The vascular effects of cilostazol

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WS Weintraub. The vascular effects of cilostazol. *Can J Cardiol* 2006;22(Suppl B):56B-60B.

Cilostazol is a phosphodiesterase III inhibitor with pharmacological effects that include vasodilation, inhibition of platelet activation and aggregation, inhibition of thrombosis, increased blood flow to the limbs, improvement in serum lipids with lowering of triglycerides and elevation of high density lipoprotein cholesterol, and inhibition of vascular smooth muscle cell growth. Cilostazol has been shown in multiple randomized clinical trials to result in decreased claudication and improved ability to walk in patients with peripheral arterial disease. In addition, cilostazol has been shown in multiple randomized clinical trials to decrease restenosis in the setting of coronary stent implantation. The purpose of the present paper was to review the vascular effects of cilostazol and to present results of the major clinical trials of the use of cilostazol in peripheral arterial disease and percutaneous coronary intervention with stent implantation.

Key Words: *Platelet inhibition; Restenosis; Vascular biology*

Cilostazol is a phosphodiesterase III inhibitor with pharmacological effects that include vasodilation, inhibition of platelet activation and aggregation, inhibition of thrombosis, increased blood flow to the limbs, improvement in serum lipids with lowering of triglycerides and elevation of high density lipoprotein cholesterol, and inhibition of vascular smooth muscle cell growth (Figure 1). Its action as an antiplatelet agent is by blocking phosphodiesterase, preventing the breakdown of cyclic AMP, which inactivates thromboxane A₂. In this regard, cilostazol may complement both acetylsalicylic acid (ASA) and ADP receptor blockers such as clopidogrel. Cilostazol is highly protein bound. It is largely excreted by the kidneys (74%), and less so by the liver (20%). Metabolism is via cytochrome P (CYP)3A4 and CYP2C19. There is no inhibition of CYP450. Pharmacokinetics do not vary with age or sex.

EFFECTS ON THE ENDOTHELIUM

Nakamura et al (1) studied the effect of cilostazol on relaxation of the rat thoracic aorta. Cilostazol induced relaxation of the phenylephrine-precontracted thoracic aorta in a concentration-dependent manner. This effect was reduced in the endothelium-denuded aorta compared with the intact endothelium, suggesting that relaxation was partly dependent on the endothelium. The cilostazol-induced relaxation of the thoracic aorta was reversed by N(G)-nitro-L-arginine, a competitive inhibitor of nitric oxide (NO) synthase. Cilostazol also increased NO in the porcine thoracic aorta. In cilostazol-treated rats, urinary excretion of nitrites, a stable metabolite of NO,

Les effets vasculaires du cilostazol

Le cilostazol est un inhibiteur II de la phosphodiesterase dont les effets pharmacologiques incluent la vasodilatation, l'inhibition de l'activation des plaquettes et l'agrégation, l'inhibition de la thrombose, l'augmentation du débit sanguin vers les membres, l'amélioration des lipides sériques accompagnée d'une diminution des triglycérides et de l'élévation du cholestérol à lipoprotéines de haute densité ainsi que l'inhibition de la croissance des cellules vasculaires des muscles lisses. De multiples essais aléatoires cliniques ont démontré que le cilostazol entraîne une diminution de la claudication et améliore la capacité de marcher chez les patients atteints d'une maladie artérielle périphérique. De plus, il réduit le risque de resténose après l'implantation d'une endoprothèse coronaire. Le présent article vise à analyser les effets vasculaires du cilostazol et à présenter les résultats des principaux essais cliniques sur l'utilisation de ce médicament dans le cas d'une maladie artérielle périphérique et d'une intervention coronaire percutanée avec implantation d'endoprothèse.

and basal production of NO of the aortic ring were greater than in control animals. These data suggest that cilostazol-induced vasodilation is dependent on NO from the endothelium.

ANTIPROLIFERATIVE EFFECTS

In a preclinical study, Ishizaka et al (2) evaluated the effect of locally administered cilostazol on neointimal formation in the balloon-injured rat carotid artery. The intimal area of the injured carotid was significantly smaller in the cilostazol-treated group than in the control group ($0.06 \pm 0.01 \text{ mm}^2$ versus $0.15 \pm 0.02 \text{ mm}^2$; $P < 0.001$). In addition, smooth muscle cells in the injured media were also significantly fewer in the cilostazol-treated group than in the controls ($4.3 \pm 0.5\%$ versus $9.1 \pm 0.9\%$ of total cells; $P < 0.001$).

