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Therapeutic Class Review
Intermittent Claudication Agents

Overview/Summary

Peripheral artery disease (PAD) affects approximately eight and a half million adults in the United States.[1] One of the most common symptoms of PAD is intermittent claudication, which results from inadequate blood flow to the limb and is characterized by pain, aching, cramping or numbness in the lower extremities that occurs with exercise and subsides with rest. Intermittent claudication can severely impact a patient's mobility and quality of life. The limitations of intermittent claudication, including total walking distance and pain-free walking distance, can often be improved with exercise, risk factor modification and medical management.[2] Risk factor modifications include smoking cessation and control of hypertension, hyperlipidemia or diabetes mellitus if indicated. An estimated 50% of patients with intermittent claudication also have significant coronary artery disease.[3] Currently, cilostazol and pentoxifylline extended-release are the only two agents Food and Drug Administration (FDA)-approved for the treatment of intermittent claudication. Cilostazol is a phosphodiesterase type III inhibitor that reversibly inhibits platelet aggregation by suppressing degradation of cyclic adenosine monophosphate (cAMP), resulting in increased cAMP in platelets and blood vessels, potentially leading to an increase in dermal blood flow of the lower extremities.[4] Upon discontinuing cilostazol, platelet aggregation returns to normal within 96 hours. Pentoxifylline is a tri-substituted methylxanthine derivative that has been shown to have hemorheologic effects. Patients with intermittent claudication have been shown to have erythrocytes that are more rigid than those found in patients without PAD.[3] Pentoxifylline reduces blood viscosity, improves erythrocyte flexibility, microcirculatory flow and tissue oxygen concentrations. Improvement in erythrocyte flexibility appears to be due to inhibition of phosphodiesterase and a resultant increase in cAMP in red blood cells.[5] Other agents that have been used in the treatment of intermittent claudication include antiplatelet agents, vasodilators, anticoagulants and calcium channel blockers.[3]

In a meta-analysis, cilostazol was shown to increase the initial claudication distance, the distance walked before the onset of pain, by 30 to 40 meters. Additionally, cilostazol increased absolute claudication distance, the total distance a patient is able to walk, by 30 to 50 meters.[6] Alternatively, studies assessing the efficacy of pentoxifylline extended-release for improvement in initial claudication distance and absolute claudication distance have not consistently demonstrated benefit. One meta-analysis found that pentoxifylline extended-release increased the pain-free walking distance by 30 meters.[5] Other studies have concluded that there is no difference between pentoxifylline extended-release and placebo in regard to improvements in walking distance.[7] Despite their specific indications for the treatment of intermittent claudication, cilostazol and pentoxifylline extended-release have the potential to be used off-label in a variety of cardiovascular conditions. Cilostazol has been used for stroke prophylaxis, prophylaxis for coronary stent stenosis and for the prevention of thromboses in patients undergoing percutaneous coronary intervention. Pentoxifylline extended-release has been studied for use in cerebrovascular disease, congestive heart failure, vascular disorders of the inner ear, stasis ulcer, male infertility and as an adjunct for the treatment of diabetes mellitus.[8] Cilostazol and its active metabolites have a half-life of approximately 11 to 13 hours, which allows for twice daily dosing.[4,8] Pentoxifylline immediate-release (not currently available in the United States) has a plasma half-life of approximately 0.4 to 1 hour, while the M-V metabolite has a slightly longer half-life of up to 1.6 hours. The half-life for the pentoxifylline extended-release formulation is not reported, but it is recommended to be administered three times daily.[5,8]

Current guidelines for the management of PAD by the American College of Cardiology recommend a supervised exercise program for all patients with intermittent claudication. Cilostazol is also recommended as an effective therapy to improve symptoms and increase walking distance in patients with lower extremity PAD and intermittent claudication. Pentoxifylline extended-release may be

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considered as second-line alternative therapy to cilostazol to improve walking distance in patients with intermittent claudication, although the clinical effectiveness of pentoxifylline as therapy is marginal and not well established.[9] The American College of Chest Physicians recommends against the use of pentoxifylline and states that cilostazol should be reserved for moderate to severe intermittent claudication, due to the established role of supervised exercise programs for this patient population. For patients with clinically manifest coronary or cerebrovascular disease, lifelong antiplatelet therapy is recommended. Despite the established cardiovascular benefits in patients with PAD, antiplatelet therapy alone has not been shown to be beneficial in the treatment of intermittent claudication.[10]

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Cilostazol (Pletal®*)	Phosphodiesterase type III inhibitor/platelet aggregation inhibitor	✔
Pentoxifylline extended-release (Pentoxil®*, Trental®*)	Hemorheologic/methylxanthine	✔

*Generic available in at least one dosage form or strength.

Indications

Table 2. Food and Drug Administration Approved Indications[4,5,8]

Generic Name	Intermittent Claudication
Cilostazol	✔
Pentoxifylline extended-release	✔

Although not Food and Drug Administration (FDA)-approved for the following indications, cilostazol has been studied and used off-label for primary and secondary stroke prophylaxis, prophylaxis for coronary stent stenosis and for the prevention of thromboses in patients undergoing percutaneous coronary intervention. Similarly, pentoxifylline extended-release has also been used off-label for cerebrovascular disease as well as congestive heart failure, vascular disorders of the inner ear, stasis ulcer, male infertility and as an adjunct therapy for diabetes mellitus.

Pharmacokinetics

Table 3. Pharmacokinetics[4,5,8]

Generic Name	Bio-availability (%)	Absorption (%)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Cilostazol	87 to 100	Not reported	74	3,4 dehydrocilostazol 4'-trans-hydroxycilostazol	11 to 13*
Pentoxifylline extended-release	20	95	95	Metabolite I,V	0.4 to 1.0†

*The half-lives for the active metabolites of cilostazol are approximately equal to that of the parent compound.
†The half-lives of Metabolites I and V vary between 1.0 to 1.6 hours.

Clinical Trials

Both cilostazol and pentoxifylline extended-release have been well studied for the treatment of intermittent claudication. Robless and colleagues conducted a meta-analysis consisting of several randomized controlled trials using cilostazol. The authors concluded that at the Food and Drug Administration (FDA)-approved dose (100 mg twice daily), cilostazol increased initial claudication distance (ICD) by an average of 31.1 meters compared to placebo (95% confidence interval [CI], 21.3 to 40.9). Additionally, cilostazol improved the absolute claudication distance (ACD) by 49.7 meters compared to placebo (95% CI, 24.2 to 75.2). Cilostazol 50 mg twice daily increased ICD by 41.3 meters (95% CI, -7.0 to 89.7) compared to placebo, however, this difference was not statistically significant.[6]

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A second meta-analysis by Thompson and colleagues confirmed the results reported by Robless et al. Patients who received either 50 or 100 mg of cilostazol twice daily had significant improvements in maximum walking distance (MWD) compared to placebo (44.0 and 50.0 vs 21.4%, respectively; *P*<0.05 for both doses compared to placebo). Pentoxifylline extended-release was used in two of the included trials and the mean improvements in MWD were similar between pentoxifylline extended-release and placebo-treated patients. Cilostazol 50 and 100 mg twice daily also improved pain-free walking distance (PFWD) compared to placebo (60 and 67 vs 40%, respectively; *P*<0.05 for both doses compared to placebo). Improvements in physical functioning scores were also noted for patients who received cilostazol, but no improvements in scores were reported for pentoxifylline extended-release and placebo-treated patients.[12]

