Escitalopram Treatment for Depressive Disorder Following Acute Coronary Syndrome: A 24-Week Double-Blind, Placebo-Controlled Trial

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ABSTRACT

Objective: Depression is common after acute coronary syndrome (ACS) and has adverse effects on prognosis. There are few evidence-based interventions for treating depression in ACS. This study investigated the efficacy and safety of escitalopram in treating depressive disorders identified 2–14 weeks after a confirmed ACS episode.

Method: A total of 217 patients with *DSM-IV* depressive disorders (121 major and 96 minor) and ACS were randomly assigned to receive escitalopram in flexible doses of 5–20 mg/d (n = 108) or placebo (n = 109) for 24 weeks. The study was conducted from 2007 to 2013. The primary outcome measure was the Hamilton Depression Rating Scale (HDRS). Secondary outcome measures included the Montgomery-Asberg Depression Rating Scale (MADRS), Beck Depression Inventory (BDI), Clinical Global Impressions-Severity of Illness scale (CGI-S), Social and Occupational Functioning Assessment Scale (SOFAS), and World Health Organization Disability Assessment Schedule-12. Cardiovascular safety outcomes included echocardiography, electrocardiography, laboratory test, body weight, and blood pressure results.

Results: Escitalopram was superior to placebo in reducing HDRS scores (mean difference = 2.3, $P = .016$, effect size = 0.38). Escitalopram was also superior to placebo in decreasing depressive symptoms evaluated by the MADRS, BDI, and CGI-S and in improving SOFAS functioning level. Escitalopram was not associated with any harmful changes in cardiovascular safety measures. Dizziness was significantly more frequently reported in the escitalopram group ($P = .018$), but there were no significant differences in any other adverse events.

Conclusions: These results indicate that escitalopram has clinically meaningful antidepressant effects with no evidence of reduced cardiovascular safety in depressive disorder following ACS.

Trial Registration: ClinicalTrials.gov identifier: NCT00419471

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Depression and acute coronary syndrome (ACS) including myocardial infarction (MI) or unstable angina are leading causes of disability.[1] Depression is common in ACS, with the prevalence of major depression ranging from 15% to 27%.[2] Both major and minor depressive disorders are associated with new cardiovascular events and cardiovascular mortality.[3]

Although there is a clear need for treating depressive disorders in patients with ACS, and a number of randomized controlled trials have evaluated pharmacologic interventions, mostly selective serotonin reuptake inhibitors (SSRIs), published results have been mixed. Early trials of paroxetine[4] and fluoxetine[5] indicated efficacy but were limited by small sample sizes and short treatment periods. In the largest trial to date, the Sertraline Antidepressant Heart Attack Randomized Trial (SADHART), 369 patients with depression following ACS were given sertraline or placebo for 24 weeks.[6] Sertraline was found to be safe, but overall efficacy was less clear and was restricted to a subgroup with recurrent or more severe depression. Mirtazapine was evaluated in a 24-week placebo-controlled trial in 91 patients with post-MI depression, as a part of the larger Myocardial Infarction and Depression-Intervention Trial (MIND-IT)[7]; however, completion was low (n = 40), and there was no effect on the primary outcome, although the intervention was found to be safe and effective on secondary outcomes. Citalopram was found to be safe and superior to placebo in reducing depressive symptoms at 12 weeks in the Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy (CREATE) trial[8]; however, the sample comprised patients with moderate-to-severe depression at a late stage after hospitalization for cardiac reasons.

Overall, randomized controlled trials have reported that SSRIs are safe in ACS, but antidepressant effects remain unclear because of small sample sizes, low completion rates, inconsistent results, and heterogeneous samples. Of the SSRIs, escitalopram was found to be safe and effective for preventing depression in nondepressed post-ACS patients.[9] However, its antidepressant efficacy was not formally assessed. Accordingly, we conducted a randomized, placebo-controlled trial of efficacy and safety of escitalopram in patients with depressive disorders after ACS.

METHOD

Study Overview and Participants

The study outline is presented in Figure 1. The Escitalopram for DEPression in Acute Coronary Syndrome (EsDEPACS)

Clinical Points

- Depression is common after acute coronary syndrome (ACS), with adverse effects on prognosis, but there is little evidence for interventions to treat depression in ACS.
- This study indicates that escitalopram has clinically meaningful antidepressant effects along with tolerability and safety in patients with depression and ACS.
- Current evidence supports escitalopram as an additional effective and safe treatment option for clinicians treating patients with depression and ACS.

trial reported here is from the larger Korean DEPression in Acute Coronary Syndrome (K-DEPACS) study, which investigates depressive disorders in patients with ACS using randomized and naturalistic prospective designs. The design and rationale of the EsDEPACS and K-DEPACS were published previously.[10] Participants were consecutively recruited from all patients 2–14 weeks after an ACS episode that had resulted in hospitalization and had been confirmed by various examinations (N = 4,809) in the Department of Cardiology of Chonnam National University Hospital, Gwangju, Korea. Detailed inclusion and exclusion criteria are described in eAppendix 1 (available at PSYCHIATRIST.COM). Those who met eligibility criteria and agreed to participate (N = 1,152) were screened for depressive symptoms with the Beck Depression Inventory (BDI)[11] as inpatients 2 weeks post-ACS and thereafter as outpatients every 4 weeks up to 12 weeks. Those with depressive symptoms (BDI score > 10) at any of these occasions received a clinical evaluation by the study psychiatrists (who were naturally aware that a BDI score > 10 had been obtained, but blind to the score itself) using the Mini-International Neuropsychiatric Interview (MINI),[12] a structured diagnostic psychiatric interview for *DSM-IV*. Of 446 patients with a diagnosis of major or minor depressive disorder, those 300 who agreed to participate were randomized. The first patient was enrolled in May 2007, and the last patient completed the follow-up evaluation in March 2013. Written informed consent was obtained, and the study was approved by the Chonnam National University Hospital Institutional Review Board. The study was registered with ClinicalTrials.gov (identifier: NCT00419471).

Baseline Evaluations

Demographic data were obtained, along with self-completed BDI and psychiatrist-administered MINI diagnoses as described. Further assessment scales were administered by 2 research nurses blinded to the BDI and MINI results. Depressive symptoms were estimated by the 17-item Hamilton Depression Rating Scale (HDRS)[13] and the Montgomery-Asberg Depression Rating Scale (MADRS).[14] Global symptomatology was assessed by the Clinical Global Impressions-Severity of Illness scale (CGI-S)[15]; functioning level, by the Social and Occupational Functioning Assessment Scale (SOFAS)[16]; and disability, by the World Health Organization Disability Assessment Schedule-12 (WHODAS-12).[17] Higher scores on BDI, HDRS, MADRS, CGI-S, and WHODAS-12 and lower scores on SOFAS indicate more severe symptomatology.

