TERESA L. CARMAN, MD*
Section of Vascular Medicine
Department of Cardiovascular Medicine
Cleveland Clinic, Cleveland, OH

BERNARDO B. FERNANDEZ, JR., MD*
Section of Vascular Medicine
Department of Cardiovascular Medicine
Cleveland Clinic Florida, Weston, FL

Contemporary management of peripheral arterial disease: II. Improving walking distance and quality of life

ABSTRACT

Intermittent claudication (IC) is the classic complaint associated with peripheral arterial disease (PAD) and can significantly limit a patient's lifestyle and workplace abilities. IC is defined as reproducible pain affecting the muscles of the lower extremities that begins and increases with activity and resolves with rest. The clinical goals of management include increasing walking distance and improving quality of life. A dedicated, supervised walking program is the foundation of IC management. In addition, two drugs have been approved by the US Food and Drug Administration for the treatment of IC: cilostazol and pentoxifylline. Other agents and treatment strategies have been investigated, and some show clinical promise.

Intermittent claudication (IC) is the classic symptom associated with peripheral arterial disease (PAD). It is defined as activity-induced, reproducible symptoms of ischemia affecting the muscles of the calves, thighs, or buttocks. IC may be described as fatigue, aching, burning, numbness, weakness, or clumsiness of the limb that begins and increases with exertion. Upon rest, the symptoms of IC resolve within approximately 5 to 10 minutes.

Depending on its severity, IC may limit patients' lifestyles and vocational abilities. For this reason, patients with PAD deserve a comprehensive approach to IC management. Dedicated exercise as well as pharmacologic therapy may improve the symptoms of IC. This article reviews the roles of exercise programs and approved medications for the management of IC and surveys evidence on emerging treatment options.

PATHOGENESIS OF IC: AN ACCUMULATION OF ANAEROBIC BYPRODUCTS

With exertion, as the metabolic requirement of the muscle increases, the impaired lower extremity blood flow in a patient with PAD cannot supply sufficient oxygen and glucose to support aerobic metabolism. This allows anaerobic byproducts to accumulate and results in the IC symptoms of muscle pain and fatigue.

HOW IS IC THERAPY ASSESSED?

Measured variables such as pain-free walking distance and maximal walking distance can be assessed and may improve with medical therapy. In addition, subjective quality-of-life measures have been shown to improve in many clinical studies of IC-related treatment. However, clinically meaningful improvement in walking distance and physical functioning is highly subjective and patient-dependent. For this reason, goal-directed medical therapy cannot be overemphasized.

EXERCISE: THE FOUNDATION OF IC THERAPY

A dedicated and supervised exercise program is of paramount importance for improving walking distance in patients with IC. Although such programs are underutilized, they should serve as the foundation for the medical management of IC. Moreover, patients may derive additional benefits from exercise independent of any functional improvements, such as lipid-lowering, glucose-lowering, and blood pressure-lowering effects.

Benefit of exercise may involve a training effect

The mechanism by which exercise rehabilitation improves walking distance is not entirely clear but appears to be related to a training effect. It has been suggested that the periods of intermittent hypoxia induced by ischemia during exercise may initiate adaptive responses within muscle.[1] These responses may include loss of muscle mass and generalized muscle wasting as well as changes in muscle fiber type. Several metabolic adaptations related to oxidative metabolism, with increased aerobic capacity and diminished anaerobic glycolysis, have also been demonstrated.[1]

Regular exercise also may promote improvement in collateral flow to the ischemic muscles. This is demonstrated by collateral development in patients with chronic occlusions. These collaterals are generally believed to represent further development of preexisting vessels due to pressure gradients across areas of occlusion

* Dr. Carman reported that she has received honoraria for teaching and speaking from Bristol-Myers Squibb and Sanofi-Aventis. Dr. Fernandez reported that he has received honoraria for teaching and speaking from Otsuka America Pharmaceutical.

