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

François Lespérance, MD
Nancy Frasure-Smith, PhD
Diana Koszycki, PhD
Marc-André Laliberté, MD
Louis T. van Zyl, MD
Brian Baker, MBChB
John Robert Swenson, MD
Kayhan Ghatavi, MD
Beth L. Abramson, MD
Paul Dorian, MD
Marie-Claude Guertin, PhD
for the CREATE Investigators

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-

For editorial comment see p 411.

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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Author Affiliations and a complete list of the CREATE Investigators appear at the end of this article.
Corresponding Author: François Lespérance, MD, Centre Hospitalier de l'Université de Montréal, 1560 Sherbrooke E, Montreal, Quebec, Canada H2L 4M1 (francois.lesperance@umontreal.ca).

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,[5,6] there have also been few adequately controlled trials evaluating whether depression treatments are effective in reducing depressive symptoms in patients with CAD.[7,8] The largest of these, the Sertraline Antidepressant Heart Attack Trial (SADHART),[8] 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.[9]

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[10] and interpersonal psychotherapy (IPT),[11] 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.[12] 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*[13] criteria for a diagnosis of current major depression based on the Structured Clinical Interview for Depression.[14] 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).[15]

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[16] 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[17] 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[14] and the Mini-Mental State Examination[16] 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),[18] the Interpersonal Relationships Inventory (IPRI; a measure of perceived social support),[19] and the 32-item version of the Functional Performance Inventory (FPI; an index of function in daily activities).[20] 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[21] and the University of Pittsburgh's late-life depression studies.[22] 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-Åsberg Depression Rating Scale.[23]

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.[24] 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.[25] Furthermore, IPT was found to be superior to CBT in treating depression in patients with human immunodeficiency virus infection,[26] 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[11] and Weissman et al.[27] Slight adaptations were made to meet the needs of CAD patients,[28] including allowing up to 4 sessions by telephone.[29] 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 audiotaped.

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.[30] 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 in-

dices 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 (ie, 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]²) 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 χ^2 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,[38] we carried out preplanned exploratory analyses[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[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[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 2×2 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 ses-

sion. 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 2×2 factorial trials,[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 changes 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

Figure 1. Flow of Participants in the CREATE Trial
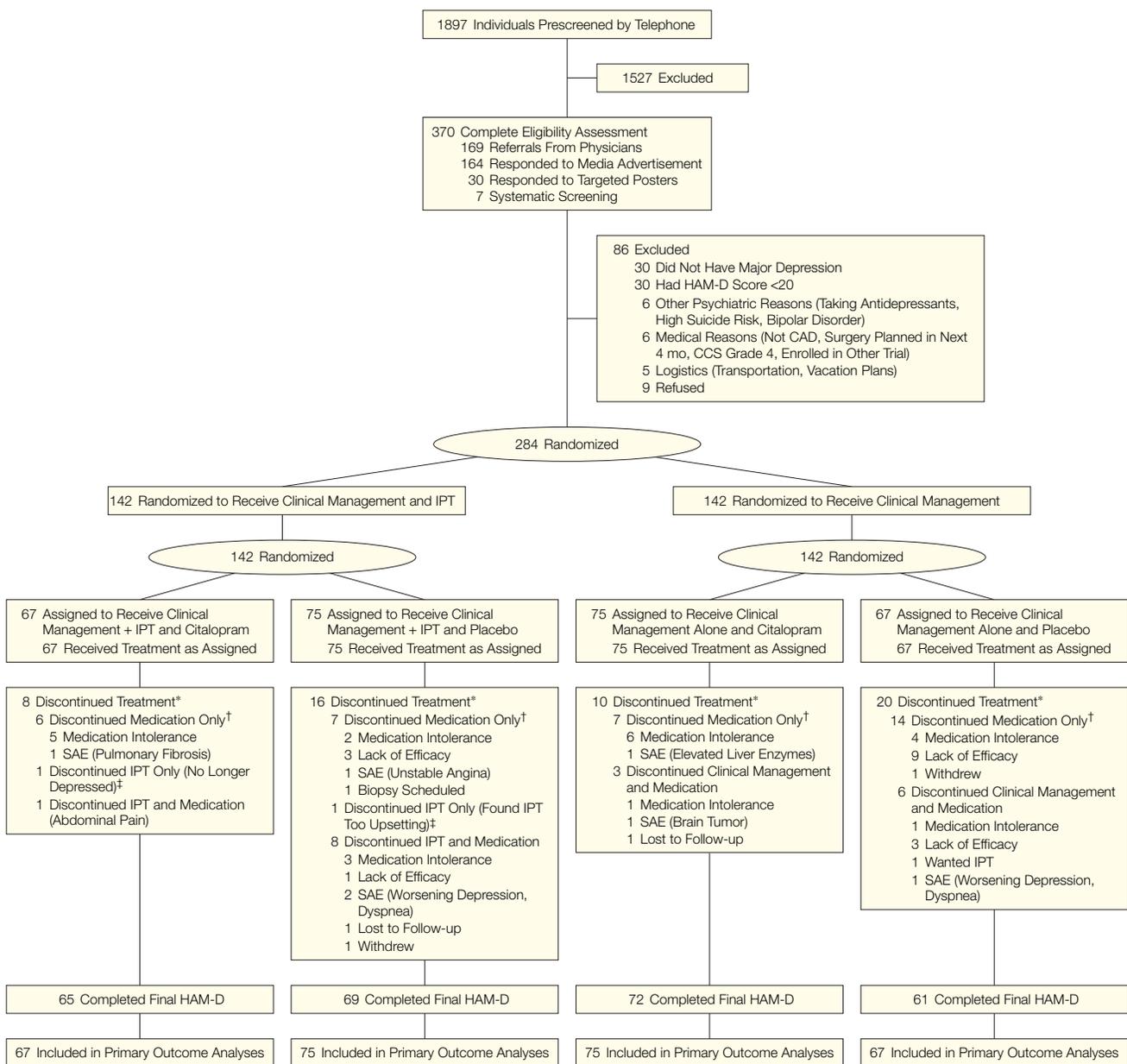
HAM-D indicates 24-item Hamilton Depression Rating Scale; CAD, coronary artery disease; CCS, Canadian Cardiovascular Society angina class; CREATE, Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy; IPT, interpersonal psychotherapy; SAE, serious adverse event.
*Patients who stopped 1 of the 2 treatments to which they had been allocated were encouraged to continue the remaining treatment.
†"Medication only" indicates that patients stopped citalopram or placebo but continued IPT or clinical management alone as allocated.
‡"IPT only" indicates that patients stopped IPT but continued citalopram or placebo as allocated.

