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Clinical Investigation

Do Patients With Arterial Occlusive Disease of Different Etiologies Benefit Equally From Cilostazol?

Burak Can Depboylu, MD; Serkan Yazman, MD; Bugra Harmandar, MD; Muruvvet Funda Tetik, MD; Hande Istar, MD; Kadir Arslan, MD; Gokhan Ilhan, MD

Department of Cardiovascular Surgery, Mugla Sitki Kocman University Faculty of Medicine, Mugla, Turkey

Abstract

Background: Cilostazol is a guideline-recommended drug that improves intermittent claudication and quality of life in patients with chronic atherosclerotic peripheral arterial disease. The drug is used for most etiologies of arterial occlusive diseases in clinical practice. This study aimed to evaluate whether patients benefit equally from cilostazol regardless of etiology.

Methods: Patients on cilostazol were divided into 4 groups according to arterial occlusive disease etiology: (1) atherosclerosis, (2) diabetic angiopathy, (3) embolism/thrombosis, and (4) Buerger disease. Patients' maximum walking distance, ankle-brachial index score and distal tissue oxygen saturation (StO_2), clinical improvement onset time, ability to reach maximum benefit time, vascular surgeries, and wounds were compared before they started cilostazol and after 12 months. Results were evaluated at a statistical significance of $P < .05$.

Results: In 194 patients, 307 target extremities were evaluated in the 4 disease groups. After cilostazol use, maximum walking distance, ankle-brachial index score, and distal StO_2 increased significantly in all groups ($P < .001$), but distal StO_2 in the diabetic angiopathy and Buerger disease groups was significantly lower than in the atherosclerosis group ($P < .001$). Ankle-brachial index and distal StO_2 differences in the Buerger disease group were significantly lower (both $P < .001$). The vascular surgery counts decreased significantly in the atherosclerosis and embolism/thrombosis groups ($P = .019$ and $P = .004$, respectively).

Conclusion: Patients with nonatherosclerotic arterial occlusive disease also benefit from cilostazol, but patients with Buerger disease or diabetic angiopathy seem to benefit less. Combining cilostazol with anticoagulant or antiaggregant agents and closer monitoring of these patients may produce better results.

Keywords: Peripheral arterial disease; cilostazol; ankle brachial index; intermittent claudication; spectroscopy, near-infrared

Introduction

Chronic atherosclerotic peripheral arterial disease (CA-PAD) of the lower extremities is seen in 4% to 12% of the population aged 55 to 70 years. It increases up to 20% in the population older than 70 years.[1,2] Cilostazol was approved by US Food and Drug Administration in 1999, the European Medicines Agency in 2002, and in Spain in 2009 to improve walking distances among patients with intermittent claudication (IC) in CA-PAD, and today, it is widely used worldwide.[3,4] Based on the positive clinical results from its use in CA-PAD, cilostazol is now also used in patients with Buerger disease, diabetic angiopathy, or arterial embolism/thrombosis that have nonatherosclerotic etiologies. Studies on the use of cilostazol in patients with Buerger disease or diabetic CA-PAD and in those on hemodialysis and the combined use of cilostazol with aspirin and/or clopidogrel are present in the literature,[5-8] but to the authors' knowledge, no comparison of cilostazol's effectiveness in atherosclerotic and nonatherosclerotic arterial occlusive diseases (AODs) has yet been performed.[9,10]

The aim of this study was to analyze the benefits of cilostazol in patients with nonatherosclerotic AOD and compare the results with use in patients with CA-PAD, the disease for which cilostazol was approved for use.

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Corresponding author: Burak Can Depboylu, MD, Mugla Sitki Kocman University, Faculty of Medicine, Department of Cardiovascular Surgery, Kotekli mahallesi, Marmaris yolu uzeri, No. 48, 48000/Mentese/Mugla, Turkey (burakdepboylu@mu.edu.tr)
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Patients and Methods

