Original Article

Cilostazol for Major Depressive Disorder After Percutaneous Coronary Intervention or Coronary Artery Bypass Grafting: A Randomized, Double-Blind, Placebo-Controlled Trial

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Highlights

- Cilostazol reduced depressive symptoms in patients after coronary revascularization.
- Its monotherapy improved depressive symptoms over six weeks versus placebo.
- Cilostazol was generally well tolerated.
- No serious safety concerns were identified during six weeks of treatment.
- Cilostazol may offer a repurposed option for depression in coronary artery disease.

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ABSTRACT

Background: Major depressive disorder (MDD) frequently occurs alongside coronary artery disease (CAD), worsening cardiovascular outcomes. Cilostazol is a phosphodiesterase 3 inhibitor used as an antiplatelet agent with potential antidepressant effects. This study evaluated the efficacy of cilostazol for treating depressive symptoms in participants with CAD.

Methods: This 6-week, double-blind, placebo-controlled clinical trial enrolled individuals with MDD and Hamilton Depression Rating Scale (HDRS) scores of 14 to 17 who had undergone percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). Participants were randomly assigned to receive cilostazol (100 mg/d) or placebo. Outcomes included HDRS scores and adverse events.

Results: Baseline characteristics were similar between the groups (all P>.05). A significant time × treatment interaction effect on HDRS scores was observed (P=.037; partial η2=0.055). The cilostazol group showed greater reductions in HDRS scores through weeks 4 and 6 (P=.012 and P=.054, respectively). Adverse effects were not serious and were comparable between the groups (all P>.05).

Conclusion: Cilostazol was beneficial and safe for treating depressive symptoms in individuals who had recently undergone PCI or CABG. Further studies are needed to support broader clinical application.

Keywords: Combination Drug Therapy; Heart; Myocardial Infarction; Neuroimmunomodulation; Randomized Controlled Trial; Drug Repositioning

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Introduction

Major depressive disorder (MDD), a common and debilitating condition affecting approximately 280 million people worldwide, is expected to become the leading cause of disability-adjusted life-years globally by 2030.[1] The disorder poses substantial challenges because of high treatment costs, persistent disability,[2] and treatment resistance in more than one-third of individuals, despite pharmacologic treatment or electroconvulsive therapy.[1,3] These factors highlight the importance of effective prevention and treatment strategies.

MDD is a common comorbidity among patients with coronary artery disease (CAD), especially after myocardial infarction (MI) and in those who have undergone percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG).[4,5] According to previous studies, MDD symptoms are observed in a large proportion of these individuals, with estimates suggesting that approximately 20% to 30% experience depressive symptoms after undergoing these interventions.[6,7] MDD is associated with physiologic disturbances, including increased heart rate,[8] reduced heart rate variability,[9] decreased baroreflex sensitivity,[10] endothelial dysfunction,[11] and reduced physical activity, all of which may increase the risk of CAD progression[12] and morbidity and mortality among individuals with CAD.[13] Among patients with CAD who undergo PCI, those with depression experience acute cardiac events at 3 times the rate of patients without depression within 1 year.[14] Previous studies have indicated that treating depression, particularly when depressive symptoms improve, can reduce cardiovascular mortality[15] and improve patients' quality of life.[16] Nonetheless, the cardiac adverse effects of standard antidepressants may limit their benefits in patients with CAD.[16–18]

Cilostazol is a medication commonly prescribed for patients with cardiovascular disease because of its antiplatelet and vasodilatory effects.[19] It is a reversible phosphodiesterase 3 (PDE3) inhibitor that modulates intracellular cyclic adenosine monophosphate levels.[19] Beneficial outcomes of cilostazol as an adjunctive treatment have been previously reported in schizophrenia, MDD, and Alzheimer disease.[20-23] These findings suggest that cilostazol, through its pharmacologic effects, might be an effective treatment approach that addresses both cardiovascular and psychologic health. Although several studies have reported antidepressant effects of cilostazol,[23-26] a gap remains in the literature regarding its specific use for treating depression in individuals with cardiac disease. Its efficacy in treating MDD in patients with CAD who had undergone PCI or CABG was evaluated in a 6-week, randomized, double-blind, placebo-controlled trial.