Ahn et al (3) studied the antiproliferative effects of cilostazol in a multicentre trial, evaluating the effect of oral cilostazol on carotid intima media thickness (IMT) in 141 patients with diabetes. The patients were randomly assigned to cilostazol 100 mg to 200 mg daily, or placebo. IMT was measured by ultrasound at zero, six and 12 months. In the cilostazol group, left common carotid artery IMT decreased from $0.94 \pm 0.03 \text{ mm}$ to $0.91 \pm 0.02 \text{ mm}$ at six months ($P < 0.05$), while in the placebo group there was little change. The right common carotid artery IMT decreased from $0.83 \pm 0.03 \text{ mm}$ to $0.82 \pm 0.01 \text{ mm}$ at six months ($P < 0.05$), and to $0.81 \pm 0.01 \text{ mm}$ at 12 months ($P < 0.05$) in the cilostazol group, while it increased from $0.87 \pm 0.03 \text{ mm}$ to $0.89 \pm 0.01 \text{ mm}$ at six months ($P < 0.05$), and to $0.90 \pm 0.01 \text{ mm}$ at 12 months ($P < 0.05$) in the placebo group.

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Cilostazol was well tolerated, the most common side effect being headache in 20%. These data suggest that cilostazol may be helpful in preventing progression of atherosclerosis in patients with diabetes.

Tsuchikane et al (4) studied the antiproliferative action of cilostazol, randomly assigning 41 patients after directional coronary atherectomy to cilostazol 200 mg daily or ASA. The medications were started before the atherectomy and continued for six months. By quantitative coronary angiography, minimal lumen diameter at follow-up was larger (2.33 ± 0.60 mm versus 1.81 ± 0.68 mm; $P=0.016$) and per cent diameter stenosis ($25 \pm 17\%$ versus $41 \pm 21\%$; $P=0.010$) was smaller with cilostazol. In addition, the per cent plaque area at follow-up was smaller with cilostazol ($56 \pm 11\%$ versus $64 \pm 14\%$; $P=0.044$). The restenosis rate was also lower in the cilostazol group (0% versus 26%; $P=0.020$).

ANTIPLATELET EFFECTS

Animal studies as early as 1985 revealed inhibition of platelet aggregation by cilostazol (5,6). Igawa et al (7) showed that cilostazol inhibited the platelet aggregation dose-dependently in the presence or absence of endothelial cells. However, the presence of endothelial cells potentiated the inhibitory effect of cilostazol on platelet aggregation. Pretreatment with ASA of the endothelial cells reversed this potentiation. The authors concluded that the endothelium-derived prostacyclin mediates the potentiation of the antiplatelet aggregatory effect of cilostazol.

Tamai et al (8) compared the effects of ASA, ticlopidine and cilostazol on bleeding time in 10 healthy adults. All three drugs inhibited platelet aggregation response to ADP, collagen, epinephrine and arachidonic acid ($P<0.05$), but not to ristocetin. ASA and ticlopidine prolonged bleeding time, while ASA also increased the maximum bleeding rate. In contrast, none of the quantitative bleeding time parameters were altered by cilostazol.

Nomura et al (9) evaluated the plasma concentrations of soluble adhesion molecules and platelet-derived microparticles (PMP) in patients with noninsulin-dependent diabetes mellitus (NIDDM) and studied the effect of cilostazol on PMP generation. NIDDM patients ($n=43$) had higher soluble adhesion molecule concentrations than control patients ($n=30$). Higher PMP levels and platelet activation markers were also noted in NIDDM patients compared with controls. Increased release of PMP from platelets was observed in diabetic plasma compared with normal plasma under high shear stress. The levels of PMP, activated platelets and soluble adhesion molecules all decreased significantly after treatment with cilostazol.

To evaluate the antiplatelet effects of cilostazol in the setting of acute myocardial infarction, Tanigawa et al (10) randomly assigned 36 patients with acute myocardial infarction after successful treatment with primary angioplasty to ASA alone, ASA plus ticlopidine or ASA plus cilostazol. Compared with stable coronary artery disease, increased shear stress-induced platelet aggregation and plasma von Willebrand factor activity were observed in patients with acute myocardial infarction before antiplatelet therapy. On day 7 after primary angioplasty, ASA did not inhibit shear stress-induced platelet aggregation, while both ASA plus ticlopidine and ASA plus cilostazol did.