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 alone (*P*=.37), and there were no differences in any of the ex-

Table 1. Baseline Characteristics of CREATE Participants*

Characteristics	Factorial Groups				IPT vs Clinical Management		Citalopram vs Placebo	
	IPT + Citalopram (n = 67)	IPT + Placebo (n = 75)	Clinical Management + Citalopram (n = 75)	Clinical Management + Placebo (n = 67)	IPT (n = 142)	Clinical Management (n = 142)	Citalopram (n = 142)	Placebo (n = 142)
Demographics								
Age, mean (SD), y	58.6 (10.44)	59.4 (9.28)	57.3 (7.83)	57.3 (8.95)	59.0 (9.81)	57.3 (8.35)	57.9 (9.15)	58.4 (9.16)
Female	26 (38.8)	18 (24.0)	7 (9.3)	19 (28.4)	44 (31.0)	26 (18.3)	33 (23.2)	37 (26.1)
Married	41 (61.2)	47 (62.7)	48 (64.0)	45 (67.2)	88 (62.0)	93 (65.5)	89 (62.7)	92 (64.8)
Education, mean (SD), y	12.8 (3.85)	12.9 (3.41)	13.6 (3.09)	13.1 (3.82)	12.9 (3.61)	13.3 (3.45)	13.2 (3.48)	13.0 (3.60)
Cardiac risk factors								
Current smoker	13 (19.4)	17 (23.0)	17 (22.7)	20 (29.9)	30 (21.3)	37 (26.1)	30 (21.1)	37 (26.2)
History of treatment for hypertension	47 (70.1)	48 (64.0)	50 (66.7)	50 (74.6)	95 (66.9)	100 (70.4)	97 (68.3)	98 (69.0)
Obesity (BMI ≥30)	26 (39.4)	35 (46.7)	40 (53.3)	26 (38.8)	61 (43.3)	66 (46.5)	66 (46.8)	61 (43.0)
Medication for diabetes	12 (17.9)	17 (22.7)	18 (24.0)	17 (25.4)	29 (20.4)	35 (24.6)	30 (21.1)	34 (23.9)
Cardiac history								
Previous myocardial infarction	40 (59.7)	54 (72.0)	49 (65.3)	41 (61.2)	94 (66.2)	90 (63.4)	89 (62.7)	95 (66.9)
Previous coronary artery bypass graft surgery	29 (43.3)	32 (42.7)	37 (49.3)	31 (46.3)	61 (43.0)	68 (47.9)	66 (46.5)	63 (44.4)
Previous coronary angioplasty	38 (56.7)	40 (53.3)	49 (65.3)	38 (56.7)	78 (54.9)	87 (61.3)	87 (61.3)	78 (54.9)
Time since most recent cardiac event†								
<6 mo	13 (19.7)	18 (24.0)	25 (33.8)	19 (28.8)	31 (22.0)	44 (31.4)	38 (27.1)	37 (26.2)
6 mo-2 y	24 (36.4)	22 (29.3)	19 (25.7)	21 (31.8)	46 (32.6)	40 (28.6)	43 (30.7)	43 (30.5)
>2 y	29 (43.9)‡	35 (46.7)	30 (40.5)‡	26 (39.4)‡	64 (45.4)‡	56 (40.0)‡	59 (42.1)‡	61 (43.3)‡
CCS angina class								
0: No angina	24 (35.8)	26 (34.7)	26 (34.7)	23 (34.3)	50 (35.2)	49 (34.5)	50 (35.2)	49 (34.5)