Dawson et al assessed the effectiveness of cilostazol vs pentoxifylline extended-release (also included in the meta-analysis by Robless) in 698 patients with intermittent claudication. After 24 weeks, the mean improvements in MWD were greater for patients treated with cilostazol compared to pentoxifylline extended-release (107 vs 64 meters; *P*=0.0005) and placebo (65 meters; *P* value not reported). There was no difference between pentoxifylline extended-release and placebo-treated patients for improvements in MWD (*P*=0.82). Cilostazol significantly increased PFWD compared to pentoxifylline extended-release (94 vs 74 meters; *P*=0.0001) and placebo (57 meters; *P* value not reported). There was no difference between pentoxifylline extended-release and placebo groups in regards to PFWD (*P*=0.07).[24] Alternatively, one recent study showed that although cilostazol increased ICD by 84% from baseline, this increase was not significantly different compared to placebo (*P*=0.98). Additionally, ACD was not significantly improved for patients receiving cilostazol twice daily compared to placebo after 24 weeks (*P*=0.22).[14]

To date, studies evaluating the effectiveness of pentoxifylline extended-release have been conflicting.[11] In a meta-analysis by Hood et al, patients treated with pentoxifylline extended-release had a significant increase in PFWD of 29.4 meters (95% CI, 13.0 to 45.9) compared to placebo. In a sensitivity analysis including only trials lasting ≥13 weeks, treatment with pentoxifylline extended-release did not significantly improve PFWD (30.8 meters; 95% CI, -4.6 to 66.3) compared to placebo. The overall weighted mean difference in ACD was statistically significant (48.4 meters; 95% CI, 18.3 to 78.6), but when only trials lasting ≥13 weeks were included, pentoxifylline extended-release did not significantly improve ACD (19.8 meters; 95% CI, -19.8 to 59.5 meters).[7] Lindgarde and colleagues found no difference between pentoxifylline extended-release and placebo for improving ICD after 24 weeks (80 vs 60%; *P*=0.268). Similarly, no difference was apparent between treatments in regards to improvements in ACD (50 vs 29%; *P*=0.094).[17]

In a small six month study by Belcaro et al (N=60), improvements in the total walking distance (TWD) were significantly greater for patients who received pentoxifylline extended-release compared to patients receiving placebo (292 vs 180%; *P*<0.02).[18] In a similar study, patients randomized to pentoxifylline had significant improvements in TWD compared to placebo (148 vs 110%; *P*<0.02) after six months of treatment. After 12 months, pentoxifylline continued to improve TWD compared to placebo (170 vs 131%; *P*<0.02).[20] DeSanctis et al also found significant increases in TWD from baseline over 12 months of treatments for patients who received pentoxifylline compared to placebo (404 vs 280%; *P*<0.05).[21] Cesarone and colleagues studied the effects of pentoxifylline extended-release over 12 months. At the completion of the study, pentoxifylline-treated patients had greater improvements in TWD compared to placebo (329.8 vs 183.0%; *P*<0.02).[22] The studies by Belcaro, DeSanctis and Cesarone all used pentoxifylline doses greater than the FDA-approved dose of 1,200 mg daily. It is also unclear if the extended-release formulation was used in the DeSanctis studies.

After 24 weeks of treatment, patients who received pentoxifylline extended-release three times daily had significantly greater improvements in ICD compared to patients taking placebo (45 vs 23%; *P*=0.016)[16]. One small study (N=31) showed that patients taking 400 mg of pentoxifylline extended-release had an average increase in MWD after 12 months compared to placebo (101 vs 9%; *P*<0.05).[23] A similar study with a crossover design found that patients taking pentoxifylline extended-release had greater improvements in MWD compared to flunarizine (values not reported; *P*<0.01).[26] Larger trials using the FDA-approved dosing showed no benefit in MWD of pentoxifylline extended-release over placebo.[16,17]

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Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Robless et al[6] Cilostazol 50 to 150 mg BID vs placebo	MA RCTs investigating the use of cilostazol in patients with stable IC for ≥6 months	N=2,332 (7 trials) 12 to 24 weeks	Primary: Change from baseline in ICD Secondary: Change from baseline in ACD, mortality, cardiovascular events, ABPI, quality of life and side effects	Primary: Compared to patients receiving placebo, treatment with cilostazol 100 mg BID was associated with a WMD in ICD of 31.1 meters (95% CI, 21.3 to 40.9). Cilostazol 50 mg BID increased ICD by 41.3 meters (95% CI, -7.0 to 89.7) compared to placebo. However, this difference was not statistically significant. Only one trial assessed the effects of cilostazol 150 mg BID on ICD. After 12 weeks of treatment, patients receiving cilostazol had a greater increase in ICD compared to placebo (WMD, 15.7 meters; 95% CI, -9.6 to 41.0). Secondary: Cilostazol 100 mg BID increased ACD by 49.7 meters (95% CI, 24.2 to 75.2) compared to placebo. Similarly, cilostazol 50 mg BID was associated with greater improvements in ACD compared to placebo (41.3 meters; 95% CI, 12.4 to 51.5). Only one trial assessed the effects of cilostazol 150 mg BID. After 12 weeks of treatment, patients who received cilostazol had a greater, yet non-significant increase in ACD compared to placebo (51.9 meters; 95% CI, -13.9 to 117.5). Total cardiovascular morbidity and all-cause mortality was 6.5% for cilostazol 100 mg BID, 6.3% for cilostazol 50 mg BID and 7.7% for placebo. In total there were 16 deaths occurring in 0.6 and 0.5% of patients in the cilostazol and placebo groups, respectively. Patients treated with cilostazol 100 mg BID had significant changes in ABPI compared to patients receiving placebo (0.06; 95% CI, 0.03 to 0.09). Patients receiving cilostazol (50 or 100 mg BID) in three trials reported improvements in the physical health components of the SF-36 questionnaires compared to patients receiving placebo. This included significant improvements in scores for physical function (P=0.002) and bodily pain (P<0.05). There were no differences between cilostazol and placebo for mental health scores. Two trials reported significant improvement in WIQ scores for patient perception of walking speed (P<0.05) with cilostazol. However, only one of the two trials reported a significant improvement in walking distance with