To evaluate the antithrombotic effects of cilostazol after stent implantation, Park et al (11) randomly assigned

Figure 1) Pharmacological profile of cilostazol. HDL-C High density lipoprotein cholesterol

490 patients to ASA plus ticlopidine or ASA plus cilostazol for one month. Major cardiac events or adverse drug effects were similar between the two groups (2.9% with ticlopidine versus 1.6% with cilostazol; $P=\text{not significant [NS]}$), as were stent thrombosis (0.4% versus 0.8%; $P=\text{NS}$), myocardial infarction (0.4% versus 0.8%; $P=\text{NS}$), severe leukopenia (1.2% versus 0%; $P=\text{NS}$), severe thrombocytopenia (0.4% versus 0%; $P=\text{NS}$) and cerebral hemorrhage (0.4% versus 0%; $P=\text{NS}$). Adverse effects led to drug withdrawal in seven (2.9%) ticlopidine patients and five (2.0%) cilostazol patients. There were no deaths during the follow-up.

Combined antiplatelet therapy was studied by Wilhite et al (12) by measuring bleeding time in 21 patients with peripheral arterial disease. Patients were placed on sequential two-week regimens of the following therapies: ASA (325 mg daily), ASA plus cilostazol (100 mg twice daily), cilostazol, cilostazol plus clopidogrel (75 mg each day), clopidogrel, clopidogrel plus ASA, and clopidogrel plus ASA plus cilostazol. Baseline bleeding time for the group was 4.29 ± 1.69 min. ASA (bleeding time 6.64 ± 3.52 min) and clopidogrel (bleeding time 10.0 ± 5.4 min) significantly prolonged the bleeding time ($P<0.01$), while cilostazol had no significant effect (bleeding time 5.41 ± 2.69 min). ASA plus clopidogrel (bleeding time 17.39 ± 4.59 min) had a more pronounced effect than either agent alone ($P<0.01$). The addition of cilostazol to either ASA (bleeding time 8.3 ± 4.27 min) or clopidogrel (bleeding time 12.7 ± 7.46 min) or in combination with ASA plus clopidogrel (bleeding time 17.92 ± 4.69 min) did not prolong bleeding time. The authors concluded that cilostazol can be used in combination with other platelet inhibitors without an additional effect on platelet function.

EFFECT OF CILOSTAZOL ON SERUM LIPIDS

Studies in rats have shown that cilostazol decreases serum triglycerides and increases high density lipoprotein cholesterol, an effect that seems to be mediated by increasing plasma lipoprotein lipase (13). Elam et al (14) studied the effect of cilostazol on plasma lipoproteins in 189 patients with peripheral arterial disease. After 12 weeks of cilostazol 100 mg twice daily, triglycerides decreased 15% ($P<0.001$), high density lipoprotein cholesterol increased by 10% ($P<0.001$) and apolipoprotein A1 increased by 5.7% ($P<0.01$). There was a trend (3%) toward decreased apolipoprotein B. Low density lipoprotein cholesterol and lipoprotein(a) concentrations were

unaffected. Cilostazol increased treadmill walking time by 35% ($P=0.0015$) and ankle-brachial index by 9% ($P<0.001$). In addition to improving the symptoms of peripheral arterial disease, cilostazol favourably modifies plasma lipids. The mechanism of this effect remains unknown.

TREATMENT OF PERIPHERAL ARTERIAL DISEASE

Cilostazol is indicated in the treatment of peripheral arterial disease. Cilostazol had been studied in 10 trials of patients with peripheral arterial disease, and has been shown to improve maximum walking distance in most of them. At 37 sites in the United States, Beebe et al (15) randomly assigned 516 men and women 40 years and older with moderately severe chronic, stable, symptomatic intermittent claudication to cilostazol 100 mg twice daily, cilostazol 50 mg twice daily or placebo for 24 weeks. Outcome measures included pain-free and maximal walking distance on a treadmill, quality of life, global assessments by patients and physicians, and cardiovascular morbidity and all-cause mortality. Cilostazol was found to be superior to placebo as early as week 4, with continued improvement through 24 weeks. At 24 weeks, patients in the cilostazol 100 mg arm had a 51% improvement in maximal walking distance ($P<0.001$ versus placebo), while the cilostazol 50 mg arm patients had a 38% improvement in maximal walking distance ($P<0.001$ versus placebo). Patients on cilostazol 100 mg had an increase in maximum walking distance from 130 m at baseline to 259 m at week 24, and from 132 m to 199 m for the cilostazol 50 mg group. Pain-free walking distance increased by 59% ($P<0.001$) and 48% ($P<0.001$) in the cilostazol 100 mg and cilostazol 50 mg groups, respectively. There were also improvements in quality of life, functional status and global health evaluations. Headache, diarrhea, dizziness and palpitations were the most commonly reported potentially drug-related adverse events and were self-limited. Seventy-five patients (14.5%) withdrew because of any adverse event, with no difference between treatment groups. In addition, there was no difference between groups in the incidence of combined cardiovascular morbidity or all-cause mortality.

