Enhanced Depression Care for Patients With Acute Coronary Syndrome and Persistent Depressive Symptoms

Coronary Psychosocial Evaluation Studies Randomized Controlled Trial

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Background: Depressive symptoms are an established predictor of mortality and major adverse cardiac events (defined as nonfatal myocardial infarction or hospitalization for unstable angina or urgent/emergency revascularizations) in patients with acute coronary syndrome (ACS). This study was conducted to determine the acceptability and efficacy of enhanced depression treatment in patients with ACS.

Methods: A 3-month observation period to identify patients with ACS and persistent depressive symptoms was followed by a 6-month randomized controlled trial. From January 1, 2005, through February 29, 2008, 237 patients with ACS from 5 hospitals were enrolled, including 157 persistently depressed patients randomized to intervention (initial patient preference for problem-solving therapy and/or pharmacotherapy, then a stepped-care approach; 80 patients) or usual care (77 patients) and 80 nondepressed patients who underwent observational evaluation. The primary outcome was patient satisfaction with depression care. Secondary outcomes were depressive symptom changes (assessed with the Beck Depression Inventory), major adverse cardiac events, and death.

Results: At the end of the trial, the proportion of patients who were satisfied with their depression care was higher in the intervention group (54% of 80) than in the usual care group (19% of 77) (odds ratio, 5.4; 95% confidence interval [CI], 2.2-12.9 [P < .001]). The Beck Depression Inventory score decreased significantly more (t155=2.85 [P = .005]) for intervention patients (change, −5.7; 95% CI, −7.6 to −3.8; df=155) than for usual care patients (change, −1.9; 95% CI, −3.8 to −0.1; df=155); the depression effect size was 0.59 of the standard deviation. At the end of the trial, 3 intervention patients and 10 usual care patients had experienced major adverse cardiac events (4% and 13%, respectively; log-rank test, χ2 = 3.93 [P = .047]), as well as 5 nondepressed patients (6%) (for the intervention vs nondepressed cohort, χ2 = 0.48 [P = .49]).

Conclusion: Enhanced depression care for patients with ACS was associated with greater satisfaction, a greater reduction in depressive symptoms, and a promising improvement in prognosis.

Trial Registration: clinicaltrials.gov Identifier: NCT00158054

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For editorial comment see page 585

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but no difference in the cardiac event rate between an-

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METHODS

RECRUITMENT, ENROLLMENT, AND INFORMED CONSENT

Participants were recruited at 5 hospital sites (Mount Sinai Hos-

pital and New York Presbyterian Hospital, New York, New York; and New Haven Hospital, Hospital of St Raphael, and Veter-

ans Affairs Connecticut Healthcare System–West Haven, New

Haven, Connecticut) from January 1, 2005, through February 29, 2008. Full details of the design and methods are provided elsewhere.25

Study participants were identified prospectively by moni-

toring hospital admissions for ACS diagnoses.26 To ensure that

only patients with persistent depressive symptoms were en-

rolled, trial eligibility required a score of 10 or higher on the

Beck Depression Inventory (BDI)26 on assessments within 1 week of

hospitalization for ACS and 3 months later. Patients with BDI scores below 5 at both assessment points who met all other eligibility criteria were included in a nondepressed observa-
tional cohort.

Exclusion criteria were assessed at the hospital visit and

2-month follow-up and included alcohol or other drug depen-
dency, dementia, current or past psychosis or bipolar disor-
der, terminal illness, unavailability for follow-up, BDI score of

45 or higher, or suicidality by self-report or determined dur-
ing a clinical interview.

The institutional review boards at all institutions approved

the protocol, and all participants provided written informed con-

sent. To ensure equipoise, the description of the study to pa-
tients and their physicians emphasized the possible benefits and

limitations of both the intervention and usual care conditions.

RANDOMIZATION

At each site, eligible patients were randomized on a 1:1 basis

within randomly ordered blocks of 4 or 6 patients according to

table of assignments prepared in advance by the trial statis-
tician (J.E.S.). Using a Web-based program, project coordi-
nators specified the strata, initials, and study identification num-
ber of the person to be randomized, and the program issued the

group assignment.

