

# Effect of Escitalopram vs Placebo Treatment for Depression on Long-term Cardiac Outcomes in Patients With Acute Coronary Syndrome

## A Randomized Clinical Trial

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**IMPORTANCE** Depression has been associated with poorer medical outcomes in acute coronary syndrome (ACS), but there are few data on the effects of antidepressant treatment on long-term prognosis.

**OBJECTIVE** To investigate the effect on long-term major adverse cardiac events (MACE) of escitalopram treatment of depression in patients with recent ACS.

**DESIGN, SETTING, AND PARTICIPANTS** Randomized, double-blind, placebo-controlled trial conducted among 300 patients with recent ACS and depression enrolled from May 2007 to March 2013, with follow-up completed in June 2017, at Chonnam National University Hospital, Gwangju, South Korea.

**INTERVENTIONS** Patients were randomly assigned to receive either escitalopram in flexible dosages of 5, 10, 15, or 20 mg/d (n = 149) or matched placebo (n = 151) for 24 weeks.

**MAIN OUTCOMES AND MEASURES** The primary outcome was MACE, a composite of all-cause mortality, myocardial infarction (MI), and percutaneous coronary intervention (PCI). Four secondary outcomes were the individual MACE components of all-cause mortality, cardiac death, MI, and PCI. Cox proportional hazards models were used to compare the escitalopram and placebo groups by time to first MACE.

**RESULTS** Among 300 randomized patients (mean age, 60 years; 119 women [39.3%]), 100% completed a median of 8.1 (interquartile range, 7.5-9.0) years of follow-up. MACE occurred in 61 patients (40.9%) receiving escitalopram and in 81 (53.6%) receiving placebo (hazard ratio [HR], 0.69; 95% CI, 0.49-0.96;  $P = .03$ ). Comparing individual MACE outcomes between the escitalopram and placebo groups, respectively, incidences for all-cause mortality were 20.8% vs 24.5% (HR, 0.82; 95% CI, 0.51-1.33;  $P = .43$ ), for cardiac death, 10.7% vs 13.2% (HR, 0.79; 95% CI, 0.41-1.52;  $P = .48$ ); for MI, 8.7% vs 15.2% (HR, 0.54; 95% CI, 0.27-0.96;  $P = .04$ ), and for PCI, 12.8% vs 19.9% (HR, 0.58; 95% CI, 0.33-1.04;  $P = .07$ ).

**CONCLUSIONS AND RELEVANCE** Among patients with depression following recent acute coronary syndrome, 24-week treatment with escitalopram compared with placebo resulted in a lower risk of major adverse cardiac events after a median of 8.1 years. Further research is needed to assess the generalizability of these findings.

**TRIAL REGISTRATION** ClinicalTrials.gov Identifier: [NCT00419471](https://clinicaltrials.gov/ct2/show/study/NCT00419471)

JAMA. 2018;320(4):350-357. doi:10.1001/jama.2018.9422

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Depression is frequently comorbid with acute coronary syndrome (ACS; including myocardial infarction [MI] and unstable angina)<sup>1</sup> and associated with poor outcomes including increased mortality and nonfatal events.<sup>2,3</sup> A clinically important question is whether antidepressant treatment mitigates these adverse effects. In randomized clinical trials of antidepressants in ACS, mostly evaluating selective serotonin reuptake inhibitors, improvement in depressive symptoms has been demonstrated repeatedly.<sup>4,5</sup> However, effects on cardiac outcomes have not generally been found within the treatment period.<sup>6-9</sup>

Considering longer-term cardiac outcomes, in an 18-month follow-up of the Myocardial Infarction and Depression-Intervention Trial (MIND-IT), no difference was found in cardiac outcomes between 209 patients receiving antidepressants (8 weeks of mirtazapine and/or subsequent open-label citalopram) and 122 patients receiving usual care.<sup>10</sup> In the 6.7-year follow-up of the Sertraline Antidepressant Heart Attack Randomized Trial (SADHART), there was also no difference in mortality between 184 patients receiving 6 months of sertraline and 177 receiving placebo.<sup>11</sup> Furthermore, the Enhancing Recovery in Coronary Heart Disease Patients (ENRICH) trial found no difference in cardiac outcomes over a 29-month follow-up between the intervention (9 months of cognitive behavioral therapy with or without 12 months of antidepressants) and usual care among 2481 patients with depression following MI.<sup>12</sup> However, in a subanalysis, 301 patients receiving selective serotonin reuptake inhibitors showed better cardiac outcomes than 1388 not receiving them.<sup>13</sup> Conversely, an observational study reported that 58 patients who received selective serotonin reuptake inhibitors had worse outcomes than 354 who did not receive them over a 3.6-year follow-up.<sup>14</sup>

Associations of antidepressant treatment with long-term cardiac outcomes in depression following ACS have therefore been inconclusive. Previous research has been limited by short follow-up periods,<sup>10,14</sup> heterogeneous antidepressant regimens and samples,<sup>13,14</sup> and limited evaluation of cardiac outcomes.<sup>11</sup> This study aimed to investigate whether the effect of escitalopram vs placebo for treating acute-phase depression in patients with recent ACS resulted in benefits in longer-term cardiac outcomes.