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				cilostazol. The side effect profile of cilostazol included symptoms of headache, diarrhea, pain, infection, rhinitis, pharyngitis, peripheral edema and nausea in 5% or more of patients receiving cilostazol. Headaches, diarrhea and peripheral edema were reported more frequently in patients receiving cilostazol (100 and 50 mg BID) compared to placebo (*P*<0.05). Patients receiving cilostazol 50 mg BID reported symptoms of rhinitis and infection more frequently than patients on placebo (*P*<0.05).
Thompson et al[12] Cilostazol 50 to 150 mg BID vs pentoxifylline extended-release 400 mg TID vs placebo	MA DB, PC, RCTs that included patients with moderate to severe IC lasting ≥6 months	N=2,702 (8 trials) 12 to 24 weeks	Primary: Change from baseline in MWD Secondary: Change from baseline in PFWD, SF-36 and WIQ scores	Primary: Compared to placebo, treatment with cilostazol increased MWD in six of the eight studies evaluated. Patients who received either 50 or 100 mg of cilostazol BID had significant improvements in MWD compared to placebo (44.0 and 50.0 vs 21.4%, respectively; *P*<0.05 for both doses compared to placebo). Pentoxifylline extended-release was used in two trials and the mean percent changes from baseline were similar between pentoxifylline extended-release and placebo-treated patients. Secondary: Compared to placebo, treatment with cilostazol increased PFWD in five of the eight studies evaluated. Patients who received either 50 or 100 mg of cilostazol BID had significant improvements in PFWD compared to placebo (60 and 67 vs 40%, respectively; *P*<0.05 for both doses compared to placebo). Patients who received cilostazol 100 mg BID had greater improvements in physical function subscale scores in all six trials compared to placebo (*P* value not reported). In the pooled analysis at the end of treatment, patients taking cilostazol scored 4.4 points higher in this section compared to patients taking placebo (*P*<0.01). However, changes in the general health subscale were not significant. For the physical function portion of SF-36, there was a greater improvement at the end of treatment in the cilostazol 100 mg BID group compared to the placebo group in all six trials. In the pooled analysis at the end of treatment, patients who were receiving cilostazol scored 2.1 points higher than those who were receiving placebo (*P*<0.01). In five of six trials there was a significantly greater improvement in the walking distance subscale for patients treated with cilostazol 100 mg BID, than in

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				those receiving placebo at the end of treatment. Patients receiving cilostazol 100 mg BID, scored 6.6 points higher than those taking placebo (*P*<0.01) in the pooled analysis at the end of treatment. Greater improvement was demonstrated in the walking speed subscale with cilostazol 100 mg BID vs placebo at the end of treatment in all six trials; the average increase was 6.1 points greater than with placebo (*P*<0.01).
Hood et al[7] Pentoxifylline 600 to 1,800 mg daily[†] vs placebo	MA DB, PC, RCTs that included patients with IC lasting 3 months to 5 years and a PFWD of ≤200 meters	N=541 (11 trials) 2 to 26 weeks	Primary: Change from baseline in PFWD and ACD Secondary: Not reported	Primary: Patients with IC who were treated with pentoxifylline had a significantly greater increase in PFWD (29.4 meters; 95% CI, 13.0 to 45.9), compared to placebo. In a sensitivity analysis including only trials lasting ≥13 weeks, treatment with pentoxifylline did not significantly improve PFWD (30.8 meters; 95% CI, -4.6 to 66.3). The overall weighted mean difference in ACD was statistically significant for pentoxifylline (48.4 meters; 95% CI, 18.3 to 78.6). In a sensitivity analysis including only trials lasting ≥13 weeks, treatment with pentoxifylline did not significantly improve ACD (19.8 meters; 95% CI, -19.8 to 59.5). Secondary: Not reported
O'Donnell et al[14] Cilostazol 100 mg BID vs placebo	DB, PC, RCT Patients aged 30 to 90 with stable IC for ≥3 months, ABI <0.9 who were also taking antiplatelet and cholesterol lowering therapies without previous use of cilostazol	N=80 24 weeks	Primary: Change from baseline in ICD and ACD Secondary: Arterial compliance, ABI, $Tcp0_2$, and quality of life	Primary: After six weeks of treatment, patients who received cilostazol had significant increases in ICD compared to patients receiving placebo (105.5 [51.3%] vs 67.5 meters [6.3%]; *P*=0.019). After 24 weeks, there was no difference noted in ICD between cilostazol when compared to placebo (82.5 [84.8%] vs 85.0 meters [66.5%]; *P*=0.98). Patients treated with cilostazol had significant increases in ACD after six weeks of treatment compared to placebo (193.1 [33.7%] vs 168.5 meters [21.5%]; *P*=0.043). After 24 weeks, there was no difference in ACD between cilostazol and placebo-treated patients (286.1 [173.1%] vs 227.1 meters [92.1%]; *P*=0.22). When improvements in walking distance were compared to baseline values, cilostazol significantly increased both ICD and ACD after six weeks of treatment (*P*<0.001 for both ICD and ACD). Improvements from baseline

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				continued to remain increased for ICD and ACD at 24 weeks (*P*<0.021 and *P*<0.001, respectively). Secondary: A greater reduction in arterial compliance was found in patients treated with cilostazol compared to placebo after six weeks (19.7 vs 26.7%, *P*=0.001) and 24 weeks (19.7 vs 27.7%, *P*=0.005). There was no difference in ABI for patients who received cilostazol or placebo after six or 24 weeks for left and right lower limbs (*P*=0.06 to *P*=0.45). Additionally, there was no difference between treatment groups in regards to $Tcp0_2$ after six and 24 weeks (*P*=0.08 to *P*=0.98). There were significant increases from baseline in the cilostazol group for SF-36 scores of physical functioning (11.0 vs –0.3%; *P*=0.013) and physical component summary (11.4 vs 5.1%; *P*=0.044) subset scores at 24 weeks. There were no differences in WIQ scores between the treatment groups after six weeks for distance or speed (*P*=0.64 and *P*=0.73, respectively) or at 24 weeks (*P*=0.41 and *P*=0.88 for distance and speed, respectively). When 24-week distance and speed scores were compared with baseline values, a significant improvement in scores occurred in the cilostazol group but no changes were noted in the placebo group (*P*=0.014 vs *P*=0.81 and *P*=0.021 vs *P*=0.74 for distance and speed with cilostazol and placebo, respectively).
O'Donnell et al[15] Cilostazol 100 mg BID vs placebo	DB, PC, RCT Patients aged 30 to 90 with stable IC and an ABI <0.9 who were also taking antiplatelet and cholesterol lowering therapies for ≥3 months	N=106 24 weeks	Primary: Change from baseline in ICD and ACD Secondary: Generation of antioxidant consumption and markers of inflammation including selectins, I-CAM, thromboxane, interleukin and hsCRP	Primary: Patients who received cilostazol had greater improvements in ICD compared to placebo after six (38.9 vs 22.7%; *P*=0.06) and 24 weeks (67.0 vs 51.6%; *P*=0.63), but the differences were not statistically significant. Patients in the cilostazol treatment group had significant improvements in ACD compared to placebo after six (77.2 vs 26.6%; *P*=0.026) and 24 weeks (161.7 vs 79.0%; *P*=0.048). Secondary: There were no significant differences in selectin, I-CAM or thromboxane levels between the treatment groups at any time point of the study. However, selectin levels were reduced in the cilostazol group before and after exercise after 24 weeks compared to baseline levels (pre-exercise; *P*=0.001 and post-exercise; *P*<0.001). No changes were seen in the placebo group. There was also no difference between cilostazol and placebo for markers of interleukin or hsCRP.