The following cardiovascular risk factors were ascertained: diagnosed hypertension and diabetes mellitus, resting blood pressure, fasting serum total cholesterol level, measured body mass index, and reported current smoking status. Diagnoses of MI or unstable angina were made. Severity of ACS was estimated by the Killip classification.[18] Echocardiography results were left ventricular ejection fraction (LVEF) and wall motion scores. Electrocardiography (ECG) variables were heart rate (beats/min), PR interval (ms), QRS duration (ms), and QTc duration (ms). Serum cardiac biomarkers troponin I and creatine kinase-MB (CK-MB) were measured. Previous history of ACS was obtained. Cardiovascular medications used were recorded.

Intervention

The efficacy and safety of flexible doses of escitalopram (5, 10, 15, or 20 mg) were investigated using a randomized, double-blind, placebo-controlled design. Patients were randomly assigned to treatment in a 1:1 ratio following computer-generated randomization codes provided by a statistician independent of recruiting clinicians. Drugs were stored at a dispensary attached to the study hospital and were provided to patients by pharmacists who were blind to patients' status. Outcome measurement (by nurses) and adverse event monitoring (by psychiatrists) were carried out blind to treatment allocation. Examinations were scheduled at baseline and at weeks 4, 8, 12, 16, 20, and 24 thereafter, with a 7-day allowable window. The initial escitalopram dose at baseline was 10 mg/d generally. After the second evaluation (week 4), the medication doses could be changed and determined by the investigators' clinical decision considering the response and tolerability. Medications were taken once daily per orally after the supper meal. Adherence was checked by pill counts at every visit and was defined as acceptable if at least 75%.

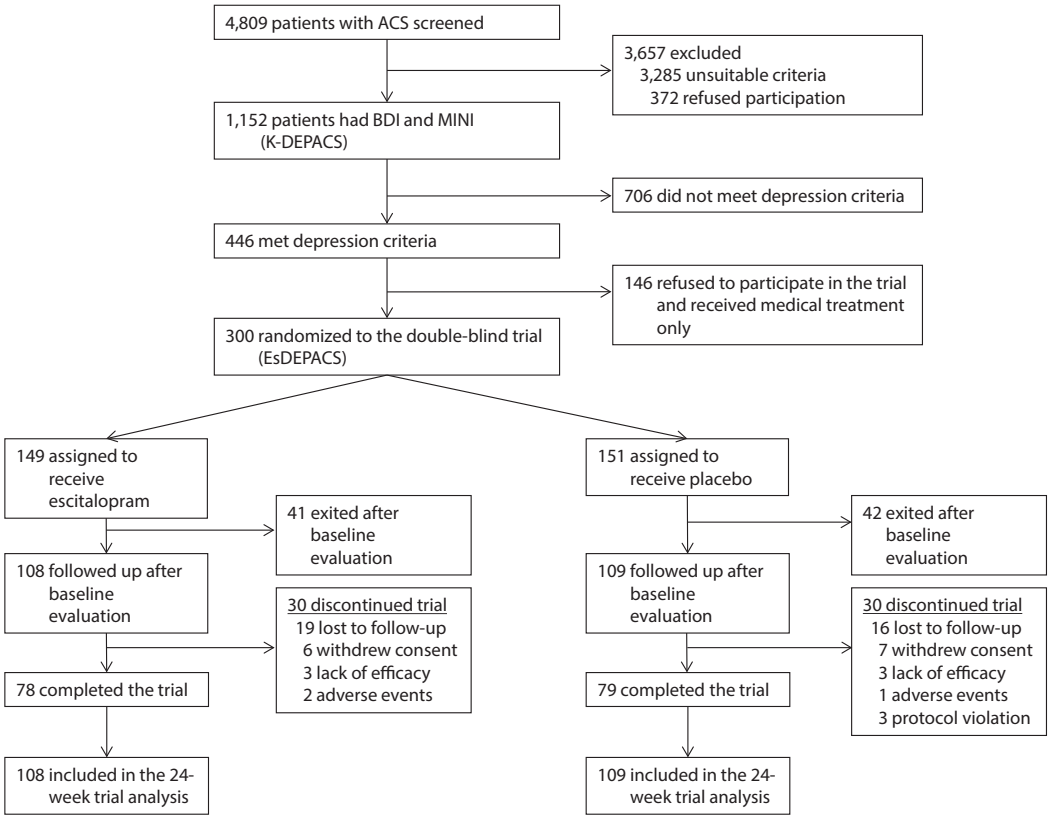
Outcomes

The primary efficacy outcome measure was the HDRS score change from baseline to endpoint. HDRS was chosen in order to maximize the comparability of our results with those from the SADHART[6] and CREATE[8] trials, in which HDRS was also used as the primary outcome. Secondary depressive outcome measures were MADRS, BDI, and CGI-S score changes from baseline to endpoint. Other efficacy outcome measures were SOFAS and WHODAS-12 score changes from baseline to endpoint. These measures were used for outcomes only and were not used as enrollment criteria.

For general safety outcomes, adverse events were recorded at all visits. Serious adverse events, both clinical and laboratory, were assessed. Reasons for discontinuation were recorded.

For cardiovascular safety outcomes, the following variables were measured: echocardiography for LVEF and wall motion; ECG for heart rate, PR interval, QRS duration, and QTc duration; laboratory tests for troponin I, CK-MB,

Figure 1. Participant Recruitment Process



Abbreviations: ACS = acute coronary syndrome, BDI = Beck Depression Inventory, EsDEPACS = Escitalopram for DEPression in Acute Coronary Syndrome, K-DEPACS = Korean DEPression in Acute Coronary Syndrome, MINI = Mini-International Neuropsychiatric Interview.

and total cholesterol; and body weight. These measures were conducted at the last follow-up (week 24) where possible. Resting blood pressure was measured at every follow-up visit.

Statistical Analysis

Subjects evaluated at least once after baseline comprised the efficacy dataset. Those who exited after baseline were excluded in later analyses, because treatment effects could not be investigated further. Baseline data were compared between escitalopram and placebo groups using *t* tests or χ^2 tests as appropriate. These factors were compared again between those followed and those not followed after the baseline evaluation.