TABLE 1
Results and recommendations from two meta-analyses of exercise programs for patients with intermittent claudication (IC)

Authors	No. studies	Key findings on effects of exercise rehabilitation	Recommended characteristics of a program for maximal improvement
Gardner/ Poehlman[3]	21	Increased mean distance to onset of IC pain by 179%, from 125.9 ± 57.3 m at baseline to 351.2 ± 188.7 m* Increased mean distance to maximal IC pain by 122%, from 325.8 ± 148.1 m at baseline to 723.3 ± 591.5 m*	• Supervised • Duration of 6 months or more • Use of walking as sole mode of exercise • 3 or more sessions per week lasting > 30 min each • Walking to the point of near-maximal pain
Bulmer/ Coombes[4]	22	Produced median improvement of 119% in pain-free walking ability (range, 14% to 276%) Produced median improvement of 83% in absolute walking ability (range, 23% to 210%)	• Supervised • Duration of 20 weeks or more • Use of intermittent-intensity treadmill walking at a pain-free threshold • 3 sessions per week lasting 45 min each

* $P < .001$

promoting hypertrophy of existing vessels rather than the development of new arteries.[2] Exercise training has also been shown to increase the number of mitochondria and capillaries in trained muscles, which may allow for increased cellular oxygen extraction, increased aerobic metabolism, and a reduction in anaerobic glycolysis.[2] Nevertheless, although many patients may derive symptom improvement from an exercise program, changes in blood flow using the ankle-brachial index and other means of measurement rarely document improvement.

Supervised, frequent, and sustained walking programs improve functionality

Many different forms of exercise rehabilitation, such as walking, polestriding (a form of walking with poles similar to cross-country skiing without the skis), resistance training, exercise cycling, and stair-climbing, have been investigated. Moreover, studies have used many different protocols, which makes interpretation of this large body of data somewhat difficult. Nevertheless, two large meta-analyses of clinical trials that used exercise rehabilitation for the treatment of IC have found substantial mean and median improvements in walking ability across 21 and 22 studies, respectively, following exercise rehabilitation (Table 1).[3,4] The authors of each meta-analysis concluded by identifying the components of an exercise program that had the greatest impact on improving walking performance, as also outlined in Table 1. Consistent with these meta-analyses, a recent prospective study among patients with PAD showed that self-directed walking exercise was associated with significantly less functional decline when performed at least three times weekly compared with only one to two times a week.[5]

All patients with PAD should be encouraged to exercise. For PAD patients with IC, the above two meta-analyses specifically support the utility of a walking program consisting of at least 3 sessions per week that ideally last 45 minutes per session. Supervised walking programs have demonstrated superior performance over unsupervised programs. Referral to a supervised PAD rehabilitation program, when available, is preferred over a self-directed walking program, and supervised programs now have a specific Current Procedural Terminology code (CPT 93668) for reimbursement.

What is the best level of exercise intensity?

The required level of exercise intensity remains somewhat unclear. In our experience, asking patients to walk to near-maximal pain may hamper participation, since repeated pain and discomfort may limit patients' adherence. We find that asking patients to walk past the point of initial onset of claudication symptoms is a good alternative, as this still allows for hypoxic stimulation to the muscles without causing undue distress.

APPROVED PHARMACOLOGIC THERAPIES

Beyond the foundational role of exercise in the management of IC, two pharmacologic agents have received US Food and Drug Administration (FDA) approval for the treatment of IC: cilostazol and pentoxifylline. Each agent should be used in conjunction with a supervised exercise program as well as with cardiovascular risk-factor modification and antiplatelet therapy, as discussed in the preceding article in this supplement.

The recently published practice guidelines for PAD

management from the American College of Cardiology and American Heart Association recommend cilostazol as an effective therapy for improving symptoms and increasing walking distance in patients with PAD and IC, and they recommend pentoxifylline as a second-line alternative to cilostazol.[6]

Cilostazol: Effects and dosing considerations

Cilostazol is a reversible phosphodiesterase 3 inhibitor that increases available cyclic adenosine monophosphate (c-AMP). The agent's mechanism of action for increasing walking distance in patients with IC is poorly understood but appears to relate to its c-AMP–mediated vascular properties. Cilostazol has vasodilatory effects, antiplatelet properties, and vascular antiproliferative effects.[7] It also reduces serum triglycerides and increases high-density lipoprotein cholesterol while exerting no effects on low-density lipoprotein cholesterol or lipoprotein(a).[8,9]

The recommended dose of cilostazol is 100 mg orally twice daily, to be taken on an empty stomach. Common side effects include gastrointestinal complaints, including nausea or change in stool characteristics (incidence of approximately 15% for each), headache (approximately 30% incidence), and palpitations (9% incidence).[10] The impact of these side effects may be lessened by reducing the starting dose to 50 mg twice daily for several weeks before increasing to the full dose. This regimen may also prove useful in elderly patients, who seem particularly vulnerable to side effects. For many patients, side effects abate with continued use of the medication.