1: Ordinary physical activity does not cause angina	22 (32.8)	30 (40.0)	23 (30.7)	23 (34.3)	52 (36.6)	46 (32.4)	45 (31.7)	53 (37.3)
2: Slight limitation of ordinary physical activity	17 (25.4)	14 (18.7)	19 (25.3)	13 (19.4)	31 (21.8)	32 (22.5)	36 (25.4)	27 (19.0)
3: Marked limitation of ordinary physical activity	4 (6.0)	5 (6.7)	7 (9.3)	8 (11.9)	9 (6.3)	15 (10.6)	11 (7.7)	13 (9.2)
Cardiac medications								
β-Blockers	46 (68.7)	55 (73.3)	48 (64.0)	45 (67.2)	101 (71.1)	93 (65.5)	94 (66.2)	100 (70.4)
Calcium channel blockers	13 (19.4)	17 (22.7)	28 (37.3)	16 (23.9)	30 (21.1)	44 (31.0)	41 (28.9)	33 (23.2)
Angiotensin-converting enzyme inhibitors	39 (58.2)	39 (52.0)	38 (50.7)	36 (53.7)	78 (54.9)	74 (52.1)	77 (54.2)	75 (52.8)
Statins	55 (82.1)	65 (86.7)	63 (84.0)	64 (95.5)	120 (84.5)	127 (89.4)	118 (83.1)	129 (90.8)
Diuretics	18 (26.9)	17 (22.7)	16 (21.3)	17 (25.4)	35 (24.6)	33 (23.2)	34 (23.9)	34 (23.9)
Aspirin	56 (83.6)	57 (76.0)	58 (77.3)	56 (83.6)	113 (79.6)	114 (80.3)	114 (80.3)	113 (79.6)
Antiplatelet drugs	16 (23.9)	15 (20.0)	19 (25.3)	20 (29.9)	31 (21.8)	39 (27.5)	35 (24.6)	35 (24.6)
Anticoagulants	6 (9.0)	10 (13.3)	5 (6.7)	6 (9.0)	16 (11.3)	11 (7.7)	11 (7.7)	16 (11.3)
Digoxin	3 (4.5)	4 (5.3)	5 (6.7)	5 (7.5)	7 (4.9)	10 (7.0)	8 (5.6)	9 (6.3)
Long-acting nitrates	9 (13.4)	13 (17.3)	7 (9.3)	8 (11.9)	22 (15.5)	15 (10.6)	16 (11.3)	21 (14.8)
Baseline depression								
HAM-D-24 score, mean (SD)	28.8 (6.39)	30.0 (6.43)	29.6 (6.43)	30.3 (7.64)	29.5 (6.42)	30.0 (7.01)	29.3 (6.40)	30.2 (7.00)
BDI-II score, mean (SD)	30.2 (8.85)	29.4 (9.83)	30.4 (9.27)	31.3 (9.34)	29.8 (9.36)	30.8 (9.28)	30.3 (9.04)	30.3 (9.62)
Duration of current depression								
4 wk-<6 mo	27 (40.3)	31 (41.3)	20 (26.7)	26 (38.8)	58 (40.8)	46 (32.4)	47 (33.1)	57 (40.1)
6 mo-2 y	26 (38.8)	28 (37.3)	33 (44.0)	30 (44.8)	54 (38.0)	63 (44.4)	59 (41.5)	58 (40.8)
>2 y	14 (20.9)	16 (21.3)	22 (29.3)	11 (16.4)	30 (21.1)	33 (23.2)	36 (25.4)	27 (19.0)
Recurrent depression	33 (49.3)	42 (56.0)	34 (45.3)	27 (40.3)	75 (52.8)	61 (43.0)	67 (47.2)	69 (48.6)
Comorbid anxiety disorder	18 (26.9)	20 (26.7)	18 (24.0)	12 (17.9)	38 (26.8)	30 (21.1)	36 (25.4)	32 (22.5)