In another trial, Dawson et al (16) randomly assigned 698 patients at 54 centres to cilostazol 100 mg twice daily, pentoxifylline 400 mg three times daily or placebo. Maximal walking distance on a treadmill was measured at baseline and at four, eight, 12, 16, 20 and 24 weeks. The maximal walking distance in the cilostazol arm was significantly greater at every postbaseline visit compared with either patients who received pentoxifylline or placebo. After 24 weeks, maximal walking distance increased by 107 m (54% increase from baseline) in the cilostazol group, compared with a 64 m improvement (30% increase) in the pentoxifylline group ($P<0.001$). The improvement with pentoxifylline was similar to placebo (65 m, 34% increase; $P=0.82$). Deaths and serious adverse event rates were similar in each group. Side effects (including headache, palpitations and diarrhea) were more common in the cilostazol arm, but drug withdrawal rates were similar with cilostazol (16%) and pentoxifylline (19%). Thus, cilostazol was shown to be better than either pentoxifylline or placebo for increasing walking distances in patients with intermittent claudication, while associated with minor side effects.

Dawson et al (17) also studied the effect of withdrawal of cilostazol and pentoxifylline on the walking ability of patients with peripheral arterial disease. Forty-five patients received

either cilostazol 100 mg twice daily, pentoxifylline 400 mg orally three times daily or placebo for 24 weeks. At 24 weeks, all groups received placebo only, and follow-up continued through week 30. There was an improvement in treadmill walking time with cilostazol, but much less with pentoxifylline or placebo. After crossover to placebo there was rapid loss of treatment benefit ($P=0.001$) for cilostazol-treated patients. This decline with crossover from cilostazol to placebo suggests that the improvement in walking time in the cilostazol arm was due to the drug.

Beebe et al (15) randomly assigned 394 patients with intermittent claudication to placebo, cilostazol 100 mg or 200 mg daily, with follow-up at 24 weeks. Patients receiving cilostazol 200 mg experienced a 21% net improvement in maximal walking distance compared with placebo ($P=0.0003$) and a 22% improvement in distance walked to the onset of symptoms ($P=0.0015$). Patients on cilostazol 100 mg had a smaller benefit. Quality of life and functional status assessments corroborated the walking time results.

Mohler et al (18) evaluated the effect of cilostazol on ankle-brachial index. Two similar randomized controlled trials were pooled. The patients walked on a treadmill at 0.89 m/s, 12.5% grade until the claudication-limited maximal walking distance was reached. Anterior and posterior tibial pressures were measured by Doppler ultrasound at baseline and at 1 min, 5 min and 9 min recovery. At 24 weeks of treatment, both resting and postexercise ankle-brachial index improved more in the cilostazol group than in the placebo group.

The reasons for these beneficial effects in patients with peripheral arterial disease are not clear, but seem to be related to the multiple benefits shown with cilostazol, including vasodilation, inhibition of platelet activation and aggregation and inhibition of thrombosis. The principal side effects of cilostazol are headache, diarrhea and palpitations. With over 12,000 patients with vascular disease studied, cilostazol has not been shown to result in an increased incidence of any vascular event.

INHIBITION OF RESTENOSIS AFTER CORONARY STENT IMPLANTATION

In one of the first studies to evaluate the effect of cilostazol on restenosis, Take et al (19) randomly assigned 68 patients to cilostazol immediately after percutaneous transluminal coronary angioplasty (PTCA) versus ASA or ticlopidine (Table 1). Follow-up coronary angiography four to six months after PTCA revealed that restenosis was significantly lower (17%) in the cilostazol group than in the noncilostazol group (40%) ($P<0.05$).

