Therapeutic Choice Is Quality Claudication Care

Exercise and claudication pharmacotherapies as the foundation to redefine conservative care.

BY MUDASSAR AHMED, MD; SARA MURRAY, MD; AND ALAN T. HIRSCH, MD

Peripheral arterial disease (PAD) affects more than 9 million Americans, and as many as 3 million experience claudication, its primary lower extremity ischemic symptom.[1] The prevalence of both PAD and claudication increases with age and exposure to common risk factors, and this prevalence is increasing.[2] The prevalence of PAD and claudication are closely associated with numerous comorbidities that also affect ambulatory function, including arthritis, neuropathy, spinal stenosis, and podiatric disease.[3,4] Thus, although classic claudication is present in approximately one in 10 people with PAD, as many as 40% of individuals with PAD have atypical leg pain.[1]

THE CLINICAL CONUNDRUM: THE COPREVALENCE OF PAD, CLASSIC CLAUDICATION, AND ATYPICAL LEG PAIN

The clinical conundrum, which is shared by individual patients, endovascular practices, health systems, and the public, is that efforts to diminish the impact of claudication symptoms are constrained by the following facts:

- Although PAD is common, classic claudication is not. The presence of lower extremity arterial stenoses, or the ankle-brachial index value, is not closely associated with the magnitude of leg symptoms. Similarly, arterial patency is sometimes less than ideally associated with improvement in exercise-associated leg pain.
- Current vascular training programs, regardless of specialty, do not provide expertise on use of exercise and pharmacological claudication interventions.
- Patients have previously had limited access to information regarding their treatment choices.
- Current health care payer policies do not provide reimbursement aligned with the relative safety and efficacy of claudication treatments, and PAD health care costs are high.[5]
- The nation's economic status is now strained by the use of technologies that may not always yield tangible health benefits.

All patients with PAD, whether classic ischemic leg symptoms are present or not, have been shown to have limited physical activity, impaired walking speed and endurance, and functional decline.[6-8] In addition, PAD is a "coronary heart disease equivalent" and is associated with a two- to threefold increased short-term risk of cardiovascular ischemic events.[9,10] In fact, the overall cardiovascular morbidity of PAD is likely now greater, on average, than that experienced by patients with clinical coronary artery disease (CAD).[11] It is imperative, therefore, that clinicians who diagnose and treat PAD implement treatments that are known to prevent future cardiovascular events, improve functional limitations, and decrease further functional deterioration. Current national guidelines recommend aggressive risk-factor modification and antiplatelet therapy for patients with PAD (Figure 1).[1] These medical interventions are well accepted but incompletely applied.[3]

This article focuses on the appropriate application of claudication medical therapies to improve claudication (Table 1). These evidence-based treatments are interventions proven to improve symptoms and are much more