## Methods

### Study Design and Participants

This article describes preplanned extended follow-up of the Escitalopram for Depression in Acute Coronary Syndrome (EsDEPACS) study, a 24-week randomized, placebo-controlled clinical trial of escitalopram for treating depression following ACS. The design of this trial has been published,<sup>15</sup> and the trial protocol is available in [Supplement 1](#). Written informed consent was collected, and the study was approved by the Chonnam National University Hospital (CNUH) Institutional Review Board. Participant recruitment and study flow are presented in [Figure 1](#).

### Baseline Evaluation

Participants were consecutively recruited from patients recently hospitalized with ACS at the Department of Cardiology of CNUH, Gwangju, South Korea. In 2005, this department was

## Key Points

**Question** Does antidepressant treatment of depression shortly after acute coronary syndrome improve long-term cardiac outcomes?

**Findings** In this randomized clinical trial that included 300 patients with recent acute coronary syndrome and depression, 24-week treatment with escitalopram compared with placebo resulted in an occurrence of major adverse cardiac outcomes of 40.9% vs 53.6% after a median follow-up of 8.1 years, a difference that was statistically significant.

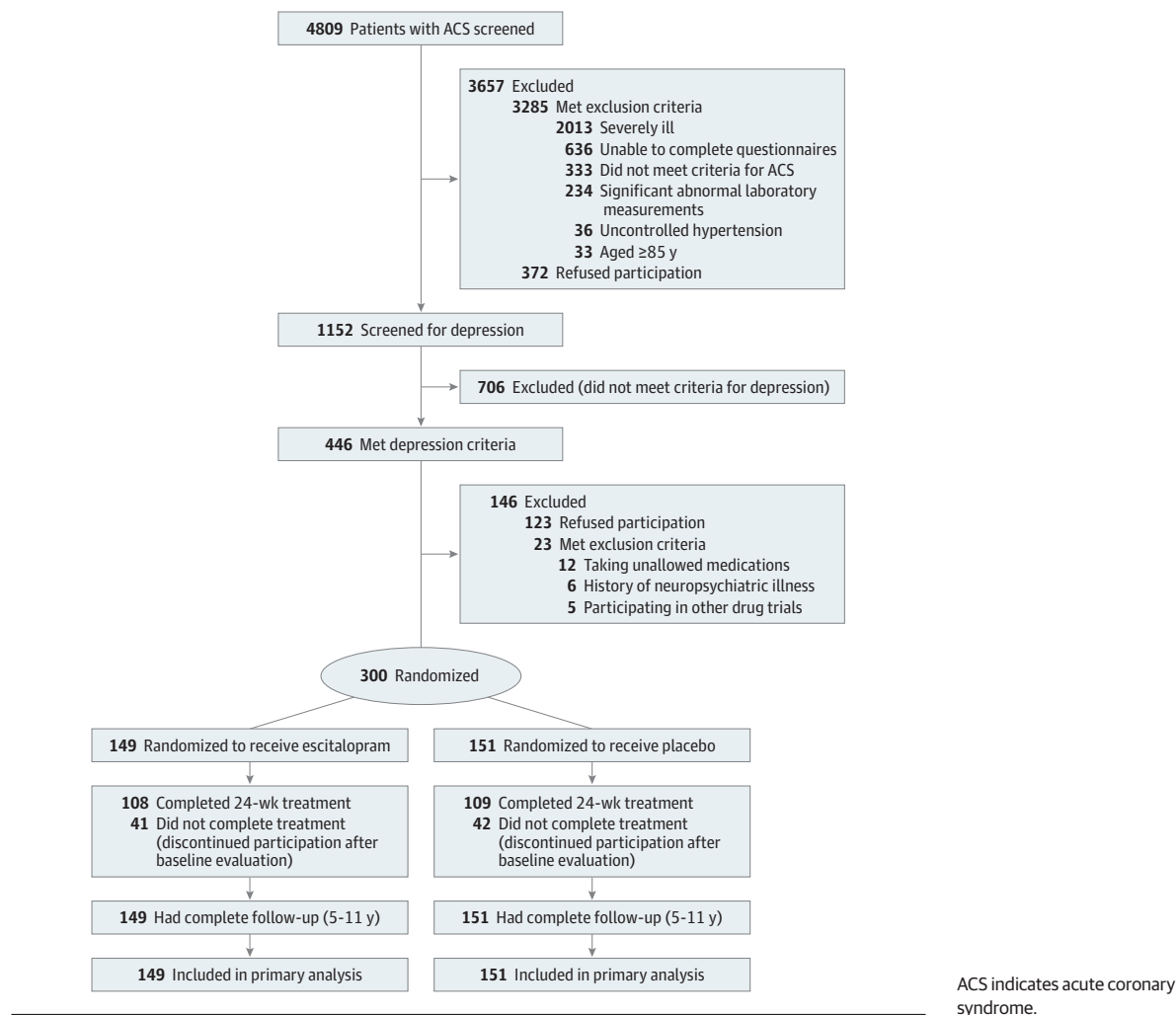
**Meaning** Treatment with escitalopram for depression following recent acute coronary syndrome may improve long-term cardiac outcomes.