A single-center, prospective cohort study of patients with Rutherford grade 0 and 1 (category 0, 1, 2, 3) AOD was undertaken. Following exclusion of patients with Rutherford grades 2 and 3 (category 4, 5, 6) disease and chronic, limb-threatening ischemia, the remaining patients were started on cilostazol 100 mg twice daily in 2019 and 2020, then allocated to 1 of 4 groups according based on etiology. The patients were followed for 1 year at 3-month intervals. Patients without diabetes but with isolated CA-PAD were included in the atherosclerosis group (AG), which had a rate of target extremity per patient of 99/60. Beyond aggravation of atherosclerosis, chronic hyperglycemia causes low-grade inflammation, vasoconstriction, thrombotic abnormalities, arterial stiffness, endothelial dysfunction, and microvascular dysfunction, leading to distal artery disease. Therefore, patients with distal diabetic angiopathy, patients with CA-PAD who use insulin or oral antidiabetics, and those with high glucose and hemoglobin A_{1c}—even if they did not use medication—were allocated to the diabetic angiopathy group (DAG), which had a rate of target extremity per patient of 87/53. Patients who were started on cilostazol because of arterial embolism or thrombosis were allocated to the embolism/thrombosis group (ETG), which had a rate of target extremity per patient of 76/53. Patients with Buerger disease were allocated to the Buerger disease group (BDG), which had a rate of target extremity per patient of 45/28.

Patients' Rutherford clinical classification, TransAtlantic Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II) classification of the accompanying atherosclerotic lesions, ankle-brachial index (ABI) score (ERKA manual sphygmomanometer; Kallmeyer Medizintechnik GmbH & Co KG; and Huntleigh DMX Digital Doppler; Huntleigh Healthcare Ltd), distal tissue oxygen saturation (Sto_2) (INVOS 5100C Cerebral/Somatic Oximeter; Covidien), and maximum walking distance (Cardioline xr450m adult treadmill ergometer [Trento], at fixed incline of 12.5% and speed of 3.2 kph) measurements were performed by at least 2 authors in the cardiovascular surgery clinic. Extremities whose ABI scores were under 0.90 were chosen as target extremities. In addition, patients were informed and received recommendations about walking exercise, dietary changes, and smoking cessation.

Afterwards, patients were called to the control outpatient clinics every 3 months unless they had new or increasing symptoms. At the outpatient control clinics, 1 author collected data on the recommended walking exercise, dietary program, smoking cessation, and side effects related to cilostazol. Then, all authors evaluated the collected data jointly. Cilostazol dose reduction was made by joint decision, when necessary. At the 12-month control visit, at least 2 authors performed the final measurements and data collection at the cardiovascular surgery clinic. Interobserver reliability was ensured through communication and information sharing among the observers (the article's authors) at every stage of measurements and data collection and also at monthly meetings. Any disagreements were solved by consulting Bugra Harmandar, MD, who is also the head of the clinic, as an impartial observer.

The obtained data from the study were analyzed using SSPS software, version 20.0 (IBM Corporation). The Kolmogorov-Smirnov test was performed to test the normality of quantitative variables. Because no assumption of normal distribution was provided, the Wilcoxon test was used to compare paired samples, and the Kruskal-Wallis H test was used to compare independent groups. Continuous variables that follow normal distribution are shown as mean (SD), and continuous variables that do not follow normal distribution are shown as median (25th-75th percentile). To analyze the categorical data, the authors used the Pearson χ^2 test. The McNemar test was used to compare the number of vascular surgeries and wound counts before and after cilostazol use. Descriptive statistics for categorical variables are presented as number (%). $P < .05$ was considered statistically significant.

Abbreviations and Acronyms

ABI	ankle-brachial index
AG	atherosclerosis group
AOD	arterial occlusive disease
BDG	Buerger disease group
CA-PAD	chronic atherosclerotic peripheral arterial disease
CAD	coronary artery disease
DAG	diabetic angiopathy group
ETG	embolism/thrombosis group
IC	intermittent claudication
Sto_2	tissue oxygen saturation
TASC II	TransAtlantic Inter-Society Consensus for the Management of Peripheral Arterial Disease

Results

In total, 307 target extremities in 194 patients were evaluated. Of the patients, 34 (18%) were female and 160 (82%) were male. The mean (SD) age was 65 (14) years, and the mean (SD) weight was 80 (15) kg. All patients had distal arterial lesions under the level of the knee. Patients' characteristics, Rutherford clinical classification, accompanying diseases, and smoking status are provided in Table I. In patient imaging studies, it was

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TABLE I. Patient Characteristics, Rutherford Clinical Classification, Accompanying Disease, and Smoking Status