For the efficacy analyses, the primary outcome measure was the HDRS score at endpoint, examined at a significance level of .05. A repeated-measures analysis of covariance in a mixed model was used with baseline HDRS scores as covariates. Multiple imputation by chained equations was used for missing data due to discontinuation after the second visit postbaseline (week 4) by treatment group, demographics (age and gender), and baseline HDRS and Killip scores. For clinical relevance, time to HDRS remission/response and numbers needed to treat between the treatment groups are described in eAppendix 2 and Supplementary eFigure 1. For the secondary outcomes on MADRS, BDI, CGI-S, SOFAS, and WHODAS-12, repeated-measures analyses of covariance in a mixed model were used with corresponding baseline scores as covariates. To maintain an overall type I error rate of .05 with 5 outcomes, a *P* value of .01 (.05/5) was used to define statistical significance by Bonferroni correction.

For general safety analyses, adverse events that occurred during the treatment period were compared between the 2 treatment groups using χ^2 tests. A repeated-measures analysis of covariance in a mixed model was used for echocardiography, ECG, laboratory tests, and body weight over the 24-week treatment period after adjustment for corresponding baseline values and Killip scores. Statistical analyses were carried out using SPSS 18.0 (IBM) and STATA 12.0 (StataCorp) software.

With respect to sample size, the EsDEPACS trial was designed to have 80% power to detect small to medium effect sizes (0.35) on the primary efficacy outcome (ie, a mean difference in HDRS scores of 2 points, assuming an SD of 5 to 6) assuming 2-sided tests at $\alpha = .05$. A sample size of 106 patients per group was calculated as required. A previous Korean naturalistic study of antidepressant treatment outcomes reported that a considerable proportion of subjects (30%) exited the study after baseline evaluation.[19] With the prediction of a 30% exit, 150 subjects per group were enrolled, for a total of 300 patients with ACS and depression.

Table 1. Baseline Characteristics of the EsDEPACS Participants[a]

	Followed Up After Baseline Evaluation			Exited After Baseline Evaluation (n = 83)
	Escitalopram (n = 108)	Placebo (n = 109)	Total (N = 217)	
Demographic characteristics				
Age, mean (SD), y	60.1 (10.9)	58.5 (10.6)	59.3 (10.8)	61.9 (10.9)
Gender, n (%) men	67 (62.0)	63 (57.8)	130 (59.9)	50 (60.2)
Education, mean (SD), y	9.4 (4.2)	9.4 (4.1)	9.4 (4.2)	9.0 (4.2)
Depression characteristics				
HDRS score, mean (SD)	15.9 (4.9)	15.1 (4.3)	15.5 (4.6)	16.4 (5.0)
MADRS score, mean (SD)	17.9 (6.9)	17.0 (5.5)	17.5 (6.3)	17.9 (6.1)
BDI score, mean (SD)	19.1 (8.6)	19.2 (7.5)	19.2 (8.1)	18.7 (7.9)
CGI-S score, mean (SD)	3.2 (1.0)	3.1 (0.9)	3.2 (0.9)	3.1 (0.8)
Previous depression, n (%)	6 (5.6)	5 (4.6)	11 (5.1)	2 (2.4)
DSM-IV diagnosis, n (%)				
Major depressive disorder	61 (56.5)	60 (55.0)	121 (55.8)	48 (57.8)
Minor depressive disorder	47 (43.5)	49 (45.0)	96 (44.2)	35 (42.2)
Cardiac risk factors, n (%)				
Hypertension	63 (58.3)	65 (59.6)	128 (59.0)	56 (67.4)
Diabetes mellitus	34 (31.5)	33 (30.3)	67 (30.9)	19 (22.9)
Hypercholesterolemia	51 (47.2)	50 (45.9)	101 (46.5)	43 (51.8)
Obesity	41 (38.0)	54 (50.0)	95 (43.8)	29 (34.9)
Current smoker	36 (33.3)	28 (25.7)	64 (29.5)	20 (24.1)
Previous ACS	6 (5.6)	8 (7.3)	14 (6.5)	5 (6.0)
Family history of ACS	5 (4.6)	4 (3.7)	9 (4.1)	8 (9.6)
Current cardiac status				
ACS diagnosis, n (%)				
Myocardial infarction	66 (61.1)	67 (61.5)	133 (61.3)	51 (61.4)
Unstable angina	42 (38.9)	42 (38.5)	84 (38.7)	32 (38.6)
Killip class > 1, n (%)	15 (13.9)	22 (20.2)	37 (17.1)	22 (26.5)
LVEF, mean (SD), %	60.1 (10.9)	62.4 (9.9)	61.3 (10.5)	60.8 (11.4)
Troponin I, mean (SD), mg/dL	9.5 (8.4)	9.5 (7.5)	9.5 (7.9)	10.1 (9.0)
Creatine kinase-MB, mean (SD), mg/dL	14.8 (14.2)	14.8 (19.9)	14.8 (17.3)	21.8 (29.1)*

[a]No significant differences were found between the escitalopram and placebo groups, and no significant differences were found between those followed up and exited after baseline evaluation except in serum creatine kinase-MB level using *t* tests or χ^2 tests as appropriate.

*$P = .043$.

Abbreviations: ACS = acute coronary syndrome, BDI = Beck Depression Inventory, CGI-S = Clinical Global Impressions Severity of Illness scale, EsDEPACS = Escitalopram for DEPression in Acute Coronary Syndrome study, HDRS = Hamilton Depression Rating Scale, LVEF = left ventricular ejection fraction, MADRS = Montgomery-Asberg Depression Rating Scale.

RESULTS

Recruitment and Baseline Characteristics

The recruitment process is described in Figure 1. Three hundred patients comprised the EsDEPACS population and were randomized, of whom 83 (28%) exited the study after baseline. The remaining 217 formed the efficacy sample, of whom 108 received escitalopram and 109 received placebo: 142 (65%) enrolled as inpatients and 75 (35%) as outpatients. Baseline characteristics of the 2 treatment groups are summarized in the first and second columns of Table 1; there were no significant differences between the 2 groups in any characteristic (all *P* values > .2). The serum CK-MB level was significantly higher in patients exiting after baseline evaluation compared to those followed up ($P = .043$), but there were no significant differences in any other characteristic at baseline between them (all *P* values > .1), as summarized in the third and fourth columns of Table 1. Between the 41 escitalopram and 42 placebo subjects who exited after baseline, there were no significant differences in any baseline characteristic (all *P* values > .05), as summarized in Supplementary eTable 1.

