# Pharmacoeconomic Analysis of Sertraline Treatment of Depression in Patients With Unstable Angina or a Recent Myocardial Infarction

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***Background:*** The prevalence of major depressive disorder in patients with acute coronary syndromes (ACSs) is high and associated with worse cardiovascular outcomes and higher health care costs. Sertraline is the only treatment for major depressive disorder studied in a placebo-controlled trial of patients with ACS and found to be safe and effective. The cost implications of providing antidepressant treatment in this population have not yet been examined. The objective was to evaluate from a payer perspective the potential reduction in costs and psychiatric and cardiovascular events and procedures following sertraline versus placebo treatment of major depressive disorder in patients hospitalized for ACS.

***Method:*** Data were analyzed from a randomized, double-blind, placebo-controlled 24-week trial (Sertraline Antidepressant Heart Attack Randomized Trial) of sertraline treatment for major depressive disorder in patients hospitalized for ACS. Main outcome measures included frequency and costs (derived from Medicare diagnosis-related group fee schedules) of psychiatric and cardiovascular events occurring during the treatment period.

***Results:*** There was a trend toward significantly fewer psychiatric or cardiovascular hospitalizations in the sertraline compared with the placebo group (55/186 vs. 76/183; p = .054). The mean per patient cost associated with psychiatric and medical events over the course of treatment was $2733 for sertraline and $3326 for placebo, but the difference was not statistically significant (p = .32). After including the costs of the sertraline ($360 over 24 weeks), there was no increase in treatment costs for sertraline compared with placebo.

***Conclusion:*** Sertraline treatment of major depressive disorder following hospitalization for a recent myocardial infarction or unstable angina appears to be a cost-effective strategy.

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Major depressive disorder is a highly prevalent illness[1] that has a large financial impact on the health care system,[2–4] as well as society.[5] Part of this financial burden results from increased morbidity and mortality when depression co-occurs with other medical illnesses. In the case of acute coronary syndromes (ACSs), myocardial infarction (MI), or unstable angina, the presence of depressive symptoms is associated with higher rehospitalization rates following the initial coronary event[6,7] in addition to higher mortality rates.[8–11] Additional health care costs during the year following an MI have been reported to be 41% higher for patients with mild to moderate depressive symptoms compared with those without depressive symptoms.[6] Given that there are approximately 1.4 million hospitalizations for ACS each year in the United States alone,[12] and that prevalence estimates of major depressive disorder following MI and ACS range from 15% to 23%,[6,8,9,13–17] these additional health care costs due to major depressive disorder can be a significant incremental financial burden.

Pharmacologic treatment of major depressive disorder with selective serotonin reuptake inhibitors (SSRIs) is generally safe and effective, although the associated medication and provider costs are not insignificant.[18] These costs, however, are partially offset by savings resulting from decreases in nonpsychiatric health care uti-

lization.[19–21] Studies examining the cost-effectiveness of programs for treatment of depression in primary care have found increases in treatment effectiveness, but moderate increases in costs, relative to treatment as usual,[22,23] even among depressed patients who were high utilizers of general medical care.[22] No published studies have demonstrated a net cost savings for any antidepressant, relative to a control group, following treatment of depression, although treatment is considered to be cost-effective.

Successful treatment of depression in an ACS sample has the potential to lessen health care costs by reducing both psychiatric and cardiovascular emergencies resulting in hospitalizations, emergency room visits, and revascularization procedures.[24] In addition, depression may be associated with an increased frequency of outpatient visits if somatic symptoms associated with depression mimic physical illness, leading to increased physician or emergency room visits and diagnostic procedures.[25] As an example, patients with depression and comorbid anxiety may seek treatment for noncardiac chest pain resulting from their anxiety and depressive symptoms and be referred for costly diagnostic procedures. Alternatively, patient compliance with medical treatment and lifestyle modification recommendations may be lower in depressed patients, and this may lead to greater numbers of cardiac events and hospitalizations.[26] Of particular interest is whether potential reductions in psychiatric and medical health care utilization that may result from alleviation of depression can translate into net cost savings in an ACS sample.