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.
‡Some participants had missing data because of silent myocardial infarctions of unknown age diagnosed by electrocardiogram.

ploratory 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

Table 2. Adjusted Mean Baseline to 12-Week Changes in Depression and Other Outcomes*

Measures	Factorial Groups				IPT vs Clinical Management			Citalopram vs Placebo		
	IPT + Citalopram (n = 67)	IPT + Placebo (n = 75)	Clinical Management + Citalopram (n = 75)	Clinical Management + Placebo (n = 67)	IPT (n = 142)	Clinical Management (n = 142)	P Value	Citalopram (n = 142)	Placebo (n = 142)	P Value
Primary outcome: 24-item HAM-D score, mean (SD)†	13.7 (9.98)	10.5 (9.96)	16.1 (9.96)	12.6 (9.97)	12.1 (9.97)	14.4 (9.97)	.06	14.9 (9.99)	11.6 (9.99)	.005
Between-group difference (96.7% CI)					−2.26 (−4.78 to 0.27)			3.33 (0.80 to 5.85)		
Secondary outcome: BDI-II score, mean (SD)‡	15.4 (10.67)	11.5 (10.68)	14.0 (10.67)	10.7 (10.68)	13.5 (10.69)	12.4 (10.69)	.37	14.7 (10.68)	11.1 (10.68)	.005
Between-group difference (98.3% CI)					1.13 (−1.90 to 4.16)			3.61 (0.58 to 6.64)		
Exploratory outcomes										
IDS score, mean (SD)§	16.8 (13.12)	12.8 (13.08)	20.4 (13.08)	14.9 (13.13)	14.8 (13.12)	17.7 (13.12)	.06	18.6 (13.12)	13.8 (13.12)	.002
Between-group difference (95% CI)					−2.91 (−5.96 to 0.15)			4.76 (1.71 to 7.81)		
17-Item HAM-D score, mean (SD)‖	9.9 (7.60)	7.7 (7.60)	11.6 (7.60)	9.3 (7.60)	8.8 (7.60)	10.5 (7.60)	.07	10.7 (7.61)	8.5 (7.61)	.02
Between-group difference (95% CI)					−1.66 (−3.43 to 0.11)			2.19 (0.42 to 3.96)		
FPI score, mean (SD)¶	−0.14 (0.41)	−0.07 (0.42)	−0.14 (0.41)	−0.02 (0.41)	−0.11 (0.42)	−0.08 (0.41)	.56	−0.14 (0.41)	−0.05 (0.42)	.05
Between-group difference (95% CI)					−0.03 (−0.13 to 0.07)			−0.10 (−0.19 to 0)		
IPRI score, mean (SD)#	−4.9 (6.61)	−2.0 (6.57)	−3.6 (6.67)	−1.9 (6.62)	−3.5 (6.63)	−2.8 (6.63)	.36	−4.3 (6.63)	−2.0 (6.63)	.004
Between-group difference (95% CI)					−0.72 (−2.26 to 0.83)			−2.31 (−3.86 to −0.77)		

Abbreviations: BDI-II, Beck Depression Inventory II; CI, confidence interval; FPI, Functional Performance Inventory; HAM-D, Hamilton Depression Rating Scale; IDS, Inventory of Depressive Severity; IPRI, Interpersonal Relationships Inventory; IPT, interpersonal psychotherapy.
*Adjusted for baseline score, fitting both main effects and 2-way interaction in an intention-to-treat, last-observation-carried-forward analysis. Negative values for the FPI and IPRI indicate improvements.
†$P=.91$ for IPT × citalopram interaction.
‡$P=.82$ for IPT × citalopram interaction.
§$P=.64$ for IPT × citalopram interaction.
‖$P=.94$ for IPT × citalopram interaction.
¶$P=.62$ for IPT × citalopram interaction.
#$P=.46$ for IPT × citalopram interaction.

Table 3. 12-Week Remission and Response Rates on the 24-Item HAM-D*

Measures	Factorial Groups				IPT vs Clinical Management			Citalopram vs Placebo		
	IPT + Citalopram (n = 67)	IPT + Placebo (n = 75)	Clinical Management + Citalopram (n = 75)	Clinical Management + Placebo (n = 67)	IPT (n = 142)	Clinical Management (n = 142)	P Value	Citalopram (n = 142)	Placebo (n = 142)	P Value
Remission (12-week 24-item HAM-D score ≤8)†	24 (35.8)	16 (21.3)	27 (36.0)	16 (23.9)	40 (28.2)	43 (30.3)	.70	51 (35.9)	32 (22.5)	.01
Odds ratio for between-group difference (95% CI)					0.90 (0.54-1.51)			1.93 (1.14-3.25)		
Response (≥50% reduction from baseline)‡	22 (49.3)	28 (37.3)	42 (56.0)	29 (43.3)	61 (43.0)	71 (50.0)	.24	75 (52.8)	57 (40.1)	.03
Odds ratio for between-group difference (95% CI)					0.75 (0.47-1.20)			1.67 (1.04-2.67)		