Methods

The trial was registered with the Iranian Registry of Clinical Trials (IRCT) (registration No. IRCT20090117001556N154; https://www.irct.ir). The study adhered to the Consolidated Standards of Reporting Trials (CONSORT) guideline.[27]

Study Design

In this 6-week, double-blind, placebo-controlled, parallel-group clinical trial, participants were randomly assigned to 1 of 2 groups: cilostazol or placebo. The study was conducted in patients attending the outpatient clinics of Imam Khomeini Hospital Complex and Baharloo Hospital, Tehran University of Medical Sciences, from December 2023 through June 2024.

Patients and the public were not directly involved in the design, conduct, or reporting of this study. Nevertheless, future research will seek to incorporate patient perspectives to enhance the relevance and acceptability of interventions.[28]

Ethics Considerations

The study was conducted in accordance with the Declaration of Helsinki and its subsequent revisions. The institutional review board of Tehran University of Medical Sciences approved the study (approval No. IR.TUMS.IKHC.REC.1402.291). All participants were informed of their right to withdraw from the trial at any time without affecting their ongoing treatment. Written informed consent was obtained from all registered participants.

Participants

Participants were male and female individuals aged 40 to 60 years with CAD who had undergone

elective PCI or CABG within the previous 3 months because of angina or left ventricular dysfunction (unrelated to MI) and were referred by their cardiologists to outpatient psychosomatic clinics because they were suspected of having depressive symptoms. Participants were interviewed by a senior psychiatrist using the Structured Clinical Interview for DSM-5 (SCID).29 Only individuals diagnosed with MDD during the interview who had baseline Hamilton Depression Rating Scale (HDRS) scores30 of 14 to 17 were included.16,31 The age range of 40 to 60 years was selected to reduce clinical heterogeneity and enhance the safety and interpretability of outcomes in this trial. An HDRS score of 14 to 17 was selected as an eligibility criterion to ensure a relatively homogeneous baseline symptom burden and to avoid including individuals with very severe depressive symptoms who might require immediate conventional antidepressant treatment. Individuals with an HDRS score greater than 17 were excluded from the study and initiated on appropriate treatment for their condition.

Exclusion criteria included (1) use of antipsychotic medications within the previous year, (2) diagnosis of another psychiatric disorder, (3) history of electroconvulsive therapy within the previous 2 months, (4) history of thyroid disease or inflammatory disease (eg, autoimmune thyroiditis, inflammatory bowel disease, systemic lupus erythematosus, psoriasis, autoimmune hepatitis, migraine, Guillain-Barré syndrome, multiple sclerosis, rheumatoid arthritis), (5) pregnancy or lactation, (6) history of allergy to cilostazol, (7) heart failure, including reduced left ventricular ejection fraction, and (8) concomitant use of medications with significant interactions with cilostazol (eg, antithrombin alpha, antithrombin III, argatroban, enoxaparin, apixaban). Individuals were excluded from the study if they experienced severe worsening of depressive symptoms or severe adverse effects at any time during the trial. A board-certified psychiatrist assessed participants to ensure adherence to the inclusion and exclusion criteria.

Intervention

Participants received either cilostazol, 100 mg, or placebo daily for 6 weeks. No other psychiatric medications or cognitive behavioral therapy were permitted during the trial. Additionally, medication adherence was monitored during each visit through pill counts and confirmed by direct inquiries from patients and their legal representatives.

The sustained-release formulation of cilostazol manufactured by Otsuka Pharmaceutical was administered once daily. This dosing schedule was selected in accordance with the characteristics of the sustained-release formulation and was consistent with a previous study.[23] This dosage is consistent with standard prescribing practices and was chosen to balance therapeutic benefits with minimal adverse effects.

This study provides a detailed description of the intervention—including dosage, administration, and monitoring—as well as a comprehensive assessment of potential harms and adverse events associated with cilostazol treatment.[28]

Sample Size Calculation

Based on a previous study[23] and assuming a mean difference (MD) of 3 in HDRS scores between the cilostazol and placebo groups, with a standard deviation (SD) of 3, a power of 85%, a 2-tailed significance level of 5%, and a 20% dropout rate, a sample size of 35 patients per group was planned.

