Effects of Citalopram and Interpersonal Psychotherapy on Depression in Patients With Coronary Artery Disease
The Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy (CREATE) Trial

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SINCE THE EARLY 1990S, STUDIES have reported prevalences of major depression between 17% and 27% in hospitalized patients with coronary artery disease (CAD).1 Most have also demonstrated that depression has a negative cardiac prognostic impact.2,3 Only 1 large randomized trial, the Enhancing Recovery in Coronary Heart Disease (ENRICHD) study,4 has tried to determine whether treating depression could improve cardiac prognosis in CAD patients. Although ENRICHD demonstrated that a combination of short-term individual cognitive behavior therapy (CBT) and a selective serotonin reuptake inhibitor (SSRI), when needed, was significantly better than usual care at reducing depressive symptoms over 6 months in depressed or socially iso-

Context Few randomized controlled trials have evaluated the efficacy of treatments for major depression in patients with coronary artery disease (CAD). None have simultaneously evaluated an antidepressant and short-term psychotherapy.

Objective To document the short-term efficacy of a selective serotonin reuptake inhibitor (citalopram) and interpersonal psychotherapy (IPT) in reducing depressive symptoms in patients with CAD and major depression.

Design, Setting, and Participants The Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy, a randomized, controlled, 12-week, parallel-group, 2 × 2 factorial trial conducted May 1, 2002, to March 20, 2006, among 284 patients with CAD from 9 Canadian academic centers. All patients met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria for diagnosis of major depression of 4 weeks’ duration or longer and had baseline 24-item Hamilton Depression Rating Scale (HAM-D) scores of 20 or higher.

Interventions Participants underwent 2 separate randomizations: (1) to receive 12 weekly sessions of IPT plus clinical management (n = 142) or clinical management only (n = 142) and (2) to receive 12 weeks of citalopram, 20 to 40 mg/d (n = 142), or matching placebo (n = 142).

Main Outcome Measures The primary outcome measure was change between baseline and 12 weeks on the 24-item HAM-D, administered blindly during centralized telephone interviews (tested at α = .033); the secondary outcome measure was self-reported Beck Depression Inventory II (BDI-II) score (tested at α = .017).

Results Citalopram was superior to placebo in reducing 12-week HAM-D scores (mean difference, 3.3 points; 96.7% confidence interval [CI], 0.80–5.85; P = .005), with a small to medium effect size of 0.33. Mean HAM-D response (52.8% vs 40.1%; P = .03) and remission rates (35.9% vs 22.5%; P = .01) and the reduction in BDI-II scores (difference, 3.6 points; 98.3% CI, 0.58–6.64; P = .005; effect size = 0.33) also favored citalopram. There was no evidence of a benefit of IPT over clinical management, with the mean HAM-D difference favoring clinical management (–2.26 points; 96.7% CI, −4.78 to 0.27; P = .06; effect size, 0.23). The difference on the BDI-II did not favor clinical management (1.13 points; 98.3% CI, −1.90 to 4.16; P = .37; effect size = 0.11).

Conclusions This trial documents the efficacy of citalopram administered in conjunction with weekly clinical management for major depression among patients with CAD and found no evidence of added value of IPT over clinical management. Based on these results and those of previous trials, citalopram or sertraline plus clinical management should be considered as a first-step treatment for patients with CAD and major depression.

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lated myocardial infarction patients, the effect size was small. The study failed to show that the ENRICHD treatment protocol was better than usual care in preventing all-cause mortality and recurrent myocardial infarctions.

While there is a clear need for additional studies evaluating interventions to prevent the cardiac prognostic impact of depression, there have also been few adequately controlled trials evaluating whether depression treatments are effective in reducing depressive symptoms in patients with CAD. The largest of these, the Sertraline Antidepressant Heart Attack Trial (SADHART), provided some evidence of the safety of sertraline in patients recently hospitalized for an acute coronary syndrome. However, the overall efficacy results were less convincing. Planned subgroup analyses showed a clear benefit of sertraline over placebo for patients with recurrent depression and those with more severe depression. Additional post hoc analyses showed that patients whose depression began before the index cardiac event benefited more from sertraline than those with more recent depression onset.

The Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy (CREATE) is the first trial specifically designed to evaluate the short-term efficacy and tolerability of 2 depression treatments in patients with CAD: citalopram, a first-line SSRI antidepressant and interpersonal psychotherapy (IPT), a short-term, manual-based psychotherapy focusing on the social context of depression. To help ensure the applicability of results to a wide group of cardiac patients, recruitment was not restricted to patients with a recent acute coronary syndrome hospitalization.

METHODS

Overview

CREATE's design and rationale were published previously. CREATE was a 2 × 2 factorial, parallel-group, 12-week trial conducted among 284 outpatients with CAD and depression. The primary aims were to document the efficacy of citalopram in comparison with matching placebo and IPT in comparison with clinical management, an established control condition for psychotherapy. This trial was conducted in 9 academic centers across Canada. All centers received ethics approval from their institutional review boards before recruiting patients. The first patient was randomized on May 1, 2002, and the last patient visit occurred on March 20, 2006.

Psychiatric Eligibility Criteria

To be eligible, patients had to be aged 18 years or older and meet Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria for a diagnosis of current major depression based on the Structured Clinical Interview for Depression. Patients had to have been depressed for 4 weeks or longer and have a baseline score of 20 or higher on the centralized, telephone-administered 24-item Hamilton Depression Rating Scale (HAM-D).

Psychiatric exclusion criteria included depression due to a general medical condition (based on clinical judgment), bipolar disorder or major depression with psychotic features, substance abuse or dependency during the previous 12 months, serious suicide risk, current use of antidepressants, lithium, or anticonvulsants for mood disorder, current treatment with any form of psychotherapy, previous absence of response to citalopram or IPT, 2 or more previous unsuccessful treatments for the index depression episode, lifetime history of early termination (<8 weeks) of citalopram or 2 other SSRIs because of adverse events, Mini-Mental State Examination score of less than 24, and clinician judgment that the patient would not adhere to the study regimen.