Patients should avoid grapefruit juice when taking cilostazol. Dose reduction should be considered in patients who are also taking drugs metabolized by the cytochrome P-450 isoenzymes (including omeprazole, erythromycin, ketoconazole, and diltiazem), as these may reduce cilostazol metabolism. Because several other phosphodiesterase inhibitors have been associated with decreased survival in patients with heart failure, cilostazol should not be used in patients with any severity of heart failure. No recommendations exist for patients known to have a decreased ejection fraction without evidence of heart failure. Whether these patients should be permitted to use the drug is unknown. To date no excess cardiovascular morbidity or mortality has been associated with cilostazol.[10] However, since other drugs are available and may be useful for IC, cilostazol may be best avoided in patients with a decreased ejection fraction.

Because of its antiplatelet properties, cilostazol has been demonstrated to prolong bleeding time.[11] In one small study, when cilostazol was combined with aspirin, clopidogrel, or both, the bleeding time was significantly prolonged.[11] While this effect has not been shown to have clinical significance in trials, discontinuing cilostazol prior to surgery or other procedures may be prudent. Cilostazol should also be withheld in patients at increased risk for bleeding or in those experiencing a bleeding event.

Pentoxifylline: Effects and dosing considerations

Pentoxifylline, a methylxanthine derivative, was approved by the FDA for the treatment of IC in 1984. Although its mechanism of action is poorly understood, it is thought to function via intracellular c-AMP phosphodiesterases. Pentoxifylline displays hemorrheologic effects including decreased blood viscosity, increased red blood cell and leukocyte deformability, reduced platelet adhesion, inhibition of neutrophil adhesion and activation, and possibly reduced fibrinogen concentrations.[6,7,12]

The recommended dose is 400 mg orally three times daily, to be taken with food. Gastrointestinal complaints are the most common side effects.[7,12] Pentoxifylline is metabolized in the liver, although the primary compound and metabolites are excreted in the urine.[12] Caution in dosing is indicated in patients with hepatic impairment or decreased renal excretion.[7,12]

Clinical trials

Cilostazol vs placebo. Several trials have compared cilostazol with placebo in patients with IC. All of them have demonstrated improvement in walking distance (both maximal walking distance and pain-free walking distance) with cilostazol. Many of the trials also have evaluated health-related quality-of-life measures using validated, self-reported questionnaires including the Walking Impairment Questionnaire (WIQ) and the Medical Outcomes Short Form-36 (SF-36).

The results of these studies are reflected in two recently published meta-analyses of randomized, placebo-controlled trials that used both treadmill walking protocols and quality-of-life questionnaires to assess cilostazol's effects.[9,13] Two dosages of cilostazol were examined—50 mg twice daily and 100 mg twice daily.

One meta-analysis included eight trials and demonstrated significantly greater increases from baseline in both maximal walking distance and pain-free walking distance with both cilostazol dose groups relative to placebo (Table 2).[9]

The other meta-analysis included six phase 3 trials and reported its results according to whether the studies used graded or constant-load treadmill protocols (graded protocols, in which the treadmill speed and/or

TABLE 2
Improvement in walking distance in a meta-analysis of eight placebo-controlled trials of cilostazol[9]

Treatment	Increase in MWD	Increase in PFWD
Placebo	21%	40%
Cilostazol 50 mg bid	44%*	60%*
Cilostazol 100 mg bid	50%*	67%*