Drug Treatments and Discontinuation

The mean (SD) time from ACS to the start of study medication was 29.0 (24.1) days. Most patients were taking 5-mg or 10-mg daily doses of treatment medication (first 4 rows of Supplementary eTable 2) at the final visit. The mean (SD) doses at the last visit were 7.6 (3.7) mg for the escitalopram group and 8.5 (3.9) mg for the placebo group, and the mean (SD) treatment durations were 138.3 (22.4) and 138.0 (22.9) days, respectively. Adherence to medications was ≥ 75% in 100 of 108 people (93%) receiving escitalopram and in 103 of 109 people (95%) receiving placebo. Frequencies of the classes of cardiovascular medications used are summarized in the lower part of Supplementary eTable 2. The mean (SD) number of concomitant cardiovascular medications was 5.5 (1.6). In each group, 30 patients (28%) discontinued allocated treatments during the study, leaving 78 escitalopram and 79 placebo patients completing the trial. Reasons for discontinuation are listed in Figure 1, the most common being loss to follow-up. Overall, there were no significant differences in any aspects related to study drug treatments, concomitant medications, or discontinuation between the escitalopram and placebo groups.

Table 2. Efficacy Results of the EsDEPACS Trial From Baseline to Endpoint

	Escitalopram (n = 108)[a]		Placebo (n = 109)[a]		Mixed Model Analysis	
	Baseline	Endpoint	Baseline	Endpoint	Difference (95% CI)	*P* Value[b]
Hamilton Depression Rating Scale (primary outcome)						
All patients	15.9 (4.9)	8.6 (6.0)	15.1 (4.3)	10.1 (5.7)	2.3 (0.7 to 4.0)	.016
Patients with major depressive disorder[c]	17.8 (5.2)	9.2 (5.9)	16.7 (4.8)	11.0 (6.2)	2.8 (0.4 to 5.3)	.046
Patients with minor depressive disorder[c]	13.5 (3.4)	7.8 (6.1)	13.1 (2.4)	9.0 (4.9)	1.6 (−0.5 to 3.8)	.174
Secondary depressive outcomes						
Montgomery-Asberg Depression Rating Scale	17.9 (6.9)	9.0 (7.8)	17.0 (5.5)	12.2 (7.4)	4.0 (1.9 to 6.2)	<.001
Beck Depression Inventory	19.1 (8.6)	9.6 (7.2)	19.2 (7.5)	12.2 (8.1)	2.5 (0.1 to 4.9)	.009
Clinical Global Impressions-Severity of Illness scale	3.2 (1.0)	2.1 (1.0)	3.1 (0.9)	2.5 (1.1)	0.5 (0.2 to 0.8)	.001
Other psychiatric outcomes						
Social and Occupational Functioning Assessment Scale	69.6 (9.2)	76.4 (8.6)	70.7 (7.0)	73.6 (8.2)	4.0 (1.5 to 6.4)	.002
World Health Organization Disability Assessment Schedule-12	34.6 (20.9)	21.6 (19.7)	32.1 (20.1)	25.0 (19.6)	6.0 (0.2 to 11.9)	.069

[a]Data shown as mean (SD).
[b]*P* values derived from repeated-measures analysis of covariance in a mixed model with the corresponding baseline scores as a covariate.
[c]Of the total sample of 217 patients, 121 had major depressive disorder, and 96 had minor depressive disorder.
Abbreviation: EsDEPACS = Escitalopram for DEPression in Acute Coronary Syndrome study.

Table 3. Adverse Events During the Treatment Period, n (%)[a]

	Escitalopram (n = 108)	Placebo (n = 109)
Any adverse events	55 (50.9)	52 (47.7)
Dizziness	15 (13.9)	5 (4.6)
Headache	11 (10.2)	6 (5.5)
Fatigue	3 (2.8)	1 (0.9)
Insomnia	5 (4.6)	2 (1.8)
Pain	10 (9.3)	15 (13.8)
Gastrointestinal disturbance	9 (8.3)	5 (4.6)
Dry mouth	6 (5.6)	4 (3.7)
Sexual dysfunction	7 (6.5)	2 (1.8)
Orthostatic hypotension	4 (3.7)	6 (5.5)
Tingling sensation	6 (5.6)	5 (4.6)
Swelling	4 (3.7)	5 (4.6)
Dyspnea	8 (7.4)	12 (11.0)
Serious adverse events	3 (2.8)	6 (5.5)
Angina	1 (0.9)	4 (3.7)
Myocardial infarction	1 (0.9)	0 (0.0)
Stroke	1 (0.9)	1 (0.9)
Fracture	1 (0.9)	2 (1.8)

[a]Dizziness was significantly more frequently reported in the escitalopram group compared to the placebo group (*P* = .018). No significant differences were found between the 2 groups in any other adverse events using χ^2 tests.

Efficacy Results

The mean HDRS scores from baseline to 24 weeks of the escitalopram and placebo groups are displayed with the sample sizes at each follow-up point in Supplementary eFigure 2. Efficacy results are summarized in Table 2. For the primary outcome measure, escitalopram was superior to placebo in reducing HDRS scores over the treatment period with an effect size of 0.38. Results from the additional analysis, comparing HDRS score changes in those who completed the 24-week trial (N = 159), are displayed in Supplementary eFigure 3. For the secondary depressive outcome measures, escitalopram was superior to placebo in decreasing depressive symptoms evaluated by MADRS, BDI, and CGI-S. For the other psychiatric outcomes, escitalopram was superior to placebo in improving SOFAS scores significantly, but differences in WHODAS-12 score trajectories did not reach statistical significance. After applying Bonferroni corrections for the secondary depressive and other psychiatric outcomes, statistical significance remained for MADRS, BDI, CGI-S, and SOFAS (all *P* values < .01). When the same analyses were repeated after excluding 11 participants with a previous history of depression, the results were not changed substantially (data not shown). Additional analyses further adjusting for concomitant cardiovascular medications did not result in substantial changes (data not shown).

Safety Results

Adverse events during the study period are summarized in Table 3. Dizziness was more frequently reported in the escitalopram group compared to the placebo group (13.9% vs 4.6%, *P* = .018). However, there were no significant differences between the 2 treatment groups in any other adverse events. Reports of these adverse events were not frequent in either the escitalopram group (3%–14%) or placebo group (1%–14%) and were mild and tolerable. Serious adverse events were rare in both treatment groups. Discontinuation from the study occurred in 2 patients from the escitalopram group (stroke and MI) and in 1 patient from placebo group (stroke).