Randomization and Blinding

A permuted block randomization method (blocks of 4, allocation ratio 1:1) was drawn upon to generate randomized codes via computer software. Randomization was performed using a computer-generated random sequence created by an independent statistician not involved in participant enrollment or assessment. Cilostazol and placebo tablets were indistinguishable in terms of size, shape, color, texture, and odor. The matching placebo was prepared and quality checked by the Institute of Medicinal Plants (ACECR), Iran. Allocation concealment was ensured by using sealed, opaque envelopes, which were opened sequentially by a study coordinator at the time of participant enrollment. Participants, care providers, and outcome assessors were all blinded to treatment allocation. Two separate groups performed random allocation and clinical assessments.

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Tools and Assessments

At the beginning of the study, all participants received a comprehensive physical examination along with tests, including a complete blood count, liver function assessment, coagulation tests (levels of prothrombin time [PT], partial thromboplastin time [PTT], and international normalized ratio [INR]), and a 12-lead electrocardiogram. In addition, vital signs, body weight, and any reported adverse events, particularly the potential risk of bleeding from anticoagulant therapy (by assessing coagulation tests), were tracked during each follow-up visit at weeks 2, 4, and 6. Patients were monitored for bleeding-related and renal safety signals during follow-up.

Participants were assessed at the start of the study and again at weeks 2, 4, and 6. The depression severity and the effects of cilostazol on symptom improvement were measured using the HDRS, a widely recognized 17-item scale that evaluates depressive symptoms, with each item rated on a 3- to 5-point scale.[30] The 6-week period is concordant with previous research on depression, where similar durations have been used to assess treatment effectiveness.[16,31–35] Since this was a primary study, minimizing patient burden and ensuring higher retention rates were also considered.

Adverse effects were assessed using a 25-item checklist, which also included 3 open-ended questions to capture any unexpected side effects.[16,31,35] Moreover, a follow-up phone call was made 1 week after starting the study to record any adverse effects. Participants were given a 24-hour medical helpline phone number for advice on any adverse effects.

Outcomes

The primary efficacy analysis was performed with the aid of a repeated-measures general linear model, and time-treatment interaction was considered the principal efficacy comparison.

Secondary outcomes included changes in HDRS scores from baseline to follow-ups, early improvement (≥20% reductions in HDRS scores within the first 2 weeks), rate of response to treatment (≥50% reductions in HDRS scores), rate of remission (HDRS scores ≤7), and frequency of adverse effects at any study time points.

Statistical Analysis

All analyses were performed using SPSS (IBM SPSS Statistics for Windows, version 27.0; Armonk, NY, IBM Corp) and R (version 4.4.0). Assumptions for each statistical test were assessed, and if violations were identified, appropriate procedures were applied. The distribution of numerical variables was evaluated using Q-Q plots. Continuous variables were presented as mean (SD). Categorical variables were presented as frequency (percentage). The independent-samples *t* test was utilized to compare numerical variables between the groups. The association between categorical variables was assessed using the χ^2 or Fisher exact test, as appropriate.

The effect of the time × treatment interaction on HDRS scores was investigated using repeated-measures analysis of variance within a general linear model, with treatment (cilostazol vs placebo) as the between-participants factor and study time points as the within-participants factor. When the Mauchly test of sphericity was significant, the Greenhouse-Geisser adjustment was employed. Data from participants who had at least 1 postbaseline visit were analyzed. Missing data were handled using the last observation carried forward (LOCF) approach. A 2-tailed *P* value less than .05 was considered statistically significant.

Results

(Figure 1) depicts the participant flow diagram. A total of 92 individuals were assessed for eligibility. Of these, 70 were randomly assigned to the 2 treatment groups (cilostazol, n=35; placebo, n=35). Four participants in the cilostazol group and 6 in the placebo group withdrew consent before week 2, leaving a final sample of 31 participants who received cilostazol and 29 who received placebo.

(Table 1) summarizes the baseline sociodemographic and clinical characteristics of the studied participants. The mean (SD) age was 56.37 (2.48) years. Most participants were male (76.7%) and had undergone PCI (83.3%). The treatment groups did not differ significantly regarding baseline characteristics (P>.05).