MWD = maximal walking distance; PFWD = pain-free walking distance
* $P < .05$ vs placebo

incline are increased during the protocol, are more demanding and typically demonstrate smaller improvements than do constant-load protocols, which use a fixed incline and speed).[13] In studies using a graded protocol, patients taking cilostazol 100 mg twice daily had a 40% increase in maximal walking distance compared with a 20% increase for placebo recipients ($P < .0001$); results were similar for pain-free walking distance ($P < .0001$ for the difference vs placebo). In studies using a constant-load protocol, maximal walking distance increased 76% in patients taking cilostazol 100 mg twice daily compared with 20% in those taking placebo ($P < .0001$); again, results were similar for pain-free walking distance ($P < .0001$). Patients randomized to cilostazol 50 mg twice daily also demonstrated improvement relative to placebo in all the evaluated parameters, but improvement was less than with the 100-mg regimen.

Both meta-analyses showed statistically significant improvements with cilostazol relative to placebo on self-reported WIQ measures of walking distance, walking speed, stair-climbing ability, and pain severity.[9,13]

Pentoxifylline vs placebo. Although the tolerability of pentoxifylline is generally good, it has been suggested that its therapeutic benefit may not be considerably greater than that of placebo.[14,15] However, a meta-analysis of 11 randomized, placebo-controlled, double-blind trials in patients with IC found that pentoxifylline increased treadmill-measured pain-free walking distance by an average of 30 meters and increased absolute claudication distance by approximately 48 meters relative to placebo.[16] The authors cautiously pointed out that 30 meters of treadmill walking is equivalent to 90 meters of walking on flat ground, suggesting that pentoxifylline may play a role in increasing functional walking distance in patients with IC.[16]

TABLE 3
Results from a 24-week comparative trial of cilostazol and pentoxifylline in moderate to severe IC[15]

Treatment	Increase in MWD (m)	Pts with > 50% increase in MWD	Increase in PFWD (m)	Pts with symptoms worsened/ unchanged
Placebo (n = 239)	65	27%	57	30%
Cilostazol 100 mg bid (n = 227)	107*	41%	94†	23%
Pentoxifylline 400 mg tid (n = 232)	64‡	27%	74‡	34%

IC = intermittent claudication; MWD = maximal walking distance; PFWD = pain-free walking distance
* $P < .001$ vs placebo and vs pentoxifylline
† $P < .001$ vs placebo and $P = .02$ vs pentoxifylline
‡ Not significantly different from placebo

Direct comparative trial. One randomized, double-blind, multicenter trial has directly compared cilostazol, pentoxifylline, and placebo in patients with moderate to severe IC.[15] As detailed in Table 3, cilostazol was associated with significantly greater increases in both maximal and pain-free walking distance at 24 weeks compared with both placebo and pentoxifylline, whereas the increases with pentoxifylline were not significantly different from those with placebo. Moreover, cilostazol recipients were more likely to have a greater than 50% improvement in walking distance and less likely to have their IC symptoms worsen or remain the same compared with both the placebo and pentoxifylline groups (Table 3). None of the treatments significantly affected patients' responses on the SF-36 or the WIQ instruments relative to baseline.[15]

Response may take several months

For both cilostazol and pentoxifylline, therapeutic benefit appears to have a relatively slow onset and improvement in function and walking distance increases over time. Most trials have evaluated improvement at 4, 12, 16, and 26 weeks of therapy. It is important to stress to patients that these medications take several months to yield improvement. Most clinicians favor a minimum of 12 weeks of therapy before declaring a patient unresponsive to one of these drugs.

As indicated above, not all patients will demonstrate

improvement. One small trial evaluated the effects of withdrawal of cilostazol or pentoxifylline in patients with IC.[17] In this study, the cilostazol (n = 16), pentoxifylline (n = 13), and placebo (n = 16) recipients all demonstrated increases from baseline in pain-free and maximal walking distance over a 24-week period; however, none of these increases was statistically significant, likely owing to the small numbers of patients enrolled. Following completion of the 24-week treatment period, the cilostazol and pentoxifylline groups were treated with placebo for 6 weeks. After withdrawal of therapy, the cilostazol group lost 49% of the improvement in walking distance that had been gained during therapy, whereas no change after crossover was seen in the pentoxifylline or placebo groups. The authors concluded that patients who respond to cilostazol will likely suffer decreased walking performance after withdrawal of the drug, returning to near-baseline walking distances, while patients whose symptoms have not improved with pentoxifylline should be withdrawn from therapy.[17] In addition, although subjective reporting of improvement is helpful, objectively documenting improvement using treadmill-based protocols may be beneficial.[17]

THERAPIES UNDER ONGOING INVESTIGATION FOR IC

In addition to the two FDA-approved therapies for IC, several other therapies and treatment strategies show promise for improving IC symptoms and walking performance in patients with PAD.