INTERVENTION AND USUAL CARE PROTOCOLS

The intervention included the following 5 essential compo-
nents adapted from the IMPACT study22: (1) an enhanced care

approach, with treatment delivered by a clinical nurse special-

ist, psychologist, social worker, and/or psychiatrist; (2) pa-

tient choice of psychotherapy and/or pharmacotherapy; (3) a

form of psychotherapy called problem-solving therapy (PST); (4) a stepped-care approach in which symptom severity was

reviewed every 8 weeks and treatment was augmented according
to predetermined decision rules23; and (5) a standardized instru-
ment used to track depressive symptoms.

Problem-solving therapy, as developed for the IMPACT

study, has been described in detail elsewhere.22,23,26 It is pro-
tocol driven, brief, problem focused, and designed to augment

the patient’s own skills. Patients are taught how to systemati-
cally evaluate and address individual psychosocial problems.

The initiation of and regular engagement in pleasant activities

chosen by the patient is encouraged. Visits initially occurred
weekly, in person or by telephone, with each visit lasting ap-
proximately 30 to 45 minutes. Visit frequency was decreased or in-
creased according to the progress of individual patients and

their preference.

Pharmacotherapy treatment choices included sertraline, es-
citalopram oxalate, venlafaxine hydrochloride, bupropion hy-
drochloride, and mirtazapine. A study psychiatrist or nurse prac-
titioner prescribed appropriate medication following standard
clinical practice. Intervention patients choosing pharma-
cotherapy were initially seen at 1- to 2-week intervals for dose ti-
tration and thereafter every 3 to 5 weeks as needed for the re-
mainder of the 6-month trial period. If a patient was already tak-
ing an antidepressant, treatment decisions were coordinated with
the prescribing physician. At the end of the trial, patients were pro-
vided with 6 further months of medication if they could not afford it but were referred to their usual care provider for follow-up. Four patients took advantage of this offer.

Stepped-care decisions for patients randomized to the intervention group were guided by responses to the 9-item Patient Health Questionnaire,27 administered at each treatment visit and formally evaluated at 8-week intervals. Patients who did not show prespecified improvement were offered the choice of switching treatments (eg, from PST to medication), adding the other treatment, or intensifying the original treatment choice, based on the treatment team’s recommendation (for details, see Burg et al23).

The control condition for the trial was usual care, as defined by the patient’s treating physicians. Physicians of the intervention and usual care patients were informed that their patients were participating in a trial and that they had elevated depressive symptoms; physicians were also told whether the patient met the criteria for a major depressive episode.

DATA COLLECTION

At the time of the index ACS hospitalization, demographic, medical history, and prognostic variables were collected, including left ventricular ejection fraction and Global Registry of Acute Coronary Events (GRACE) score risk.28 At 3 months, just before randomization, a structured clinical interview (Depression Interview and Structured Hamilton questionnaire)29 was conducted by telephone to assess the presence of a current major depressive episode and psychiatric exclusion criteria. All other measures at hospitalization, 3 months after hospitalization, and at the end of the 6-month intervention (month 9) were assessed in person. Measures at months 5 and 7 were obtained by telephone. Interviewers and those collecting medical outcome data were blinded to intervention assignment.

OUTCOME MEASURES

The primary outcome was satisfaction with depression care because previous treatments may not have been acceptable to patients with CHD.13 Patients were asked, “Over the last 2 months, how would you rate the quality of professional care you have received for your symptoms of distress or depression?” Patients responded on a 5-point Likert scale (1, excellent; 5, poor) or indicated that they had received no care for these symptoms; these were presented regularly in a blinded fashion to the Data and Safety Monitoring Board.

STATISTICAL ANALYSIS

Differences between the intervention and usual care groups and between the trial participants and nondepressed cohort at baseline were evaluated using a $t$ test for continuous variables and $\chi^2$ analysis for categorical variables. When baseline medical covariate data were incomplete for the GRACE and Charlson indexes, a regression-based approach was used to impute the best linear predicted score based on the available items.