The cardiovascular safety results are summarized in Table 4. Except for the analysis of changes in blood pressure, which included all 217 subjects, these analyses were carried out in subgroups of 157 subjects who completed the trial and 20 subjects who discontinued after the postbaseline visits, for a total of 177 of 217 subjects (82%). There were no statistically significant differences in any of the cardiovascular safety outcomes between the 2 treatment groups. Additional analyses further adjusting for concomitant cardiovascular medications did not result in substantial changes (data not shown).

DISCUSSION

Principal findings of the EsDEPACS 24-week, randomized, double-blind, placebo-controlled study indicate that escitalopram was effective for treating depressive disorders in patients with recently developed ACS. This was found not only for the primary outcome (HDRS) but also for several secondary depressive outcomes (MADRS, BDI, CGI-S) and on improvement in social and occupational functioning (SOFAS). Escitalopram was also found to be safe and well

Table 4. Cardiovascular Safety Results From the EsDEPACS Trial at Baseline and Endpoint

	Escitalopram (n = 91)[a]		Placebo (n = 86)[a]		
	Baseline	Endpoint	Baseline	Endpoint	*P* Value[b]
Echocardiography results					
Left ventricular ejection fraction, %	60.1 (11.2)	62.3 (12.9)	61.6 (10.1)	63.9 (8.1)	.578
Wall motion, score	19.2 (5.4)	18.1 (4.2)	18.5 (4.0)	17.3 (2.9)	.310
Electrocardiography results					
Heart rate, beats/min	72.5 (13.8)	67.5 (10.0)	74.2 (17.3)	68.2 (9.0)	.759
PR interval, ms	168.2 (25.6)	163.9 (24.5)	171.5 (25.1)	166.1 (21.6)	.739
QRS duration, ms	97.6 (17.9)	97.7 (16.3)	92.8 (14.8)	93.6 (14.0)	.576
QTc duration, ms	438.7 (39.1)	424.4 (29.8)	443.6 (41.9)	421.1 (33.3)	.258
Laboratory results					
Troponin I, mg/dL	9.6 (8.9)	0.2 (0.6)	10.0 (8.0)	0.3 (1.3)	.504
Creatine kinase-MB, mg/dL	14.3 (14.0)	12.0 (6.1)	15.5 (21.1)	12.1 (5.3)	.859
Total cholesterol, mg/dL	180.4 (37.5)	158.1 (38.5)	177.3 (42.2)	154.0 (34.7)	.474
Body weight, kg	64.0 (10.4)	64.6 (11.3)	67.0 (12.2)	66.9 (12.6)	.124
Blood pressure, mm Hg (n = 217)	n = 108		n = 109		
Systolic	122.9 (15.5)	122.2 (17.3)	122.6 (15.3)	122.0 (17.8)	.921
Diastolic	77.8 (10.3)	78.5 (11.7)	76.7 (10.6)	75.8 (11.8)	.165

[a]Data shown as mean (SD).
[b]*P* values derived from repeated-measures analysis of covariance in a mixed model with corresponding baseline values and Killip score as covariates.

tolerated, and no significant associations were found with any harmful changes in cardiovascular measurements.

To our knowledge, this is the first trial to evaluate the efficacy and safety of escitalopram for treating depression following ACS. Several study design issues should be considered prior to interpretations. First, we included minor depressive disorder in this study a priori, based on previous research indicating significant negative effects on cardiac prognosis and therefore a need for treatment.[20,21] Furthermore, several meta-analyses have suggested that antidepressant effects are substantial only in severely depressed patients,[22] although other studies have demonstrated antidepressant efficacy as sufficiently robust to recommend treatment for patients with nonsevere depressive symptoms.[23] Because of this inclusion criterion, levels of depression in EsDEPACS participants were less severe (mean baseline HDRS score = 16) than in the SADHART, MIND-IT, and CREATE trials (mean baseline HDRS scores, 17–23).[6–8] No attempt was made to stratify the randomization by depression severity, but the severity was similar between randomization arms. Second, we recruited participants a relatively short time after an ACS episode (2–14 weeks, mean = 29 days), focusing on this period because of previous research showing that depression at this acute stage of ACS frequently persists and is associated with worse cardiac prognosis.[24]

Bearing in mind these considerations, a robust effect of escitalopram was found. The difference in favor of escitalopram over placebo was clinically relevant, with an effect size of 0.38 for mean change from baseline to endpoint. This effect size was greater than that reported in the CREATE trial (0.33),[8] possibly due to the longer treatment period (24 weeks in EsDEPACS vs 12 weeks in CREATE). Our positive finding was largely supported by secondary outcomes on 3 other depression assessment scales different from the HDRS in some aspects: the MADRS excludes somatic symptoms of depression, the BDI is a self-report measure, and the CGI-S assesses global symptomatology. Furthermore, escitalopram was associated with significantly improved functioning level, consistent with CREATE study findings.[8]

In the SADHART and CREATE studies, antidepressant effects were more apparent in participants with prior histories of depression,[6,8] whereas in our study, the main findings were not different when analyses were repeated after excluding patients with previous history of depression. The difference between those studies and ours might be due to the fact that previous depression was infrequently reported (4.7%) in our participants compared to the previous studies (40%–50%), although the prevalence in our study is consistent with a nationwide Korean epidemiologic study reporting a 1-year prevalence of major depression of 1.8%.[25]

Low escitalopram doses (mean = 7.6 mg/d) were used, lower than doses in the CREATE trial (citalopram 33–34 mg/d, equivalent to escitalopram 16–17 mg/d).[8] Ethnic differences have been reported in response to psychotropic medications, and lower doses have been suggested as sufficient for achieving similar responses in East Asians compared to Caucasians.[26] However, this finding may be also be related to the milder depression severity in EsDEPACS compared to CREATE.[8]

Escitalopram was generally safe and well tolerated, and only dizziness was significantly more frequently reported in the escitalopram group. This finding differs from CREATE, which reported higher frequencies of adverse events in the citalopram treatment group.[8] The difference may be due to the relatively low doses used in EsDEPACS. In addition, we found no evidence for harmful effects of escitalopram over placebo on any cardiovascular profiles evaluated by echocardiography, ECG, laboratory results, body weight, and blood pressure. Recently, there has been concern about the use of higher doses of citalopram and escitalopram in relation to QTc prolongation, a surrogate marker of cardiotoxicity.[27] In EsDEPACS, we found no group difference in QTc duration. Although this finding may be related to the low escitalopram doses used, similar results were found in the CREATE study with higher citalopram doses.[8] Serious cardiovascular adverse events occurred in less than 5% of both groups.