nominated by the Korean Circulation Society to serve as the central coordinating center for the Korea Acute Myocardial Infarction Registry (KAMIR).<sup>16</sup> KAMIR is a nationwide prospective, multicenter, online registry (<http://kamir5.kamir.or.kr/>) designed as a surveillance platform to track clinical outcomes of patients with acute MI without exclusion criteria to reflect real-world practice; this enables prospective associations to be evaluated for a range of exposures or interventions with long-term cardiac outcomes. From November 2005 to December 2015, 53 966 individuals had been registered nationally and 44 758 (82.9%) were followed up for cardiac events at 1 year.<sup>16-18</sup> Information was collected in a standardized proforma across sites. The study described herein focused solely on participants recruited from CNUH, which adopted a more intensive surveillance approach, with information gathered by personnel exclusively for this study, backed up by KAMIR network resources. This allowed complete follow-up for all 24-week trial participants. Preplanned monitoring of the obtained information was conducted by additional personnel at the Clinical Trial Centre of CNUH with expertise in data quality control and checked for completeness and accuracy once per year after registration. All missing or uncertain outcome data were complemented or amended through manual checks of electronic records and supplementary telephone calls where required.

Patients were treated by study cardiologists based on international guidelines for management of ACS.<sup>19</sup> Inpatients who had had ACS in the previous 2 weeks (mean, 6.3 [SD, 2.4] days) and who met eligibility criteria (eAppendix 1 in [Supplement 2](#)) and agreed to participate were screened for depressive symptoms with the Beck Depression Inventory (BDI)<sup>20</sup> at baseline and thereafter as outpatients every 4 weeks up to 12 weeks. Those with a BDI score greater than 10 on any of these occasions received a clinical evaluation by a study psychiatrist using the Mini International Neuropsychiatric Interview (MINI),<sup>21</sup> a structured diagnostic psychiatric interview applying *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition) (DSM-IV) criteria, which yield diagnoses of major or minor depressive disorder.<sup>22</sup>

Information was collected on characteristics that could potentially affect cardiac outcomes.<sup>23</sup> Demographic data were obtained on age, sex, education, marital status, living alone, accommodation, and employment status. For evaluating depressive symptoms, the self-completed BDI and psychiatrist-administered MINI diagnoses were ascertained as described, and history of depression was also recorded. Cardiovascular

Figure 1. Participant Flow in the Escitalopram for Depression in Acute Coronary Syndrome Study



risk factors ascertained included diagnosed hypertension and diabetes mellitus, hypercholesterolemia by fasting serum total cholesterol level ( $>200$  mg/dL [ $5.18$  mmol/L]), obesity by measured body mass index, reported current smoking status, and personal and family histories of ACS. Cardiac severity status was identified using ACS diagnosis (MI or unstable angina), Killip classification,<sup>24</sup> New York Heart Association functional classification,<sup>25</sup> left ventricular ejection fraction, QTc duration, and serum levels of troponin I and creatine kinase MB.

### 24-Week Randomized Clinical Trial

Among participants with a baseline diagnosis of major or minor depressive disorder, those who met eligibility criteria and agreed to participate were randomized to a 24-week, double-blind, randomized clinical trial of escitalopram vs placebo. The first patient was enrolled in May 2007 and the last patient completed the 24-week follow-up evaluation in March 2013. Examinations were scheduled at baseline and at weeks 4, 8, 12, 16, 20, and 24 thereafter. The study drug dosage was 10 mg/d initially and could be changed (from 5 mg/d to 20 mg/d) according to the investigators' clinical decision, taking into

account response and tolerability after the second evaluation. Mean doses at the last visit were 7.6 (SD, 3.7) mg for the escitalopram group and 8.5 (SD, 3.9) mg for the placebo group. Adherence was checked by pill counts at every visit and was defined as acceptable if at least 75%. Adherence to medication was 93.3% and 95.4% in patients receiving escitalopram and placebo, respectively. At the end of 24 weeks of double-blind treatment, the study was completed, study medication was tapered down, and patients were unblinded.