Outcome Analyses

Descriptive statistics based on the raw data at baseline were used to characterize the sample. Linear and nonlinear (ie, logistic) multilevel repeated-measures modeling procedures were used to generate full-information maximum-likelihood estimates of all treatment effects (outcome at 9 months or change in outcome from months 3 to 9, after the 6-month intervention). By including all subjects and all available data, this approach yields intent-to-treat estimates that are valid under the assumption that the missing data are missing at random, conditional on the observed data.23,31 Wald $\chi^2$ statistics were used to test the statistical significance of group differences at 9 months and the differential change between groups (group × time interaction). The primary outcome was the percentage of patients who rated their depression care as excellent or very good at 9 months. Change in the BDI score was a secondary outcome. Effect size was calculated as the group difference in BDI change divided by the pooled SD at baseline. Kaplan-Meier survival curves for MACEs were estimated and compared using the log-rank test. All analyses were performed using SAS statistical software (version 9.2; SAS Institute Inc, Cary, North Carolina), including PROCs MIXED, NLMIXED, LIFETEST, and PHREG procedures.

Power Analysis

The 2-sided $\alpha$ was set at 0.05, and power was set at 0.90. The sample size was chosen to ensure this level of power to detect a 30% group difference (intervention vs usual care groups) in the proportion of patients who were satisfied with their depression care at the conclusion of the 6-month trial. This required enrolling 80 patients per group, allowing for 20% loss (eg, 64 per group with 9-month outcome data would provide a power of $\geq0.93$ to detect any 30% group difference in satisfaction, eg, 90% vs 60%, 65% vs 35%, or 35% vs 5%).

BASELINE CHARACTERISTICS

Patients randomized to the intervention and usual care groups were similar on all baseline variables (Table 1). In contrast, compared with those in the trial, patients in the nondepressed cohort differed on measures of depression (by definition), were less likely to be female, were more likely to be Hispanic, had more years of education, and were more likely to be married. Their index ACS was also more likely to be an ST-segment elevation or a non–ST-segment elevation myocardial infarction than unstable angina. Finally, the nondepressed cohort had significantly higher GRACE28 scores than the persistently depressed groups.
INTERVENTION IMPLEMENTATION

TREATMENT PREFERENCES AND INTERVENTION IMPLEMENTATION

Of the 80 patients randomized to intervention, 60 (75%) initially chose PST, 16 (20%) chose antidepressant medication, and 2 (2.5%) chose both; two patients did not state a treatment preference (Figure 1). Thirteen patients (16%) did not receive any study treatment. The mean (SD) number of treatment sessions delivered by phone ranged between 0% and 40%h

The sample sizes were 73 in the usual care, 78 in the intervention, and 76 in the nondepressed groups.

Table 2

PREVALENCE OF ANTIDEPRESSANT AND PSYCHOTHERAPY USE BEFORE AND AFTER THE TRIAL

Approximately one-third of the trial participants (35%) reported taking antidepressants at the 3-month randomization; at the end of the trial this was 48% in the treatment group, but remained at 30% in the usual care group (odds ratio, 4.48; 95% confidence interval [CI], 1.05-19.2 [P = .04, intention-to-treat estimates]). Participation in psychotherapy was 11% and 20%, respectively, before randomization; at the end of the trial it had increased to 39% in the intervention group, with a decline to 12% in the usual care group (odds ratio, 10.1; 95% CI, 2.32-44.3 [P = .002, intention-to-treat estimates; therefore, patient numbers not presented]).

PRIMARY TRIAL OUTCOME

The percentage of patients reporting depression care as excellent or very good at month 3 (ie, randomization) was modestly and not significantly different between groups (P = .18) (Table 2). At 9 months, however, 54% of patients in the intervention group reported this level of satisfaction with depression care compared with 19%
SECONDARY TRIAL OUTCOMES

Depressive symptoms decreased significantly in both the intervention (mean change, −5.7; 95% CI, −7.6 to −3.8) and usual care (mean change, −1.9; 95% CI, −3.8 to −0.1) groups (Table 3). The group difference in depressive symptom decrease was also significant (mean group difference, −3.8; 95% CI, −6.5 to −1.2; \( t_{155}=2.85 \) [\( P=.005 \)]), representing a depression effect size of 0.59 (95% CI, 0.18–1.00). Table 3 also shows that the depressive symptom effects seemed to generalize across men, women, Hispanic patients, and African American patients. In an analysis of the 3-, 5-, 7- and 9-month depressive symptoms, group differences emerged 4 months into the trial (at month 7, \( t_{155}=2.88 \) [\( P=.004 \)] and remained significant at the end of the trial (\( t_{155}=2.99 \) [\( P=.003 \)]).

