

Heart Rate Variability in Acute Coronary Syndrome Patients With Major Depression

Influence of Sertraline and Mood Improvement

Alexander H. Glassman, MD; J. Thomas Bigger, MD; Michael Gaffney, PhD; Louis T. Van Zyl, MB, ChB, MMed (Psych)

Context: Major depressive disorder (MDD) associated with acute coronary syndrome (ACS) increases the risk of mortality. Decreased heart rate variability (HRV), also a predictor of mortality, is reduced in patients with MDD after ACS, and has been suggested to be a mediator of MDD mortality after ACS. Although selective serotonin reuptake inhibitors may reduce mortality post-ACS, little is known about their effects on HRV.

Objective: To examine the influence of both sertraline and improvement in mood on HRV.

Methods: The Sertraline Antidepressant Heart Attack Randomized Trial assessed HRV from 24-hour Holter electrocardiogram recordings at baseline in 290 patients and from a second recording in 258 of these patients 16 weeks after randomization to sertraline or placebo. Frequency domain measures of HRV included high-frequency power, low-frequency power, very low-frequency power, ultra low-frequency power, and total power. Depression severity was measured by the Hamilton Rating Scale for Depression. Clinical response was measured with the Clinical Global Impressions Improvement scale.

Results: At baseline, prior episodes of MDD were associated with lower HRV. Sertraline significantly increased ultra low-frequency power, while improvement in mood was associated with higher low-frequency power independent of treatment. However, the expected recovery in HRV following ACS was not observed in patients with MDD. Higher ultra low-frequency during sertraline treatment and higher low-frequency power in patients whose mood improved resulted primarily from these measures decreasing in their comparison groups.

Conclusions: Heart rate variability recovery is impaired in depressed patients after ACS. Previously reported differences in baseline HRV between patients with and without depression after ACS grew larger in the 16 weeks following a coronary event. Both sertraline treatment and symptomatic recovery from depression were associated with increased HRV compared with placebo-treated and nonrecovered post-ACS control groups, respectively, but this results primarily from decreased HRV in the comparison groups.

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Author Affiliations:

Departments of Psychiatry (Dr Glassman) and Medicine (Dr Bigger), Columbia University College of Physicians and Surgeons, New York, New York; Pfizer Inc, New York, New York (Dr Gaffney); and Department of Psychiatry, Queens University, Kingston, Ontario, Canada (Dr Van Zyl).

THE 2005 EVIDENCE REPORTS/Technology Assessment from the Agency for Health Care Research and Quality found 17 studies that assessed the influence of depression on mortality following a coronary event.¹ Depression following myocardial infarction was consistently associated with about a 3-fold increase in cardiac mortality, and evidence continues to accumulate.²⁻⁴ The association between depression and cardiovascular morbidity and mortality is clear, and multiple mechanisms have been suggested. Depression has regularly been demonstrated to lower adherence to prescribed medication and secondary prevention measures.^{5,6} Plasma norepinephrine,⁷ autonomic activity,^{8,9} heart rate variability (HRV),^{10,11} platelet biomark-

ers,¹²⁻¹⁴ and inflammatory markers¹⁵⁻¹⁷ as well as omega-3 fatty acids differ between patients with clinical depression and nondepressed patients after myocardial infarction and also influence the risk for ischemic heart disease.¹⁸ The possibility also exists that depression and vascular disease share certain vulnerability genes.¹⁹

Enhancing Recovery in Coronary Heart Disease (ENRICH), a large National Heart, Lung, and Blood Institute trial, found that cognitive behavioral therapy, compared with usual care, reduced depression but not mortality in patients with depression after myocardial infarction.²⁰ Though the trial was neither randomized nor controlled, 20% of the 1853 patients with depression in both the cognitive behavioral therapy and usual care arms received an antidepressant; those individuals had a statistically significant 42%