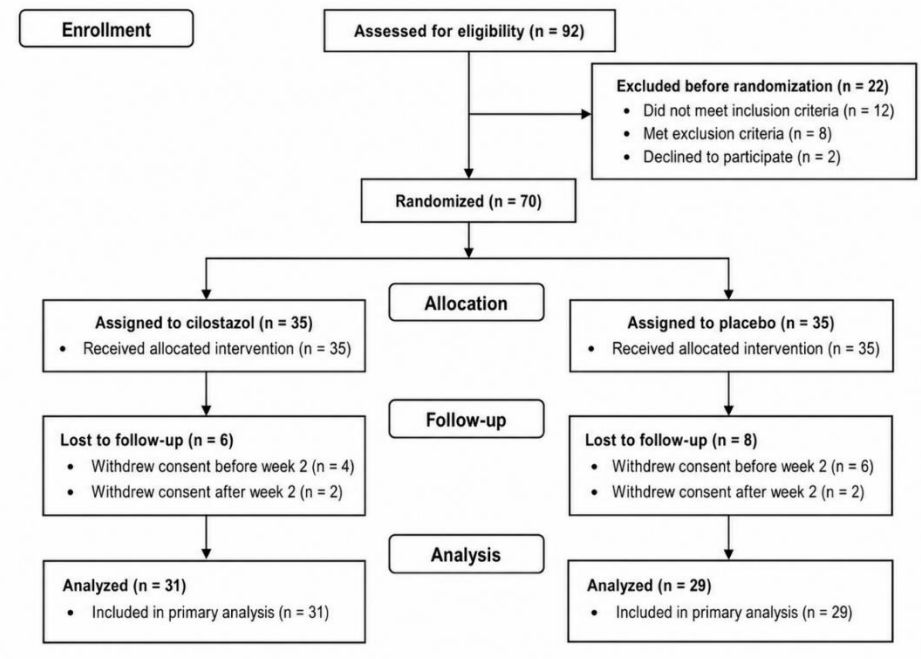

Figure 1. Participants' flow diagram

Table 1. Baseline characteristics of participants

Variable	Total (N = 60)	Cilostazol (n = 31)	Placebo (n = 29)	P
Age, mean (SD), y	56.37 (2.48)	56.23 (2.62)	56.52 (2.36)	.65
Male sex, No. (%)	46 (76.7)	23 (74.2)	23 (79.3)	.763
Marital Status, No. (%)				.81
Single	5 (8.3)	3 (9.7)	2 (6.9)	
Married	47 (78.3)	23 (74.2)	24 (82.8)	
Divorced	8 (13.3)	5 (16.1)	3 (10.3)	
Education, No. (%)				.06
≤12 y	47 (78.3)	21 (67.7)	26 (89.7)	
>12 y	13 (21.7)	10 (32.3)	3 (10.3)	
Smoking Status, No. (%)				.31
Nonsmoker	35 (58.3)	16 (51.6)	19 (65.5)	
Smoker	25 (41.7)	15 (48.4)	10 (34.5)	
Coronary Revascularization Type, No. (%)				.73
PCI	50 (83.3)	25 (80.6)	25 (86.2)	
CABG	10 (16.7)	6 (19.4)	4 (13.8)	
Baseline HDRS score	15.25 (0.97)	15.32 (0.95)	15.17 (1.00)	.55

*Mean (SD) and frequency (%) were used to summarize normally distributed continuous and categorical variables, respectively. Independent-samples *t* tests were utilized to compare normally distributed continuous variables between the groups. The χ^2 or Fisher exact test was applied to assess the association between categorical variables, as appropriate.
CABG: coronary artery bypass grafting; HDRS: Hamilton Depression Rating Scale; PCI: percutaneous coronary intervention

Longitudinal Changes in HDRS Scores Across the Treatment Groups

(Table 2 and Figure 2) present the changes in HDRS scores over the 6-week follow-up categorized by the treatment groups. The primary repeated-measures analysis revealed a significant interaction between time and treatment (cilostazol vs placebo) (F=3.35; df=2.05; P=.04; partial η^2=0.055), indicating significantly different reductions in the average HDRS scores between the groups over time. Mean (SD) HDRS reductions in the cilostazol group compared with the placebo group were −1.68 (1.66) vs −1.17 (1.10) until week 2 (P=.17; Cohen d=0.356), −3.64 (2.20) vs −2.31 (1.75) until week 4 (P=.01; Cohen d=0.668), and −5.13 (2.86) vs −3.86 (2.03) until week 6 (P=.05; Cohen d=0.508).