The EsDEPACS trial has several limitations. First, 83 of 300 randomized subjects (28%) exited the study after baseline evaluation. Since their serum CK-MB levels were significantly higher compared to those of patients who were followed up, it can be assumed that more severe ACS pathology might be associated with the attrition. However, there were no significant differences in any other baseline variables of depressive status. Furthermore, we anticipated such an exit and increased the sample size for randomization

when designing this trial. Second, the study completion rate was 73%. This rate was the same as the completion rate in the 24-week SADHART study (73%)[6] and higher than that in the 24-week MIND-IT mirtazapine trial (43%),[7] although lower than in the 12-week CREATE study (81%).[8] There were no significant differences in the rate of or reasons for discontinuation between the escitalopram and placebo groups. A third limitation is that recruitment was carried out at a single site, unlike previous studies using multicenter recruitment.[6 8] This aspect of the study may limit the generalizability, and therefore replication of these findings in multicenter settings may be needed. However, a single-center study has strengths in terms of consistency in evaluating and treating patients.

In conclusion, clinically meaningful antidepressive effects were found for escitalopram compared to placebo in depressive disorder occurring with ACS, along with high tolerability and safety. As stated earlier, there have been very few evidence-based treatment options for depression in ACS to date, despite the high prevalence and negative impact of depression in these patient groups. The EsDEPACS trial supports an additional effective and safe treatment option for clinicians treating these patients.

Drug names: citalopram (Celexa and others), escitalopram (Lexapro and others), fluoxetine (Prozac and others), mirtazapine (Remeron and others), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft and others).

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Supplementary Material

Article Title: Escitalopram Treatment for Depressive Disorder Following Acute Coronary Syndrome: A 24-Week Double-Blind, Placebo-Controlled Trial

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List of Supplementary Material for the article

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eAppendix 1. Inclusion and exclusion criteria

Inclusion criteria were as follows: i) aged 18~85 years; ii) confirmed ACS by investigation (the presence of ST-segment elevation MI was determined by >30 min of continuous chest pain, a new ST-segment elevation ≥2 mm on at least two contiguous electrocardiographic leads, and creatine kinase-MB more than three times normal; the presence of non-ST-segment elevation MI was diagnosed by chest pain and a positive cardiac biochemical marker without new ST-segment elevation; and the presence of unstable angina was determined by chest pain within the preceding 72 h with or without ST-T wave changes or positive cardiac biochemical markers); iii) BDI>10; iv) major or minor depressive disorder according to DSM-IV criteria; iv) ability to complete study questionnaires; v) ability to understand the study objectives and sign informed consent. Exclusion criteria were: i) occurrence of ACS while hospitalized for another reason; ii) ACS developing less than 3 months after a coronary artery bypass graft procedure; iii) uncontrolled hypertension (systolic blood pressure (BP) >180mmHg or diastolic BP >100mmHg); iv) resting heart rate <40/min; v) severe physical illnesses threatening life or interfering with the recovery from ACS; vi) persistent clinically significant laboratory abnormalities; vii) concomitant use of class I antiarrhythmic medications, reserpine, guanethidine, clonidine, methyldopa, lithium, anticonvulsants, antipsychotics, or antidepressants; viii) history of neuropsychiatric illnesses such as dementia, Parkinson's disease, brain tumor, psychosis, bipolar disorder, alcoholism, or other substance dependence; ix) pregnancy; x) participating in other drug trials.

eAppendix 2. Methods and Results for time to Hamilton Rating Scale for Depression (HAMD) remission/response analyses

Remission was defined as a HAMD score ≤7, and response was defined as a HAMD score reduction of >50% over the treatment period. Remission/response statuses were recorded at each follow-up point. Achieving remission or response was defined only when the remission or response was maintained to the 24 week study endpoint or to the last follow-up examination if earlier, with the date of the first observed remission or response point applied as the timing of remission or response. Log-rank tests in Kaplan Meyer models were conducted to compare the cumulative proportion of participants with remission/response between the treatment groups. For clinical relevance 'numbers needed to treat (NNT)' were calculated for the remission/response proportion (as 100 divided by the difference in percentages) at each follow-up point, indicating the number of patients receiving escitalopram which would be required for one extra person to achieve remission/response. Cox proportional hazards models were used to assess the time to remission/response with the baseline HAMD scores as a covariate.

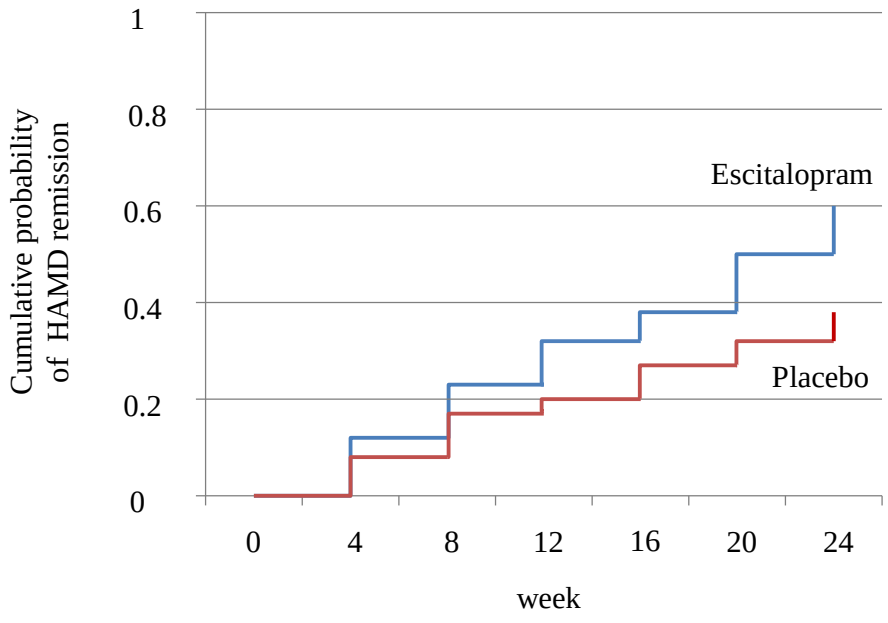
Results on time to achieve HAMD remission/response and NNT between the treatment groups are displayed in supplementary eFigure 1. Patients in escitalopram group had significantly earlier remission and response with NNT=5 at week 20 and 4 at week 24.