Variable	AG	DAG	ETG	BDG
Patient count, No. (%)				
Total	60 (100)	53 (100)	53 (100)	28 (100)
Single limb disease	21 (35)	19 (36)	31 (59)	11 (39)
Double limb disease	39 (65)	34 (64)	22 (41)	27 (61)
Target limb counts, No.	99	87	76	45
Sex, No. (%)				
Female	7 (12)	14 (26)	11 (21)	2 (7)
Male	53 (88)	39 (74)	42 (79)	26 (93)
Age, mean (SD), y				
Female	71 (9)	68 (10)	65 (22)	41 (11)
Male	70 (9)	69 (11)	67 (11)	46 (10)
Weight, mean (SD), kg				
Female	66 (13)	74 (18)	66 (13)	55 (1)
Male	81 (7)	86 (24)	82 (10)	84 (8)
Rutherford clinical classification, No. (%)				
Grade 0, category 0	0 (0)	0 (0)	2 (4)	0 (0)
Grade 1, category 1	0 (0)	1 (2)	1 (2)	0 (0)
Grade 1, category 2	22 (37)	25 (47)	16 (30)	6 (21)
Grade 1, category 3	38 (63)	27 (51)	34 (64)	22 (79)
Accompanying diseases, No. (%)				
Hyperlipidemia[a]	35 (58)	18 (34)	30 (57)	9 (32)
Hypertension[b]	22 (37)	26 (49)	25 (47)	3 (11)
CAD[c]	22 (37)	14 (26)	17 (32)	5 (18)
Arrhythmia[d]	2 (3)	6 (11)	14 (26)	2 (7)
COPD	10 (17)	5 (9)	6 (11)	0 (0)
Stroke	6 (10)	5 (9)	5 (9)	0 (0)
Chronic renal insufficiency	5 (8)	3 (6)	2 (4)	1 (4)
Carotid artery stenosis	3 (5)	3 (6)	1 (2)	0 (0)
Smoking, No. (%)	42 (70)	29 (55)	29 (55)	24 (86)

AG, atherosclerosis group; BDG, Buerger disease group; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; DAG, diabetic angiopathy group; ETG, embolism/thrombosis group.

[a] Patients who have low-density lipoprotein cholesterol >130 mg/dL, total cholesterol >200 mg/dL, triglycerides >150 mg/dL, or use antihyperlipidemic medication.
[b] Patients who have blood pressure >140/90 mm Hg or are using antihypertensive medication.
[c] Patients who have narrowing or blockage in the coronary arteries and who underwent percutaneous coronary intervention or coronary bypass grafting or are on medication for CAD.
[d] Patients who have atrial fibrillation or are on medication for atrial fibrillation.

observed that even though the main occlusive disease etiology was different from atherosclerosis, a specific portion of the patients had accompanying multisegmental atherosclerotic lesions. In the BDG and DAG, these additional atherosclerotic lesions may have increased ischemia. In the ETG, the thrombus may have developed on a chronic atherosclerotic background and determined the occlusion level; it may also have been the reason for incomplete or unsuccessful embolectomy procedures. Therefore, the authors decided to include patients' additional atherosclerotic lesions and TASC II classifications to better evaluate the effects of the lesions cumulatively in all groups. Imaging methods used to di-

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TABLE II. Imaging Methods Used to Diagnose the AOD and TASC II Classification of the Patients' Arterial Lesion

Imaging method	No. (%)
CTA	105 (54)
CDUS	44 (23)
MRI-A	19 (10)
DSA	1 (1)
CTA + CDUS	13 (7)
MRI-A + CDUS	12 (6)

TASC II classification	AG, No. (%)	DAG, No. (%)	ETG, No. (%)	BDG, No. (%)
Patient count	60 (100)	53 (100)	53 (100)	28 (100)
Aortoiliac segment				
A	7 (12)	6 (11)	8 (15)	1 (4)
B	7 (12)	1 (2)	2 (4)	1 (4)
C	16 (27)	7 (13)	4 (8)	1 (4)
D	3 (5)	3 (6)	3 (6)	1 (4)
Lesion free	27 (45)	36 (68)	36 (68)	24 (86)
Femoropopliteal segment				
A	3 (5)	5 (9)	6 (11)	3 (11)
B	25 (42)	24 (45)	10 (19)	7 (25)
C	24 (40)	2 (4)	26 (49)	5 (18)
D	7 (12)	1 (2)	7 (13)	0 (0)
Lesion free	1 (2)	21 (40)	4 (8)	13 (46)
Infrapopliteal segment				
A	19 (32)	21 (40)	32 (60)	8 (29)
B	29 (48)	21 (40)	14 (26)	12 (43)
C	6 (10)	9 (17)	7 (13)	3 (11)
D	6 (10)	2 (4)	0 (0)	5 (18)
Lesion free	0 (0)	0 (0)	0 (0)	0 (0)