Table 2. Comparison of longitudinal change in HDRS scores across treatment groups

Measurement Point	Total (N = 60)	Cilostazol (n = 31)	Placebo (n = 29)	P
Baseline	15.25 (0.97)	15.32 (0.95)	15.17 (1.00)	.55
Week 2	13.82 (1.63)	13.65 (1.99)	14.00 (1.13)	.40
Week 4	12.25 (2.36)	11.68 (2.61)	12.86 (1.90)	.049
Week 6	10.73 (2.69)	10.19 (3.08)	11.31 (2.09)	.11

*Data are presented as mean (SD) for normally distributed continuous variables. Independent-samples *t* tests were used for between-group comparisons.
HDRS: Hamilton Depression Rating Scale

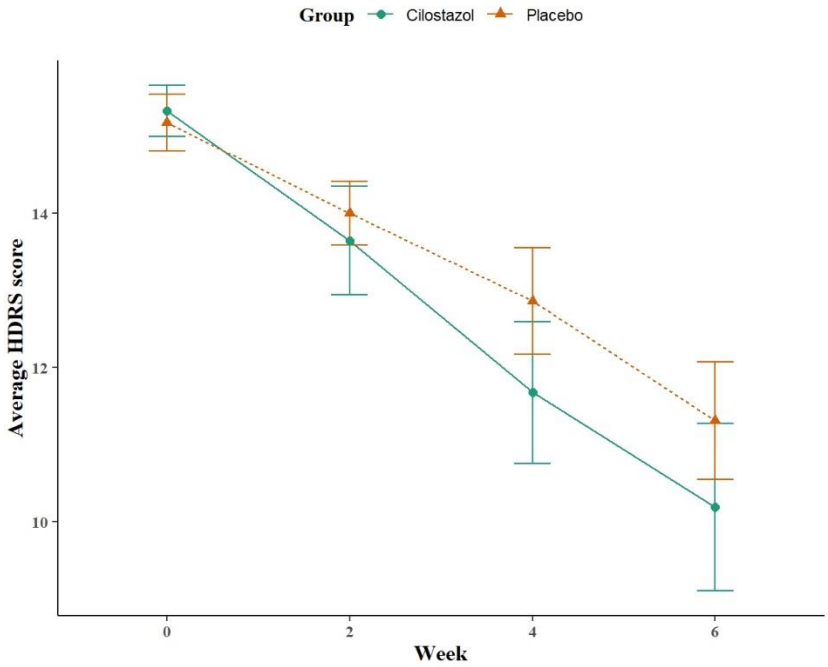

Figure 2. Longitudinal changes in Hamilton Depression Rating Scale (HDRS) scores across treatment groups during the trial. The error bars represent 95% confidence intervals.

Improvement, Response, and Remission Across Treatment Groups

As shown in (Table 3), there were no significant differences in the proportion of early improvers or remitters between groups (P=.26 and P=.20, respectively). Although the cilostazol group tended to have a higher responder rate at week 6 compared with placebo, this difference did not reach statistical significance (P=.05).

Table 3. Improvement, treatment response, and remission across treatment groups

Outcome	Total (N=60)	Cilostazol (n=31)	Placebo (n=29)	P
Early improvers‡	8 (13.3)	6 (19.4)	2 (6.9)	.26
Responders, week 2§	0	0	0	NA
Responders, week 4§	0	0	0	NA
Responders, week 6§	8 (13.3)	7 (22.6)	1 (3.4)	.053
Remitters, week 6‖	6 (10.0)	5 (16.1)	1 (3.4)	.20

*Frequency (%) was used to summarize categorical variables. The Fisher exact test was utilized to assess the association between categorical outcomes and groups.
‡Early improvers were defined as the proportion of individuals with an HDRS reduction rate of ≥20% at week 2. The HDRS reduction rate at week 2 was calculated as follows: [(week 0 – week 2) / week 0] × 100.
§Responders were defined as the proportion of individuals with an HDRS reduction rate of ≥50% at each follow-up. The HDRS reduction rate was calculated as follows: [(week 0 – week X) / week 0] × 100.
‖Remitters were defined as the proportion of individuals with an HDRS score of ≤7 at each time point.

Adverse Events Across Treatment Groups

No severe or unexpected adverse effects were reported, and no bleeding-related adverse events or clinically apparent renal complications were observed during the follow-up period. No participant discontinued the study because of an adverse event. Dizziness, nausea, and cough were the most frequently reported adverse effects in the cilostazol group; each was observed in 16.1% of participants. In the placebo group, nausea and headaches were the most commonly reported symptoms, each affecting 13.7% of participants. Potential side effects commonly associated with cilostazol (eg, headache or palpitations) were monitored, but their incidence was comparable between the groups and did not result in unblinding. No statistically significant differences in adverse events were observed between the treatment groups (Table 4).