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Porter et al[16] Pentoxifylline extended-release 400 mg TID vs placebo	DB, MC, PC, PG, RCT Patients with a diagnosis of COAD and IC for ≥6 months who were able to walk 50 to 510 meters in 9.5 minutes	N=128 24 weeks	Primary: Change from baseline in ICD and ACD Secondary: Strength of peripheral pulses, pain, coldness, cramps, tightness, tiredness, and paresthesia	Primary: There was no difference in the change in ICD between pentoxifylline extended-release and placebo after 12 weeks of treatment (56 vs 32%; *P*=0.55). After 24 weeks of treatment, patients who received pentoxifylline extended-release had significantly greater improvements in ICD compared to patients receiving placebo (45 vs 23%; *P*=0.016). There was no difference in the change in ACD between pentoxifylline extended-release and placebo after 12 weeks of treatment (36 vs 33%; *P*=0.097) Although the improvements in ACD between the treatment groups were not as high after 24 weeks, pentoxifylline extended-release treatment was significantly more effective at increasing ACD from baseline compared to placebo (32 vs 20%; *P*=0.035). Secondary: With regard to the subjective parameters, only the incidence of paresthesias showed a greater reduction (*P*<0.05) in the pentoxifylline extended-release group over 24 weeks of the study. Coldness in the lower limbs was significantly improved after 12 weeks of treatment (*P*<0.01), but this difference was not apparent after 24 weeks. There were no significant differences between pentoxifylline extended-release and placebo for the other variables assessed.
Lindgarde et al[17] Pentoxifylline extended-release 400 mg TID vs placebo	DB, MC, PC, PG, RCT Patients ≥40 years of age with moderate to severe COAD and IC for ≥6 months and an ICD of 50 to 200 meters	N=150 24 weeks	Primary: Change from baseline in ICD and ACD Secondary: Not reported	Primary: There was no difference between pentoxifylline extended-release and placebo for improving ICD after 24 weeks (80 vs 60%; *P*=0.268). Similarly, there was no difference between patients in either treatment group in regards to improvements in ACD (50 vs 29%; *P*=0.094) at the conclusion of the study. In a subset analysis of patients with an ankle to arm pressure ratio of ≤0.8 (87% of the included population) and duration of disease ≥1 year (85% of the included population), pentoxifylline extended-release was significantly more effective for improving ICD (99 vs 47%; *P*=0.011) and ACD (63 vs 30%; *P*=0.023), compared to placebo. Secondary: Not reported

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Belcaro et al[18] Pentoxifylline extended-release 400 mg QID vs placebo	DB, PC, RCT Patients aged 45 to 75 with severe IC lasting ≥3 months, controlled diabetes for ≥5 years, resting ABI <0.8, TWD <100 meters and a decrease in ankle pressure of 15 mm Hg after standard exercise on a treadmill	N=60 6 months	Primary: Change from baseline in TWD Secondary: Not reported	Primary: After three months of treatment, patients in both the pentoxifylline extended-release and placebo groups had significant increases in TWD from baseline (122 and 99 meters, respectively; *P*<0.05). After six months of treatment, the increase in TWD was significantly improved for patients who received pentoxifylline extended-release compared to patients receiving placebo (161 [292%] vs 103 meters [180%]; *P*<0.02). Secondary: Not reported
Incandela et al[19] Pentoxifylline 600 mg QID[†] vs placebo	DB, PC, RCT Patients with severe IC lasting ≥3 months who were experiencing pain at night, with an ABI <0.6, TWD <50 meters and a decrease in ankle pressure of 30 mm Hg after standard exercise on a treadmill	N=20 10 days	Primary: Change from baseline in skin flux, after exercise flux, $TcpO_2$ and PCO_2 after five days of treatment and exercise Secondary: Not reported	Primary: After 10 days of treatment, patients who received pentoxifylline had significant increases in skin flux (2.1 vs 0.6), after exercise flux (3.4 vs 0.8) and $TcpO_2$ (61 vs 56 mm Hg) compared to placebo (*P*<0.05 for all comparisons). Moreover, PCO_2 was significantly decreased in pentoxifylline treated patients compared to patients who received placebo (28 vs 30 mm Hg; *P*<0.05). All changes in the pentoxifylline group were significantly improved compared to baseline values (*P*<0.05). Secondary: Not reported
DeSanctis et al[20] Pentoxifylline 600 mg TID[†] vs placebo	DB, PC, RCT Patients aged 50 to 65 with IC lasting ≥3 months, resting ABI <0.8, TWD >400 meters and a decrease in ankle	N=194 12 months	Primary: Change from baseline in TWD Secondary: Not reported	Primary: Patients receiving either pentoxifylline or placebo experienced significant increases in TWD from baseline after both six and 12 months (*P*<0.02 and *P*<0.05, respectively). After six months of treatment, patients in the pentoxifylline group had a greater increase in TWD compared to patients who received placebo (822 [148%] vs 638 meters [110%]; *P*<0.02). After 12 months, TWD was significantly increased for patients receiving pentoxifylline compared to placebo (943 [170%] vs 755 meters [131%]; *P*<0.02).

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	pressure of 20 mm Hg after standard exercise on a treadmill			Secondary: Not reported
DeSanctis et al[21] Pentoxifylline 600 mg TID[†] vs placebo	DB, PC, RCT Patients aged 45 to 75 with severe IC lasting ≥4 months, resting ABI <0.8, TWD 50 to 200 meters and a decrease in ankle pressure of 15 mm Hg after standard exercise on a treadmill	N=120 12 months	Primary: Change from baseline in TWD, skin flux and after exercise flux Secondary: Not reported	Primary: Patients receiving either pentoxifylline or placebo experienced significant increases in TWD from baseline after both six and 12 months of treatment (*P*<0.05). After six months, patients randomized to pentoxifylline had greater increases in TWD compared to placebo (177 [268%] vs 133 meters [198%]; *P*<0.05). After 12 months, improvements in TWD remained significantly improved for pentoxifylline compared to placebo (267 [404%] vs 188 meters [280%]; *P*<0.05). Compared to placebo, pentoxifylline improved skin flux (1.9 vs 1.2; *P*<0.02) and after exercise flux (4.4 vs 3.3; *P*<0.02) after 12 months. Secondary: Not reported
Cesarone et al[22] Pentoxifylline extended-release 400 mg QID vs placebo	DB, PC, RCT Patients aged 45 to 75 with severe IC lasting ≥4 months, resting ABI <0.8, TWD 50 to 200 meters and a decrease in ankle pressure of 15 mm Hg after standard exercise on a treadmill	N=200 40 weeks	Primary: Change from baseline in TWD and PFWD Secondary: Not reported	Primary: Patients receiving either pentoxifylline extended-release or placebo experienced significant increases in TWD and PFWD from baseline after 20 and 40 weeks of treatment (*P*<0.05 and *P*<0.02, respectively). After 20 weeks of treatment, patients randomized to pentoxifylline extended-release had a significant increase in TWD compared to patients who received placebo (221 [254%] vs 155 meters [158%]; *P*<0.05). After 12 months, pentoxifylline extended-release-treated patients continued to have greater improvements in TWD compared to placebo (287 [329.8%] vs 180 meters [183.0%]; *P*<0.02). Compared to placebo, patients receiving pentoxifylline extended-release had significant increases in PFWD after 20 weeks of treatment (155 [360.5%] vs 106 [252.4%]; *P*<0.05). The improvement with pentoxifylline extended-release continued throughout week 40 of the study (166 [386%] vs 155 meters [369%]; *P*<0.02). Secondary: Not reported