Supplementary eFigure 1. Time to Hamilton Rating Scale for Depression (HAMD) remission/response and numbers needed to treat (NNT) between the EsDEPACS treatment groups

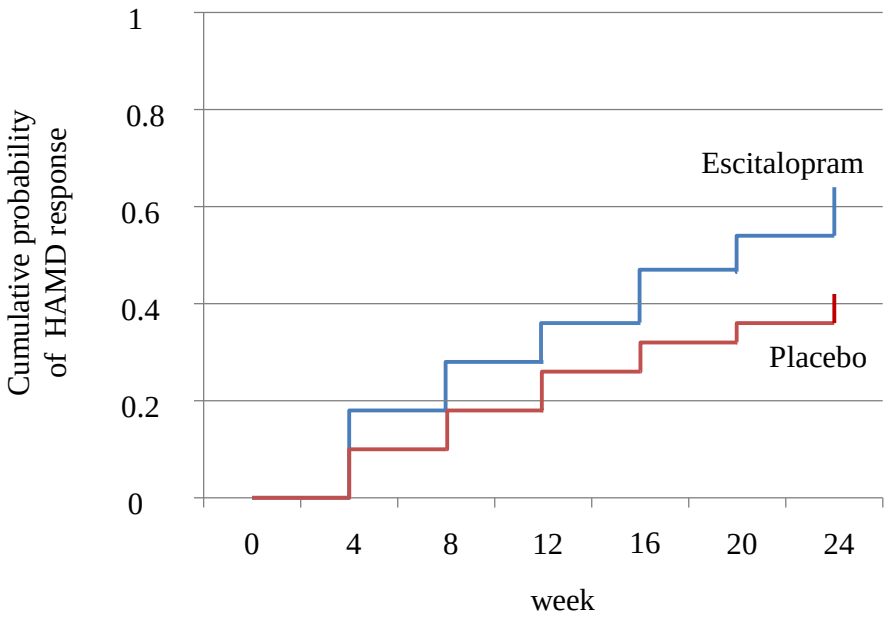
Figure legends:

The cumulative proportions of participants with remission were driven from Kaplan Meyer models. Hazard ratios (95% confidence intervals) [HR (95% CI)] and p-values were drawn from Cox regression hazard ratio tests after adjustment for baseline HAMD scores. NNT indicates the number of patient in the escitalopram group which would be required for one more person to achieve remission or response.

EsDEPACS, Escitalopram for DEPression in Acute Coronary Syndrome study.



Number at risk							
Escitalopram	108	96	84	69	53	42	31
Placebo	109	101	91	83	71	62	56
NNT	-	25	16.7	7.1	7.7	5.3	4.5



HR (95% CI) = 1.89 (1.32-2.89)
p=0.003

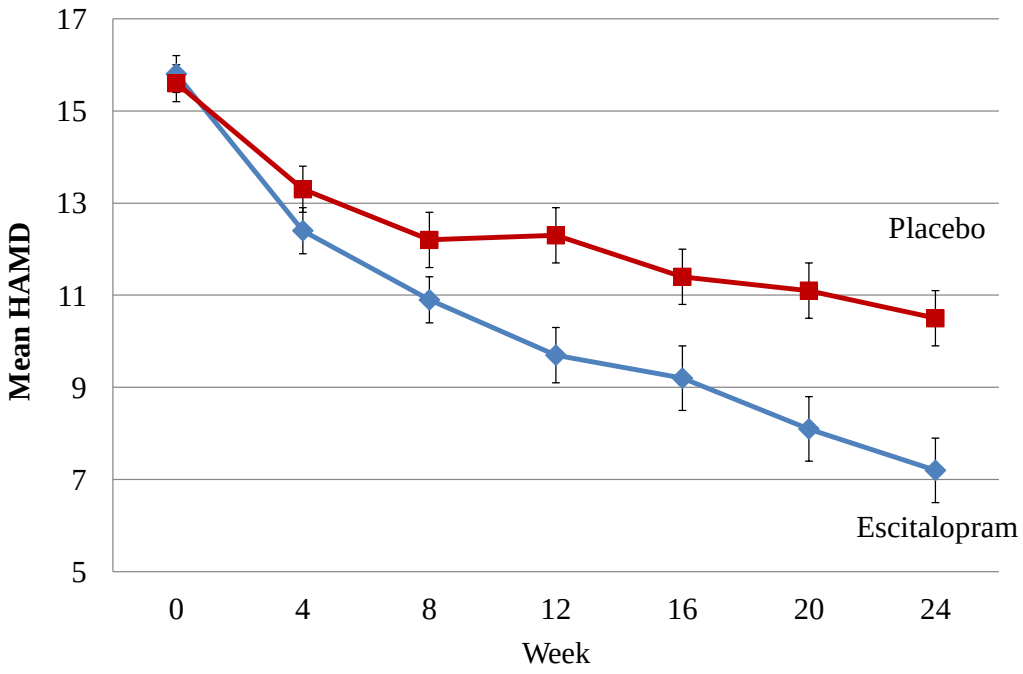
Number at risk

Escitalopram	108	89	78	65	56	50	39
Placebo	109	98	89	83	74	70	63
NNT	-	12.5	10	10	6.3	5.6	4.5

Supplementary eFigure 2. Mean Hamilton Rating Scale for Depression (HAMD) scores from baseline to 24 weeks between the EsDEPACS treatment groups with the sample sizes at each follow-up point

Figure legends:

EsDEPACS, Escitalopram for DEPression in Acute Coronary Syndrome study.