The primary outcome was remission of depressive symptoms, defined by a Hamilton Depression Rating Scale (HAM-D) score of 7 or lower at the trial end.<sup>26</sup> In pretrial analyses, a sample size of 106 patients per group was estimated as sufficient to detect a mean difference in HAM-D scores of 2 points, assuming an SD of 5.5, 2-sided tests,  $\alpha = .05$ , and 80% power; therefore, assuming 30% loss to follow-up, a total of 300 patients was specified as a target for recruitment. The presence of any antidepressant use after the trial was ascertained at 1 year after the index ACS. The results of this 24-week trial have been published; escitalopram was superior to placebo in reducing depressive symptoms.<sup>9</sup>

### Long-term Follow-up for Cardiac Outcomes

Comprehensive evaluations for cardiac outcomes were possible for this study because KAMIR manages and records detailed data electronically on hospital admissions, deaths, recurrent MI, and percutaneous coronary intervention (PCI). Long-term follow-up was initiated after the patients were enrolled for this trial. Because previous studies in this field have shown conflicting results,<sup>10-14</sup> there was no appropriate reference for power calculation within the designated sample size. The KAMIR study reported a 10.9% incidence of major adverse cardiac events (MACE) over 1 year<sup>16</sup>; therefore, approximately 50% MACE incidence was expected during a 5-year follow-up. Assuming 2-sided tests,  $\alpha = .05$ , and a follow-up sample size of 300, the expected power was 70% and 96% for detecting 10% and 15% group differences, respectively. Each patient's status was evaluated and recorded at every hospital visit using the KAMIR protocol administered by KAMIR researchers. At least 2 researchers were exclusively assigned to this study during the entire study period specifically to obtain accurate data on long-term cardiac outcomes. These researchers made telephone contact with patients or their family members the day before each expected hospital visit to facilitate continued participation and to maximize follow-up. For those transferred to other hospitals, the researchers verified the patient's status through a telephone call to the hospital and using the KAMIR database shared between the hospitals. When reasons for loss to follow-up could not be identified in the hospital records, mainly deaths outside of the hospital (3% of all participants), deaths were confirmed through telephone contact with a family member and through death certification in the National Registration Records, with which it was confirmed that all patients were registered. Emigration did not occur for any cohort member. As described, assertive maximization of outcome information collection was carried out at the Clinical Trial Centre of CNUH, including checks for completeness and accuracy each year after the registration and manual supplementary data collection via records checks and telephone follow-up where indicated. Through these measures, all baseline participants were thus successfully and completely followed up for these outcomes. Because a patient could have more than 1 event, all patients were followed up to the present evaluation point or until death, and nonhierarchical end-point analyses were used.

### Outcome Measures

The primary end point was MACE, which was a composite of all-cause mortality, MI, and PCI. Four secondary end points were (1) all-cause mortality; (2) cardiac death (defined as sudden death with no other explanation available, death due to arrhythmia or after MI or heart failure, or death caused by heart surgery or endocarditis); (3) MI; and (4) PCI. An independent end-point committee composed of study cardiologists adjudicated all potential events and was blinded to the participants' randomization status.

### Statistical Analysis

Baseline demographic and clinical characteristics were compared between the escitalopram and placebo groups using *t* tests or  $\chi^2$  tests. The primary analysis included all randomized participants and was based on follow-up data at a median of 8.1 years after

trial commencement. Kaplan-Meier models were used to calculate the cumulative proportion of participants experiencing a composite MACE according to the date of the first event for each patient. Cox proportional hazards models were used to compare the escitalopram and placebo groups by time to first composite MACE. Two sensitivity analyses were carried out: (1) excluding patients taking antidepressants at the 1-year post-ACS examination to exclude the possible medication effects of the 24-week trial on long-term cardiac outcomes and (2) restricting the analysis to those with impaired left ventricular ejection fraction (<55%) at baseline. Secondary analyses were performed for individual MACE components in the same analytic models. Schoenfeld residuals tests were carried out to test the proportional hazards assumptions for primary and secondary outcomes.

Post hoc analyses were conducted in the subsample who completed the trial. To evaluate the effects of treatment and remission status, Cox proportional hazards models were used to compare time to first MACE after the 24-week trial. Individual associations with treatment group (escitalopram vs placebo) and remission status (remission vs no remission) were estimated separately.

All analyses were repeated after adjustment for variables that have been associated with cardiac outcomes in previous research.<sup>23</sup> All statistical tests were 2-sided with a significance level of  $P < .05$ . Statistical analyses were carried out using SPSS version 21.0 (IBM) and Stata version 12.0 (Stata Corp).