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Roekaerts et al[23] Pentoxifylline extended-release 400 mg TID vs placebo	DB, PC, PG, RCT, XO Elderly patients with IC due to peripheral occlusive artery disease with a TWD of 20 to 1,000 meters in the XO group and 80 to 360 meters in the parallel group	N=36 12 and 6 months for the XO and parallel group components of the study, respectively	Primary: Change from baseline in TWD and PFWD Secondary: Not reported	Primary: In the XO component of the study, patients who received pentoxifylline extended-release had significant increases from baseline in MWD after 12 months (two XO periods) compared to placebo (618 [101%] vs 64 meters [9%]; *P*<0.05). The maximum walking time was also significantly improved for patients treated with pentoxifylline extended-release (1,006 [96%] vs 121 seconds [10%]; *P*<0.05). The change from baseline in PFWD was significantly increased for patients who received pentoxifylline extended-release compared to placebo after six months (569 [124%] vs 123 meters [28%]; *P*<0.05). Additionally, the increase in pain-free walking time was greater with pentoxifylline extended-release compared to placebo (1,000 [127%] vs 198 seconds [27%]; *P*<0.05). In the parallel group component of the study, treatment with pentoxifylline extended-release increased MWD and PFWD by 121 and 138%, respectively, compared to placebo (-15 and -25%; *P* values not reported). Additionally, patients who received pentoxifylline extended-release had greater increases in maximum walking time and pain free walking time compared to placebo (123 and 139% vs -14 and -25%, respectively; *P* values not reported). Secondary: Not reported
Dawson et al[24] Cilostazol 100 mg BID vs pentoxifylline extended-release 400 mg TID vs placebo	DB, MC, PC, RCT Patients with moderate to severe symptoms of IC that had been present for ≥6 months with an ABI <0.9 and ≥10 mm Hg decrease in ankle pressure after walking on a treadmill	N=698 24 weeks	Primary: Change from baseline in MWD Secondary: Change from baseline in PFWD, resting Doppler limb pressures and quality of life	Primary: At 24 weeks, the improvements in MWD were significantly greater for patient treated with cilostazol compared to pentoxifylline extended-release (107 vs 64 meters; *P*=0.0005) and placebo (65 meters; *P* value not reported). There was no difference between pentoxifylline extended-release and placebo-treated patients for improvements in MWD (*P*=0.82). After 24 weeks of treatment the number of patients who had unchanged or worsening MWD was lower for patients treated with cilostazol compared to pentoxifylline extended-release and placebo (23 vs 34 and 30%, respectively; *P* value not reported). Secondary: After 24 weeks, treatment with cilostazol significantly increased PFWD from baseline compared to pentoxifylline extended-release (94 vs 74 meters; *P*=0.0001) and placebo (57 meters; *P* value not reported). There was no difference in PFWD between patients receiving pentoxifylline extended-

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				release or placebo (74 vs 57 meters; *P*=0.07). In the affected limb, ABI increased slightly for patients who were treated with cilostazol (0.04) or pentoxifylline extended-release (0.05) but not placebo (-0.01). The increase in pressure in the cilostazol group was significant compared to placebo (*P*<0.01). None of the treatments significantly affected SF-36 scores. Moreover, there was no difference between treatments in regards to WIQ scores for distance or speed. In subjective assessments by patients, more patients treated with cilostazol reported their outcomes as successful relative to baseline compared to patients receiving pentoxifylline extended-release (51 vs 39%; *P*=0.004) and placebo (34%; *P*<0.001).
Ciocon et al[25] Pentoxifylline extended-release 400 mg TID vs ASA 325 mg QD	AC, DB, RCT Patients ≥65 years old experiencing leg claudication with diagnosed peripheral vascular disease, ankle to arm pressure ratio of <0.8 and who were naive to ASA or pentoxifylline for the previous 6 months	N=90 6 weeks	Primary: Change in MWD, VAS scores for level of walking pain and activity levels Secondary: Not reported	Primary: After six weeks of treatment, patients who received pentoxifylline extended-release were able to walk significantly further than patients who received ASA (2.0 vs 1.2 miles; *P*<0.05). There were no differences from baseline in VAS pain scores for patients receiving pentoxifylline extended-release or placebo. Patients in the ASA treatment group had a non-significant decrease in pain scores after six weeks (*P* values not reported). Additionally, there was no change from baseline in level of activity scores in either treatment group (*P* values not reported). Secondary: Not reported
Perhoniemi et al[26] Pentoxifylline extended-release 400 mg TID vs flunarizine* 5 mg TID	AC, DD, RCT, XO Patients aged 45 to 80 with moderate claudication and a MWD of 500 meters	N=31 6 months	Primary: Change from baseline in MWD and PFWD Secondary: Not reported	Primary: During both XO treatment periods, both treatment groups had significantly improved MWD compared to baseline values in the placebo run-in period (values not reported; *P*<0.01 for both comparisons). Furthermore, PFWD was also increased for both treatments compared to baseline, but the improvement was only significant with pentoxifylline extended-release (values not reported; *P*<0.01). There was no significant difference between flunarizine and pentoxifylline extended-release in regards to either MWD or PFWD (*P* values not reported).

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: Not reported
Panchenko et al[27] Pentoxifylline 600 mg QD[†] vs indobufen* 400 mg QD	OL, PG, RCT Patients with a clinical diagnosis of peripheral occlusive artery disease and IC	N=71 6 months	Primary: Change from baseline in MWD and PFWD Secondary: Not reported	Primary: After one month of treatment, MWD was significantly increased from baseline in both the pentoxifylline (44 meters; *P*<0.05) and indobufen (56 meters; *P*<0.001) treatment groups. At three months, improvements in MWD continued to improve for both pentoxifylline and indobufen treatment groups patients (73 and 105 meters, respectively; *P*<0.01 for both comparisons). At the six month final evaluation, indobufen was significantly more effective than pentoxifylline for increasing MWD from baseline in patients with IC (143 [108%] vs 41 meters [35%], respectively; *P*=0.008). After one month of treatment, PFWD was significantly increased from baseline in both the pentoxifylline (28 meters; *P*<0.05) and indobufen (35 meters; *P*<0.001) treatment groups. At three months, improvements in PFWD continued to improve in both the pentoxifylline and indobufen treatment groups (50 and 80 meters, respectively; *P*<0.01 for both comparisons). At the six month final evaluation, pentoxifylline significantly increased the PFWD from baseline (27 meters; *P*<0.001). Patients who received indobufen increased PFWD by 104 meters compared to baseline (*P*<0.01). No direct comparison was made for the change in PFWD between treatment groups after six months. Secondary: Not reported