Medical Eligibility Criteria

Patients had to have established CAD based on hospital chart evidence of a previous acute myocardial infarction or cardiac revascularization or coronary angiography showing 50% blockage or more in at least 1 major coronary artery. Randomization could not occur less than 1 week following discharge for a cardiac hospitalization, and patients had to have stable CAD based on clinical judgment (eg, no worsening of angina or congestive heart failure symptoms in the past week). We also excluded patients with coronary artery bypass graft surgery planned during the next 4 months, those with a Canadian Cardiovascular Society Angina Class of 4 (severe limitations), those participating in other trials, and those unable to speak English or French.

Recruitment and Baseline Interview

Patients were recruited through physician referrals, advertisements in medical centers and mass media, and screening in outpatient clinics. Following a short telephone screening interview, potentially eligible patients were invited for further outpatient evaluation.

After study explanation and provision of written informed consent, the Axis I Disorders modules of the Structured Clinical Interview for Depression and the Mini-Mental State Examination were administered by a trained clinician. The baseline evaluation also included assessment of sociodemographic variables, medical history, and current medications, and the study psychiatrist reviewed the medical chart to confirm eligibility. Patients completed the Beck Depression Inventory II (BDI-II), the Interpersonal Relationships Inventory (IPRI; a measure of perceived social support), and the 32-item version of the Functional Performance Inventory (FPI; an index of function in daily activities). These self-reports were repeated at the 6- and 12-week visits. Height, weight, and supine blood pressure were measured, and all patients had a 12-lead electrocardiogram and thyroid function test. Potentially eligible patients were scheduled for the centralized 24-item HAM-D assessment. Those with a score of 20 or higher were assigned an appointment for their first study session and randomization.
Randomization
Participants underwent 2 separate randomizations: once to receive IPT plus clinical management vs clinical management only and once to receive citalopram vs matching placebo pill. This resulted in 4 groups: (1) IPT plus clinical management and citalopram; (2) IPT plus clinical management and placebo pill; (3) clinical management only and citalopram; and (4) clinical management only and placebo pill. Randomizations were stratified by therapist using blocks of 4 for the randomization to active medication vs placebo and a single block of 5, followed by randomly permuted blocks of 2, 4, 6, and 8, for randomization to IPT vs clinical management. The allocation sequences were computer generated and concealed in sequentially numbered, site-specific, sealed opaque envelopes stored at the coordinating center until randomization.

Prior to the first study appointment, the coordinating center verified all eligibility criteria by telephone and facsimile. After confirming eligibility, the therapist completed the first clinical management session and then telephoned the coordinating center, where the randomization envelope was opened.

Blinding
The medication portion of the trial was completed in a double-blind fashion, with all therapists, patients, site psychiatrists, telephone raters, and coordinating center personnel blinded to patients’ group assignment. Code-break cards were provided to site pharmacies. The telephone raters for the primary outcome assessment were not involved in assessing adverse effects and were blinded to patients’ allocation to IPT vs clinical management alone. Patients were instructed not to divulge their IPT/clinical management assignment to the raters. At the end of the 12-week visit, patients completed a self-report question asking them to guess which treatment they had received (placebo or active medication; “don’t know” was not allowed).

Drug Administration and Concomitant Psychotropic Medication
Citalopram and matching placebo were provided as 20-mg tablets. Patients began taking 10 mg/d for 1 week and then increased to 20 mg/d. If the centralized 24-item HAM-D score at 6 weeks was not 8 or lower, the dose was increased to the maximum of 40 mg/d. If tolerated, this dose was maintained through the end of the trial. New prescriptions of benzodiazepines were not permitted. Short-term use of diphenhydramine or zopiclone was allowed for major sleep difficulties.

Clinical Management and End-of-Study Visit
All participants took part in weekly individual clinical management sessions with the same therapists who carried out IPT. The clinical management approach was based on the protocol used in the National Institute of Mental Health Treatment of Depression Collaborative Research Program and the University of Pittsburgh’s late-life depression studies. Clinical management involved semistructured 20- to 25-minute visits including information about depression and medication use, reassurance, and encouragement of adherence to medication and the study protocol. Medication adverse effects were evaluated weekly using a checklist of symptoms frequently reported with SSRI use plus open-ended questions about cardiovascular symptoms or signs. Therapists also screened for serious adverse events and suggested strategies to help deal with adverse effects. Clinical depression status was monitored at each session with the Montgomery-Asberg Depression Rating Scale.

Therapists kept site psychiatrists informed of patients’ status. Therapists were trained to adhere to clinical management and taught to avoid specific psychotherapeutic actions, including interpretations of behavior or feelings and exploration of interpersonal issues. Up to 4 clinical management sessions could be done by telephone. All sessions were digitally recorded for quality control. A few days after the 12-week or final session, patients had a follow-up visit, including measurement of blood pressure and weight and an electrocardiogram, and met with a study psychiatrist to plan poststudy care.

Interpersonal Psychotherapy
Interpersonal psychotherapy is the only other short-term, semistructured psychotherapy aside from CBT that is recommended in depression treatment guidelines. Interpersonal psychotherapy deals with problems common in patients with CAD, including interpersonal conflicts, life transitions, grief, and loss. It also addresses social isolation, a factor that has been linked to increased mortality and morbidity in some studies of patients with CAD. Furthermore, IPT was found to be superior to CBT in treating depression in patients with human immunodeficiency virus infection, a group also dealing with comorbid physical and emotional problems.