reduction in death or recurrent myocardial infarction.²¹ The Sertraline Antidepressant Heart Attack Randomized Trial (SADHART) demonstrated the safety and efficacy of sertraline treatment in 369 acute coronary syndrome (ACS) patients and observed a reduction in death and recurrent myocardial infarction similar to that seen in ENRICHED.²² Although randomized and controlled, SADHART was not powered to detect an effect on mortality and, as would be expected, the observed effect was not statistically significant. A study testing whether sertraline could prevent the onset of depression in 137 poststroke patients without depression also showed a trend of selective serotonin reuptake inhibitors (SSRIs) to reduce life-threatening events.²³ While treatment was randomized and controlled, the observations of reduced morbidity and mortality were post hoc and not evaluated blindly. These 3 studies are each inconclusive, but together they strongly suggest that SSRIs reduce medical morbidity and mortality following myocardial infarction and raise the issue of mechanisms that might underlie this reduced mortality.²⁴

Low HRV predicts death after myocardial infarction.^{25,26} It is reduced in depressed compared with nondepressed patients after myocardial infarction¹⁰ and has been proposed to be a mediator of the increased mortality associated with depression.²⁷ During an acute coronary episode, HRV drops and then recovers substantially though incompletely during the next few months.²⁸ Only 1 small study has examined HRV response to antidepressant drug treatment. The study involved 27 depressed patients after myocardial infarction who were treated with an SSRI or placebo and concluded that sertraline facilitated HRV recovery.²⁹ SADHART obtained paired baseline and 16-week, 24-hour Holter electrocardiogram recordings in 258 of the 369 patients randomized to sertraline or placebo and offered the opportunity to both replicate this facilitated recovery and to examine whether it was caused by the drug, clinical response, or both. Our hypothesis in 1997 was that (1) baseline HRV would be lower in major depressive disorder (MDD) patients with more severe symptoms and/or with prior episodes of MDD and (2) sertraline would increase HRV more than placebo. The 2001 publication by McFarlane et al²⁹ suggested to us that depression might impair HRV recovery following myocardial infarction and we also sought to examine this possibility in the SADHART data.

METHODS

STUDY DESIGN

Safety, efficacy, quality of life, and cost-benefit analyses as well as the details of the methods of SADHART have been previously published.^{22,30,31} In brief, SADHART recruited patients with MDD who were hospitalized for ACS. Institutional review or ethics boards at each participating center approved the study and all patients gave written informed consent for 24 weeks of double-blind, randomized treatment with either sertraline or placebo. Enrollment began in April 1997 and follow-up assessments were completed by April 2001. An independent data and safety monitoring board observed the study.

Heart rate variability measures from 24-hour Holter electrocardiogram recordings were obtained at baseline from 290

of the 369 patients enrolled in SADHART. Paired baseline and week 16 recordings were available in 258 cases. Randomization was stratified by left ventricular ejection fraction (<30% vs \geq 30%) and depression severity (Hamilton Rating Scale for Depression score³² <18 or \geq 18 and presence or absence of \geq 2 previous episodes). Patients in the sertraline group received a mean dosage of 69 mg/d. Pill counts assessed compliance.

SUBJECT SELECTION

Men and women aged 18 years or older who were hospitalized for ACS were initially identified by medical record review or referral and were screened for MDD by a psychiatrist using the Diagnostic Interview Schedule.³³ Patients were excluded (1) if they had a systolic blood pressure greater than 180 mm Hg or a diastolic blood pressure greater than 100 mm Hg; (2) if they anticipated cardiac surgery during the next 6 months; (3) if an index event developed fewer than 3 months after coronary artery bypass graft surgery; (4) if they had a resting heart rate of less than 40 beats/min or daytime sinus pauses of more than 3.5 seconds; (5) if they had myocardial infarction or unstable angina of nonatherosclerotic etiology; (6) if they had moderate to severe heart failure as indicated by Killip class III or IV status; (7) if they had persistent clinically significant laboratory abnormalities; (8) if they had significant renal dysfunction, hepatic dysfunction, or other significant noncardiac disease; (9) if they were women of childbearing potential and were not using adequate contraception; (10) if they currently used class I antiarrhythmic medications; (11) if they used reserpine, guanethidine, clonidine, or methyl dopa; (12) if they used anticonvulsant or neuroleptic drugs; (13) if they used antidepressants or regularly used benzodiazepine or had alcohol or substance abuse or dependence in the past 6 months; (14) if they had psychotic symptoms, history of psychosis, bipolar disorder, organic brain syndrome, or dementia; (15) if they had a significant suicide risk; or (16) if they began psychotherapy in the 3 months prior to screening.