Patient-reported adverse events were similar overall between the intervention and usual care groups, except that the usual care patients were significantly more likely to report experiencing a non–depression-related psychiatric problem than those in the intervention group (68 vs 59; \( \chi^2=5.38 \) [\( P=.02 \)]). Patients in the intervention group had fewer MACE events (3 events [4%]) than did those in the usual care group (10 [13%]) or the nondepressed observational cohort (5 [6%]). Figure 2 shows the Kaplan-Meier curves for the 3 groups (log-rank test for the usual care vs intervention groups, \( \chi^2=3.93 \) [\( P=.047 \); for the intervention vs nondepressed group, \( \chi^2=0.48 \) [\( P=.49 \)]. No significant site differences were detected for any of the primary or secondary outcomes.

### Table 2. Satisfaction With Depression Care 3 and 9 Months After ACS

<table>
<thead>
<tr>
<th>Variable</th>
<th>Usual Care Group (n=77)</th>
<th>Intervention Group (n=80)</th>
<th>OR (95% CI)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rated depression care as excellent or very good at 3 mo, % (95% CI)b</td>
<td>13.2 (6.5-19.6)</td>
<td>21.6 (12.9-29.7)</td>
<td>1.8 (0.8-4.5)</td>
<td>.18</td>
</tr>
<tr>
<td>Rated depression care as excellent or very good at 9 mo, % (95% CI)b</td>
<td>18.8 (10.4-26.7)</td>
<td>54.2 (41.9-63.6)</td>
<td>5.4 (2.2-12.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Patients receiving no care at 3 mo, No. (%)</td>
<td>56/76 (74)</td>
<td>53/74 (72)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Patients receiving no care at 9 mo, No. (%)</td>
<td>43/69 (62)</td>
<td>19/70 (27)</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

Abbreviations: ACS, acute coronary syndrome; CI, confidence interval; ellipses, not applicable; OR, odds ratio.

*a Data on depression care were missing for 7 patients at 3 months and for 18 patients at 9 months.

*b Numbers of patients are not provided because these percentages are derived from an intent-to-treat, multilevel, repeated-measures logistic regression analysis.
In light of the damaging impact of depression on quality of life and prognosis in patients with CHD, rates of detection and effective treatment for depression remain unacceptably low in this patient population. It was in this spirit that the COPES trial was undertaken. The enhanced-care, patient-preference, stepped approach used herein was associated with substantial improvement in satisfaction with depression care and a significant reduction in depressive symptoms. In addition, although the study was not powered for this outcome, the intervention in depressive symptoms. In addition, although the study was not powered for this outcome, the intervention led to a promising difference in MACEs between randomized groups, with the MACE rate in the intervention group resembling that in the nondepressed cohort.

LIMITATIONS

First, patients selected for this trial did not include all patients with ACS. We excluded those with cognitive impairments, other life-threatening conditions, and, most important, other psychiatric conditions such as alcohol or other drug dependence and bipolar disorder. Because these comorbid conditions are highly prevalent in depressed patients, our findings might not be applicable to all patients with ACS and depressive symptoms. Second, we had a relatively small sample size, and the MACE rate was, expectedly, quite small. Thus, further trials of enhanced depression care are required to determine whether this type of treatment can improve post-ACS prognosis. Third, our patients were not blinded to their treatment status. We made every effort to blind the end-point committee and the outcome assessors by asking patients not to reveal their group and by ensuring that assessors were not in contact with the therapist team, but this is only a single-blind trial. Fourth, we chose usual care as our control condition rather than placebo or another active control, such as clinical management. Thus, we did not account for nonspecific effects of treatment. Fifth, 13 of the 80 patients randomized to treatment never attended a first depression care visit. Another 7 terminated treatment before their care provider advised it, suggesting that, although the acceptance of our depression intervention was more than 50%, there is room for improvement. Recent studies using telephone-delivered cognitive behavioral therapy and combined psychotherapy with pharmacotherapy by telephone provided suggestions for novel delivery methods to further test in patients with ACS. Sixth, we did not collect cost data, which would have aided in the evaluation of this intervention. Finally, our 6-month treatment may have been too brief; we saw significant differences in depressive symptoms only after 4 months of treatment. The American College of Physicians recommended that clinicians continue treatment for 4 to 9 months after a satis-