Table 4. Frequency of adverse events across treatment groups

Adverse Event	Cilostazol (n=31)	Placebo (n=29)	P
Dizziness	5 (16.12)	3 (10.34)	.71
Back pain	3 (9.67)	1 (3.44)	.61
Nausea	5 (16.12)	4 (13.79)	.99
Sore throat	3 (9.67)	1 (3.44)	.61
Headaches	4 (12.90)	4 (13.79)	.99
Cough	5 (16.12)	3 (10.34)	.71

*Frequency (%) was used to summarize categorical variables. The Fisher exact test was applied to assess the association between categorical outcomes and groups.

Discussion

This 6-week, randomized, double-blind, placebo-controlled trial investigated the effectiveness of cilostazol (100 mg/d) in reducing depressive symptoms in individuals following coronary revascularization procedures. By comparison with placebo, cilostazol led to a significantly greater reduction in HDRS scores over time. Relative improvement rates were higher in the cilostazol group than in the placebo group. No significant differences in adverse events were observed between the groups.

The present findings are supported by animal studies. One animal study investigated whether cilostazol had antidepressant effects in chronic mild stress-treated mice after ischemic stroke. The findings showed that cilostazol could reduce the rate of poststroke depression by inhibiting neurodegeneration in both the primary stroke lesion and secondary extrafocal areas while also increasing neurogenesis.[25] In another animal study, cilostazol demonstrated prophylactic antidepressant effects in Wistar rats subjected to stress.[36]

Clinical findings have also been consistent with these findings. In a 6-week, double-blind, placebo-controlled study involving individuals with moderate to severe MDD, cilostazol was evaluated as an adjunct to sertraline. The results showed that the cilostazol group had significantly greater improvements in depression severity than the placebo group.[23] In another randomized clinical trial of 431 individuals with acute ischemic stroke, cilostazol was reported to have reduced depression-related scores. Participants received either conventional stroke treatment alone (cilostazol-free group) or conventional treatment with cilostazol (200 mg/d) and were monitored for 6 months. By the end of the trial, the cilostazol-treated group demonstrated significantly lower scores on both the National Institutes of Health Stroke Scale (NIHSS) and the 24-item HDRS than the cilostazol-free group.[26] Further, in a case series involving 7 individuals older than 65 years, cilostazol was prescribed after inadequate response to conventional antidepressant medications. Over 10 weeks, 6 of the 7 participants exhibited substantial improvements in depressive symptoms.[24] These results chime with findings from our trial, reinforcing the possibility that cilostazol may have antidepressant effects in patients with cardiovascular disease.

Cilostazol, which is traditionally used for its cardiovascular benefits, has shown promise in alleviating depressive symptoms. Although the

mechanisms underlying the antidepressant effects of cilostazol have yet to be fully understood, emerging evidence suggests that its ability to enhance cerebral blood flow and modulate neurotransmitter systems (eg, serotonin and norepinephrine) may play a crucial role in improving mood regulation.[26]

Neuroinflammation has been suggested as a key factor in the pathophysiology of MDD.[37] Inflammatory cytokines reduce brain-derived neurotrophic factor (BDNF) expression and increase tryptophan oxidation, thereby disrupting the serotonin production pathway.[38] Moreover, the primary mechanism of cilostazol involves inhibiting cyclic adenosine monophosphate degradation, which leads to vasodilation and improved blood flow.[19,39] This modulation can activate several protein kinases, including protein kinase A. Protein kinase A activation can contribute to phosphorylation of proteins such as cyclic adenosine monophosphate response element-binding protein (CREB), involved in long-term memory, synaptic plasticity, and neuronal health.[40,41] Cilostazol has been shown to enhance cyclic adenosine monophosphate signaling. This enhancement leads to activation of CREB, BDNF, and its receptor tropomyosin receptor kinase B (TrkB), all of which are essential for neurogenesis and synaptic plasticity.[25,42] Cilostazol has also been shown to promote neurogenesis in the hippocampus and striatum, which are critical brain regions for mood regulation.[25] Other possible mechanisms whereby cilostazol exerts antidepressant effects include improving cerebral blood flow, reducing neuroinflammation through inhibition of microglial activation, and modulating neurotransmitter systems implicated in mood regulation.[43]