The goal of this study was to examine this issue using a secondary analysis of data from the Sertraline Antidepressant Heart Attack Randomized Trial (SADHART).[27] Specifically, the costs of antidepressant medication and the potential cost savings from the reduction in psychiatric and cardiovascular hospitalizations and procedures for sertraline compared with placebo treatment in the SADHART sample of depressed patients with MI or unstable angina were evaluated. The primary hypothesis was that treating the depression would reduce both the number of psychiatric hospitalizations and the frequency of cardiovascular-related hospitalizations and procedures and thereby result in cost-savings for sertraline relative to placebo.

A secondary hypothesis was that patients who responded to sertraline would have lower costs than patients who were treated with sertraline but who did not achieve an antidepressant response based on the Clinical Global Impressions-Improvement scale (CGI-I)[28] criteria.

## METHOD

### Study Design

The SADHART trial has been described in detail in a previous article.[27] In summary, patients who were hospitalized for ACSs and who met DSM-IV criteria for major depressive disorder were randomly assigned to 24 weeks of treatment with either sertraline (N = 186) or placebo (N = 183). Figure 1 gives the disposition of all patients throughout the trial. Patients were recruited from 40 outpatient cardiology centers and psychiatry clinics in the United States, Europe, Canada, and Australia. All subjects provided written informed consent, and the protocol was approved by the relevant institutional review board at each participating site.

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

### Medical Events and Service Utilization

Medical event data for this study were obtained from serious adverse events reports that were collected for all patients who were hospitalized during the study. All serious adverse events were reviewed and adjudicated by blinded physician raters from the Duke University Clinical Research Institute, Clinical Events Committee (Durham, N.C.). Hospital records and discharge summaries for those patients were reviewed by a rater who was also blinded to treatment group in order to extract reasons for the hospitalization and service utilization. A decision tree was constructed using these data to describe the patterns of utilization seen in the SADHART study.

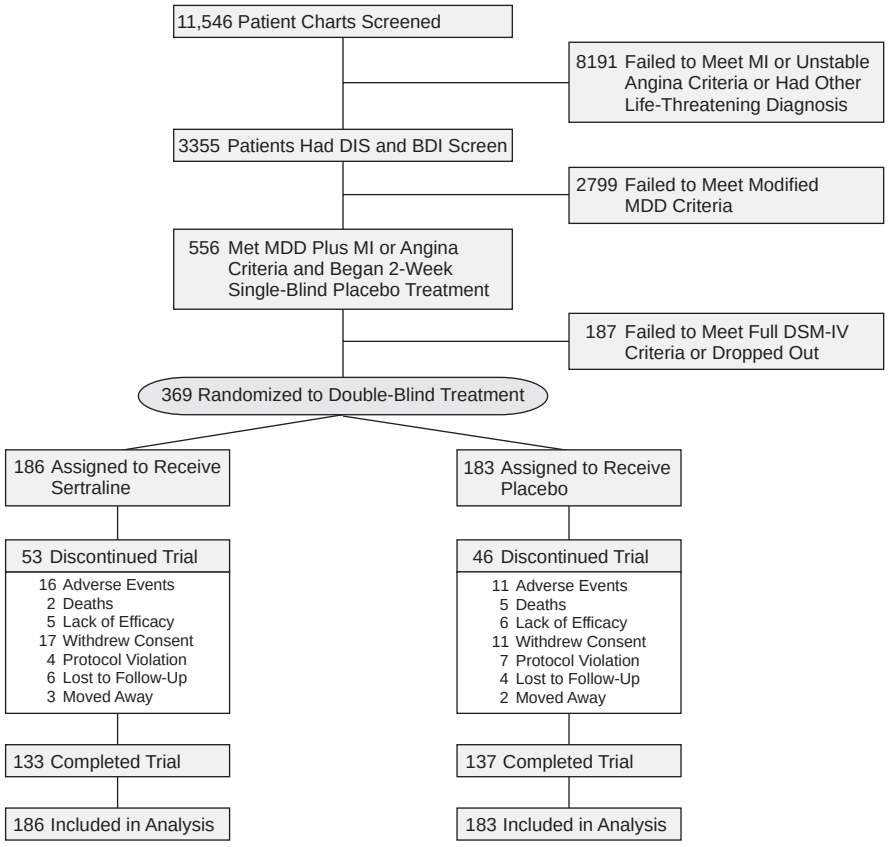
Events that occurred during the course of the study or in the 30 days following the end of the study were included in the analysis. Events occurring in the 30 days following the study were included because they may be attributable to treatment effects, and the U.S. Food and Drug Administration requires information on serious adverse events to be collected for that time period. Events that had been planned prior to the start of the study were excluded.