For patients randomized to IPT, each IPT session immediately followed a clinical management session. The IPT was administered by certified therapists who followed the treatment guidelines of Klerman et al and Weissman et al. Slight adaptations were made to meet the needs of CAD patients, including allowing up to 4 sessions by telephone. Interpersonal psychotherapy and clinical management sessions were conducted by doctoral- or master’s-level clinicians with at least 4 years of psychotherapy experience (mean, 15.8 years; SD, 9.01 years). Prior to the trial, 6 of the 14 therapists had formal training and significant experience with IPT. Before study initiation, the remaining 8 therapists participated in didactic IPT workshops and individual supervision of IPT with 2 to 3 depressed patients with CAD. As in the clinical management alone group, all clinical management and IPT sessions were audi-taped.

Efficacy Measures
To minimize bias in ascertaining the primary outcome, which is crucial in
psychotherapy trials, and to reduce measurement error, the 24-item HAM-D was administered centrally by telephone at baseline and at 6 and 12 weeks by trained clinical psychologists (n=5) blinded to treatment group. Our approach was based on that used by the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial.28 Ratings were audiotaped for quality assurance. For exploratory comparison with STAR*D results, the Inventory of Depressive Severity (IDS)31 was also completed during these interviews. The secondary outcome, the BDI-II, and 2 other exploratory outcomes, the index of function in daily activities (FPI) and the measure of perceived social support (IPRI), were assessed at baseline and following the 6- and 12-week study visits.

Protocol Adherence

Efforts were made to maintain patients in their assigned groups, including allowing flexible visit schedules and reducing citalopram/placebo dosages. However, if intolerable adverse effects, worsening of depression, or logistic constraints became problematic, patients were allowed to continue with medication (citalopram/placebo) only or weekly IPT/clinical management only.

Tolerability and Safety Issues

An independent data and safety monitoring board monitored recruitment and data completeness by site, as well as safety information after completion of the first 50 and 140 participants. The safety of each treatment was judged according to the occurrence of serious adverse events as defined by US Food and Drug Administration regulations.32 In CREATE, serious adverse events also included significant worsening of depression or suicide risk, significant lengthening of QTc intervals (>525 milliseconds) and serious bleeding. All serious adverse events were classified as cardiovascular or noncardiovascular by the event committee, blinded to treatment allocation. Other safety indices included electrocardiogram findings and blood pressure changes between the baseline and end-of-study visits. The tolerability of treatments was evaluated in terms of nonserious adverse events.

Sample Size

Because we included a secondary outcome, the BDI-II, the study-wise error rate (α = .05) was partitioned as suggested by Davis,33 with a lower probability level (α = .017) used to test the secondary outcome than the primary outcome (HAM-D; α = .033). The strength of 2 × 2 factorial designs is that when clinically significant treatment interactions are not expected, each treatment can be compared with its respective control condition with the same sample size as a study evaluating 1 treatment.34 Clinically significant interactions occur when there is evidence of treatment synergism or a ceiling effect of either treatment. In addition to assuming no interaction between IPT/clinical management and citalopram/placebo and partitioning the error rate, the power calculations were based on the following assumptions: detection of medium effect sizes (0.5) for both treatments (i.e., 2 to 3 points on the 24-item HAM-D, assuming an SD of 4 to 6), 2-sided tests, and intention-to-treat analyses for all randomized patients. Using the program PS Power and Sample Size,35 these assumptions yielded a total sample of 88 per group for α = .017 and 80% power for the secondary outcome. In addition, as suggested by Donner,36 the sample size was increased to take into account missing outcome data and incomplete exposure to the intended treatments. We expected missing 12-week assessments among 5% of participants or less (n=0.95) and treatment discontinuation of 20% or less (n=1−0.20)12 in each group. These assumptions increased the sample size calculation to 140 per group, or a total of 280 participants. This sample size provided 87% power for testing the primary outcome and 80% power for testing the secondary outcome. There were no interim efficacy analyses.

Statistical Analysis

SPSS software, version 14.0 (SPSS Inc, Chicago, Ill) was used for analyses. Baseline characteristics among treatment groups (IPT vs clinical management alone and citalopram vs placebo) were compared using analysis of variance for continuous measures and the Pearson χ2 test for categorical variables. All analyses were based on the intention-to-treat principle, with the last-observation-carried-forward approach applied for missing data. All statistical tests were 2-tailed. With the exception of the primary and secondary analyses, for which the experiment-wise α was partitioned into α = .017 and α = .033 for the secondary (BDI-II) and primary (HAM-D) outcomes, respectively, all other analyses used α = .05.

The primary efficacy analysis involved a 2 × 2 analysis of covariance assessing the main effects and interaction of IPT and citalopram on the baseline to 12-week changes in the 24-item HAM-D scores, with the baseline HAM-D score included as the covariate. Similar analyses of covariance were carried out for the secondary outcome, the BDI-II, and for the exploratory outcomes, the IDS, the FPI, and the IPRI. To explore the timing of treatment impact, parallel analyses were completed using the 6-week last-observation-carried-forward scores as the outcome.

For comparison with other antidepressant trials, multiple logistic regression was used to compare remission rates (24-item HAM-D scores ≤8),37 and response rates (percentage with ≥50% reduction in HAM-D scores) at 12 weeks. These analyses first assessed the significance of interactions between IPT vs clinical management alone and citalopram vs placebo in predicting the dichotomous outcome of interest, by adding the interaction term to a model involving both main effects and testing its significance using the likelihood ratio test. In the absence of significant interactions, individual logistic regression analyses for each main effect were carried out.

Although the power to detect treatment-control differences within vari-
ous subgroups was inevitably less than for the main analyses.\textsuperscript{38} we carried out preplanned exploratory analyses\textsuperscript{12} assessing possible modifications of treatment impact in relation to previous depression, comorbid anxiety disorder, and continuous measures of baseline social support (IPRI), functional status (FPI), and cognitive function (Mini-Mental State Examination). Because the subgroups were preplanned and exploratory in nature, no adjustment was made for multiple analyses.