## Results

### Recruitment and Baseline Characteristics

Of 4809 patients with ACS screened, 1152 were recruited to undergo depression screening with the BDI and MINI, through which 446 participants were identified as having a baseline *DSM-IV* diagnosis of major ( $n = 202$ ) or minor ( $n = 246$ ) depressive disorder. Among these patients, 300 were included in the trial and randomized to receive either escitalopram ( $n = 149$ ) or placebo ( $n = 151$ ) (Figure 1). In the recruiting process, higher participation rates were noted in patients with more severe depressive symptoms, resulting in a frequency of major depressive disorder of 57.0% (85/149) among the escitalopram group and 55.6% (84/151) among the placebo group, compared with 22.6% (33/146) in patients who met inclusion criteria but were not randomized. Baseline demographic and clinical characteristics are described in the Table and were similar between the escitalopram and placebo groups. Severity of ACS was relatively mild; 81% of patients were in Killip class 1 and 89% were in New York Heart Association class I. Because randomization resulted in similar distributions of measured covariates between the allocation groups, analyses were reported without adjustment, consistent with other research in this field.<sup>27</sup>

### Primary Outcome

All participants were followed up for 5 to 11 years until death or June 2017 (median follow-up, 8.1 [interquartile range, 7.1-9.0] years; mean, 8.4 [SD, 1.2] years). Before the end of the 24-week trial, 12 patients experienced MACE. Figure 2 shows cumulative risk of the primary end point (composite MACE) in the



**Table. Baseline Characteristics by Randomization Group Among 300 Patients With Depression After Acute Coronary Syndrome**

Characteristics	Escitalopram (n = 149)	Placebo (n = 151)
<b>Demographics</b>		
Age, mean (SD), y	60.0 (11.2)	60.1 (10.5)
Men, No. (%)	88 (59.1)	93 (61.6)
Education, mean (SD), y	9.4 (4.2)	9.2 (4.1)
Unmarried, No. (%)	18 (12.1)	29 (19.2)
Living alone, No. (%)	12 (8.1)	16 (10.6)
Rented accommodation, No. (%)	21 (14.1)	34 (22.5)
Unemployed, No. (%)	71 (47.7)	73 (48.3)
<b>Depression</b>		
Beck Depression Inventory score <sup>a</sup>	16 (13-22)	17 (14-23)
Mean (SD)	18.8 (8.3)	19.2 (7.7)
Median (IQR)	16 (13-22)	17 (14-23)
DSM-IV diagnosis of major depressive disorder, No. (%)	85 (57.0)	84 (55.6)
Previous depression, No. (%)	6 (4.0)	7 (4.6)
<b>Cardiac risk factors, No. (%)</b>		
Hypertension	90 (60.4)	94 (62.3)
Diabetes mellitus	44 (29.5)	41 (27.2)
Hypercholesterolemia	73 (49.0)	71 (47.0)
Obesity	59 (39.6)	65 (43.0)
Current smoker	43 (28.9)	42 (27.8)
Previous acute coronary syndrome	8 (5.4)	11 (7.3)
Family history of acute coronary syndrome	9 (6.0)	8 (5.3)
<b>Current cardiac status</b>		
Acute coronary syndrome diagnosis of myocardial infarction, No. (%)	92 (61.7)	92 (60.9)
Killip class >1, No. (%) <sup>b</sup>	24 (16.1)	35 (23.2)
NYHA class >I, No. (%) <sup>c</sup>	15 (10.1)	18 (11.9)
LVEF, mean (SD), %	60.4 (11.0)	61.9 (10.4)
LVEF <55%, No. (%)	34 (22.8)	33 (21.9)
QTc duration, mean (SD), ms	433.3 (39.7)	438.9 (38.3)
Peak troponin I, mean (SD), mg/dL	6.7 (8.5)	7.7 (8.0)
Peak creatine kinase MB fraction, mean (SD), mg/dL	17.2 (22.0)	16.3 (20.8)

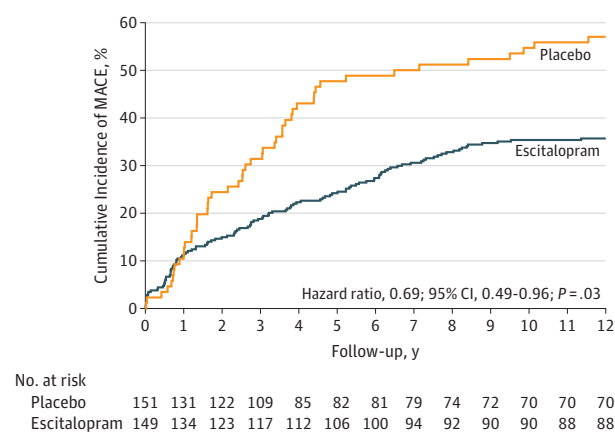
Abbreviations: DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition); IQR, interquartile range; LVEF, left ventricular ejection fraction.

<sup>a</sup> The Beck Depression Inventory consists of 21 items with a total score ranging from 0 to 63, with higher scores indicating more severe depressive symptoms.

