activity in ACS provokes depression, this might explain the high frequency of depression associated with ACS and our observation that a first episode of MDD related to ACS has the same or, as others have reported,[40-42] even greater morbidity and mortality than recurrent MDD.[9] Some first episodes of MDD beginning after ACS are probably reactive and improve spontaneously. However, others may be provoked by vascular disease with high levels of inflammation, show little improvement, and carry a high risk of dying.[43] Although some studies[26,27,44] have found that inflammatory markers are increased in depression, other recent findings suggest that inflammatory markers associated with depression contribute only modestly to new coronary events.[45,46] To our knowledge, there are no published studies testing whether inflammatory markers in ACS are associated with new episodes of major depression. Establishing inflammation as a causal factor in depression associated with ACS could provide a rationale for the use of anti-inflammatory drugs in post-ACS depression.[47,48]

A limitation of all studies of psychosocial risk factors in coronary syndromes is that many patients refuse to be interviewed,[5,18,42] especially older women.[5,42] Participation is further limited in placebo-controlled trials like SADHART because ethical concerns preclude randomization of patients already taking antidepressants for fear of causing relapse. Exclusion of these subjects could confound conclusions about variation between the sexes, as well as differences between first-episode and recurrent MDD. Almost 15% of patients otherwise eligible for SADHART were excluded because they were already taking antidepressants. Usual treatment trials also exclude patients with a HAM-D severity score of less than 18 to increase the chance of finding drug-placebo differences. The primary objective of SADHART was to determine safety (not efficacy), and patients with mild MDD were not excluded. This resulted in a high placebo response rate and reduced the overall drug-placebo difference. Some authors have perceived the efficacy in SADHART as modest or even unconvincing.[49] Nevertheless, our group believes that the modest overall drug effect was due to the high placebo response rate among participants with milder depression.[8] In any case, inclusion of very mild MDD had the advantage of a more representative range of post-ACS depression than usual treatment studies.

Extensive evidence indicates that medically healthy individuals experiencing depression are at increased risk to develop coronary events,[50] and the association between depression and adverse cardiac events is stronger in patients with ACS.[51] How much the presence of depression increases cardiac risk compared with the extent that cardiac disease increases the risk for depression is unclear. Depression is a syndrome with multiple pathways to a similar clinical picture.[52] In patients with active coronary heart disease, it seems likely that the association with depression is a 2-way street, and each can aggravate the other. Regardless of whether the inflammatory state is contributing to the onset of depression, depression impairs quality of life and needs to be treated. Even without definitive evidence that they reduce mortality,[53] SSRIs (especially in more severe depression) are efficacious[8] and safe[2,3,39] and improve the quality of a patient's life.[54] More severe baseline depression or lack of response should be red flags warning the clinician of more malignant cardiovascular disease and a greater likelihood of nonadherence with guideline cardiovascular drug therapy. Additional evaluation is needed to determine whether anti-inflammatory therapy will reduce depression and whether treatment of depression improves adherence to cardiovascular guideline therapy.

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