**Table 3. Reduction in Depressive Symptoms 3 and 9 Months After ACS**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Usual Care Group (n=77)</th>
<th>Intervention Group (n=80)</th>
<th>Intervention vs Usual Care Group</th>
<th>Nondepressed Cohort (n=80)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Depression symptom score at 3 mo</td>
<td>Depression symptom score at 3 mo</td>
<td>Depression symptom score at 3 mo</td>
<td>Depression symptom score at 3 mo</td>
</tr>
<tr>
<td></td>
<td>19.6 (18.2 to 21.1)</td>
<td>19.0 (17.5 to 20.4)</td>
<td>-0.7 (-2.7 to 1.4)</td>
<td>0.64 .52</td>
</tr>
<tr>
<td></td>
<td>Depression symptom score at 9 mo</td>
<td>Depression symptom score at 9 mo</td>
<td>Depression symptom score at 9 mo</td>
<td>Depression symptom score at 9 mo</td>
</tr>
<tr>
<td></td>
<td>17.7 (15.6 to 19.7)</td>
<td>13.2 (11.1 to 15.3)</td>
<td>-4.5 (-7.4 to -1.6)</td>
<td>3.03 .003</td>
</tr>
<tr>
<td></td>
<td>Change in depressive symptom score overall</td>
<td>Change in depressive symptom score overall</td>
<td>Change in depressive symptom score overall</td>
<td>Change in depressive symptom score overall</td>
</tr>
<tr>
<td></td>
<td>-1.9 (-3.8 to -0.1)</td>
<td>-5.7 (-7.6 to -3.8)</td>
<td>-3.8 (-6.5 to -1.2)</td>
<td>2.85 .005</td>
</tr>
<tr>
<td></td>
<td>Men only (n=73)</td>
<td>Men only (n=73)</td>
<td>Men only (n=73)</td>
<td>Men only (n=73)</td>
</tr>
<tr>
<td></td>
<td>-1.2 (-3.9 to -1.5)</td>
<td>-4.8 (-7.6 to -2.0)</td>
<td>-3.6 (-7.5 to 0.3)</td>
<td>1.83 .07</td>
</tr>
<tr>
<td></td>
<td>Women only (n=84)</td>
<td>Women only (n=84)</td>
<td>Women only (n=84)</td>
<td>Women only (n=84)</td>
</tr>
<tr>
<td></td>
<td>-2.6 (-5.1 to 0.0)</td>
<td>-6.5 (-9.1 to -4.0)</td>
<td>-4.0 (-7.6 to -0.3)</td>
<td>2.16 .03</td>
</tr>
<tr>
<td></td>
<td>Hispanic only (n=68)</td>
<td>Hispanic only (n=68)</td>
<td>Hispanic only (n=68)</td>
<td>Hispanic only (n=68)</td>
</tr>
<tr>
<td></td>
<td>-1.6 (-4.4 to 1.3)</td>
<td>-5.1 (-7.9 to -2.2)</td>
<td>-3.5 (-7.6 to 0.5)</td>
<td>1.71 .09</td>
</tr>
<tr>
<td></td>
<td>African American only (n=29)</td>
<td>African American only (n=29)</td>
<td>African American only (n=29)</td>
<td>African American only (n=29)</td>
</tr>
<tr>
<td></td>
<td>-1.5 (-5.3 to -2.4)</td>
<td>-7.9 (-12.7 to -3.1)</td>
<td>-6.4 (-12.6 to -0.2)</td>
<td>2.05 .04</td>
</tr>
</tbody>
</table>

Abbreviations: ACS, acute coronary syndrome; ellipses, not applicable.

Data are presented as mean (95% confidence interval) unless otherwise indicated. Depressive symptom scores were assessed using the Beck Depression Inventory. Multilevel linear mixed models were used to estimate a group × time interaction effect.
factory response in patients with a first episode of major depressive disorder. For patients who have had 2 or more episodes of depression, an even longer duration of therapy may be beneficial. The depression and cardiac outcomes reported herein might be strengthened by longer depression treatment.