Abbreviations: CI, confidence interval; HAM-D, Hamilton Depression Rating Scale; IPT, interpersonal psychotherapy.
*Intention-to-treat, last-observation-carried-forward analysis.
†$P=.80$ for IPT × citalopram interaction.
‡$P=.96$ for IPT × citalopram interaction.

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
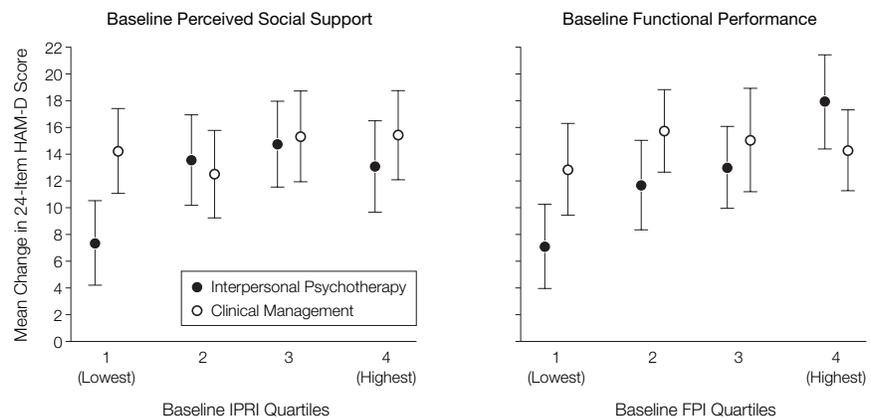
IPRI indicates Interpersonal Relationships Inventory; FPI, Functional Performance Inventory. Error bars indicate 95% confidence intervals. Mean data are adjusted for baseline 24-item HAM-D (Hamilton Depression Rating Scale) score, fitting main effects of interpersonal psychotherapy/clinical management, citalopram/placebo, and baseline social support or functional performance scores, plus all 2-way interactions by intention-to-treat, last-observation-carried-forward analysis. From lowest to highest, quartiles (means) were defined as 13 to 27 (30.48), 38 to 45 (42.03), 46 to 50 (48.21), and 51 to 63 (53.91) for the IPRI and as 0.53 to 1.59 (1.23), 1.63 to 2.00 (1.82), 2.03 to 2.38 (2.21), and 2.41 to 3.00 (2.61) for the FPI. $P=.03$ for interaction between continuous IPRI score and interpersonal psychotherapy/clinical management; $P=.003$ for interaction between continuous FPI score and interpersonal psychotherapy/clinical management.

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

Type of Event	IPT + Citalopram (n = 67)	IPT + Placebo (n = 75)	Clinical Management + Citalopram (n = 75)	Clinical Management + Placebo (n = 67)
Cardiovascular				
Myocardial infarction	0	2	0	1
Congestive heart failure	1*	1	1	0
Worsening angina	2	1	0	1
Stroke	1	0	0	0
Other cardiovascular	1	0	0	0
Total No. (%) of patients with cardiovascular serious adverse events	5 (7.5)	4 (5.3)	1 (1.3)	2 (3.0)
Noncardiovascular				
Fractures/falls	0	1	2	1
Significantly worsening depression/suicidal ideation	0	1	0	3
Other noncardiovascular	8*†	2‡	2§	3‖
Total No. (%) of patients with serious adverse events	13 (19.4)	8 (10.7)	5 (6.7)	9 (13.4)

Abbreviation: 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.

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, dyspnea, 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 (48.6% vs 30.3%; P = .002), 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[43] and other placebo-controlled antidepressant trials,[44] including those evaluating citalopram.[45] Similar to the results of SADHART,[8,9] 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*