AG, atherosclerosis group; AOD, arterial occlusive disease; BDG, Buerger disease group; CDUS, color doppler ultrasonography; CTA, computed tomography angiography; DSA, digital subtraction angiography; DAG, diabetic angiopathy group; ETG, embolism/thrombosis group; MRI-A, magnetic resonance imaging angiography; TASC II, TransAtlantic Inter-Society Consensus for the Management of Peripheral Arterial Disease.

agnose AOD and TASC II classifications of the patients' arterial lesions are provided in Table II.

The mean (SD) admission time of patients in the ETG to our hospital was 25.60 (15.40) hours. Embolism/thrombosis regions were the common femoral artery in 6 extremities, the superficial femoral artery in 19 extremities, the popliteal artery in 24 extremities, and the crural arteries in 27 extremities. Because of their previous cardiovascular disease, severe peripheral arterial lesions, applied vascular surgeries, and atrial fibrillation, cilostazol was combined with aspirin in 100 patients, with clopidogrel in 19 patients, with new oral anticoagulants in 7 patients, and with warfarin in 5 patients. Despite the authors' insistence, 21 patients in the AG, 9 patients in the DAG, 16 patients in the ETG, and 8 patients in the BDG continued smoking. According to the patients' feedback and controls, clinical improvements began to be seen at a mean (SD) of 4.62 (2.93) weeks and reached a maximum at a mean (SD) of 10.71 (5.78) weeks after cilostazol was started. Headache (n = 41 [21.1%), diarrhea (n = 25 [12.9%]), and nausea (n = 21 [10.8%]) were the most commonly seen early side effects, which continued until maximum improvements were reached. Edema (n = 40 [20.6%]), ecchymosis (n = 18 [9.3%]), and petechiae (n = 11 [5.7%]) were the most commonly seen late side effects after maximum

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improvements had been reached. Cilostazol doses were reduced to 50 mg twice daily in 5 patients because of diarrhea, in 3 patients because of nausea, and in 6 patients because of headache in the first month; and in 2 patients because of edema in the fourth month and in 1 patient because of ecchymosis in the sixth month. Measurement comparisons were performed at the end of mean (SD) 13.24 (1.84) months because of the COVID-19 pandemic. Maximum walking distance, ABI, and Sto_2 values increased significantly in all groups, but there was no significant difference among the groups regarding maximum walking distance increase ($P = .441$). Ankle-brachial index scores after cilostazol use in the ETG were significantly higher than in the DAG ($P = .037$). After cilostazol use, Sto_2 in the DAG and BDG were significantly lower than in the AG ($P < .001$). Differences in ABI in the BDG was significantly lower than in the DAG and ETG ($P < .001$). The Sto_2 difference in the BDG was significantly lower than in the AG, DAG, and ETG ($P < .001$) (Table III). Although vascular surgery counts decreased in all groups after cilostazol use, the decrease in the AG and ETG were statistically significant ($P = .019$ and $P = .004$, respectively). Although the wound counts decreased after cilostazol use in all groups, however, no statistically significant result was obtained (Table IV).

TABLE III. Descriptive Statistics and Comparison Results of MWD, ABI, Distal Sto_2, ABI Difference, and Distal Sto_2 Difference in the AG, DAG, ETG, and BDG Before and After Cilostazol Use[a]