In addition, although not planned in the original protocol, we also examined subgroups based on sex (because of subgroup results from ENRICHD\textsuperscript{39} and results of baseline comparisons of the sex distribution) and therapist experience (results of a recent CBT trial suggested that outcomes were better with more experienced therapists\textsuperscript{40}). All subgroup analyses added the main effect of the variable being assessed, as well as its interactions with IPT or clinical management alone and citalopram or placebo, to the basic $2 \times 2$ factorial analysis of covariance including the 2 main treatment effects and their interaction. Significant interactions were considered indicative of heterogeneity of treatment effects between subgroups, and data for the interactions were further explored examining adjusted mean changes within subgroups based on the overall analysis of covariance models. To examine significant interactions involving continuous variables, the variables were stratified into quartiles and examined graphically.

**RESULTS**

As shown in Figure 1, 1897 patients participated in telephone prescreening for key eligibility criteria. Of these, 370 were invited for a complete assessment and 284 gave written informed consent, completed baseline assessments, and were randomized.

**Protocol Adherence**

All 284 randomized patients received at least 1 dose of study medication and attended at least 1 clinical management or clinical management + IPT session. However, 54 patients discontinued 1 or both allocated treatments during the study. Reasons for discontinuation are listed in Figure 1. More discontinued their study medication than their weekly IPT or clinical management sessions. The most frequent reason for discontinuation among patients randomized to citalopram was intolerance of adverse effects, while lack of efficacy was the most common reason for those receiving placebo. However, the number of patients stopping because of intolerance did not differ between the citalopram and placebo groups. Participation in the IPT and clinical management sessions was very high, with 86% of patients completing the 12 planned sessions and only 17 patients completing less than 10 sessions. Nine patients (8 receiving clinical management alone and 1 IPT) had more than 4 sessions by telephone. The mean duration of IPT sessions was 48.1 minutes (SD, 8.40 minutes). Finally, the mean citalopram dose at the last visit was 33.1 mg (SD, 10.82 mg), not different from the mean final placebo dose (34.2 mg; SD, 9.91 mg; $P = .38$).

Two patients had their randomization codes broken. Centralized ratings at 12 weeks were obtained for 94% of randomized participants. Although patients were asked not to inform the rater of their assignment to IPT or clinical management alone, 4 clinical management patients mentioned their group assignment. Finally, at the end of the 12-week visit, 63% of patients randomized to citalopram and 61% of those randomized to placebo guessed their treatment group correctly.

**Baseline Characteristics**

The baseline demographic, medical, and psychiatric characteristics of participants are shown in Table 1. As recommended for $2 \times 2$ factorial trials,\textsuperscript{41,42} the characteristics in each of the 4 groups are shown, along with those for patients randomized to IPT vs clinical management and those randomized to citalopram vs placebo. The groups appear well-balanced. The only significant difference involved a lower proportion of women randomized to clinical management alone than to IPT ($P = .01$).

The mean age of participants was 58.2 years (SD, 9.13 years), and 25% were women. Most had a history of myocardial infarction or at least 1 revascularization procedure. The timing of the most recent cardiac hospitalization discharge ranged from 3 weeks to 31 years (median, 18.9 months) prior to randomization. As shown in Table 1, most had their most recent cardiac event more than 6 months before randomization. Patients took a mean of 7.5 (SD, 3.61) different medications. The mean baseline 24-item HAM-D score of 29.7 (SD, 6.71) and BDI-II score of 30.2 (SD, 9.32) reflect a moderately to severely depressed group. For comparison with other studies, the mean baseline 17-item HAM-D score was 22.8 (SD, 5.09) and the mean IDS-30 was 39.8 (SD, 8.33). Almost half of the participants had had previous depression, and one quarter had a comorbid anxiety disorder. The duration of the index depression episode was more than 6 months in more than 60% of the sample.

**Efficacy Results**

The efficacy results appear in Table 2 and Table 3. Because there was no evidence of interaction between therapy (IPT vs clinical management alone) and medication (citalopram vs placebo) for any outcome variables (all $P$ values > .45), all subsequent comparisons involved only the main effects of therapy and medication.

Citalopram was superior to placebo in reducing depressive symptoms in all efficacy measures. The mean difference between citalopram and placebo in baseline to 12-week change on the 24-item HAM-D score was 3.3 points, an effect size of 0.33. The effect sizes were similar for the secondary outcome, the BDI-II (0.33), and for the IDS (0.37) and for perceived social support (IPRI; 0.33). The effect size for the index of functional performance in daily activities (FPI) was slightly lower (0.21). The remission rates, response rates, and mean changes on the
17-item HAM-D score also consistently favored citalopram over placebo (Table 3). Finally, the superiority of citalopram was apparent by 6 weeks (mean 24-item HAM-D change from baseline to 6 weeks, adjusted for baseline score, 11.02 for citalopram vs 8.44 for placebo; mean difference between groups, 2.58; 95% confidence interval, 0.55-4.60; \( P = .01 \)).