<sup>b</sup> Killip class is ranked from 1 to 4, with higher rank indicating more severe clinical signs of heart failure.

<sup>c</sup> New York Heart Association (NYHA) class is ranked from I to IV, with higher rank indicating more severe limitation of activity due to symptoms.

escitalopram and placebo groups. A significant difference was found: composite MACE incidence was 40.9% (61/149) in the escitalopram group and 53.6% (81/151) in the placebo group (hazard ratio [HR], 0.69; 95% CI, 0.49-0.96;  $P = .03$ ). The model assumption was met (Schoenfeld  $P = .48$ ). The estimated statistical power to detect the observed difference in MACE incidence rates between the 2 groups was 89.7%. When the same analyses were repeated after excluding patients taking antidepressants at the 1-year point after ACS ( $n=5$  for escitalopram and  $n=3$  for placebo), the results were not changed substantially; composite MACE incidences were 40.3% (58/144) in the escitalopram group and 53.4% (79/148) in the placebo group (HR, 0.69;

**Figure 2. Cumulative Incidence of MACE (Primary Outcome)**

MACE indicates major adverse cardiac events, a composite of all-cause mortality, myocardial infarction, and percutaneous coronary intervention. Median follow-up was 8.1 (IQR, 7.0-9.0) years for the escitalopram group and 8.2 (IQR, 7.1-8.9) years for the placebo group.

95% CI, 0.48-0.96;  $P = .03$ ). In patients with impaired left ventricular ejection fraction (<55%) at baseline, composite MACE occurred in 23/34 (55.8%) escitalopram participants and 24/33 (72.7%) placebo participants, which was not statistically significant either for this composite outcome ( $P = .12$ ) or individual MACE outcomes (all  $P > .30$ ).