ASSESSMENTS

Heart rate variability was assessed from 24-hour Holter electrocardiogram recordings analyzed by the core Research Holter Laboratory at Columbia University. The 24-hour cassette recordings were digitized and scanned on a Marquette Holter Analysis System (GE Healthcare, Chalfont St Giles, England) that automatically identified all QRS complexes and labeled them as normal, ventricular complexes, supraventricular complexes, or noise. The labels assigned automatically by the scanner were reviewed and edited by experienced technicians. A cardiologist in the laboratory reviewed the results of each analysis. Frequency domain measures of NN (normal-normal complexes) variability were calculated on these edited files.

Frequency domain measures of HRV included high-frequency power (0.15-0.4 Hz), low-frequency power (0.04-0.15 Hz), very low-frequency power (0.0033-0.04 Hz), ultra low-frequency power (0.0033 Hz), and total power. These values were transformed to their natural logarithm and used for analysis. There is more than a 0.9 correlation between ultra low-frequency power and total power³⁴ and therefore tables and text usually report high-frequency, low-frequency, very low-frequency, and ultra low-frequency powers while omitting total power.

Depression severity was measured by the Hamilton Rating Scale for Depression. Treatment response was measured with the Clinical Global Impressions Improvement scale.³⁵ Responders were defined as having a Clinical Global Impressions Improvement score of 1 (very much improved) or 2 (much improved).

Table 1. Demographics for 290 Patients With Baseline Heart Rate Variability Measures^a

Characteristic	Patients Treated With Sertraline (n = 142)	Patients Given Placebo (n = 148)
Mean age (SD), y	57.1 (11.2)	57.7 (10.3)
Male sex	90 (61)	93 (65)
Mean LVEF (SD), %	53.1 (10.5)	52.5 (12.8)
Previous MI	64 (44)	60 (42)
Diabetes	42 (29)	42 (29)
MI rather than UA	114 (78)	94 (66)
Mean HAM-D score (SD)	19.7 (5.3)	19.5 (5.5)
Previous MDD episode	83 (56)	72 (50)
Onset before hospitalization	84 (57)	73 (51)

Abbreviations: HAM-D, Hamilton Rating Scale for Depression; LVEF, left ventricular ejection function; MDD, major depressive disorder; MI, myocardial infarction; UA, unstable angina.

^aValues are presented as number of patients (percentage) unless otherwise indicated.

The occurrence of cardiovascular events (death, stroke, myocardial infarction, or hospitalization for severe angina or congestive heart failure) was tracked during the course of the 24-week treatment period. A clinical events committee, blinded to treatment assignment, adjudicated final determination of all serious adverse events, including any cardiovascular event.

STATISTICAL METHODS

Baseline clinical and demographic variables were compared for the sertraline and placebo groups using χ^2 statistics for categorical variables and *t* tests or analysis of variance for continuous variables. Analysis of change in HRV from baseline to week 16 was examined using analysis of covariance. The model consisted of the baseline HRV score as the covariate and the following 2 factors (and the interaction between them): treatment group (sertraline or placebo) and response (responders or nonresponders). Thus, the effect of treatment on the 16-week HRV change is adjusted for the effects of response and baseline HRV. Similarly, the effect of response on the 16-week HRV change is adjusted for the effects of treatment and baseline HRV. Heart rate variability measurements were transformed to their natural logarithms. Baseline and week 16 means are presented on the logarithm scale. The mean changes in the HRV measurements on the logarithm scale are reverse transformed to obtain the mean percentage change (geometric mean) on the absolute scale. Total power was not included in this analysis because it is nearly completely redundant with ultra low-frequency power scores and could cause multicollinearity problems in the regression analysis.²⁵ All tests of statistical significance were 2 tailed.