Statins

In addition to their role in reducing cardiovascular events in patients with PAD (see preceding article), the HMG-CoA reductase inhibitors ("statins") have demonstrated beneficial effects in terms of increasing walking distance and improving leg function in patients with PAD in a small number of trials.

In a study of 60 patients, simvastatin increased the time to onset of IC symptoms compared with placebo at both 6 and 12 months.[18] In another trial, conducted among 86 patients with IC, those randomized to simvastatin 40 mg/day had a statistically significant increase in pain-free and maximal walking distance at 6 months compared with those randomized to placebo.[19]

Another research team randomized 354 patients with IC to placebo or to atorvastatin 10 mg or 80 mg daily and found that pain-free walking time increased by 63% after 12 months in patients taking atorvastatin 80 mg/day compared with 38% in placebo recipients ($P = .025$).[20] Differences in the increase in maximal walking time did not reach statistical significance, however, and no significant differences were noted in the ankle-brachial index (ABI) or in SF-36 or WIQ scores.[20]

In a study of 641 men and women with and without PAD, those subjects who were taking statins had significantly better performance on tests of 6-minute walk distance and 4-meter walking velocity and a significantly better summary performance score than did the subjects who were not taking statins.[21] Among the 392 subjects with PAD (ABI < 0.90), statin use was associated with improvements in 4-meter walking velocity and in the summary performance score after adjusting for confounding variables.[21]

Although the precise mechanism by which statins may increase exercise tolerance and improve walking ability remains unknown, it likely relates to the statins' pleiotropic effects on vascular endothelium, which extend far beyond lipid reduction. It is likely that many of these effects may play a role in PAD.[22]

ACE inhibitors

Angiotensin-converting enzyme (ACE) inhibitors also may benefit patients with PAD by improving endothelial function. Few studies have investigated ACE inhibitors for IC, however, and all have been small. In the most recent trial, a 24-week randomized study among 40 patients with symptomatic PAD, ramipril 10 mg/day was associated with significant increases in mean pain-free walking time and maximal walking time compared with placebo.[23]

Therapeutic angiogenesis

Therapeutic angiogenesis has been shown to promote collateral blood vessel formation and improve blood flow. Trials using vascular endothelial growth factor (VEGF) gene transfer began in 1994. Since then, a number of differently engineered and recombinant angiogenic growth factors, including VEGF, basic fibroblast growth factor, hepatocyte growth factor, and hypoxia-inducible factor-1, have been studied, both in critical limb ischemia and in IC. Unfortunately, clinical outcomes have not been overwhelmingly positive, and some trials have been confounded by significant side effects such as skin rash, edema, and proteinuria.[6,7,14,24]

The only study to date to demonstrate some positive results, the TRAFFIC trial,[25] investigated the use of recombinant fibroblast growth factor-2 (rFGF-2). The study randomized 190 patients to placebo or either single-dose or double-dose intra-arterial infusion of rFGF-2. The single-dose arm demonstrated a significant increase in peak walking time at 90 days relative to the placebo arm, but this difference was not maintained at 180 days. Moreover, the time to onset of IC symptoms was not different between the treat-

ment arms and no subjective differences were identified using the WIQ or SF-36 questionnaires.

Trials of therapeutic angiogenesis are continuing and are using a variety of vectors and transfer methods.