*Agent not available in the United States.
[†] The formulation of pentoxifylline is unclear and could not be determined from the study evaluated. Studies with the extended-release notation clearly indicated that the extended-release formulation was being used by noting the brand name Trental® which is marketed as the extended-release formulation in the United States.
Drug regimen abbreviations: BID=twice daily, QD=once daily, QID=four times daily, TID=three times daily
Study abbreviations: AC=active-controlled, CI=confidence interval, DB=double-blind, DD=double-dummy, MA=meta-analysis, OL=open label, PC=placebo-controlled, PG=parallel-group, RCT=randomized controlled trial, XO=crossover
Miscellaneous abbreviations: ABI=ankle-brachial index, ABPI=ankle brachial pressure index, ACD=absolute claudication distance, ASA=acetylsalicylic acid, hsCRP=high-sensitivity c-reactive protein, IC=intermittent claudication, I-CAM=intracellular cell-adhesion molecules, ICD=initial claudication distance, mm HG=millimeters of mercury, MWD=maximum walking distance, PCO_2=partial pressure of carbon dioxide, PFWD=pain-free walking distance, SF-36=Medical outcomes study questionnaire 36-item short form, $Tcp0_2$=transcutaneous oxygen, TWD=total walking distance, VAS=visual analog scale, WIQ=walking impairment questionnaire, WMD=weighted mean difference

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Table 5. Special Populations [4,5,8]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Cilostazol	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and efficacy in children have not been established.	In patients with severe renal impairment (creatinine clearance <25 mL/minute), caution is recommended, however, no dosage adjustment required.	Not studied in hepatic dysfunction.	C	Unknown
Pentoxifylline extended-release	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients.* Safety and efficacy in children have not been established.	Dose reductions to 400 mg twice daily in patients with moderate renal dysfunction and to 400 mg once-daily with severe renal dysfunction with close monitoring for toxicities due to metabolite accumulation is recommended.†	No dosage adjustment required.	C	Yes (% unknown)

* No dose adjustment is recommended, however, clinical studies did not include sufficient numbers of patients aged 65 and older.
†Recommended dose per MicroMedex. The package insert states Trental® has not been studied in hepatic or renal dysfunction.

Adverse Drug Events

The most common adverse reactions, as reported in the manufacturer prescribing information, are noted in Table 6. The most frequently reported adverse event in clinical trials of cilostazol was headache, which occurred in 27 to 34% of patients. It was the only adverse event resulting in discontinuation of therapy in≥ 3% of patients.[3] Following headache, diarrhea and abnormal stools were the most commonly reported adverse events. Rare cases of thrombocytopenia or leucopenia have been reported and progressed to agranulocytosis when cilostazol was not immediately discontinued. Agranulocytosis, however, was reversible upon discontinuation of cilostazol. Pentoxifylline extended-release was generally well tolerated in clinical trials. The most commonly reported adverse effects in patients receiving pentoxifylline were nausea, dizziness and dyspepsia. The overall incidence of the other adverse events were similar to placebo.[4]

Table 6. Adverse Drug Events (%)[4,5,8]

Adverse Event	Cilostazol	Pentoxifylline Extended-Release
Cardiovascular		
Angina/chest pain	-	0.3
Arrhythmia/palpitation	5 to 10	1.7*
Congestive heart failure	2	-
Flushing	-	2.3*
Hypotension	-	✔
Tachycardia	2 to 4	✔
Central Nervous System		
Anorexia	-	✔
Dizziness	9 to 10	1.9 to 11.9

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Adverse Event	Cilostazol	Pentoxifylline Extended-Release
Drowsiness	-	1.1*
Headache	27 to 34	1.2
Nervousness	-	1.7*
Thirst	-	✔
Tremor	-	0.3
Vertigo	1 to 3	1 to 3
Digestive System		
Abdominal discomfort	4 to 5	4*
Abnormal stools	12 to 15	-
Constipation	-	✔
Diarrhea	12 to 19	3.4*
Dyspepsia	6	2.8
Flatulence	2 to 3	0.6
Hematemesis	✔	-
Nausea	6 to 7	2.2
Vomiting	-	1.2
Metabolic and Nutritional		
Peripheral edema	7 to 9	✔
Weight change	-	✔
Musculoskeletal		
Back pain	6 to 7	-
Myalgia	2 to 3	-
Ophthalmic		
Blurred vision	-	2.3*
Conjunctivitis	-	✔
Scotoma	-	✔
Respiratory		
Blood in eye	✔	-
Cough	3 to 4	-
Epistaxis	✔	-
Pharyngitis	7 to 10	-
Rhinitis	7 to 12	-
Sore throat	-	✔

* Adverse event reported with pentoxifylline immediate-release formulation, unavailable in the United States.
- Incidence not reported.
✔ Adverse event reported in <2% of cases.

Contraindications/Precautions[4,5,8]

Cilostazol is contraindicated in patients with class III and IV heart failure and the Black Box Warning detailing the contraindication is outlined below. Cilostazol is also contraindicated in patients with haemostatic disorders or active pathologic bleeding, such as bleeding peptic ulcer and intracranial bleeding. Similarly, pentoxifylline extended-release is contraindicated in patients with recent cerebral or retinal hemorrhages, as well as for patients with previous intolerances to methylxanthines such as caffeine and theophylline. There is limited information with respect to the efficacy or safety of the concurrent use of cilostazol and clopidogrel, a platelet-aggregation inhibiting drug indicated for use in patients with peripheral arterial disease. Although it cannot be determined whether there was an additive effect on bleeding times, during concomitant administration with cilostazol and clopidogrel, caution is advised. Patients who are concomitantly taking warfarin and pentoxifylline extended-release should have more frequent monitoring of prothrombin times, while patients with other risk factors complicated by hemorrhage (surgery, ulceration, etc) should have periodic examinations for bleeding, including hematocrit and hemoglobin.

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Black Box Warning for Cilostazol[4]

WARNING
Contraindication Cilostazol and several of its metabolites are inhibitors of phosphodiesterase III. Several drugs with this pharmacologic effect have caused decreased survival compared to placebo in patients with class III-IV congestive heart failure. Cilostazol is contraindicated in patients with congestive heart failure of any severity.