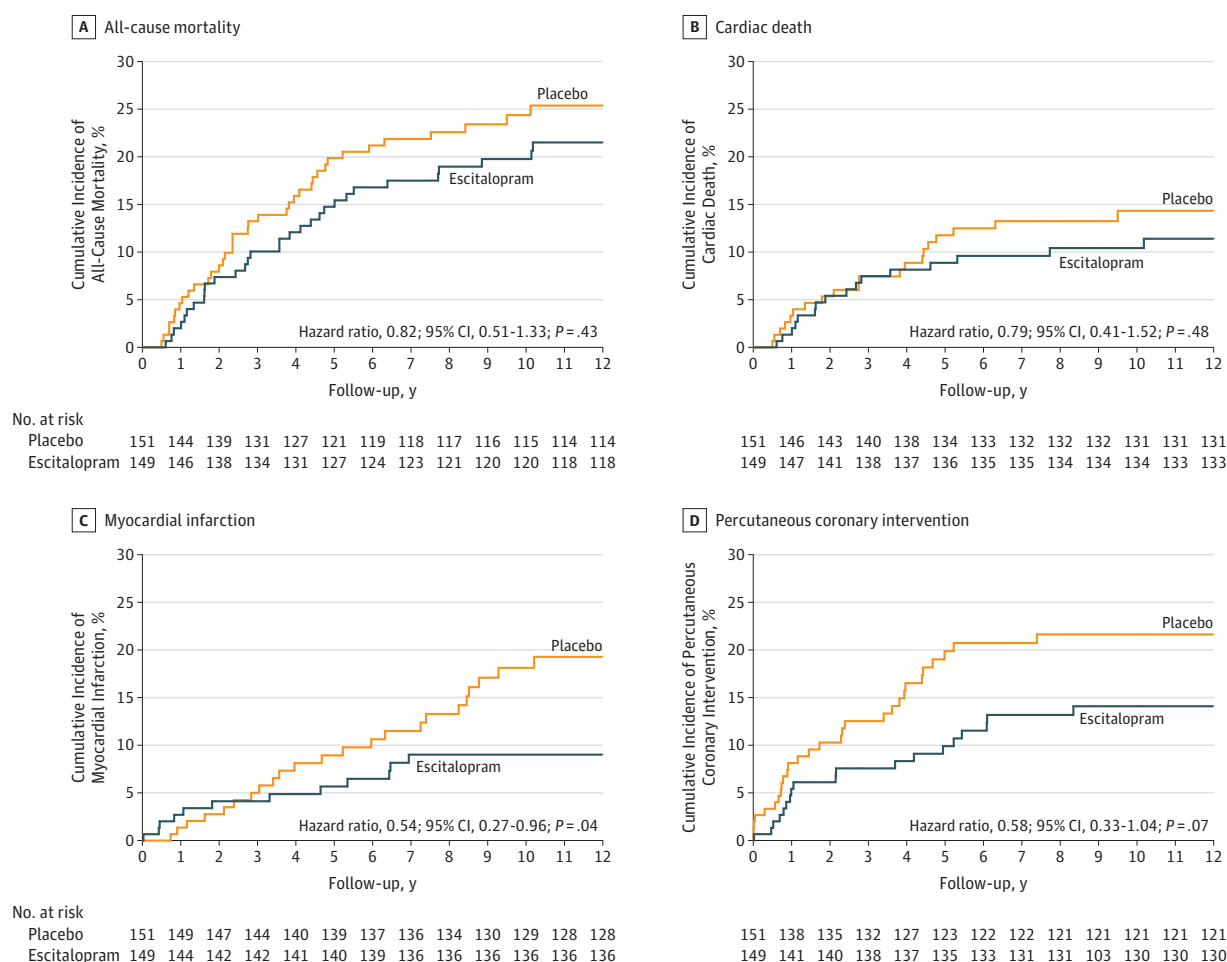
### Secondary Outcomes

Figure 3 shows cumulative risks in the escitalopram and placebo groups for secondary end points (individual MACE components). A significant difference was found in the incidence of MI at 8.7% in the escitalopram group and 15.2% in the placebo group (HR, 0.54; 95% CI, 0.27-0.96;  $P = .04$ ). However, there were no significant differences in the incidences of other individual MACE components between the escitalopram and placebo groups: 20.8% and 24.5%, respectively, for all-cause mortality (HR, 0.82; 95% CI, 0.51-1.33;  $P = .43$ ); 10.7% and 13.2% for cardiac death (HR, 0.79; 95% CI, 0.41-1.52;  $P = .48$ ); and 12.8% and 19.9% for PCI (HR, 0.58; 95% CI, 0.33-1.04;  $P = .07$ ). Model assumptions were all met (Schoenfeld  $P > .45$ ).

### Post Hoc Outcomes

Associations of depression treatment and remission status with times to first MACE are summarized in eTable 1 in Supplement 2. Of 300 randomized patients, 217 (108 receiving escitalopram and 109 receiving placebo) completed the 24-week trial. The serum creatine kinase MB fraction was significantly higher in patients who did not complete the 24-week trial vs those who completed it ( $P = .04$ ), but there were no significant differences in any other characteristic at baseline (all  $P > .05$ ). Remission was achieved in 57 (52.3%) of 108 escitalopram patients and in 38 (34.9%) of 109 placebo participants who completed the 24-week trial. Of the completers, 7 experienced MACE before the end of the 24-week trial, so the remaining 210 were included in the long-term follow-up analysis. With respect to the association with treatment group, those randomized to escitalopram had significantly lower hazards of composite MACE, MI,

**Figure 3. Cumulative Incidence of the Individual MACE Components of All-Cause Mortality, Cardiac Death, Myocardial Infarction, and Percutaneous Coronary Intervention**



Cardiac death was defined as sudden death with no other explanation available, death due to arrhythmia or after myocardial infarction or heart failure, or death caused by heart surgery or endocarditis.

and PCI compared with those randomized to placebo. With respect to the association with remission status, the group with remission had significantly lower hazards of composite MACE, all-cause mortality, and PCI compared with those without remission. Because all multiplicative interaction terms between treatment group and remission status on MACE were not statistically significant (all  $P > .12$ ), the effect sizes should not be interpreted as different. Results of adjusted analyses are reported in eTables 2 and 3 in [Supplement 2](#).

## Discussion

In this median 8.1-year follow-up of a randomized 24-week clinical trial of treatment for depression in patients with recent ACS, MACE incidence was significantly lower in patients receiving escitalopram than those receiving placebo.

These results should be considered in relation to those from 2 previous randomized clinical trials with supplementary follow-up, MIND-IT and SADHART, which reported no signifi-

cant difference between antidepressant and control treatment on MACE.<sup>10,11</sup> In the present study, the beneficial effect of escitalopram over placebo was observed for composite MACE and MI outcomes but not for any mortality outcomes. In post hoc analyses, all-cause mortality was associated with nonremission status irrespective of treatment allocation. Findings from the SADHART 6.7-year follow-up and from the present 8.1-year follow-up were similar in that mortality differed not by treatment group but by remission status, although SADHART evaluated only all-cause mortality as an outcome.<sup>11</sup> MIND-IT reported no significant difference in any composite or individual MACE measure between antidepressant intervention and care as usual; however, its follow-up duration was relatively short (18 months) and composite MACE incidence was low (13.4%).<sup>10</sup> Although the present finding has not been reported previously in ACS, similar results were reported in a poststroke depression cohort; 12-week antidepressant treatment allocation was associated with improved survival over a 9-year follow-up.<sup>28</sup>