L-Carnitine and propionyl-L-carnitine

L-Carnitine and propionyl-L-carnitine have been investigated for IC in several studies and appear to enhance skeletal muscle metabolism. Both compounds have been shown to improve exercise performance, increase pain-free and maximal walking time, and increase muscle strength in patients with PAD.[26–28] No serious adverse events have been documented with either compound. In a 6-month randomized study comparing propionyl-L-carnitine (2 g/day orally) with placebo in 155 patients with IC, time to onset of claudication increased by 39% from baseline in the propionyl-L-carnitine group compared with 14% in the placebo group ($P < .001$).[27] Peak walking time also improved significantly more with propionyl-L-carnitine.[27] Treatment with propionyl-L-carnitine also significantly improved WIQ assessments of perceived walking distance and speed as well as SF-36 assessments of physical role functioning, bodily pain, and transition to a better health state.[27] Propionyl-L-carnitine therapy remains under investigation for IC and PAD.

L-Arginine

L-Arginine, a substrate for nitrous oxide synthase, is a precursor of endothelium-derived nitrous oxide, a potent endogenous vasodilator. It also appears to be a competitive inhibitor of asymmetric dimethylarginine, a nitric oxide synthase inhibitor.[29,30] Supplementation with L-arginine (by intravenous infusion and orally) has been investigated in patients with IC, but results have been inconsistent. A recent pilot study evaluated 3-g, 6-g, and 9-g L-arginine supplements along with placebo in patients with PAD and demonstrated improvement in both pain-free and maximal walking distance in all groups, including the placebo group. The 3-g dose group had the greatest improvement in maximal walking distance, and this dose is expected to serve as a foundation for future investigations.[29]

OTHER INVESTIGATED THERAPIES

Prostaglandin derivatives have undergone trials for IC and critical limb ischemia. Amendt recently published a meta-analysis of 13 prospective, randomized, controlled trials evaluating prostaglandins in patients with IC.[31] Nine of the studies employed intravenous or intra-arterial infusion of prostaglandin E_1 (PGE_1), and four studies used the oral agents beraprost, iloprost, or AS-013 (an oral PGE_1 prodrug). PGE_1 was more effective than the other prostaglandins and placebo in increasing pain-free walking distance and maximal walking distance. However, intravenous or intra-arterial infusion therapy is clinically impractical and further study may be warranted.

Two of the studies in this meta-analysis evaluated oral beraprost in comparison with placebo. In one trial, patients who were randomized to 6 months of beraprost therapy (n = 209) demonstrated statistically significantly greater increases in both pain-free and maximal walking distance compared with patients randomized to placebo (n = 213).[32] These results, however, were not confirmed by a larger subsequent placebo-controlled trial.[33] In addition, anticipated adverse events related to the prostanoid, such as headache, vasodilation, diarrhea, pain, and nausea, were statistically more frequent in the beraprost group than in the placebo group.[33]

Further investigation of prostaglandins for IC is required before their use can be endorsed.

Naftidrofuryl and buflomedil are approved for the treatment of IC in Europe but are not currently available in the United States. Naftidrofuryl (nafronyl oxalate) is a serotonin antagonist; buflomedil is an alpha$_1$/$_2$-adrenergic antagonist. In a meta-analysis of six randomized, blinded clinical trials, naftidrofuryl demonstrated a significant increase in pain-free and maximal walking distance relative to placebo.[34]

Immunomodulation therapy has been explored in light of findings that patients with PAD have elevated serum markers of inflammation including high-sensitivity C-reactive protein (hs-CRP), interleukin-6, monocyte chemoattractant protein-1, and soluble intercellular adhesion molecule type-1.[35,36] The SIMPADICO trial investigated a novel immunomodulation therapy for the treatment of IC. While hs-CRP levels were reduced in patients following therapy, there were no changes in pain-free or maximal treadmill walking distance or in quality-of-life measures.[37]

Other experimental therapies. Chelation therapy, anticoagulation, vitamin E, ginkgo biloba, ketanserin, glutathione, policosanol, ticlopidine, calcium channels blockers such as verapamil and nifedipine, and many other therapies have been investigated in patients with IC.[6,7,14,38] At this time, none of these agents is advocated for the treatment of IC.