Although patients improved with both IPT and clinical management, there was no evidence of superiority for IPT. We planned to reject the null hypothesis if the \( P \) value for the primary outcome, the 24-item HAM-D score, was .033 or less and/or the \( P \) value for the secondary outcome, the BDI-II...
score, was .017 or less. For the HAM-D, the difference between IPT and clinical management alone approached the threshold of .033 (P = .06) but favored clinical management over IPT. The mean changes on the BDI-II showed no difference between IPT and clinical management (P = .37), and there were no differences in any of the ex-

Table 1. Baseline Characteristics of CREATE Participants

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>IPT + Citalopram (n = 67)</th>
<th>IPT + Placebo (n = 75)</th>
<th>Clinical Management Citalopram (n = 75)</th>
<th>Clinical Management Placebo (n = 67)</th>
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<tbody>
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<td>Demographics</td>
<td></td>
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<tr>
<td>Age, mean (SD), y</td>
<td>58.6 (10.44)</td>
<td>59.4 (9.28)</td>
<td>57.3 (7.83)</td>
<td>57.3 (8.95)</td>
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<tr>
<td>Female</td>
<td>26 (38.8)</td>
<td>18 (24.0)</td>
<td>7 (9.3)</td>
<td>19 (28.4)</td>
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<td>Married</td>
<td>41 (61.2)</td>
<td>47 (62.7)</td>
<td>48 (64.0)</td>
<td>45 (67.2)</td>
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<td>Education, mean (SD), y</td>
<td>12.8 (3.85)</td>
<td>12.9 (3.41)</td>
<td>13.6 (3.09)</td>
<td>13.1 (3.82)</td>
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<td>Cardiac risk factors</td>
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<tr>
<td>Current smoker</td>
<td>13 (19.4)</td>
<td>17 (23.0)</td>
<td>17 (22.7)</td>
<td>20 (29.9)</td>
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<td>History of treatment for hypertension</td>
<td>70.1 (70.1)</td>
<td>64.0 (64.0)</td>
<td>56.6 (74.6)</td>
<td>70.4 (70.4)</td>
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<td>Obesity (BMI ≥30)</td>
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<td>35 (46.7)</td>
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<td>Medication for diabetes</td>
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<td>17 (22.7)</td>
<td>18 (24.0)</td>
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<td>Previous coronary angioplasty</td>
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<td>40 (53.3)</td>
<td>49 (65.3)</td>
<td>38 (56.7)</td>
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<td>Time since most recent cardiac event†</td>
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</tr>
<tr>
<td>&lt;6 mo</td>
<td>19 (28.8)</td>
<td>25 (33.8)</td>
<td>25 (33.8)</td>
<td>20 (29.9)</td>
</tr>
<tr>
<td>&gt;6 mo-2 y</td>
<td>24 (36.4)</td>
<td>22 (29.3)</td>
<td>19 (25.7)</td>
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<td>CCS angina class</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>0: No angina</td>
<td>24 (35.8)</td>
<td>26 (34.7)</td>
<td>26 (34.7)</td>
<td>23 (33.4)</td>
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<td>1: Slight limitation of ordinary physical activity</td>
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<tr>
<td>2: Moderate limitation of ordinary physical activity</td>
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<tr>
<td>3: Marked limitation of ordinary physical activity</td>
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<td>Cardiac medications</td>
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<tr>
<td>β-Blockers</td>
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<td>55 (73.3)</td>
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<td>45 (67.2)</td>
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<td>64 (65.0)</td>
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<td>16 (21.3)</td>
<td>17 (25.4)</td>
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<td>Aspirin</td>
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<td>58 (77.3)</td>
<td>56 (83.6)</td>
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<td>Anticoagulants</td>
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<td>10 (13.3)</td>
<td>5 (6.7)</td>
<td>6 (9.0)</td>
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<td>4 (5.3)</td>
<td>5 (6.7)</td>
<td>7 (5.7)</td>
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<td>Long-acting nitrates</td>
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<td>13 (17.3)</td>
<td>7 (9.3)</td>
<td>8 (11.9)</td>
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<td>Baseline depression</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAM-D-24 score, mean (SD)</td>
<td>28.8 (6.39)</td>
<td>30.0 (6.43)</td>
<td>29.6 (6.43)</td>
<td>30.3 (7.64)</td>
</tr>
<tr>
<td>BDI-II score, mean (SD)</td>
<td>30.2 (8.85)</td>
<td>29.4 (9.83)</td>
<td>30.4 (9.27)</td>
<td>31.3 (9.34)</td>
</tr>
<tr>
<td>Duration of current depression</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 wk-&lt;6 mo</td>
<td>27 (40.3)</td>
<td>31 (41.3)</td>
<td>20 (26.7)</td>
<td>26 (38.8)</td>
</tr>
<tr>
<td>6 mos-2 y</td>
<td>26 (38.8)</td>
<td>28 (37.3)</td>
<td>33 (44.0)</td>
<td>30 (44.8)</td>
</tr>
<tr>
<td>Recurrent depression</td>
<td>33 (49.3)</td>
<td>42 (56.0)</td>
<td>35 (45.3)</td>
<td>36 (45.3)</td>
</tr>
<tr>
<td>Cardiovascular disorder</td>
<td>18 (26.9)</td>
<td>20 (26.7)</td>
<td>18 (24.0)</td>
<td>12 (17.9)</td>
</tr>
</tbody>
</table>

Abbreviations: BDI-II, Beck Depression Inventory-II; BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; CCS, Canadian Cardiovascular Society; HAM-D-24, 24-item Hamilton Depression Rating Scale; IPT, interpersonal psychotherapy.

*Data are presented as No. (%) unless otherwise indicated.

†Cardiac events include myocardial infarction, coronary artery bypass graft surgery, percutaneous coronary angioplasty, cardiac catheterization, and hospital admission for congestive heart failure.

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CITALOPRAM AND PSYCHOTHERAPY FOR DEPRESSION IN CORONARY ARTERY DISEASE

Exploratory outcomes. Finally, remission and response rates did not differ between the IPT and clinical management groups.

Because of the greater percentage of women in the IPT group than in the clinical management group, we carried out analyses of covariance assessing the potential differential impact of treatment on changes in depression outcomes in men and women. The interaction between therapy (IPT/clinical management alone) and sex was not significant for either the 24-item HAM-D score (P = .72) or the BDI-II score (P = .90). Similarly, neither of the interactions between medication (citalopram/placebo) and sex were significant (for...
HAM-D, \( P = .57 \); for BDI-II, \( P = .23 \), indicating similar treatment effects in women and men.