In another early study evaluating the effect of cilostazol in preventing restenosis, Yamasaki et al (20) randomly assigned 36 patients undergoing bare-metal coronary stent implantation to cilostazol or ASA for six months. At follow-up, minimal luminal diameter was greater with cilostazol than ASA ($P<0.001$). Late loss and loss index were smaller with cilostazol than with ASA ($P<0.001$).

Kozuma et al (21) randomly assigned 130 patients undergoing elective bare-metal coronary artery stent implantation to cilostazol 200 mg/day treatment or ticlopidine 200 mg/day treatment. Angiographic follow-up was performed at six months, and clinical follow-up at one year. In the ticlopidine group, there was one sudden death and one myocardial infarction resulting from subacute occlusion. Adverse effects were observed in

three patients in the cilostazol group and six in the ticlopidine group. Late loss in the cilostazol group was smaller than in the ticlopidine group (0.58 ± 0.52 mm versus 1.09 ± 0.65 mm; $P < 0.0001$). The restenosis rate was also lower in the cilostazol group than in the ticlopidine group (16% versus 33%; $P = 0.044$). At one year, the target vessel revascularization rate was 23% in the cilostazol group and 42% in the ticlopidine group ($P = 0.03$).

Tsuchikane et al (22) randomly assigned 211 patients to cilostazol 200 mg daily for three months or ASA after PTCA. At six months, the minimal lumen diameter, measured by quantitative coronary arteriography, was larger (1.65 ± 0.55 mm versus 1.37 ± 0.58 mm; $P < 0.0001$) and diameter stenosis was lower ($34 \pm 18\%$ versus $46 \pm 19\%$; $P < 0.0001$) in the cilostazol group. Restenosis and target lesion revascularization rates were also lower with cilostazol (18% versus 40%; $P < 0.001$; and 11% versus 29%; $P < 0.001$).

Somewhat less certain results were noted by Park et al (23). These investigators randomly assigned 409 patients undergoing elective coronary stenting to receive ASA plus ticlopidine or ASA plus cilostazol, starting two days before stenting. Ticlopidine was given for one month and cilostazol for six months. There were no cases of stent thrombosis. The restenosis rate was 27% in the ticlopidine group and 23% with cilostazol ($P = \text{NS}$). Interestingly, in the subgroup with diabetes, the restenosis rate was 50% with ticlopidine and 22% with cilostazol ($P < 0.05$). Clinical events during follow-up did not differ between the two groups.

The utility of cilostazol has been studied as an agent to prevent restenosis in patients undergoing percutaneous coronary intervention (PCI). The effect of cilostazol on restenosis was studied in the prospective Randomized Antiplatelet trial of Cilostazol versus Ticlopidine in patients undergoing coronary Stenting (RACTS) trial. In this trial, patients undergoing coronary artery stenting with bare-metal stents were randomly assigned to cilostazol plus ASA or ticlopidine plus ASA. A total of 397 patients at seven medical centres in China were studied. Angiographic and clinical follow-up were performed at six and nine months, respectively. On follow-up angiography, there was a strong trend to a larger minimum luminal diameter with cilostazol (2.3 mm versus 2.1 mm; $P = 0.057$), and less late loss (0.80 mm versus 0.96 mm; $P = 0.12$). There was also a strong trend to less binary restenosis, defined as 50% diameter narrowing at follow-up (29% versus 37%; $P = 0.086$). There was no difference in overall stent thrombosis. Target vessel revascularization was less frequent with cilostazol (23% versus 33%; $P < 0.05$). There was no difference between the arms in bleeding, headache requiring drug discontinuation or nausea. The reasons for the beneficial actions of cilostazol in the RACTS trial are not clear, but may be related to the antiproliferative actions of cilostazol. The RACTS trial was one of the major trials setting the stage for the Cilostazol for RESTenosis (CREST) trial.

The combined effects of cilostazol and probucol on restenosis was studied by Sekiya et al (24). Using a factorial design, 126 patients were randomly assigned one week before stenting to control, probucol 500 mg daily, cilostazol 200 mg daily or probucol plus cilostazol. Treatment continued from five days pre-stent until six month follow-up. The restenosis rate per segment was 32% in controls, 17% for probucol, 12% for the cilostazol group ($P < 0.05$ versus control) and 9.5% for combined treatment ($P < 0.05$ versus control). While severely underpowered, there was no difference in event rates.