RESULTS

Baseline Holter electrocardiogram recordings were obtained in 290 (79%) SADHART patients a mean 3 weeks after their hospital admission and were repeated in 258 patients 16 weeks later. Baseline measures of HRV decreased significantly with age, diabetes, and impairment of left ventricular ejection function (data not shown). **Table 1** presents baseline characteristics by treatment. Among the 290 cases in which Holter electrocardio-

Table 2. Natural Logarithm of Heart Rate Variability by Treatment^a

Spectral Component	Baseline, Mean (SD)	Week 16, Mean (SD)	Change, %
Patients Given Placebo (n = 133)			
Ln ULF	9.07 (0.80)	8.96 (0.79)	- 10.1 ^b
Ln VLF	6.78 (1.02)	6.72 (1.01)	- 5.1
Ln LF	5.51 (1.15)	5.46 (1.24)	- 5.6
Ln HF	4.65 (1.12)	4.68 (1.08)	2.9
Patients Treated With Sertraline (n = 125)			
Ln ULF	8.89 (0.75)	8.99 (0.89)	9.7
Ln VLF	6.74 (0.88)	6.66 (0.94)	- 8.1
Ln LF	5.47 (1.15)	5.35 (1.13)	- 11.2 ^b
Ln HF	4.57 (1.02)	4.47 (1.02)	- 9.2

Abbreviations: HF, high-frequency power; LF, low-frequency power; ULF, ultra low-frequency power; VLF, very low-frequency power

^aMean changes in heart rate variability on the logarithm scale are reverse transformed to obtain mean percentage change (geometric mean) on the absolute scale.

^b*P* values < .05 for baseline to week 16.

gram recordings were obtained, there were no significant baseline differences between patients treated with sertraline or placebo (Table 1). These 290 baseline cases as well as the 258 patients who had repeat HRV measures available very closely resembled the patients who did not have recordings.

BASELINE HRV MEASURES AND DEPRESSION CHARACTERISTICS

The response ratio (drug-placebo response) of post-ACS depression to sertraline has been shown to be associated with pretreatment severity of the present depressive episode, history of prior MDD episodes, and the onset of the present episode before or after hospitalization.³¹ Recently, prior MDD episodes have been associated with both an increasing cardiac risk profile and an increased risk of cardiac events.³⁶ Accordingly, we tested whether baseline HRV measures varied by these characteristics. There was no association between depression severity and onset of the present episode before or after hospitalization and any measure of HRV. Previous MDD episodes were associated with lower baseline very low-frequency power (*P* = .04) and had a borderline association with lower ultra low-frequency power (*P* = .07). Baseline HRV measures were not associated with subsequent improvement in depression either in the sertraline or placebo group.

HRV CHANGE WITH SERTRALINE, REMISSION OF DEPRESSION, AND RECOVERY FROM ACS

Contrary to previous studies in unselected patients with depression after myocardial infarction,²⁸ no significant increases in any HRV measure from baseline to 16 weeks were seen in patients receiving either sertraline or placebo. In 6 of the 8 measures examined, 16-week HRV variables were actually numerically lower than at baseline (**Table 2**) and these decreases were statistically significant (*P* < .05) for ultra low-frequency power in patients

Table 3. Independent Influence of Treatment and Depression Response on HRV From Baseline to Week 16^a

HRV Spectral Power	Mean Change (%)		P Value
	Sertraline	Placebo	
Ln ULF	0.086 (9.1)	- 0.113 (- 10.7)	.02
	Improved Mood	Not Improved	
Ln LF	- 0.012 (-1.2)	- 0.220 (- 19.7)	.05

Abbreviations: HRV, heart rate variability; LF, low-frequency power; ULF, ultra low-frequency power.

^aThe effect of treatment is adjusted for the effects of response and baseline HRV by analysis of covariance. Similarly, the effect of response is adjusted for treatment and baseline HRV. Each remained significant.