Drug Interactions

Table 7. Drug Interactions[4,5,8]

Generic Name	Interacting Medication or Disease	Potential Result
Antiplatelet agents (all)	Selective serotonin norepinephrine reuptake inhibitors	Concurrent use of selective serotonin norepinephrine reuptake inhibitors and antiplatelet agents may result in an increased risk of bleeding.
Antiplatelet agents (all)	Selective serotonin reuptake inhibitors	Concurrent use of selective serotonin reuptake inhibitors and antiplatelet agents may result in an increased risk of bleeding.
Cilostazol and pentoxifylline	Antiplatelet agents (all)	Concurrent use of cilostazol or pentoxifylline and antiplatelet agents may result in an increased risk of bleeding.
Cilostazol	Strong inhibitors of cytochrome P450 3A4 (i.e., erythromycin and ketoconazole)	Concurrent use of cilostazol and strong cytochrome 3A4 inhibitors may result in an increased risk of cilostazol adverse events. If given with medications that are strong inhibitors of cytochrome 3A4, a cilostazol dose of 50 mg twice daily is recommended.
Cilostazol	Strong inhibitors of cytochrome P450 2C19 (i.e., omeprazole)	Concurrent use of cilostazol and strong cytochrome 2C19 inhibitors may result in increased risk of cilostazol adverse events. If given with medications that are strong inhibitors of cytochrome 2C19, a cilostazol dose of 50 mg twice daily is recommended.
Cilostazol	Ginkgo biloba	Concurrent use of cilostazol and ginkgo biloba may result in an increased risk of bleeding.
Pentoxifylline	Non-steroidal anti inflammatory agents	Concurrent use of pentoxifylline and non-steroidal anti inflammatory agents may result in an increased risk of bleeding.
Pentoxifylline	Cimetidine	Concurrent use of pentoxifylline and cimetidine may result in pentoxifylline toxicity.
Pentoxifylline	Insulin	Concurrent use of pentoxifylline and insulin may result in an increased risk of hypoglycemia.
Pentoxifylline	Theophylline	Concurrent use of pentoxifylline and theophylline may result in an increased risk of theophylline toxicity.
Pentoxifylline	Warfarin	Concurrent use of pentoxifylline and warfarin may result in an increased risk of bleeding.

Dosage and Administration

Cilostazol should be administered at least half an hour before or two hours after breakfast and dinner. A dose of 50 mg twice daily should be considered during coadministration with inhibitors of cytochrome P450 3A4 such as erythromycin, diltiazem and ketoconazole, and during coadministration with inhibitors of cytochrome P450 2C19 such as omeprazole. Pentoxifylline extended-release should be administered three times daily in conjunction with meals in order to reduce the risk of gastrointestinal adverse events. Patients may respond as early as two to four weeks after the initiation of therapy, but treatment for eight to 12 weeks may be needed before a beneficial effect is experienced.

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Table 8. Dosing and Administration[4,5,8]

Generic Name	Adult Dose	Pediatric Dose	Availability
Cilostazol	Intermittent claudication: Tablet: initial, 50 to 100 mg BID; maintenance, 100 mg BID	Safety and efficacy in children have not been established.	Tablet: 50 mg 100 mg
Pentoxifylline extended-release	Intermittent claudication: Extended-release tablet: initial, 400 mg BID* or TID; maintenance, 400 mg TID	Safety and efficacy in children have not been established.	Extended-release tablet: 400 mg

BID=twice daily, TID=three times daily
*Dosing of 400 mg BID is only recommended for patients who experience central nervous system or gastrointestinal side effects, and should not be used as maintenance dosing for most patients.

Clinical Guidelines

Table 9. Clinical Guidelines

Clinical Guideline	Recommendations
The American College of Chest Physicians: **Antithrombotic Therapy for Peripheral Artery Occlusive Disease: Evidence-Based Clinical Practice Guidelines 8TH Edition (2008)**[10]	Chronic limb ischemia and intermittent claudication • In peripheral artery disease, patients with clinically manifest coronary or cerebrovascular disease, lifelong antiplatelet therapy in comparison to no antiplatelet therapy is recommended. • In those without clinically manifest coronary or cerebrovascular disease, aspirin (75 to 100 mg/day) is recommended over clopidogrel. In patients who are aspirin intolerant, treatment with clopidogrel over ticlopidine is recommended. • In patients with peripheral artery disease and intermittent claudication, the use of anticoagulants to prevent vascular mortality or cardiovascular events is not recommended. • For patients with moderate-to-severe disabling intermittent claudication who do not respond to exercise therapy, and who are not candidates for surgical or catheter-based intervention, treatment with cilostazol is recommended. • Cilostazol should not be used in those with less-disabling claudication. Because of the cost of cilostazol therapy, and the safety and efficacy of an exercise program, cilostazol treatment should be reserved for patients with moderate to severe claudication who have tried and failed an exercise program and are not candidates for vascular surgical or endovascular procedures. The use of pentoxifylline is not recommended. • For patients with intermittent claudication, the use of anticoagulants is not recommended. • For patients with limb ischemia, the use of prostaglandins is not recommended. • In patients who suffer from acute arterial emboli or thrombosis, immediate systemic anticoagulation with unfractionated heparin, over no anticoagulation is recommended. In patients undergoing embolectomy systemic anticoagulation with unfractionated heparin with long-term anticoagulation with vitamin K antagonists is recommended. • In patients with short-term (<14 days) thrombotic or embolic disease, intraarterial thrombolytic therapy is recommended, provided patients are at low risk of myonecrosis and ischemic nerve damage developing during the time to achieve revascularization by this method. • For patients undergoing major vascular reconstructive procedures, intravenous unfractionated heparin, prior to the application of vascular cross clamps is recommended. • For all patients undergoing infrainguinal arterial reconstruction, aspirin (75 to 100 mg, begun preoperatively) is recommended. The use of

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Clinical Guideline	Recommendations
	perioperative dextran, heparin, or long-term anticoagulation with vitamin K antagonists for all extremity reconstructions is not routinely recommended. • For patients receiving routine autogenous vein infrainguinal bypass, aspirin (75 to 100 mg, begun preoperatively) is recommended. The routine use of vitamin K antagonists is not recommended in patients undergoing infrainguinal vein bypass. For those at high risk of bypass occlusion and limb loss, vitamin K antagonists plus aspirin should be used. • For patients receiving routine prosthetic infrainguinal bypass, aspirin (75 to 100 mg, begun preoperatively) is recommended and the routine use of vitamin K antagonists in patients undergoing prosthetic infrainguinal bypass is not recommended. • In patients undergoing carotid endarterectomy, aspirin, 75 to 100 mg, given preoperatively to prevent perioperative ischemic neurologic events is recommended. Lifelong postoperative aspirin (75 to 100 mg/day) is recommended. • In non-operative patients with asymptomatic carotid stenosis (primary or recurrent), lifelong aspirin, 75 to 100 mg/day is recommended. In this patient group, dual antiplatelet therapy with aspirin and clopidogrel is not recommended.
The Trans-Atlantic Inter-Society: **Consensus Document on the Management of Peripheral Artery Disease (2007)**[27]	• Supervised exercise should be made available as part of the initial treatment for all patients with peripheral arterial disease. • The most effective programs employ treadmill or track walking that is of sufficient intensity to bring on claudication, followed by rest, over the course of a 30 to 60 minute session. Exercise sessions are typically conducted three times a week for three months. • A three to six month course of cilostazol should be first-line pharmacotherapy for the relief of claudication symptoms, as evidence shows both an improvement in treadmill exercise performance and in quality of life. • While early trials of pentoxifylline were positive on the endpoint of improvement in treadmill exercise performance, later studies demonstrated that pentoxifylline was no more effective than placebo for improving treadmill walking distance or functional status assessed by questionnaires. Several meta-analyses have concluded that the drug is associated with modest increases in treadmill walking distance over placebo, but the overall clinical benefits were questionable. The clinical benefits of pentoxifylline in improving patient assessed quality of life have not been extensively evaluated. • Naftidrofuryl* can also be considered for treatment of claudication symptoms as it has shown benefit on treadmill performance and quality of life in studies of patients with intermittent claudication. • L-carnitine and propionyl-L-carnitine interact with skeletal muscle oxidative metabolism, and these drugs are associated with improved treadmill performance. Propionyl-L-carnitine (an acylform of carnitine) was more effective than L-carnitine in improving treadmill walking distance. • Aspirin and other antiplatelet agents (clopidogrel) are important in the long-term treatment of patients with peripheral artery disease to reduce their risk of cardiovascular events with well established efficacy. However, no studies have shown a benefit of antiplatelet or anticoagulant drugs in the treatment of claudication. • Arteriolar vasodilators were the first class of agents used to treat claudication, including drugs that inhibit the sympathetic nervous system (alpha blockers), direct-acting vasodilators (papaverine), β_2-adrenergic