SUMMARY

Exercise rehabilitation with a supervised treadmill walking program should serve as the foundation for the comprehensive medical management of IC. In addition, two drugs, cilostazol and pentoxifylline, have

been FDA-approved for the treatment of IC in conjunction with an exercise program. Favorable increases in walking distance and subjective improvement in quality-of-life measures have been demonstrated with cilostazol, whereas results with pentoxifylline are less convincing. Both drugs are fairly well tolerated, with minor side effects reported. Other pharmacologic agents and therapeutic angiogenesis are undergoing investigation for the treatment of IC, but their efficacy and potential role remain to be better defined.

REFERENCES

1. Clanton TL, Klawitter PF. Invited review: adaptive responses of skeletal muscle to intermittent hypoxia: the known and the unknown. J Appl Physiol 2001; 90:2476–2487.
2. McCombs PR, Subramanian S. The benefits of exercise in intermittent claudication: effects on collateral development, circulatory dynamics and metabolic adaptations. Ann Vasc Surg 2002; 16:791–796.
3. Gardner AW, Poehlman ET. Exercise rehabilitation programs for the treatment of claudication pain: a meta-analysis. JAMA 1995; 274:975–980.
4. Bulmer AC, Coombes JS. Optimising exercise training in peripheral arterial disease. Sports Med 2004; 34:983–1003.
5. McDermott MM, Liu K, Ferrucci L, et al. Physical performance in peripheral arterial disease: a slower rate of decline in patients who walk more. Ann Intern Med 2006; 144:10–20.
6. Hirsch AT, Haskal ZJ, Hertzer NR, et al. ACC/AHA 2005 practice guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic). Circulation 2006; 113:e463–e654.
7. Jacoby D, Mohler III ER. Drug treatment in intermittent claudication. Drugs 2004; 64:1657–1670.
8. Elam MB, Heckman J, Crouse JR, et al. Effect of the novel antiplatelet agent cilostazol on plasma lipoproteins in patients with intermittent claudication. Arterioscler Thromb Vasc Biol 1998; 18:1942–1947.
9. Thompson PD, Zimet R, Forbes WP, Zhang P. Meta-analysis of results from eight randomized, placebo-controlled trials on the effect of cilostazol on patients with intermittent claudication. Am J Cardiol 2002; 90:1314–1319.
10. Pratt CM. Analysis of the cilostazol safety database. Am J Cardiol 2001; 87(Suppl):28D–33D.
11. Wilhite DB, Comerota AJ, Schmieder FA, Throm RC, Gaughan JP, Rao AK. Managing PAD with multiple platelet inhibitors: the effect of combination therapy on bleeding time. J Vasc Surg 2003; 38:710–713.
12. Windmeier C, Gressner AM. Pharmacologic aspects of pentoxifylline with emphasis on its inhibitory actions on hepatic fibrosis. Gen Pharmacol 1997; 29:181–196.
13. Regensteiner JG, Ware Jr JE, McCarthy WJ, et al. Effect of cilostazol on treadmill walking, community-based walking ability, and health-related quality of life in patients with intermittent claudication due to peripheral arterial disease: meta-analysis of six randomized controlled trials. J Am Geriatr Soc 2002; 50:1939–1946.
14. Dean SM. Pharmacologic treatment for intermittent claudication. Vasc Med 2002; 7:301–309.
15. Dawson DL, Cutler BS, Hiatt WR, et al. A comparison of cilostazol and pentoxifylline for treating intermittent claudication. Am J Med 2000; 109:523–530.
16. Hood SC, Moher D, Barber GG. Management of intermittent claudication with pentoxifylline: meta-analysis of randomized controlled trials. CMAJ 1996; 155:1053–1059.
17. Dawson DL, DeMaioribus CA, Hagino RT, et al. The effect of withdrawal of drugs treating intermittent claudication. Am J Surg 1999; 178:141–146.
18. Aronow WS, Nayak D, Woodworth S, Ahn C. Effect of simvastatin versus placebo on treadmill exercise time until the onset of intermittent claudication in older patients with peripheral arterial disease at six months and at one year after treatment. Am J Cardiol 2003; 92:711–712.