Measures	Factorial Groups				IPT vs Clinical Management		P Value for Baseline to 12-wk Change	Citalopram vs IPT		P Value for Baseline to 12-wk Change
	IPT + Citalopram	IPT + Placebo	Clinical Management + Citalopram	Clinical Management + Placebo	IPT	Clinical Management		Citalopram	Placebo	
Systolic blood pressure, mean (SD), mm Hg										
Baseline	128.5 (18.76)	128.3 (18.20)	126.2 (18.68)	128.4 (19.72)	128.4 (18.41)	127.2 (19.12)	.01	127.3 (18.69)	128.3 (18.86)	.80
12 wk	128.9 (17.32)	131.9 (21.68)	126.5 (15.24)	123.7 (16.06)	130.4 (19.58)	125.2 (15.62)		127.7 (16.26)	127.9 (19.55)	
Diastolic blood pressure, mean (SD), mm Hg										
Baseline	75.9 (10.13)	75.9 (9.92)	75.2 (12.05)	76.3 (10.47)	75.9 (9.99)	75.7 (11.32)	.13	75.5 (11.13)	76.1 (10.15)	.29
12 wk	76.7 (8.64)	75.8 (10.56)	74.9 (9.22)	74.2 (9.18)	76.2 (9.61)	74.6 (9.17)		75.8 (8.96)	75.0 (9.91)	
Heart rate, mean (SD), beats/min†										
Baseline	65.4 (10.92)	63.0 (11.83)	64.1 (10.46)	64.1 (13.17)	64.1 (11.3)	64.1 (11.72)	.19	64.7 (10.66)	63.5 (12.42)	.66
12 wk	63.3 (11.04)	63.6 (11.08)	62.4 (8.10)	61.7 (10.18)	63.5 (11.02)	62.1 (9.07)		62.8 (9.59)	62.7 (10.6)	
PR interval, mean (SD), ms†										
Baseline	167.2 (21.04)	166.0 (25.54)	168.1 (27.53)	170.0 (29.75)	166.6 (23.29)	169.0 (28.46)	.61	167.7 (24.56)	167.9 (27.59)	.20
12 wk	167.5 (22.73)	168.5 (27.3)	167.3 (28.96)	171.5 (31.03)	168.0 (24.99)	169.2 (29.86)		167.4 (26.07)	169.9 (29.05)	
QRS interval, mean (SD), ms†										
Baseline	94.6 (14.75)	98.8 (15.86)	98.7 (19.24)	93.7 (12.98)	96.8 (15.42)	96.4 (16.82)	.94	96.7 (17.30)	96.5 (14.77)	.15
12 wk	93.8 (15.40)	98.7 (15.82)	97.3 (19.47)	94.2 (13.88)	96.4 (15.75)	95.9 (17.17)		95.7 (17.66)	96.6 (15.07)	
QT interval, mean (SD), ms†										
Baseline	401.0 (33.54)	414.8 (37.66)	410.4 (47.48)	406.3 (42.68)	408.1 (36.25)	408.5 (45.24)	.94	405.9 (41.53)	410.8 (40.11)	.34
12 wk	411.9 (36.93)	411.6 (39.27)	413.0 (35.72)	410.6 (34.24)	411.8 (38.01)	411.9 (34.94)		412.4 (36.17)	411.2 (36.9)	
QTc interval, mean (SD), ms†										
Baseline	413.7 (23.09)	419.2 (21.81)	418.8 (31.40)	413.2 (16.21)	416.5 (22.52)	416.2 (25.73)	.30	416.3 (27.76)	416.4 (19.59)	.18
12 wk	417.8 (22.30)	417.8 (18.18)	418.4 (25.20)	411.9 (15.12)	417.8 (20.20)	415.5 (21.40)		418.1 (23.77)	415.1 (17.03)	

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 persons[46,47] and in patients with cerebrovascular disease[48] 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[49] 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.[5,6,50,51] 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.

It may contain nonpharmacological elements essential to improving depression in patients with CAD, including regular monitoring of mood and physical symptoms. We do not know whether less frequent clinical management or clinical management delivered by those without psychotherapy training would be equally effective.

The limitations of the CREATE trial include the recruitment of participants through advertisements and exclusion of those unwilling to accept randomization, with both factors reducing the generalizability of results. However, adherence to study protocol was very good. We obtained 12-week, blinded, centralized depression ratings for 94% of participants. Furthermore, most patients participated in all 12 weekly IPT or clinical management sessions. By chance, more women were randomized to receive IPT than clinical management alone, but there was no difference between men and women in their responses to citalopram/placebo or IPT/clinical management. Finally, we carried out multiple exploratory subgroup analyses and did not adjust for the number of these comparisons. Although most of these analyses were preplanned, some of the significant differences may have occurred by chance, and these results would need confirmation in future trials to establish their validity.