**COMPARISON OF COPES WITH OTHER DEPRESSION INTERVENTION TRIALS IN PATIENTS AFTER ACS**

Although some previous trials have shown statistically significant reductions in depressive symptoms, there were no improvements in cardiovascular outcomes. One possible explanation is that the depression treatment effects resulting from the modalities tested were not large enough to alter the increased risk of cardiovascular events and mortality conferred by depression. In fact, previous trials had 1 common finding: only clinically modest depression differences between the treatment and control groups. One plausible reason for this finding is that the treatments were unacceptable to patients with CHD. A patient’s willingness to engage in, adhere to, and continue depression treatment can determine whether the treatment succeeds or fails. Most of the depression interventions used in previous trials involving patients with CHD were originally validated with treatment-seeking outpatients with psychiatric problems; therefore, acceptance by the broader population of patients with CHD cannot be assumed. Previous studies have shown that fewer patients drop out of PST compared with other psychological therapies.

Another possible explanation for the lack of improved cardiac prognosis with previously tested depression interventions is that the treatments were not sufficiently powerful. Recent systematic reviews of single-modality antidepressant or psychotherapy treatments in other patient populations showed only modest efficacy compared with placebo or usual care. Larger effect sizes have been found with multimodal or stepped-care depression treatment interventions. Until this trial, enhanced-care, stepped algorithms had not been tested in patients with CHD, but the results in other medical populations were promising. We thus chose to test this treatment modality in the COPES trial. We found a reasonable depression effect size (0.59) that compares favorably with those of previous interventions designed to reduce depression in patients with CHD (0.20-0.38).

Large reductions in depressive symptoms in the control group are an issue in trials enrolling depressed patients with and without ACS. Depression is a relapsing-remitting disease; hence, substantial reductions in symptoms and/or spontaneous remission can occur. Also, medical providers increasingly recognize depressive symptoms in patients with ACS, and some patients’ symptoms respond to the conventional depression treatment offered. For these reasons, we chose to include a 3-month observation period to identify patients with persistent depressive symptoms and thereby decrease the likelihood of a large reduction in depressive symptoms in the control group. We had a smaller reduction in depressive symptoms in the control group compared with other trials of depressed patients with CHD, possibly as a result of this strategy.

It is not known whether only a subset of patients who are depressed after ACS is at risk for ACS recurrence or mortality. We excluded more patients than we enrolled because of depressive symptom improvement, and this could be viewed as a limitation because we targeted a small sample without psychiatric diagnoses. Most observational cohort studies demonstrating depression-associated risk of ACS recurrence or mortality used a BDI score of 10 or higher to characterize depression rather than conventional psychiatric diagnoses. Participants with persistently elevated BDI scores (≥10) in these studies were found to be at risk of death. In the COPES trial, we similarly targeted patients with a BDI score of 10 or higher rather than just those meeting the diagnostic criteria for a psychiatric disorder. As expected with initial tests of whether reducing a risk factor offsets cardiac event rates, the impact of depression treatments on MACES and other cardiac risks is disparate among the trials of depression treatment in patients with CHD. The results reported herein for the COPES trial offer promising approaches for a larger trial.

Treating depression effectively in patients with CHD may be daunting, but trials to determine the best way to manage these 2 highly prevalent and disabling diseases need to continue. In the secondary prevention of cardiovascular disease, stepped-care models of depression treatment with patient preference may offer an effective approach to improve depressive symptoms and satisfaction with care; whether this type of treatment can definitively improve cardiac prognosis awaits a larger trial.

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**Author Contributions:** Dr Schwartz had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. **Study concept and design:** Davidson, Rieckmann, Clemow, Schwartz, Shimbo, Kronish, Hegel, and Burg. **Acquisition of data:** Davidson, Clemow, Medina, Albanese, Kronish, and Burg. **Analysis and interpretation of data:** Davidson, Rieckmann, Clemow, Schwartz, Shimbo, Kronish, and Burg. **Drafting of the manuscript:** Davidson, Schwartz, Shimbo, and Burg. **Critical revision of the manuscript for important intellectual content:** Davidson, Rieckmann, Clemow, Schwartz, Shimbo, Medina, Albanese, Kronish, Hegel, and Burg. **Statistical analysis:** Schwartz and...
Shimbo. Obtained funding: Davidson, Schwartz, Shimbo, and Burg. Administrative, technical, and material support: Davidson, Clemow, Medina, Albanese, Kronish, and Burg. Study supervision: Davidson, Rieckmann, Hegel, and Burg.

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