Variable	AG	DAG	ETG	BDG	*P* value[b]
Patient count, No. (%)	60 (100)	53 (100)	53 (100)	28 (100)	–
MWD before starting cilostazol, median (25th-75th percentile), m	80 (60-100)^{AB}	100 (60-122.5)^{B}	50 (40-100)^{A}	62.5 (5-83.7)^{A}	.004
MWD after cilostazol use, median (25th-75th percentile), m	250 (200-315)	240 (180-310)	235 (170-350)	220 (130-295)	.441
P value	<.001	<.001	<.001	<.001	
ABI before starting cilostazol, median (25th-75th percentile)	0.48 (0.41-0.52)^{A}	0.44 (0.32-0.50)^{B}	0.44 (0.37-0.50)^{AB}	0.50 (0.36-0.63)^{A}	.003
ABI after cilostazol use, median (25th-75th percentile)	0.55 (0.51-0.60)^{AB}	0.55 (0.47-0.59)^{A}	0.58 (0.51-0.71)^{B}	0.53 (0.37-0.71)^{AB}	.037
P value	<.001	<.001	<.001	.001	
Sto_2 before starting cilostazol, median (25th-75th percentile)	45 (40-52)^{A}	40 (31-43)^{B}	40 (32-44)^{B}	42 (30-51)^{AB}	<.001
Sto_2 after cilostazol use, median (25th-75th percentile)	51 (46-57)^{A}	47 (39-52)^{B}	49.5 (44-58.3)^{AB}	44 (31-56.5)^{B}	<.001
P value	<.001	<.001	<.001	<.001	
ABI difference, median (25th-75th percentile)	0.07 (0.04-0.11)^{AB}	0.09 (0.05-0.15)^{B}	0.09 (0.04-0.25)^{B}	0.05 (0.03-0.07)^{A}	<.001
Sto_2 difference, median (25th-75th percentile)	7 (2-11)^{A}	7 (4-12)^{A}	6 (2-17.3)^{A}	3 (0-5)^{B}	<.001

ABI, ankle-brachial index; AG, atherosclerosis group; BDG, Buerger disease group; DAG, diabetic angiopathy group; ETG, embolism/thrombosis group; MWD, maximum walking distance; Sto_2, distal oxygen saturation.

[a] Similar uppercase letters in the same row indicate no statistical difference between groups; different uppercase letters indicate the statistical difference between groups.
[b] $P < .05$ was considered statistically significant.

Discussion

As a result of this study, significant increases in maximum walking distance, ABI, and Sto_2 values were seen in all 4 groups (Table III). In the meta-analysis by Bedenis et al,[2] which included 15 clinical trials of 3,718 participants, the authors stated that "cilostazol improves both initial and absolute IC distances." Similarly, Kaya et al[11] found a 28% to 63% improvement in IC distances; in 4 different studies, only cilostazol 100 mg twice daily was used. In addition, they reported that they found a significant increase in ABI, which they considered a moderate improvement in terms of clinical significance. In the study by O'Donnell et al,[12] however, the authors could not find any difference in ABI levels at

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TABLE IV. The Comparison of the AG, DAG, ETG, and BDG According to Vascular Surgery and Presence of Wounds, Before and After Cilostazol Usea

Variable	AG, No. (%)	DAG, No. (%)	ETG, No. (%)	BDG, No. (%)	*P* value[a]
Patient count	60 (100)	53 (100)	53 (100)	28 (100)	–
Vascular surgery before starting cilostazol	17 (28)^{A}	4 (8)^{B}	28 (53)^{C}	4 (14)^{AB}	<.001
Vascular surgery after cilostazol use		19 (10)			
Redo	2 (3)	0 (0)	8 (15)	0 (0)	–
New	4 (7)	3 (6)	5 (9)	3 (11)	
Total	6 (10)^{AB}	3 (6)^{B}	13 (25)^{A}	3 (10.7)^{AB}	.024
P value	.019	.999	.004	.999	
Wound counts before starting cilostazol	16 (16)^{A}	3 (3)^{B}	7 (9)^{AB}	4 (9)^{AB}	.035
Wound counts after cilostazol use					
Healed	8 (50)	3 (100)	4 (57)	3 (75)	–
New	4 (7)	2 (4)	3 (6)	0 (0)	
Total	12 (12)	2 (2)	6 (8)	1 (2)	.052
P value	.125	.999	.999	.250	

AG, atherosclerosis group; BDG, Buerger disease group; DAG, diabetic angiopathy group; ETG, embolism/thrombosis group.

[a] Similar uppercase letters in the same row indicate no statistical difference between groups; different uppercase letters indicate the statistical difference between groups.
[b] $P < .05$ was considered statistically significant.

6 or 24 weeks of cilostazol treatment. Boezeman et al[13] evaluated foot oxygenation with near-infrared spectroscopy after endovascular revascularization; the authors found a significant increase in ABI and a 20% increase in Sto_2 4 weeks after endovascular revascularization. Komiyama et al[14] evaluated tissue oxygenation with spatially resolved spectroscopy. They determined that the decrease in muscle Sto_2 at the end of exercise correlated with the severity of IC. Although no significant difference was found among the AG, DAG, and BDG in this study, the authors considered the significantly higher ABI and ABI difference ($P = .037$ and $P < .001$, respectively) found in the ETG to be the result of the embolectomy procedures performed in patients.