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

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

Author Affiliations: Department of Psychiatry, Université de Montréal (Drs Lespérance, Frasure-Smith, and Laliberté), Research Centre, Centre Hospitalier de l'Université de Montréal (Drs Lespérance and Frasure-Smith), Research Centre (Drs Lespérance and Frasure-Smith), Department of Psychosomatic Medicine (Dr Laliberté), and Coordinating Centre (Dr Guertin), Montreal Heart Institute, and Department of Psychiatry and School of Nursing, McGill University (Dr Frasure-Smith), Montreal, Quebec; Department of Psychiatry, University of Ottawa (Drs Koszycki and Swenson), University of Ottawa Institute of Mental Health Research, Royal Ottawa Hospital (Dr Koszycki), University of Ottawa Heart Institute (Dr Swenson), and Department of Psychiatry of the Ottawa Hospital (Dr Swenson), Ottawa, Ontario; Department of Psychiatry, Queen's University and Kingston General Hospital Canada, Kingston, Ontario (Dr van Zyl); Department of Psychiatry, University Health Network and University of Toronto (Dr Baker), Department of Medicine, University of Toronto (Drs Abramson and Dorian), and Division of Cardiology (Drs Abramson and Dorian) and Cardiac Prevention Centre and Women's Cardiovascular Health (Dr Abramson), St Michael's Hospital, Toronto, Ontario; and Department of Psychiatry, Dalhousie University, Capital District Health Authority, Halifax, Nova Scotia (Dr Ghatavi).
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Study concept and design: Lespérance, Frasure-Smith, Koszycki, Laliberté, van Zyl, Baker, Swenson, Abramson, Dorian, Guertin.
Acquisition of data: Lespérance, Laliberté, van Zyl, Baker, Swenson, Ghatavi, Abramson, Dorian.
Analysis and interpretation of data: Lespérance, Frasure-Smith, Koszycki, Laliberté, Baker, Swenson, Abramson, Dorian, Guertin.
Drafting of the manuscript: Lespérance, Frasure-Smith.
Critical revision of the manuscript for important intellectual content: Lespérance, Frasure-Smith, Koszycki, Laliberté, van Zyl, Baker, Swenson, Ghatavi, Abramson, Dorian, Guertin.
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CREATE Investigators: *Study Chair and Co-chair:* François Lespérance, MD (chair); Nancy Frasure-Smith, PhD (co-chair). *Steering Committee:* François Lespérance, MD; Nancy Frasure-Smith, PhD; Diana Koszycki, PhD; Marc-André Laliberté, MD; Louis T. van Zyl, MD; Brian Baker, MBChB; John Robert Swenson, MD; Kayhan Ghatavi, MD; Jean Leblanc, MD; Beth L. Abramson, MD. *Coordinating Center*

(Montreal Heart Institute): Ginette Gravel, MSc; Martine Habra, PhD; Johanne Lalancette. *Therapist Training and Rating Center* (University of Ottawa): Diana Koszycki, PhD (director); Manon Bertrand. *Centralized Depression Raters*: Manon Bertrand; Lana Pratt, PhD; Wendy Smith, PhD; Jennifer Ellison; Marie-Pierre Leduc, MPs. *Centralized Electrocardiogram Rating* (St Michael's Hospital, Toronto): Beth L. Abramson, MD. *Event Committee*: Paul Dorian, MD; François Lespérance, MD. *Study Biostatisticians* (Montreal Heart Institute): Marie-Claude Guertin, PhD; Jean Lambert, PhD. *Data and Safety Monitoring Board* (University of Florida, Gainesville): David S. Sheps, MD, MSPH (chair); Pierre Blier, MD, PhD; Sue McGorray, MD. *Citalopram/Placebo Coordination* (Lundbeck Canada Inc): Jean Proulx. *Consultants*: Charles F. Reynolds III, MD (University of Pittsburgh); Melanie M. Biggs, PhD (University of Texas South Western Medical Center, Dallas). *Clinical Centers*: Montreal Heart Institute: Marc-André Laliberté, MD (principal investigator); François Lespérance, MD; Marie-Pierre Leduc, MPs; Aline Masson, MSc; Elaine Kennedy, MPs; Sylvie Bouchard, PhD. Sacré-Cœur Hospital (Montreal): Jean Leblanc, MD (principal investigator); Jocelyne Julien, MPs; Line Roy. Kingston General Hospital: Louis T. van Zyl, MD (principal investigator); Joan Bowie; Pilsu-qua Lloyd. Hotel-Dieu Hospital (Kingston): Susan Finch, MD; Joan Bowie; Paul Kasurak, MSW; Pilsu-qua Lloyd; Bethmarie Michalska, MA; Eleanor Rosenzweig, MSW, MTS. Providence Continuing Care Centre–Mental Health Services (Kingston): Paul Kasurak, MSW. St Michael's Hospital (Toronto): Beth L. Abramson, MD; Shree Bhalerao, MD; Paul Dorian, MD; Laurie Gillies, PhD; Edward McAnanama, BMR(OT), MEd, MSc; Lara Ross; Brigitta Zile. Ottawa Heart Institute: John Robert Swenson, MD (principal investigator); Rebecca Cohen, PhD; Élyse Sévigny; J. David Smith, PhD. Calgary Health Region: Margaret Oakander, MD (principal investigator); Maureen Milligan, PhD; Bette Moxham; Linda Seyler. Capital District Health Authority (Halifax): Kayhan Ghatavi, MD (principal investigator); Gordon Butler, PhD (co–principal investigator); Bonnie Moore. University Health Network (Toronto): Brian Baker, MBChB (principal investigator); Susan Abbey, MD.
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Synovial Lactic Acid and Septic Arthritis