TABLE 1
Restenosis trial results

Author (reference)	Patients (n)	Comparator	Restenosis cilostazol (%)	Restenosis control (%)	P
Take et al (19)	68	ASA or ticlopidine	17	40	<0.05
Kozuma et al (21)	130	Ticlopidine	16	33	<0.0001
Tsuchikane et al (22)	211	ASA	18	40	<0.0001
Park et al (23)	409	Ticlopidine	23	27	NS
Ge et al (31)	397	Ticlopidine	29	37	0.086
Sekiya et al (24)	126	Placebo	32	12	<0.05
Douglas et al (26)	705	Placebo	34	22	0.0021

ASA Acetylsalicylic acid; NS Not significant

The CREST trial

CREST was a prospective, randomized, double-blind, placebo-controlled trial comparing cilostazol with placebo to prevent restenosis following PCI with bare-metal stent implantation in a native coronary artery as evaluated by quantitative coronary angiography at six months (25). All patients were treated with clopidogrel for one month and remained on ASA throughout the study period. A total of 704 patients with critical coronary stenosis, but without a recent myocardial infarction, were recruited at 19 sites. Clinical and quantitative coronary angiographic follow-up data were obtained at six months. The primary end point was minimal luminal diameter of the first lesion stented per patient as assessed by quantitative coronary angiography at an angiographic core laboratory. The patients were well randomized, with no difference in demographic or clinical characteristics. The initial stent procedure yielded similar results in the two arms, with similar acute gain, final per cent stenosis and final minimal luminal diameter. The primary end point, the minimal luminal diameter of the analysis segment, was significantly larger in the cilostazol-treated group compared with the placebo group due to significantly less late loss in cilostazol-treated patients (0.57 mm versus 0.75 mm; $P = 0.002$). The restenosis rate was significantly lower in the cilostazol group (22%) compared with the placebo group (34%; $P = 0.0021$) (26). The rates of occurrence of death, myocardial infarction, stroke, bleeding, target vessel revascularization and rehospitalization were not shown to be different in the two groups. Cilostazol was shown to decrease the rate of restenosis in major subgroups, including patients with diabetes and small vessels. The mechanism by which cilostazol decreased restenosis is not clear, but may be related to decreased cellular proliferation (2-4).

The reduction in restenosis observed in cilostazol-treated patients in CREST was greater than observed in the pivotal STent RESTenosis Study (STRESS) and the BELgian Netherlands STent (BENESTENT) study, both of which compared stents with balloon angioplasty, where binary restenosis was reduced by 27% and 31%, respectively (27,28). While the suppression of late lumen loss by cilostazol was not as large as with drug-eluting stents, it was similar (29). Moreover, cilostazol proved effective in reducing restenosis in the worrisome subgroups with diabetes and small vessels. Of particular importance, patients treated with cilostazol did not experience increased bleeding compared

with placebo in spite of concomitant use of clopidogrel for 30 days and ASA for the duration of the study. Similarly, there was no difference in serious adverse cardiac events, stroke or rehospitalization during six month follow-up. While the reduction in restenosis experienced with cilostazol treatment was not associated with lowered target vessel revascularization, this trial was underpowered to examine clinical events. In addition, a decision to repeat intervention after follow-up diagnostic angiography was made independently, by the patients' physicians. Cutlip et al (30) reported that in multicentre trials, follow-up angiography led to 44% more repeat interventions than studies without mandated angiography. This suggested that some nonischemia-producing lesions were treated after follow-up diagnostic angiography. Repeat intervention in clinically 'silent' lesions is also suggested in the CREST trial by a target vessel revascularization rate of 16%, approximating the restenosis

rate observed in some subgroups. In contrast, in previous trials (27,28), ischemia-driven target vessel revascularization has been reported in approximately 50% of patients with angiographic restenosis. Thus, cilostazol is a drug of considerable promise. Additional trials could focus on cilostazol in nonstented lesions, vein grafts, in-stent restenosis, peripheral and carotid stents, and as a supplement to drug-eluting stents, especially in high-risk patients.

CONCLUSIONS

Cilostazol is a phosphodiesterase III inhibitor with a profound pharmacological profile. It is widely used in the treatment of peripheral arterial disease, has been used as an alternative to ADP blockers in patients undergoing PCI, and has been definitively shown to prevent restenosis after PCI with bare-metal stents. Many more trials would be required to fully analyze the utility and safety of this compound.

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