Events were categorized as either cardiac or psychiatric related, or as related to other medical conditions. Data on the use of outpatient services including rehabilitation were not included since those data were not routinely included in serious adverse events reports and discharge summaries and were not captured on the study case report forms.

### Cost Data

Direct medical costs, including inpatient hospitalizations, emergency room visits, and cardiac procedures such as percutaneous coronary interventions, percutaneous transluminal coronary angioplasty, and coronary artery bypass graft surgery, were included in the analysis from the perspective of a third-party payer. Indirect costs such as lost productivity and absenteeism were not included.

**Figure 1. Disposition of Patients in the Sertraline Antidepressant Heart Attack Randomized Trial[a]**




[a]Reprinted with permission from Glassman et al.[27]
Abbreviations: BDI = Beck Depression Inventory, DIS = Diagnostic Interview Schedule, MDD = major depressive disorder, MI = myocardial infarction.

Cost data were obtained from the 2001 Medicare fee schedule. Medicare costs were chosen on the basis of their ease of availability and applicability across the United States. During patient admissions, detailed descriptions of medical tests and procedures performed were captured in the medical record and categorized with the appropriate diagnosis-related group (DRG). Utilization data were translated into cost estimates using the mean reimbursement rate paid by the U.S. Health Care Financing Administration program for each DRG.[29] An implicit assumption in this is that the cost of a specific procedure is the same in both the sertraline and placebo groups. Although this may not be the case, detailed information on resource utilization while in the hospital was not available. However, there is no a priori reason to expect that there would be sufficient differences to meaningfully affect the results.

Consent was not obtained to collect hospital bills for the patients in the SADHART study. When the study was designed in 1995, the focus was on safety and efficacy, and cost analyses were not anticipated. Therefore, individual hospital costs or charge data were not available. However, use of those data would still have been problematic because many of the procedures were performed in large academic medical centers, and this would overestimate the mean costs of these procedures. In addition, this was an international study, and costs would have varied greatly by country. The Medicare fee schedule was chosen because it is based on the patient's diagnosis rather than specific utilization while in the hospital. DRG payments are based on the mean cost of the full hospital stay for a given diagnosis and thus should be generalizable across the United States. For the Medicare population, DRG payments represent the true cost to Medicare. For the under age 65 years population, payments will vary by insurer and provider, so there is no single national cost.

The cost of sertraline was based on the mean wholesale price for 2002 for 50 mg or 100 mg of sertraline, which is flat priced ($360 for 50 mg/day or 100 mg/day of sertraline for 24 weeks). This estimate was based on the final mean daily dose (68.8 mg; SD = 40.1) of sertraline taken in the study. Perfect compliance was assumed since this would tend to overestimate rather than underestimate the true medication costs.

### Statistical Analysis

Comparability of the treatment groups at baseline was assessed using 2-way analyses of variance including effects for treatment group, study center, and treatment-by-center interaction for continuous measures and Cochran-Mantel-Haenszel tests for categorical measures.

The distribution of cardiovascular/psychiatric events that required a hospitalization ranged from 0 to 4 for each patient. These events were compared for sertraline versus placebo using a z test based upon a Poisson distribution. Costs were compared using Wilcoxon nonparametric methodology.

## RESULTS

### Demographic and Clinical Characteristics of Patients

Among those patients randomly assigned to treatment, there were no significant differences in demographic characteristics, type of event leading to the index hospitalization (MI or unstable angina), or cardiovascular risk factors in patients taking sertraline or placebo (Table 1). In both treatment groups, the majority of patients were white, and there were similar numbers of men and women. About half had experienced at least 1 previous episode of major depressive disorder, and approximately 40% had experienced a previous MI.