19. Mondillo S, Ballo P, Barbati R, et al. Effects of simvastatin on walking performance and symptoms of intermittent claudication in hypercholesterolemic patients with peripheral vascular disease. Am J Med 2003; 114:359–364.
20. Mohler ER III, Hiatt WR, Creager MA. Cholesterol reduction with atorvastatin improves walking distance in patients with peripheral arterial disease. Circulation 2003; 108:1481–1486.
21. McDermott MM, Guralnik JM, Greenland P, et al. Statin use and leg functioning in patients with and without lower-extremity peripheral arterial disease. Circulation 2003; 107:757–761.
22. Liao JK. Effects of statins on 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibition beyond low-density lipoprotein cholesterol. Am J Cardiol 2005; 96(Suppl):24F–33F.
23. Ahimastos AA, Lawler A, Reid CM, Blombery PA, Kingwell BA. Ramipril markedly improves walking ability in patients with peripheral arterial disease. Ann Intern Med 2006; 144:660–664.
24. Morishita R, Aoki M, Ogihara T. Does gene therapy become pharmacotherapy? Exp Physiol 2005; 90:307–313.
25. Lederman RJ, Mendelsohn FO, Anderson RD, et al. Therapeutic angiogenesis with recombinant fibroblast growth factor-2 for intermittent claudication (the TRAFFIC study): a randomised trial. Lancet 2002; 359:2053–2058.
26. Hiatt WR. Carnitine and peripheral arterial disease. Ann NY Acad Sci 2004; 1033:92–98.
27. Hiatt WR, Regensteiner JG, Creager MA, et al. Propionyl-L-carnitine improves exercise performance and functional status in patients with claudication. Am J Med 2001; 110:616–622.
28. Barker GA, Green S, Askew CD, Green AA, Walker PJ. Effect of propionyl-L-carnitine on exercise performance in peripheral arterial disease. Med Sci Sports Exerc 2001; 33:1415–1422.
29. Oka RK, Szuba A, Giacomini JC, Cooke JP. A pilot study of L-arginine supplementation on functional capacity in peripheral arterial disease. Vasc Med 2005; 10:265–274.
30. Gornik HL, Creager MA. Arginine and endothelial and vascular health. J Nutr 2004; 134(10 Suppl):2880S–2887S.
31. Amendt K. PGE_1 and other prostaglandins in the treatment of intermittent claudication: a meta-analysis. Angiology 2005; 56:409–415.
32. Lièvre M, Morand S, Besse B, Fiessinger JN, Boissel JP. Oral beraprost sodium, a prostaglandin I2 analogue, for intermittent claudication. Circulation 2000; 102:426-431.
33. Mohler ER III, Hiatt WR, Olin JW, Wade M, Jeffs R, Hirsch AT. Treatment of intermittent claudication with beraprost sodium, an orally active prostaglandin I_2 analogue. J Am Coll Cardiol 2003; 41:1679–1686.
34. Girolami B, Bernardi E, Prins MH, et al. Treatment of intermittent claudication with physical training, smoking cessation, pentoxifylline, or nafronyl: a meta-analysis. Arch Intern Med 1999; 159:337–345.
35. Nylænde M, Kroese A, Stranden E, et al. Markers of vascular inflammation are associated with the extent of atherosclerosis assessed as angiographic score and treadmill walking distances in patients with peripheral arterial occlusive disease. Vasc Med 2006; 11:21–28.
36. Bassuk SS, Rifai N, Ridker PM. High-sensitivity C-reactive protein: clinical importance. Curr Probl Cardiol 2004; 29:439–493.
37. Olin JW, Hiatt WR, Mohler E, et al. A multicenter, randomized, double-blind, placebo-controlled study of immune modulation therapy in patients with symptomatic peripheral arterial disease: the SIMPADICO trial. Late-breaking oral presentation at the 55th Annual Scientific Session of the American College of Cardiology; March 13, 2006; Atlanta, GA.
38. Dawson DL. Comparative effects of cilostazol and other therapies for intermittent claudication. Am J Cardiol 2001; 87(Suppl):19D–27D.

Address: *Teresa L. Carman, MD, Section of Vascular Medicine, Department of Cardiovascular Medicine, Cleveland Clinic, 9500 Euclid Avenue, S60, Cleveland, OH 44195; carmant@ccf.org.*