**Subgroup Analyses**

Preplanned analyses of covariance to assess potential differential citalopram treatment effects on changes in the 24-item HAM-D in relation to baseline variables showed that none of the interactions between medication (citalopram/placebo) and comorbid anxiety disorder (\( P = .21 \)), baseline social support (\( P = .69 \)), baseline functional performance (\( P = .87 \)), baseline cognitive function (\( P = .58 \)), or therapists’ prior IPT experience (\( P = .89 \)) were significant. These results do not suggest heterogeneity in citalopram’s impact across subgroups. There was, however, some evidence of an interaction with past depression (\( P = .07 \)). Further exploration showed that while citalopram appeared to be superior to placebo in patients experiencing a recurrent depression (mean change from baseline to 12 weeks, adjusted for baseline score, 16.29 for citalopram and 10.63 for placebo; mean difference between groups, 5.66; 95% confidence interval, 2.43–8.89), there was little evidence of impact in those with a first depression (mean change for citalopram, 13.34 vs 12.26 for placebo; mean difference, 1.08; 95% confidence interval, –2.26 to 4.42). Those with a first episode did not differ from those with recurrent depression in the proportion with a cardiac hospitalization in the 6 months prior to baseline (28.4% vs 25.2%; \( P = .55 \); \( P = .27 \) for interaction of previous depression with citalopram/placebo) or in mean baseline 24-item HAM-D scores (those with a first episode, 29.6 [SD, 6.8]; those with a recurrent episode, 29.8 [SD, 6.7]; \( P = .80 \); \( P = .95 \) for interaction of previous depression with citalopram/placebo).

There were also no interactions between IPT/clinical management and past depression (\( P = .55 \)), comorbid anxiety disorder (\( P = .94 \)), baseline cognitive function (\( P = .88 \)), or therapists’ prior IPT experience (\( P = .85 \)). Significant interactions did occur between IPT/clinical management and baseline social support (\( P = .03 \)) and functional performance scores (\( P = .003 \)). Figure 2 shows these interactions with baseline scores stratified into quartiles. Clinical management was clearly superior to IPT for patients with low baseline perceived social support (IPRI) and for those reporting low functioning in daily activities (FPI).

**Safety and Tolerability**

Cardiovascular events were not common in this sample of patients with CAD recruited as outpatients and treated for 12 weeks. There were only 12 cardiovascular and 23 noncardiovascular serious adverse events (Table 4).

![Figure 2. Effects of Interpersonal Psychotherapy Plus Clinical Management vs Clinical Management Alone by Baseline Level of Perceived Social Support and Functional Performance](image-url)

**Table 4. Serious Adverse Events During 12 Weeks of Follow-up**

<table>
<thead>
<tr>
<th>Type of Event</th>
<th>IPT + Citalopram (n = 67)</th>
<th>IPT + Placebo (n = 75)</th>
<th>Clinical Management + Citalopram (n = 75)</th>
<th>Clinical Management + Placebo (n = 67)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>1*</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Worsening angina</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Stroke</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Noncardiovascular</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fractures/falls</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Significantly worsening</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>depression/suicidal ideation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other noncardiovascular</td>
<td>8†</td>
<td>2†</td>
<td>2§</td>
<td>3†</td>
</tr>
<tr>
<td>Total No. (%) of patients with cardiovascular serious adverse events</td>
<td>5 (7.5)</td>
<td>4 (5.3)</td>
<td>1 (1.3)</td>
<td>2 (3.0)</td>
</tr>
</tbody>
</table>

Abbreviations: IPT, interpersonal psychotherapy.

*One patient in the IPT + citalopram group had 2 serious adverse events: congestive heart failure and abdominal pain.
†Including 1 instance each of anemia, small bowel obstruction, worsening of preexisting pulmonary fibrosis, papillary carcinoma of the thyroid, skin rash, hematoma, skin rash and breathing difficulty, and partial complex seizure.
‡Including 2 instances of noncardiac chest pain.
§Including 1 each of brain tumor and elevated liver enzymes.
||Including 1 each of intestinal perforation and acute diverticulitis, hypoglycemia, and noncardiac chest pain.

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There were no differences between citalopram and placebo in any blood pressure or electrocardiographic measures, including QTc intervals (Table 5). However, patients receiving IPT experienced a slight increase in systolic blood pressure at 12 weeks in comparison with a slight decrease among patients receiving clinical management alone.

There were no differences among groups in rates of reported nausea, headache, muscle soreness/joint pain, angina, dyspepsia, restlessness, dry mouth, increased bleeding tendencies, tremor, or edema. The following were reported more frequently by patients receiving citalopram than by those receiving placebo: dizziness (47.9% vs 33.1%; \( P = .01 \)), diarrhea (49.3% vs 23.9%; \( P < .001 \)), somnolence (43.7% vs 25.4%; \( P = .001 \)), sweating (39.4% vs 23.9%; \( P = .005 \)), palpitations (25.4% vs 14.8%; \( P = .03 \)), and decreased libido or sexual difficulties (21.1% vs 7.0%; \( P = .001 \)). Patients randomized to IPT reported fatigue more frequently than those randomized to clinical management only (47.9% vs 33.1%; \( P = .01 \)).

**COMMENT**

CREATE is, to our knowledge, the first randomized controlled trial evaluating the acute-phase efficacy of both an SSRI antidepressant and a short-term form of psychotherapy for treatment of major depression in patients with CAD. Although citalopram was superior to placebo, IPT was not better than clinical management, its control condition, in reducing depression levels as assessed by either independent clinical rating or self-report. The difference in favor of citalopram is clinically relevant, with an effect size of 0.33 for mean changes between baseline and 12 weeks on both the 24-item HAM-D and the BDI-II, and was similar in patients treated with IPT and those receiving clinical management alone. Finally, the benefits of citalopram extended to changes in perceived social support and daily function.