given placebo and low-frequency power in patients given sertraline. Earlier studies of consecutive post-myocardial infarction patients indicated that HRV increased approximately 50% in the first 3 months following the coronary event with only limited further recovery at 6 or 12 months.²⁸ Patients with MDD treated with sertraline experienced a 9% increase at 16 weeks in ultra low-frequency power that was statistically significant compared with the placebo group. The statistical advantage of sertraline over placebo was the result of a 10% decrease in ultra low-frequency power in the placebo group at 16 weeks (as would be expected, total power was also significantly greater in patients taking SSRIs). Improvement in depression was examined separately in patients treated with placebo or sertraline (data not shown). Clinical response, compared with nonresponse (Clinical Global Impressions Improvement score of 1 or 2 vs 3 or 4), was associated with higher low-frequency power. The association of mood response and low-frequency power was the result of a statistically significant 20% decrease in low-frequency power with poor mood response ($P = .02$). Sertraline's effects on ultra low-frequency power remained significant after adjusting for the patient's response to treatment and the increase in low-frequency power seen with improving mood was also independent of whether the patient was treated with sertraline or placebo (**Table 3**).

Both SADHART and McFarlane et al²⁹ observed a less than 10% HRV recovery in patients given sertraline and essentially a 10% decrease in patients given placebo. McFarlane et al²⁹ observed a 28% HRV recovery in 11 non-depressed patients after myocardial infarction. In a large, unselected post-myocardial infarction sample collected during the same period, Jokinen et al³⁷ observed a 33% HRV recovery (**Figure**).

COMMENT

We describe 2 previously unreported observations concerning HRV and major depression in the 4 months following an acute coronary episode. First, and perhaps most importantly, major depression severely impairs HRV recovery following an acute coronary event (Figure). Second, sertraline compared with placebo treatment, and improvement in mood compared with nonresponse were

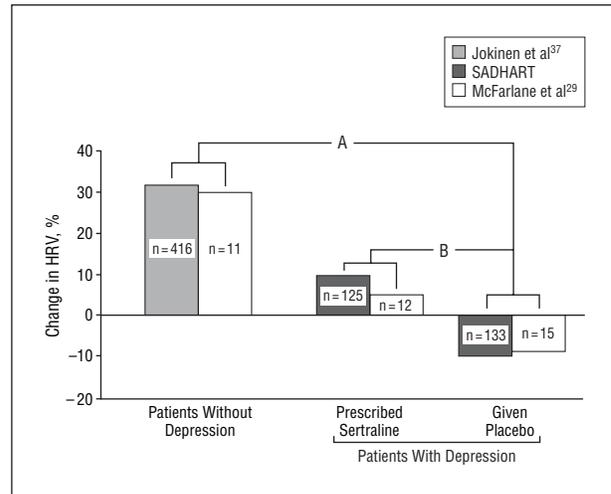


Figure. Heart rate variability (HRV) recovery following myocardial infarction in the Sertraline Antidepressant Heart Attack Randomized Trial (SADHART) and studies by Jokinen et al³⁷ and McFarlane et al.²⁹ Comparison A contrasts 2 samples of acute coronary syndrome (ACS) patients who were not depressed with the depressed patients given placebo after ACS from the current study and that by McFarlane et al.²⁹ Patients who were not depressed after ACS showed substantial HRV recovery, while HRV in depressed ACS patients given placebo actually decreased from baseline. Comparison B contrasts 2 studies of ACS patients with major depressive disorder who were randomized to receive placebo or sertraline (SADHART [the current study] vs McFarlane et al²⁹). In both, the differences between sertraline treatment and placebo were significant and the percentage changes in each from baseline were almost identical. All 3 studies collected patients from September 1996 through December 1999.

associated with improved HRV. This improvement occurs in different HRV spectral components and each is independent of the other. Significance with both sertraline and improving mood occurs when compared with the control condition, not when compared with baseline HRV measurements. There is no significant recovery in any spectral component from baseline. Significance occurs because ultra low-frequency power in patients given placebo and low-frequency power in non-responding patients decrease from baseline.