To the Editor: In their Rational Clinical Examination article, Dr Margaretten and colleagues[1] concluded that the synovial fluid white blood cell count and the corresponding percentage of polymorphonuclear cells are the most useful markers in identifying septic arthritis while waiting for the Gram stain and culture test results. Synovial fluid glucose, protein, and lactate dehydrogenase were not found to be helpful.

In the past, synovial fluid lactic acid measurement was proposed as a useful test in the rapid differentiation between septic and nonseptic arthritis. For example, in the study by Riordan et al,[2] lactic acid seemed to be more sensitive than Gram stain (especially if antibiotics had been administered before joint aspiration) and could be measured even when the synovial fluid was too thick for a cell count to be performed. In addition, synovial fluid lactic acid can be assessed rapidly in a blood gas analyzer and may be available to clinicians even before the synovial fluid cell count and differential. It would be helpful if the authors' literature search provided data on the value of this easy-to-obtain and seemingly useful test.

Petros Kopterides, MD
petkop@ath.forthnet.gr
Critical Care Department
"Attikon" University Hospital
Athens, Greece

1. Margaretten ME, Kohlwes J, Moore D, Bent S. Does this adult patient have septic arthritis? *JAMA*. 2007;297(13):1478-1488.
2. Riordan T, Doyle D, Tabaqchali S. Synovial fluid lactic acid measurement in the diagnosis and management of septic arthritis. *J Clin Pathol*. 1982;35(4):390-394.

In Reply: Our search of the literature identified 6 studies[1-5] that address synovial fluid lactic acid as a clinical test for septic arthritis. Previous studies[6] suggest that although synovial lactic acid dehydrogenase (LDH) by enzymatic analysis may be sensitive for detecting bacterial infection, it is not specific, and elevated synovial LDH levels may be observed in noninfectious inflammatory and crystal-induced arthropathies, such as rheumatoid arthritis and gout.

The identified studies were heterogeneous in their measurement of lactic acid. Brook et al,[1] Gratacós et al,[2] and Riordan et al[5] evaluated lactic acid concentration by gas liquid chromatography, while Mossman et al[3] and Shmerling et al[4] assessed LDH by enzymatic analysis. Furthermore, Gratacós et al evaluated D-lactic acid, an optical isomer of L-lactic acid. The other studies did not identify if they were referring to D-lactic acid, L-lactic acid, or both. Most studies of synovial lactic acid were excluded from our meta-analysis because of their heterogeneity, and they did not evaluate a clinical test of interest.

The studies by Shmerling et al[4] were included because they were of high study quality and level of evidence. As stated in our article, the studies by Shmerling et al[4] showed synovial LDH had 100% sensitivity but poor specificity with only half the cases being septic arthritis, resulting in many false-positive test results. These results may suggest that a low level of synovial fluid LDH would exclude the diagnosis of septic arthritis, but the negative likelihood ratio of 0.10 (95% confidence interval, 0.00-1.60) is not statistically significant.

Gas liquid chromatography assay of lactic acid may be more useful than enzymatic analysis of LDH. Although there are limited data from small numbers of patients to support the usefulness of synovial lactic acid measurement, such as in Riordan et al,[5] we believe that there is not enough evidence to encourage it as a routine test to diagnose septic arthritis at this time. However, synovial lactic acid estimation by gas liquid chromatography deserves further study.

Mary E. Margaretten, MD
mary.margaretten@ucsf.edu
Division of Rheumatology
Jeffrey Kohlwes, MD, MPH
Stephen Bent, MD
Department of Medicine
University of California
San Francisco

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CORRECTION

Data Error in Table: In the Original Contribution entitled "Effects of Citalopram and Interpersonal Psychotherapy on Depression in Patients With Coronary Artery Disease" published in the January 24, 2007, issue of *JAMA* (2007;297(4):367-379), a data error occurred in Table 3 on page 374. In the column labeled "IPT + Citalopram" under "Factorial Group," the number of patients in the "Response" row should have been 33. The percentage (49.3%) is correct. The correction does not change the results of the analysis.