In a study of patients with diabetic angiopathy, Gardner et al[15] found a 46.07% decrease in calf muscle Sto_2 1 minute after exercise. The median calf muscle Sto_2, which was 51% during rest, decreased by as much as 9% during exercise in these patients. They also concluded that elevated glucose level plays a role in impaired peripheral circulation and vascular dysfunction in patients with symptomatic CA-PAD, which leads to decreased muscle Sto_2.[15] Yong et al[5] evaluated the effects of aspirin combined with cilostazol in patients with diabetes and Buerger disease. They concluded that higher levels of serum inflammatory factors caused by diabetes and Buerger disease trigger the occurrence of thrombus and lead to endothelial dysfunction.[5] Moreover, Klein-Weigel and Richter[16] reported that Buerger disease relates to tobacco use and pro- and anti-inflammatory cytokines. The significantly lower Sto_2 levels in the DAG and BDG ($P < .001$) obtained in the current study were also thought to be associated with high glucose levels, tobacco use, and increased inflammation. With the significantly lower ABI and Sto_2 differences ($P < .001$ and $P < .001$, respectively) in the BDG combined with the earlier results, the authors concluded that nonatherosclerotic AOD etiologies also benefit from cilostazol, but patients in the DAG and BDG seemed to benefit less.

de Donato et al[17] reported that cilostazol was the only medical treatment that prevents restenosis in lower-limb revascularization and significantly reduces repeat revascularizations. In this study, vascular surgery counts also decreased significantly in the AG and ETG ($P = .019$ and $P = .004$, respectively), but repeat operation counts were high in the ETG because of embolectomy procedures performed on patients with significant atherosclerotic stenosis. Femoropopliteal bypass was the most commonly performed procedure as a repeat operation. Mii et al[18] achieved a 92% wound healing rate in patients administered cilostazol after infrainguinal bypass at 1 year. In addition, the median wound healing time was shorter than in those who did not receive cilostazol (45 vs 78 days).[18] Colak et al[19] found faster wound healing, higher rates of response to treatment, and better symptom improvement in patients with CA-PAD and diabetic foot ulcer who received cilostazol than those who received aspirin. In this study, although wound counts decreased in all groups after cilostazol use, when the healed and new wounds were combined, no sig-

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nificant difference was observed among the groups in wound counts after cilostazol use.

According to the CASTLE study by Hiatt et al,[20] headache (10.5%), diarrhea (10.9%), and palpitations (5.3%) were the most common side effects of cilostazol. Edema, headache, and diarrhea most commonly led to drug discontinuation.[20] In the study by Kaya et al,[11] 11.2% of patients experienced cilostazol side effects, but they did not cause any patient to discontinue the treatment, although cilostazol doses were reduced in some patients. In this study, headache, diarrhea, and nausea were the most common early side effects, whereas edema, ecchymosis, and petechiae were the most common late side effects. All side effects were treated according to symptoms without discontinuation of cilostazol.

Limitations

This study had some limitations. First, although the entire study was completed in a single cardiovascular surgery clinic, the same physician did not perform all controls for all patients included in the study. The authors attempted to eliminate this limitation through communication and information sharing, as stated in the "Patients and Methods" section. Second, patients could not use cilostazol alone because of existing comorbidities, previous surgical interventions, or surgeries performed during the study period. These patients were often prescribed additional anticoagulant or antiaggregant medications, as well. Patients' compliance with the diets recommended for diabetes and hyperlipidemia and their smoking status were followed according to patient statements. Finally, the results obtained for the other groups were compared with the AG, which served as the control group because atherosclerosis is the indication for which the drug was approved.

Conclusion

This study showed that cilostazol is an effective and well-tolerated agent in nonatherosclerotic etiologies of AOD as well as for CA-PAD. Patients with Buerger disease or diabetic angiopathy, however, seem to benefit less from cilostazol. Variable glucose levels, dietary disruption, and tobacco use contributed to this outcome because these conditions increase inflammation. Combined use of cilostazol with other anticoagulant or antiaggregant agents and closer monitoring of the patients may provide better results in these patients.

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