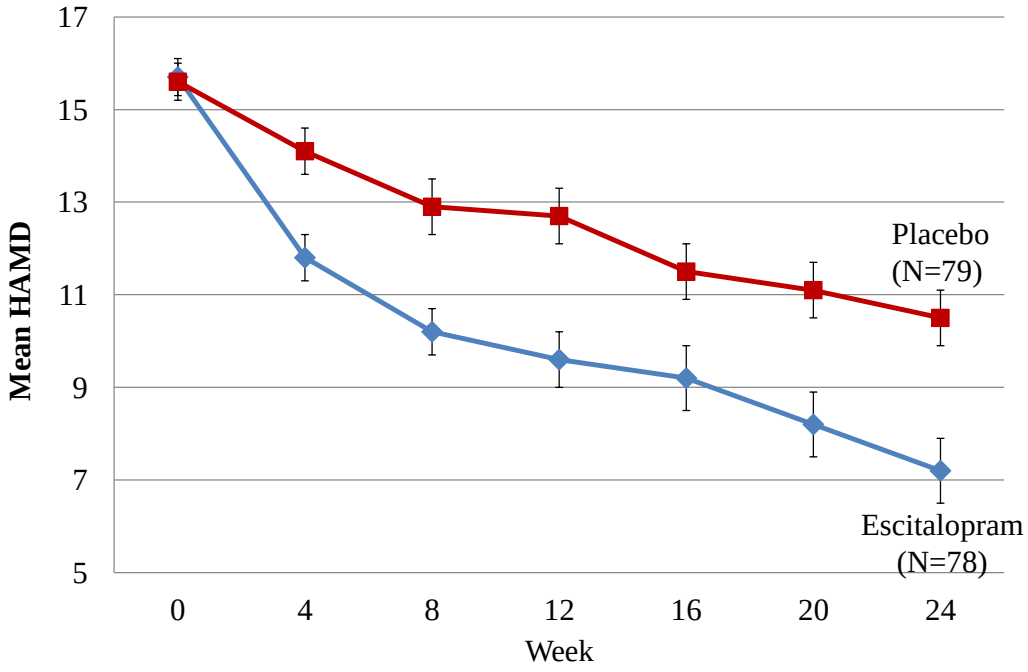


Sample size							
Escitalopram	149	108	101	86	81	79	78
Placebo	151	109	101	87	81	80	79

Supplementary eFigure 3. Mean Hamilton Rating Scale for Depression (HAMD) scores over the treatment period in those completed the 24 weeks trial.

Figure legends:

Statistics for group by time interaction after adjustment for baseline HAMD score are F=6.627 and p-value=0.011.



Mean (SD) HAMD scores

Escitalopram	15.7 (5.0)	11.8 (5.5)	10.2 (5.2)	9.6 (5.6)	9.2 (5.4)	8.2 (5.4)	7.2 (5.1)
Placebo	15.6 (4.7)	14.1 (5.3)	12.9 (5.3)	12.7 (5.9)	11.5 (6.1)	11.1 (6.0)	10.5 (6.1)

Supplementary eTable1. Baseline characteristics of the EsDEPACS subjects exited after baseline.

	Total (N=83)	Escitalopram (N=41)	Placebo (N=42)
Demographic characteristics			
Age, mean (SD) year	61.9 (10.9)	59.7 (12.2)	64.2 (9.2)
Gender, N (%) men	51 (61.4)	21 (51.2)	30 (71.4)
Education, mean (SD) year	9.0 (4.2)	9.4 (4.2)	8.6 (4.1)
Depression characteristics			
HAMD, mean (SD) score	16.4 (5.0)	15.9 (4.4)	17.0 (5.6)
MADRS, mean (SD) score	17.9 (6.1)	18.4 (6.0)	17.5 (6.3)
BDI, mean (SD) score	18.7 (7.9)	18.1 (7.6)	19.1 (8.1)
CGI-s, mean (SD) score	3.1 (0.8)	3.1 (0.8)	3.0 (0.8)
Previous depression, N (%)	2 (2.4)	0 (0)	2 (4.8)
DSM-IV diagnosis, N (%)			
Major depressive disorder	48 (57.8)	24 (58.5)	24 (57.1)
Minor depressive disorder	35 (42.2)	17 (41.5)	18 (42.9)
Cardiac risk factors, N (%)			
Hypertension	56 (67.4)	27 (65.9)	29 (69.0)
Diabetes mellitus	19 (22.9)	10 (24.4)	8 (19.0)
Hypercholesterolemia	43 (51.8)	22 (53.7)	21 (50.0)
Obesity	29 (34.9)	18 (43.9)	11 (26.2)
Current smoker	21 (25.3)	7 (17.1)	14 (33.3)
Previous ACS, N (%)	5 (6.0)	2 (4.9)	3 (7.1)
Family history of ACS, N (%)	8 (9.6)	4 (9.8)	4 (9.5)

Current cardiac status			
ACS diagnosis, N (%)			
Myocardial infarction	51 (61.4)	26 (63.4)	25 (59.5)
Unstable angina	32 (38.6)	15 (36.6)	17 (40.5)
Killip class >1, N (%)	22 (26.5)	9 (22.0)	13 (31.0)
LVEF, mean (SD) %	60.8 (11.4)	61.2 (11.1)	60.4 (11.7)
Troponin I, mean (SD) mg/dL	10.1 (9.0)	10.1 (8.9)	10.2 (9.1)
CK-MB, mean (SD) mg/dL	21.8 (29.1)	23.6 (34.6)	20.1 (22.9)

No significant differences were found between the escitalopram and placebo groups using t-tests or χ^2 tests as appropriate.

Abbreviations: EsDEPACS, Escitalopram for DEPression in Acute Coronary Syndrome study; HAMD, Hamilton Depression Rating Scale; MADRS, Montgomery Asberg Depression Rating Scale; BDI, Beck Depression Inventory; CGI-s, Clinical Global Impression Scale-severity scale; DSM-IV, Diagnostic and Statistical Manual 4th edition; ACS, acute coronary syndrome; LVEF, left ventricular ejection fraction; CK-MB, Creatine kinase-MB.

Supplementary eTable2. Treatment drugs and cardiovascular medications. Data are N (%).

	Escitalopram (N=108)	Placebo (N=109)
Dosages of treatment drugs at last visit		
5mg	62 (57.4)	50 (45.9)
10mg	40 (37.0)	47 (43.1)
15mg	1 (0.9)	7 (6.4)
20mg	5 (4.6)	5 (4.6)
Cardiovascular medications during the treatment period		
Calcium channel blockers	38 (35.2)	48 (45.0)
Nitrates	87 (80.6)	89 (81.7)
Beta blockers	77 (71.3)	80 (73.4)
Angiotensin converting enzyme inhibitors	36 (33.3)	43 (39.4)
Angiotensin 2 receptor blocker	58 (53.7)	58 (53.2)
Statins	88 (81.5)	84 (77.1)
Aspirin	99 (91.7)	98 (89.9)
Antiplatelets	83 (76.9)	79 (72.5)
Diuretics	25 (23.1)	21 (19.3)

No significant differences were found between the two groups using χ^2 tests.