No significant differences were found between sertraline and placebo on any of the cardiovascular safety measures, including left ventricular ejection fraction, blood pressure, heart rate, ventricular premature complex runs, and electrocardiographic variables including QTc interval. For the total sample, subjects treated with sertraline showed a significant improvement on the clinical CGI-I compared with placebo, but not on the Hamilton Rating Scale for Depression (HAM-D).[30] In the protocol-defined more severe/recurrent depression subgroup (HAM-D score ≥ 18 and 2 or more prior episodes of major depressive disorder), and in the subgroup of patients with at least 1 prior episode of major depressive disorder, patients treated with sertraline had significantly greater improvement on the HAM-D and the CGI-I than patients treated with placebo. The relative risks of a recurrent MI, death, worsening of angina, or congestive heart failure, or the composite of these variables (RR = 0.77; 95% CI = 0.51 to 1.16), were all lower for sertraline compared with placebo, but the confidence intervals for all of these variables were wide, and the results were not statistically significant.

### Rehospitalizations

There was a trend (p = .054) toward significantly fewer psychiatric or cardiovascular hospitalizations in the sertraline-treated group than in the placebo-treated group (55/186 sertraline vs. 76/183 placebo; z = 1.925, p = .054; Table 2). Forty-four patients in the sertraline group had at least 1 hospitalization for a cardiovascular or psychiatric event during the SADHART trial compared with 51 patients in the placebo-treated group, but this difference was not statistically significant. Fewer patients in the sertraline group had multiple hospitalizations compared with the placebo-treated group (8 vs. 18), but the difference was not statistically significant. The vast majority of the hospitalizations were for cardiovascular events or procedures.

**Table 1. Baseline Characteristics of Patients in the Sertraline Antidepressant Heart Attack Randomized Trial[a]**

| Variable | Sertraline Group (N = 186) | Placebo Group (N = 183) |
|---|---|---|
| Demographic | | |
| Age, mean (SD), y | 56.8 (11.1) | 57.6 (10.4) |
| Men, % | 63 | 64 |
| Race, % | | |
| White | 74 | 79 |
| Black | 12 | 14 |
| Hispanic | 14 | 7 |
| Marital status, % | | |
| Currently married or cohabiting | 55 | 72 |
| Single | 7 | 3 |
| Divorced or separated | 23 | 15 |
| Widowed | 14 | 9 |
| Cardiac | | |
| Cardiac event leading to current hospitalization, % | | |
| Myocardial infarction | 76 | 71 |
| Unstable angina | 24 | 29 |
| Cardiovascular history, % | | |
| Congestive heart failure | 12 | 16 |
| Prior coronary artery revascularization (CABG/PTCA) | 43 | 42 |
| Prior myocardial infarction (excluding index myocardial infarction) | 43 | 41 |
| Depression | | |
| HAM-D (17-item) total score, mean (SD) | 19.6 (5.3) | 19.6 (5.4) |
| History of prior episodes of major depressive disorder, N (%) | | |
| None | 89 (48) | 93 (51) |
| 1 | 37 (20) | 38 (21) |
| ≥ 2 | 60 (32) | 53 (29) |

[a]There were no significant between-group differences at baseline.
Abbreviations: CABG = coronary artery bypass graft surgery, HAM-D = Hamilton Rating Scale for Depression, PTCA = percutaneous transluminal coronary angioplasty.

### Service Utilization During Rehospitalization

The type of services provided during rehospitalizations differed between the sertraline-treated and placebo-treated groups. For example, patients taking placebo had numerically more cardiac catheterizations and more revascularization procedures (Table 2). Patients in the placebo group also had numerically more visits to the emergency room than did patients in the sertraline group (40 visits vs. 26 visits). None of these differences reached statistical significance.

### Costs Associated With Service Utilization

Excluding medication costs, the mean cost per patient in the sertraline-treated group was $2733 (SD = $6764) compared with $3326 (SD = $7195) in the placebo group

Table 2. Number of Psychiatric and Cardiovascular Events Among Patients With a Rehospitalization in the Sertraline Antidepressant Heart Attack Randomized Trial

| Event | Sertraline Group (N = 186) | Placebo Group (N = 183) | z[a] | p Value |
|---|---|---|---|---|
| Hospitalizations (for a cardiovascular or psychiatric event) | 55 | 76 | 1.925 | .054 |
| Emergency room visits | 26 | 40 | | |
| 1st event | 18 | 25 | | |
| 2nd event | 5 | 11 | | |
| 3rd event | 2 | 3 | | |
| 4th event | 1 | 1 | | |
| Cardiac catheterization and revascularization procedures | | | | |
| Total | 41 | 48 | | |
| PTCA | 7 | 3 | | |
| PTCA with stent | 4 | 13 | | |
| CABG | 9 | 6 | | |
| Cardiac catheterization | 21 | 26 | | |

[a]Based on a Poisson distribution.
Abbreviations: CABG = coronary artery bypass graft surgery, PTCA = percutaneous transluminal coronary angioplasty.