Several issues should be considered in the interpretation of apparent divergence between results of the current study and

previous studies. First, treatment effects on depression differed in the previous 2 studies, which did not find significant differences between antidepressant and control groups in primary outcomes, but only in subgroups with recurrent or more severe depression<sup>11</sup> or in only 1 of the secondary outcomes.<sup>7</sup> This might account for the absence of an effect on longer-term cardiovascular outcomes, whereas it was reported that escitalopram had superiority over placebo in reducing depressive symptoms during the 24-week trial,<sup>9</sup> sustained at 1-year follow-up.<sup>29,30</sup> Citalopram, the racemate of which escitalopram is the S-(+) enantiomer, has also been found to be superior to placebo for reducing depressive symptoms in patients with ACS,<sup>8</sup> although longer-term follow-up results have not yet been published. Therefore, escitalopram may have modifying effects on disease prognosis in ACS-associated depressive disorder through reduction of depressive symptoms. In addition, escitalopram may positively affect common mediators of ACS and depression including brain-derived neurotrophic factor and proinflammatory cytokines<sup>31,32</sup> and may normalize autonomic and platelet dysfunction, which have adverse effects on cardiac outcomes.<sup>33,34</sup>

Second, the levels of depressive symptoms in this study's participants were less severe (mean baseline HAM-D score, 15.9) than in MIND-IT or SADHART (mean baseline HAM-D scores, 18.1 and 19.6, respectively).<sup>10,11</sup> Of potential relevance, previous research has indicated that even minor depressive symptoms may have significant negative effects on cardiac prognosis.<sup>35</sup>

Third, the antidepressant dosage was lower in this study (escitalopram had a mean dosage of 7.6 mg/d [fluoxetine-equivalent dosage, 16.9 mg/d]) than in the SADHART study (sertraline had a mean dosage of 68.8 mg/d [fluoxetine-equivalent dosage, 27.9 mg/d]).<sup>11</sup> However, ethnic differences have been reported in response to psychotropic medications, and lower dosages have been suggested as sufficient for achieving similar responses in East Asian vs white patients.<sup>36</sup> Fourth, initial antidepressant treatment duration in the present study (24 weeks) was the same as that of SADHART,<sup>11</sup> but longer than that of MIND-IT (8 weeks)<sup>10</sup> and thus potentially relevant for the latter difference. Fifth, considering severity of heart disease, antidepressants have been reported to be ineffective for reducing depressive symptoms<sup>37,38</sup> and all-cause mortality<sup>39</sup> in pa-

tients with heart failure, a more severe form of heart disease than ACS. Severity of ACS in the present study's participants was relatively low, which might render it easier to demonstrate positive effects on both depressive and long-term cardiac outcomes. In the subgroup analysis with impaired left ventricular ejection fraction, no statistical group difference was observed in outcomes, although small numbers had diminished statistical power.

### Limitations

This study has several limitations. First, recruitment was carried out at a single site, unlike previous multicenter studies.<sup>10,11,13</sup> This may limit the generalizability of findings, although it facilitates consistency of evaluation and treatment. Findings were also drawn exclusively from a Korean population, and replication is needed in other ethnic groups. Second, differential attrition should be considered for the subgroup completing the 24-week trial. Higher serum creatine kinase MB levels were associated with attrition, potentially implicating more severe ACS pathology; however, there were no significant attrition associations with other baseline variables. Moreover, follow-up data on MACE are believed to be complete for the primary analysis. Third, the small numbers of participants experiencing individual MACE components (8.3% for cardiac death in particular) limit power and therefore generalizability, although the incidence of composite MACE (47.3%) was sufficient. Fourth, no attempt was made to investigate depression occurrence or antidepressant use after the 1-year follow-up, which could also affect long-term cardiac outcomes. However, the number of participants using any antidepressant was small at 1 year after ACS, and principal findings were not changed substantially after excluding this group.

### Conclusions

Among patients with depression following recent ACS, 24-week treatment with escitalopram compared with placebo resulted in a lower risk of MACE after a median of 8.1 years. Further research is needed to assess the generalizability of these findings.

### ARTICLE INFORMATION

**Accepted for Publication:** June 13, 2018.

**Author Contributions:** Drs J.-M. Kim and Yoon had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

**Concept and design:** J.-M. Kim, J. H. Kim, Ahn, Jeong, Yoon.

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**Conflict of Interest Disclosures:** All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Stewart reports receipt of research funding from Janssen and Roche and co-supervision of a PhD candidate with GlaxoSmithKline. No other disclosures were reported.

**Funding/Support:** This study was funded by a National Research Foundation of Korea grant (NRF-2015M3C7A1028899) and was supported by the Basic Science Research Program through the National Research Foundation of Korea funded by the Ministry of Science, ICT and Future Planning (grant NRF-2016R1A2A2A05919518). Dr Stewart is partly funded by the National Institute for Health Research Biomedical Research Centre at South

London and Maudsley NHS Foundation Trust and King's College London. H. Lundbeck A/S provided the study drug.

**Role of the Funder/Sponsor:** The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

**Additional Contributions:** We thank all patients who consented to be screened for the DEPACS study and those who participated in this study.

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