Because we required a baseline 24-item HAM-D score of 20 or higher, our participants were more severely depressed than patients included in SADHART and ENRICHD. However, the CREATE patients’ baseline depression scores and response rates were similar to those of STAR*D \(^*\) and other placebo-controlled antidepressant trials, including those evaluating citalopram. \(^*\) Similar to the results of SADHART, \(^*\) we found the benefits of SSRIs for patients with CAD to be clearer for recurrent episodes of major depression than for first episodes. This differential benefit involved both a more

---

**Table 5. Cardiac Safety Data for CREATE Participants by Group**

<table>
<thead>
<tr>
<th>Measures</th>
<th>Factorial Groups</th>
<th>IPT vs Clinical Management</th>
<th>( P ) Value for Baseline to 12-wk Change</th>
<th>Citalopram vs IPT</th>
<th>( P ) Value for Baseline to 12-wk Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure, mean (SD), mm Hg</td>
<td>Base</td>
<td>( \Delta ) Citalopram</td>
<td>( \Delta ) Placebo</td>
<td>IPT vs Clinical Management</td>
<td>Citalopram vs IPT</td>
</tr>
<tr>
<td>Baseline 128.5 (18.76)</td>
<td>1288 (18.20)</td>
<td>1262 (18.68)</td>
<td>1284 (19.72)</td>
<td>1284 (18.41)</td>
<td>1272 (19.12)</td>
</tr>
<tr>
<td>12 wk 128.9 (17.32)</td>
<td>1319 (16.68)</td>
<td>1265 (15.24)</td>
<td>1237 (16.06)</td>
<td>1304 (19.58)</td>
<td>1252 (15.62)</td>
</tr>
<tr>
<td>Diastolic blood pressure, mean (SD), mm Hg</td>
<td>Base</td>
<td>( \Delta ) Citalopram</td>
<td>( \Delta ) Placebo</td>
<td>IPT vs Clinical Management</td>
<td>Citalopram vs IPT</td>
</tr>
<tr>
<td>Baseline 75.9 (10.13)</td>
<td>75.9 (9.92)</td>
<td>75.2 (12.09)</td>
<td>76.3 (10.47)</td>
<td>75.9 (9.99)</td>
<td>75.7 (11.32)</td>
</tr>
<tr>
<td>12 wk 76.7 (8.64)</td>
<td>75.8 (10.56)</td>
<td>74.9 (9.22)</td>
<td>74.2 (9.18)</td>
<td>76.2 (9.61)</td>
<td>74.6 (9.17)</td>
</tr>
<tr>
<td>Heart rate, mean (SD), beats/min(^*)</td>
<td>Base</td>
<td>( \Delta ) Citalopram</td>
<td>( \Delta ) Placebo</td>
<td>IPT vs Clinical Management</td>
<td>Citalopram vs IPT</td>
</tr>
<tr>
<td>Baseline 65.4 (10.92)</td>
<td>63.0 (11.83)</td>
<td>64.1 (10.48)</td>
<td>64.1 (13.17)</td>
<td>64.1 (11.3)</td>
<td>64.1 (11.72)</td>
</tr>
<tr>
<td>12 wk 63.3 (11.04)</td>
<td>63.6 (11.08)</td>
<td>62.4 (8.10)</td>
<td>61.7 (10.16)</td>
<td>63.5 (11.02)</td>
<td>62.1 (9.07)</td>
</tr>
<tr>
<td>PR interval, mean (SD), ms(^+)</td>
<td>Base</td>
<td>( \Delta ) Citalopram</td>
<td>( \Delta ) Placebo</td>
<td>IPT vs Clinical Management</td>
<td>Citalopram vs IPT</td>
</tr>
<tr>
<td>Baseline 167.2 (21.04)</td>
<td>166.0 (25.54)</td>
<td>168.1 (27.53)</td>
<td>170.0 (29.75)</td>
<td>166.6 (23.29)</td>
<td>169.0 (28.46)</td>
</tr>
<tr>
<td>12 wk 167.5 (22.73)</td>
<td>168.5 (27.3)</td>
<td>167.3 (28.96)</td>
<td>171.5 (31.03)</td>
<td>168.0 (24.99)</td>
<td>169.2 (29.86)</td>
</tr>
<tr>
<td>QRS interval, mean (SD), ms(^+)</td>
<td>Base</td>
<td>( \Delta ) Citalopram</td>
<td>( \Delta ) Placebo</td>
<td>IPT vs Clinical Management</td>
<td>Citalopram vs IPT</td>
</tr>
<tr>
<td>Baseline 94.6 (14.75)</td>
<td>98.8 (15.88)</td>
<td>98.7 (19.24)</td>
<td>93.7 (12.98)</td>
<td>96.8 (15.42)</td>
<td>96.4 (18.62)</td>
</tr>
<tr>
<td>12 wk 93.8 (15.40)</td>
<td>98.7 (15.82)</td>
<td>97.3 (19.47)</td>
<td>94.2 (13.88)</td>
<td>96.4 (15.75)</td>
<td>96.9 (17.17)</td>
</tr>
<tr>
<td>QT interval, mean (SD), ms(^+)</td>
<td>Base</td>
<td>( \Delta ) Citalopram</td>
<td>( \Delta ) Placebo</td>
<td>IPT vs Clinical Management</td>
<td>Citalopram vs IPT</td>
</tr>
<tr>
<td>Baseline 401.0 (33.54)</td>
<td>414.8 (37.66)</td>
<td>410.4 (47.48)</td>
<td>406.3 (42.68)</td>
<td>406.1 (36.25)</td>
<td>406.5 (45.24)</td>
</tr>
<tr>
<td>12 wk 411.9 (36.93)</td>
<td>411.6 (39.27)</td>
<td>413.0 (35.72)</td>
<td>410.6 (34.24)</td>
<td>411.8 (38.01)</td>
<td>411.9 (34.94)</td>
</tr>
<tr>
<td>QTc interval mean (SD), ms(^+)</td>
<td>Base</td>
<td>( \Delta ) Citalopram</td>
<td>( \Delta ) Placebo</td>
<td>IPT vs Clinical Management</td>
<td>Citalopram vs IPT</td>
</tr>
<tr>
<td>Baseline 413.7 (23.09)</td>
<td>419.2 (21.81)</td>
<td>418.8 (31.40)</td>
<td>413.2 (16.21)</td>
<td>416.5 (22.52)</td>
<td>416.2 (25.73)</td>
</tr>
<tr>
<td>12 wk 417.8 (22.30)</td>
<td>417.8 (18.18)</td>
<td>418.4 (25.20)</td>
<td>411.9 (15.12)</td>
<td>417.8 (20.20)</td>
<td>415.5 (21.40)</td>
</tr>
</tbody>
</table>