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Clinical Guideline	Recommendations
	agonists (nylidrin*), calcium channel blockers (nifedipine) and angiotensin-converting enzyme inhibitors. These drugs have not been shown to have clinical efficacy in randomized, controlled trials. • L-arginine has the ability to enhance endothelium-derived nitric oxide and, thus, improve endothelial function. One study of nutritional supplementation with L-arginine improved pain-free but not peak walking time. However, a recent study of L-arginine treatment in acute myocardial infarction showed no clinical benefit and excess mortality.
The American College of Cardiology/American Heart Association: **Practice Guidelines for the Management of Patients with Peripheral Artery Disease (2005)**[9]	Exercise and lower extremity peripheral artery disease rehabilitation • A program of supervised exercise training is recommended as an initial treatment modality for patients with intermittent claudication. • Supervised exercise training should be performed for a minimum of 30 to 45 minutes, in sessions performed at least three times/week for a minimum of 12 weeks. • The usefulness of unsupervised exercise programs is not well established as an effective initial treatment modality for patients with intermittent claudication. Medical and pharmacological treatment for claudication • Cilostazol (100 mg orally twice daily) is indicated as an effective therapy to improve symptoms and increase walking distance in patients with lower extremity peripheral artery disease and intermittent claudication (in the absence of heart failure). • A therapeutic trial of cilostazol should be considered in all patients with lifestyle-limiting claudication (in the absence of heart failure). • Pentoxifylline (400 mg three times daily) may be considered as second-line alternative therapy to cilostazol to improve walking distance in patients with intermittent claudication. • The clinical effectiveness of pentoxifylline as therapy for intermittent claudication is marginal and not well established. • The effectiveness of L-arginine for patients with intermittent claudication is not well established. • The effectiveness of propionyl L-carnitine as a therapy to improve walking distance in patients with intermittent claudication is not well established. • The effectiveness of ginkgo biloba as a therapy to improve walking distance in patients with intermittent claudication is not well established. • Oral vasodilator prostaglandins such as beraprost* and iloprost are not effective medications to improve walking distance in patients with intermittent claudication. • Vitamin E is not recommended as a treatment for patients with intermittent claudication. • Chelation (e.g. ethylenediaminetetraacetic acid) is not indicated for treatment of intermittent claudication and may have harmful adverse effects.

*Agent not currently available in the United States.

Conclusions

Intermittent claudication is one of the most frequent symptoms of peripheral artery disease, often presenting with pain, aches, cramping and numbness in the lower extremities, and significantly limiting patient mobility and quality of life.[2] The two medications currently approved by the Food and Drug Administration (FDA) for this indication include cilostazol and pentoxifylline extended-release, both which are available generically. The immediate-release formulation of pentoxifylline is not available in the United States and has only been used in clinical trials. The recommended dose for cilostazol is 100 mg twice

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daily, while pentoxifylline extended-release is given as 400 mg three times daily.[4,5,8] Both agents have been used off-label in other cardiovascular conditions. The labeling for cilostazol contains a Black Box Warning concerning its use in patients with class III or IV heart failure. Other drugs that inhibit phosphodiesterase have been shown to decrease survival in patients with heart failure, but cilostazol specifically has not.[4]

Current evidence supports the use of cilostazol for the treatment of intermittent claudication, while the evidence for pentoxifylline extended-release is conflicting. A meta-analysis including eight studies of cilostazol found that treatment with cilostazol increased the maximum walking distance (MWD) by 44 to 50% and increased pain-free walking distance by 60 to 67%, both compared to placebo.[11] In a large meta-analysis of 11 trials, pentoxifylline was shown to increase pain-free walking distance in patients with intermittent claudication by approximately 30 meters. When studies lasting ≤13 weeks were excluded, there was no difference between pentoxifylline extended-release and placebo in regards to pain-free walking distances.[7] Other studies have shown that pentoxifylline extended-release increases initial claudication distance and absolute claudication distance, but the doses used were typically above the approved dosing, or had a small sample size.[18-22] Pentoxifylline extended-release does increase maximum walking distance and absolute claudication distance from baseline; however, due to the high percentage of improved placebo-treated patients, the differences were not significant. In the only study to directly compare cilostazol, pentoxifylline extended-release and placebo, there were no differences in maximum walking distance between patients receiving pentoxifylline extended-release and placebo.[13]

According to current guidelines by the American College of Chest Physicians, cilostazol should be used in patients with moderate-to-severe disabling intermittent claudication who do not respond to exercise therapy, and who are not candidates for surgical or catheter-based intervention.[10] This recommendation is based on the cost of therapy and the documented efficacy of exercise regimens. Additionally, the organization recommends against the use of pentoxifylline in patients with intermittent claudication. Similarly, the American College of Cardiology recommends the use of cilostazol to improve symptoms and increase walking distance in patients with lower extremity peripheral artery disease and intermittent claudication (in the absence of heart failure). The organization also recommends that pentoxifylline be considered as second-line alternative therapy to cilostazol to improve walking distance in patients with intermittent claudication, although the clinical effectiveness of pentoxifylline is not well established.[9] The Trans-Atlantic Inter-Society notes that early studies of pentoxifylline were promising, but more recent studies showed it was no more efficacious than placebo. [27]

Appendix I: Utilization Within This Drug Class for DVHA: October 1, 2010 to March 31, 2011

Medication	Unique utilizers	# of Rx's	Market Share (%)	Plan Cost $	Avg $/Rx
Cilostazol	32	55	64%	$2,755.68	$50.10
Pentoxifylline ER	17	31	36%	$1,116.13	$36.00
Class Total:	**----**	**86**	**100%**	**$3,871.81**	**$45.02**

Recommendations

In recognition of the role of cilostazol and pentoxifylline extended-release for improving walking distances in patients with intermittent claudication, comparable safety profiles between the agents, the availability of generics, and low utilization within the class, the creation of a new managed category is not recommended. Cilostazol is currently listed as preferred in the "Platelet Aggregation Inhibitors" managed category. Pentoxifyline extended-release is available without restrictions.

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