(p = .32). The difference in costs is a result of the lower number of events (emergency room visits and rehospitalizations) in the sertraline group.

After including the cost of sertraline treatment ($360 over 24 weeks), the cost for sertraline-treated patients increased to $3093 compared with $3326 in the placebo group, suggesting that sertraline treatment of major depressive disorder in an ACS population would not increase total treatment costs.

### Effect of Depression or Cardiovascular Subtype on Service Utilization

There were no meaningful or statistically significant differences in psychiatric-related or cardiovascular-related event costs for patients with recurrent depression compared with those with single episodes. Sertraline-treated patients who met CGI-I criteria for depression response had lower costs than patients who received sertraline but who did not meet response criteria ($2269 vs. $3617; p = .09). Although only 28.7% of the patients entered the study because of a hospitalization for unstable angina, they accounted for 40.2% of the total costs of psychiatric-related or cardiovascular-related events.

## DISCUSSION

The current study examined the costs associated with psychiatric and cardiac events and their related health care services that occurred during 6 months of sertraline compared with placebo treatment for major depressive disorder within a sample of patients who had recently been hospitalized for an acute MI or unstable angina. The results suggest that, in addition to relieving symptoms of depression,[27] sertraline treatment of major depressive disorder following a recent MI or unstable angina can be accomplished without increasing treatment costs. There may or may not be a net cost savings due to reduction in costs associated with psychiatric and medical events and related procedures; however, a larger study powered on this outcome is needed to address this hypothesis.

Response to sertraline was associated with a lower cost compared with nonresponse, although the difference only trended toward statistical significance (p = .09). Responders may be more representative of patients who continue on treatment in a clinical setting than the entire sertraline-treated group, because nonresponders are likely to discontinue treatment.

The treatment of depression can be costly when the depression is relatively severe and the treatment must be coordinated by a mental health specialist. However, most depressions are of mild to moderate severity, and treatment by a primary care physician is practical and appropriate, reducing the costs considerably. Several studies have found that decreases in nonpsychiatric health care utilization can partially offset such costs,[19–21] but this research has consistently suggested a net cost increase to the individual and health care system when major depressive disorder is treated by a mental health specialist or within primary care.[22,23] This study is therefore unusual in demonstrating no increase in costs from the treatment of major depressive disorder. It is important to consider that the goal of depression treatment should never be limited to reducing costs, but instead should be to enable the patient to return to normal functioning and well-being.

Although sertraline displayed a modest, but not statistically significant, advantage in the incidence of cardiac events over 6 months of treatment,[27] when the total number of cardiac or psychiatric hospitalizations was combined, there proved to be a trend (p = .054) toward a reduced risk of rehospitalization for patients treated with sertraline compared with those treated with placebo. When the costs of these hospitalizations and the procedures performed while in the hospital were incorporated, there was a numerical, but not statistically significant, decrease in costs in the sertraline group. This suggests that treatment can be accomplished without an increase in costs, but whether that potential savings would reach significance if the sample size were larger is not clear. Whether these results are unique for treatment of major depressive disorder in a population with ACS, or would also occur for patients with major depressive disorder that is comorbid with other serious medical conditions, is not known. One study of a broad range of high utilizers of medical care, however, found a moderate cost increase from the treatment of depression.[22]

The current study examined costs from the point of view of a third-party payer, specifically using Medicare costs. These results are likely to be generalizable to other third-party payers, including managed care organizations,

because the results are based on underlying event rates in the sertraline and placebo groups. The specific dollar amounts of the costs will vary based on the plan-specific cost structure. The results here are likely to underestimate the true differences, because we did not include some additional costs that would be related to the cardiovascular procedures, such as the use of outpatient rehabilitation services and concomitant medications. The costs of cardiac rehabilitation services in particular can be substantial.[31]

In addition, our cost calculations assumed perfect compliance with medication, which was not the case in the trial. If there had been perfect compliance, the benefits of treatment might have been greater than seen in this study.