Heart rate variability is a well-recognized measure reflecting fluctuations in autonomic activity and is a moderately strong and independent predictor of death.^{25,38,39} However, the effect of antidepressant drug treatment on HRV is complex. Heart rate variability could change in medically healthy depressed patients as a pharmacological effect of the antidepressant drug, a consequence of improvement in depressive illness, or a combination of both. The same is true of depressed patients with stable heart disease. Available data are limited and contradictory, and the effects of improving mood and drug treatment are often not distinguished. Tricyclic antidepressants decrease HRV owing to their anticholinergic effects.⁴⁰ Studies of SSRIs have found either increased HRV or no change.^{41,42} A single report of cognitive behavioral therapy in stable heart disease suggested some improvement in HRV among patients with more severe depression.⁴³ Studies of electroconvulsive therapy tend to show increased HRV with clinical improvement.^{44,45} However, the HRV measures used are inconsistent and there are contradictions.⁴⁶

Measures of HRV are stable in both medically healthy, depressed patients and depressed patients with stable heart

disease. In contrast, during ACS episodes among unselected patients, HRV falls abruptly and, among survivors, recovers gradually but incompletely in the ensuing weeks.^{28,37} Earlier studies show that, after myocardial infarction, HRV values increase approximately 50% between 3- and 12-week measurements.²⁸ In post-ACS patients with depression, improvement in HRV could therefore result from the pharmacological action of an antidepressant drug, from an improving mood independent of the drug, or as a result of recovery from the acute cardiac injury. In the only previous study of antidepressant drug treatment on HRV after myocardial infarction, McFarlane et al²⁹ compared 12 depressed patients treated with sertraline, 15 depressed patients given placebo, and 11 nondepressed controls. He observed that, compared with placebo, sertraline increased HRV and concluded that sertraline facilitated the rate of HRV recovery. The sample was too small to control for the influence of mood changes on HRV.

With 258 patients, SADHART is by far the largest data set examining the effects of antidepressants on HRV and offered an opportunity not only to validate the observations made by McFarlane et al²⁹ but also to examine the influence of improvement in depression independent of drug treatment. As in McFarlane and colleagues²⁹ study, sertraline increased HRV more than placebo. Patients treated with sertraline in SADHART experienced a 9% increase in ultra low-frequency power, far less than previously observed in large, unselected post-myocardial infarction samples.^{25,37} Statistical significance occurred because ultra low-frequency power decreased 10% in MDD patients given placebo. Although McFarlane et al²⁹ did not emphasize it, placebo cases also decreased 9% from their baseline values (Figure).

The other significant difference from baseline to week 16 was that low-frequency power increased in patients whose depression improved compared with those who did not improve, regardless of whether they received sertraline or placebo. However, again, it was not that low-frequency power increased as mood improved, but rather that low-frequency power declined by almost 20% from baseline in those whose mood failed to improve. Our original expectation was, like that of McFarlane et al,²⁹ that sertraline would increase HRV recovery. Strikingly, rather than the expected recovery, most HRV measures actually decreased compared with their baseline. Low-frequency power decreased significantly in patients whose depression failed to improve ($P=.02$) and ultra low-frequency power decreased significantly in patients treated with placebo (10.1%, $P<.05$) (Table 2). To our knowledge, no one has ever reported that HRV measures in ACS patients with depression actually worsen in the months following ACS.

The baseline observations were also not what we expected. We recently reported that severity of the present MDD episode, prior episodes of MDD, and onset of MDD before or after hospitalization were all independent predictors of sertraline response among patients with depression following ACS.³¹ We anticipated these characteristics would also be associated with baseline HRV, because they tend to separate more classic or biological depression from the more reactive cases following myocardial infarction.

However, severity of the depressive episode and onset in the hospital were not associated with differences in any spectral component of HRV. Previous episodes of MDD were associated with lower baseline very low-frequency power ($P=.04$) and had a borderline association with lower baseline ultra low-frequency power ($P=.07$). Consistent with this adverse impact of prior depressive episodes, a recent study of 505 women with coronary disease found that a prior history of depression treatment predicted an increase in life-threatening cardiac events.³⁶