Furthermore, studies of poststroke depression and vascular depression suggest that cilostazol reduces depressive symptoms by protecting brain regions affected by ischemia against neurodegeneration. This protection is thought to occur through regulation of pathways involved in apoptosis, such as suppression of phosphatase and tensin homolog phosphorylation and enhancement of Akt and casein kinase 2 (CK2) signaling.[44] Lastly, increased insulin-like growth factor 1 levels and modulation of oxidative stress pathways such as nuclear factor erythroid 2-related factor 2 (Nrf2) also contribute to the cognitive and mood-enhancing effects of cilostazol.[36]

In addition to its effects on depression, various studies have explored the effects of cilostazol on other psychiatric conditions. Research by Sakurai et al[45] indicated that cilostazol might help prevent cognitive decline in patients diagnosed with both Alzheimer disease and cerebrovascular disease. In a case-control study, Tai et al[22] found that use of cilostazol as an adjunctive therapy in individuals with Alzheimer disease might help slow cognitive decline associated with the disease. Moreover, several studies have underscored the potential therapeutic benefits of cilostazol in addressing cognitive deficits in individuals with schizophrenia.[21,46] In an animal study, posttraumatic stress disorder-related anxiety symptoms were also found to be diminished with cilostazol pretreatment.[47] These findings suggest that cilostazol may provide additional benefits beyond its primary uses, warranting further investigation into its potential role in treating various psychiatric disorders.

Regarding adverse events, no significant differences were observed between groups in this study, and no severe or unexpected adverse effects were reported. Previous studies have reported unexpected adverse effects of cilostazol, particularly in individuals with pre-existing cardiovascular conditions. For instance, a prior study observed significant prolongation of ventricular repolarization parameters—such as QTd, QTc, and Tpe—potentially increasing the risk of major adverse cardiovascular events, including sudden cardiac death.[48] Two case reports involving older adults documented cilostazol-induced ventricular tachycardia, leading to discontinuation of treatment.[42,49] In a separate case series involving 7 older adults with MDD, although significant improvements in depressive symptoms were observed, cilostazol had to be discontinued in 3 cases because of mild adverse effects, such as headache and palpitations. Notably, no meaningful changes were observed in brain imaging or electroencephalographic findings.[24] On the other hand, evidence supporting the beneficial cardiac effects of cilostazol is also well documented.[50,51] Given these contradictory findings, the adverse effect profile of cilostazol has not been fully clarified. Therefore, careful consideration is essential to ensure safe use,

particularly in more vulnerable populations. The lack of significant differences in adverse events could be attributable to the small sample size and does not completely rule out the possibility of such differences.

The present study has some limitations. First, the relatively small sample size may affect the generalizability of our findings on efficacy. Second, the restriction of enrollment to individuals aged 40 to 60 years may limit the generalizability of the findings to older patients with chornic CAD, who constitute a substantial proportion of the affected population. Third, the single-center design and relatively short follow-up period may affect the external validity and long-term applicability of results. Potential biases include reliance on subjective and self-reported measures and the use of last observation carried forward for missing data, which may underestimate variability. In addition, although the HDRS was administered by a trained psychiatrist using the original English version, formal psychometric validation of the instrument in an Iranian population has not been specifically established and should be considered when interpreting the findings. Moreover, formal bleeding-risk stratification and detailed single or dual antiplatelet therapy status were not prospectively captured in the study dataset. Future research with more extended follow-up periods is necessary to provide more accurate insights into the safety and long-term efficacy of cilostazol.

Conclusions

Cilostazol was associated with significantly greater improvement in depressive symptoms over time compared with placebo in participants who had recently undergone PCI or CABG, as demonstrated by the primary repeated-measures analysis. Although secondary analyses at individual time points did not consistently reach statistical significance, the findings support the potential antidepressant effects of cilostazol and warrant further investigation in larger, adequately powered trials. Cilostazol was generally well tolerated in this small sample, and no serious adverse events were observed during follow-up.

Declarations:

Ethical Approval

The protocol for this study was approved by the National Committee for Ethics in Biomedical Research at Tehran University of Medical Sciences (ethical approval code: IR.TUMS.IKHC.REC.1402.291).

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Conflict of Interest

The authors report no conflict of interest.

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