Meta-analytic results of previous studies indicate that treatment of major depressive disorder can improve work functioning.[32] For a larger societal point of view, improvements in work functioning should translate to increased productivity that may provide a financial benefit that accrues following treatment of major depressive disorder. Given that the mean age was 57 years in the study, many of the patients were still of working age. Employment status was not, however, consistently available from study records.

The limitations of the results presented here are common to all pharmacoeconomic analyses that are performed in the context of a randomized clinical trial designed to evaluate the safety and efficacy of a drug treatment. These include the implementation of specific inclusion and exclusion criteria and other procedures that may limit the generalizability of the results to actual clinical practice settings. However, this trial was conducted at multiple sites across Europe, Canada, Australia, and the United States and included patients with a large variety of comorbid illnesses. The broad spectrum of patients included in this study suggest that the results are generalizable to many patient populations.

Another limitation is that the trial was conducted with adequate statistical power to detect improvements in depressive symptoms, not to detect differences in medical costs. Much larger sample sizes are typically needed to detect statistically significant differences in cost offsets. A sample size of 2000 patients per treatment would be needed to achieve 80% statistical power to detect the difference found here ($593) between sertraline and placebo in mean per patient cost associated with psychiatric and medical events, and an even larger sample would be needed to detect the difference of $233 between treatment groups when the cost of sertraline is included.

A further limitation is that the cost analysis is based upon Medicare DRG schedules, although not all of the sample were Medicare recipients. Medicare DRG costs were chosen because they are standardized, readily available, and applicable across the United States and were derived based on the relative resource utilization of different procedures and the complexity of treating different diagnoses. Other cost schedules can be readily applied to the event data to arrive at alternative costs for the sertraline and placebo groups. The inclusion of data from a multinational trial may have introduced significant heterogeneity in service utilization that could have contributed variance to the cost analysis. The use of the same depression treatment protocol and the inclusion only of costs of major events should have limited this variation. The relatively small sample size precluded meaningful cross-national comparisons. A final limitation is that the 6-month treatment period limited our ability to detect the full magnitude of cost differences. It is likely that follow-up periods of 1 year or longer are necessary to fully assess the medical and psychiatric utilization rates and corresponding costs following an acute ACS-related hospitalization.

An emerging body of research has examined the cost-effectiveness of currently used cardiovascular interventions.[33–37] Newer interventions have led to substantial benefits including reduced mortality, reduced length of stay, and improved quality of life. Frequently, these benefits tend to come at increased incremental costs. Since the goal of treatment is improved health of the patient, not cost savings, increased costs should not be viewed as a drawback. However, it is important that the value of the treatment be commensurate with the costs. One commonly used cutoff for cost-effectiveness is $50,000 for each additional quality-adjusted-life-year gained.[38]

Many commonly used cardiovascular interventions, including coronary stents,[39] coronary artery bypass grafting,[35] early invasive treatment,[40] HMG-CoA reductase inhibitors,[41] and β-blockers,[42] have been shown to be cost-effective and have been adopted as standard practice because the improved outcomes are achieved at an acceptable cost. The intervention examined in the current study stands out because it is not associated with a significant cost increase. The cost-neutral nature of depression treatment in this population suggests that programs to screen and treat depression in patients hospitalized for ACS are in the best interest of both the patient and the payer and should be adopted as the standard of care.

In conclusion, pharmacoeconomic analyses of combined psychiatric and cardiac costs during the SADHART trial suggest that treatment of major depressive disorder in an ACS population may reduce the frequency of cardiovascular/psychiatric events and related procedures and may be accomplished without increasing health care costs. The high annual number of hospitalizations for ACS in the United States (approximately 1.4 million)[12] and the estimated 15% to 23% prevalence of major depressive disorder in ACS patients[8,9,13–17] suggest that further study of treatment outcomes and costs in a larger population is warranted.

These preliminary pharmacoeconomic data, taken together with the previously published data demonstrating the efficacy and safety of sertraline treatment of major

depressive disorder in ACS,[25] provide a strong rationale for the routine identification and treatment of depression in this at-risk population.

*Drug name:* sertraline (Zoloft).

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