**Abbreviation:** IPT, interpersonal psychotherapy.

*Based on 12-lead electrocardiogram results.

\( P > .05 \) for all interactions of therapy by medication.
pronounced citalopram response and a reduced placebo response for patients with recurrent depression in contrast with those with a first depression episode. Neither the timing of the most recent cardiac hospitalization nor the severity of baseline depression differed between these groups. Although the apparently lower impact on first depression episodes may be a function of the reduced power within that subgroup, it is also possible that SSRIs may actually have less impact in comparison with placebo among persons experiencing first episodes of major depression late in life, in the context of CAD or other cardiovascular diseases. Recent clinical trials of antidepressants in elderly persons46,47 and in patients with cerebrovascular disease48 have reported limited clinical benefit of antidepressants over placebo. Additional trials are required to refine the clinical indications for antidepressants for depression in patients with comorbid medical conditions.

We found no citalopram-placebo difference on any blood pressure or electrocardiographic variables, including mean QTc intervals. None of the serious adverse events involved significant lengthening of QTc intervals or serious bleeding. In fact, less than 5% of patients experienced serious cardiovascular adverse events, precluding drawing conclusions about the cardiovascular impact of citalopram. Although tricyclic antidepressants are contraindicated in patients with CAD;99 and other newer antidepressants have not been extensively evaluated, large-scale secondary prevention trials would be needed to definitively establish both the potential cardiovascular benefits and safety of SSRIs.5,6,30,51 However, with a cardiovascular event rate of 10%, a sample of some 7000 participants would be needed to document a difference in event rates of more than 20% between SSRI treatment and placebo.

We were unable to document any benefit of adding weekly IPT sessions to approximately 20 minutes of clinical management, a nonpsychotherapeutic intervention involving systematic evaluation of medication adverse effects and depression symptoms. CREATE is not the first trial that failed to document a clear benefit of IPT in comparison with an adequate control condition.52-54 In fact, the results of preplanned CREATE subgroup analyses suggest that clinical management may even be better than IPT for patients with low baseline social support or poor day-to-day functioning.

These results are reminiscent of the National Institute of Mental Health Treatment of Depression Collaborative Research Program, in which IPT was not superior to clinical management in patients with high baseline social dysfunction (the social and leisure subscale of the Social Adjustment Scale).55 Although IPT was designed to address interpersonal issues and improve interpersonal functioning, CAD patients with low levels of support or poor daily functioning may have difficulty dealing directly with the combination of cardiac and interpersonal issues that IPT sessions entail and may do better with the lower demands of regular medical management.

The lack of superiority of IPT to clinical management in reducing levels of depressive symptoms in our trial does not imply that other forms of psychotherapy, in particular CBT, would not perform better than clinical management. Although ENRICHD demonstrated that CBT, with sertraline for more severely depressed patients or those not responding to the initial phase of CBT, was superior to usual care, there is no way of knowing whether CBT was a necessary ingredient for the improvement of depressive symptoms. It is possible that the additional clinical monitoring and support provided to patients randomized to CBT was the active ingredient for improving their depressive symptoms. Besides illustrating the necessity of independent outcome assessment in psychotherapy trials, our results underscore the importance of a careful choice of controls.56 Although clinical management is not a psychotherapy per se, in combination with other studies,57 the current results suggest that it is not an inert intervention.

CONCLUSIONS

In conclusion, this randomized controlled trial used a factorial design to evaluate the 12-week efficacy of both a pharmacologic and a psychotherapeutic treatment in patients with CAD who were experiencing a major depressive episode. We found a clinically meaningful antidepressant effect of citalopram in comparison with placebo but no demonstrable benefit of the psychotherapeutic intervention, IPT, over clinical management alone. Citalopram (or sertraline, as previously shown in the SADHART trial) plus clinical management should be considered for the initial acute-phase treatment for major depression in patients with CAD. It remains to be demonstrated that any

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form of psychotherapy is superior to clinical management in reducing depression symptoms in this group.

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Author Contributions: Drs Lespérance and Frasure-Smith had access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Acquisition of data: Lespérance, Laliberté, van Zyl, Baker, Swenson, Ghatavi, Abramson, Dorian.

Analysis and interpretation of data: Lespérance, Frasure-Smith, Koszycyi, Laliberté, van Zyl, Baker, Swenson, Ghatavi, Abramson, Dorian, Guertin.

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Study supervision, Lespérance, Frasure-Smith, Koszycyi, Laliberté, van Zyl, Baker, Swenson, Ghatavi, Abramson, Dorian.

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Critical review of the manuscript for intellectual content: Lespérance, Frasure-Smith, Koszycyi, Laliberté, van Zyl, Baker, Swenson, Ghatavi, Abramson, Dorian, Guertin.

Study design, conduct, management, analysis, or interpretation of data: Abramson, Dorian, Guertin.

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33. Davis CE. Secondary endpoints can be validly analyzed, even if the primary endpoint does not provide clear statistical significance. Control Clin Trials. 1997;18:557-560.