That ultra low-frequency power would increase in patients given sertraline compared with those given placebo was an a priori hypothesis and replicates the finding of McFarlane et al.²⁹ The finding that low-frequency power is higher in responders than nonresponders regardless of treatment is post hoc and needs replication. That HRV measurements in SADHART's post-ACS patients with depression failed to increase as much as expected could conceivably result from improved ACS treatment since the original large studies of HRV recovery after myocardial infarction.²⁵ Treatment changes might result in smaller infarcts and less severe reduction of initial post-myocardial infarction HRV, and recovery might no longer produce 50% increases. However, McFarlane and colleagues²⁹ 11 post-ACS controls without depression were collected during the same years as the SADHART sample yet still showed a 28% increase in SDNN (standard deviation of the mean of qualified NN-interval; a time domain measure of HRV that correlates 99% with ultra low-frequency power and total power⁴⁷). More convincingly because of the sample size, the 416 unselected post-myocardial infarction patients in the study by Jokinen et al,³⁷ also collected during the same period, showed HRV recoveries of 33%. Even if HRV increases are no longer 50%, it is very unlikely that the decreases in HRV that we observed in patients with MDD are now the norm among post-ACS patients without depression.

No study, including SADHART, has measured HRV before and after a coronary event. To what degree the drop in HRV in patients with depression parallels post-myocardial infarction patients without depression and to what degree they were already low is unknown. Although the 22-week data in the study by McFarlane et al²⁹ suggests that recovery is not just delayed, there is too little long-term data to address this issue.

Another caution involves generalizing from a restricted sample. SADHART was a safety study of sertraline treatment in patients with MDD and required a placebo-treated comparison group. Patients already treated with an antidepressant or considered a significant suicide risk were excluded. In addition, less than 60% of eligible patients agreed or were able to participate. On average, patients who were not enrolled had more severe depression. SADHART did not find an association between HRV and baseline depression severity nor found whether the present episode began before or after hospitalization, but this might stem from the restricted range of severity examined.

Although sertraline treatment increases ultra low-frequency power compared with placebo and recovery from depression improves low-frequency power compared with nonrecovery, patients treated with sertraline post-ACS ex-

perienced only one-third as much HRV recovery as patients without MDD, and thus even SSRI treatment may not fully eliminate the autonomic risk associated with MDD.

An obvious question is what mechanisms underlie these HRV predictors of cardiac mortality. That increased sympathetic and decreased parasympathetic tone increase cardiac risk is well established.⁴⁸ However, HRV reflects not just tone, but also fluctuations in autonomic activity that stem from a multiplicity of factors reflecting peripheral systemic and central nervous system as well as sinus node physiology.⁴⁹ Despite extensive study, the mechanism making low-frequency fluctuations of R-R intervals so strongly predictive of mortality remains obscure. There is evidence that measures of HRV decrease with increasing inflammatory markers.^{50,51} Abnormal inflammatory markers have consistently been associated with depression, though the specific abnormality has been inconsistent.^{15-17,52} Recently, C-reactive protein, like HRV, has been found to be persistently abnormal in depressed compared with nondepressed patients after myocardial infarction.⁵³ Whether the persistent inflammatory abnormalities in depression bear any relationship to the absence of HRV recovery is at present unknown. What is clear is that depression is associated with biological changes involving increased heart rate, inflammatory response, plasma norepinephrine, platelet reactivity, decreased heart rate variability, and now absent post-ACS HRV recovery, all of which is associated with life-threatening consequences. Understanding why these characteristics so strongly associate with depression is crucial to understanding the nature of depression itself. Depression generally precedes the onset of coronary disease^{31,54} and vascular disease is not the usual cause of depression. However, whether the vascular risk factors associated with depression stem from the neurobiology of depression or whether the risk of vascular disease and depression share common antecedents that increase the risk for both conditions⁵⁵ is a crucial issue in understanding the pathways that lead to both depression and vascular disease.

These data indicate that the baseline differences in HRV between patients with and without depression after ACS, which have previously been documented,¹⁰ actually grow larger in the months following a coronary event, because HRV in depressed patients fails to improve. From a clinician's point of view, patients with depression after myocardial infarction, especially those with prior episodes, should be both carefully watched and aggressively treated, because they are at an elevated cardiac risk and less likely to get better spontaneously. Whether the improvement in ultra low-frequency power with sertraline, low-frequency power with remission of depression, or a combination of the two moderate the medical risk associated with lower HRV can only be established with a sample large enough to evaluate medical end points.

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Correspondence: Alexander H. Glassman, MD, Department of Clinical Psychopharmacology, New York State Psychiatric Institute, 1051 Riverside Dr, New York, NY 10032 (ahg1@columbia.edu).

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