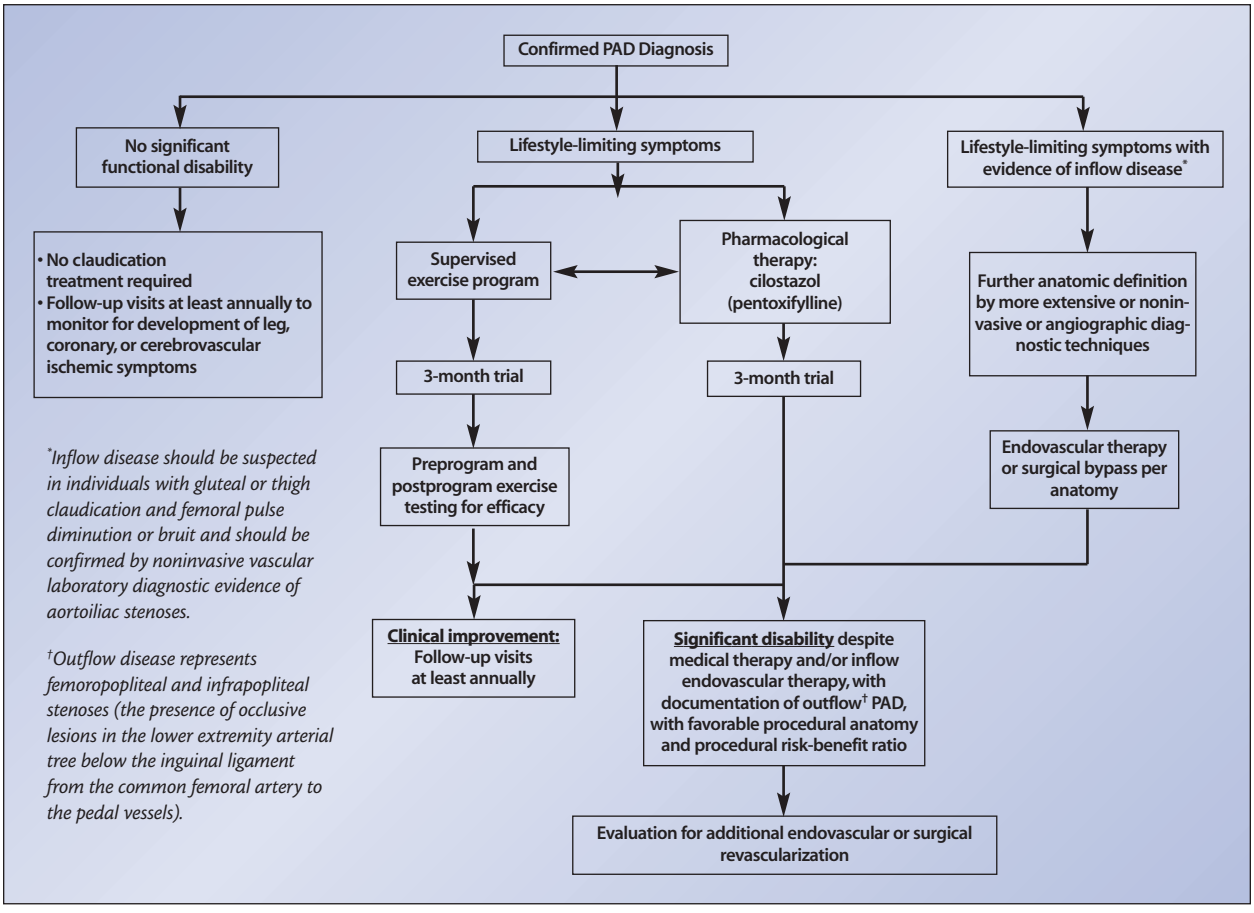

Figure 1. PAD guideline claudication treatment algorithm. (Reprinted with permission from Hirsch AT, et al. Circulation. 2006;113:1474-1547.)

powerful than the traditionally described conservative medical care standard that was once synonymous with nonrevascularization. Medical management of claudication is active, effective, low risk, cost effective, and is not conservative care.[12]

PAD EXERCISE REHABILITATION AS A PRIMARY CLAUDICATION THERAPY

Claudication leads to functional status limitations due to an exercise-associated supply-demand mismatch and equally to the profound deconditioning experienced by nearly all PAD patients over time. The biological substrate of claudication and deconditioning are well known, and functional limitations are due—beyond the decreased leg blood flow—to dysfunction of the leg as an end organ, including neurological, skeletal muscle, metabolic, gait, and other impairments. Ultimately, patients experience difficulty performing routine daily activities, and functional independence is diminished. It is vital to prevent this cycle of disability because a main claudication treatment goal is to improve functional status.[13]

Supervised exercise training is associated with improvements in walking ability and improvements in atherosclerosis risk factors. The data underlying this improvement are unambiguous, and supervised exercise has thus been emplaced as a class 1A first-line therapy for all individuals with claudication, regardless of age, ankle-brachial index value, or PAD anatomy. A meta-analysis of randomized and nonrandomized trials of exercise training by Gardner et al showed improvements in mean walking distances of 180% in pain-free walking distance and 130% for maximal walking distance.[14] Another meta-analysis by Bulmer and Coombes demonstrated median improvements in pain-free walking distance and absolute walking distance of 80% and 120%, respectively.[15] This augmentation of walking ability has been shown to correlate with performance of routine daily activities and in subjective functional improvement.[16,17]

The mechanism of benefit with exercise training is

multifactorial and is science based via several mechanisms that are known to occur in humans.[13] Clinicians who are expert in the care of claudication should be familiar with this pathophysiology and should not presume that exercise is merely reconditioning nor achieves its benefits by conjectural recruitment of collateral blood flow. There is no direct evidence that either angiogenesis or collateral blood flow recruitment can explain the magnitude of improvement that is documented in response to exercise training. There is evidence that exercise training is associated with improved endothelial arteriolar function, and this mechanism could support improved muscle blood flow.

The evidence base also supports the role of exercise training in improving glycemic control, dyslipidemia, and hypertension, as well as lowering concentrations of inflammatory markers when exercise is sustained. Exercise improves hemorrheology and elicits consistent improvements in muscle metabolism and oxygen extraction. Exercise improves fibrinolysis,[18] and indirect evidence suggests that training is associated with improved walking economy. Despite the complexity of these mechanisms, the totality of evidence for potent biological effects and major clinical improvement in both objective walking time and functional status is as robust as for any claudication treatment.

Supervised exercise therapy, as stated previously, is a class 1A, first-line claudication therapy. Referral to a supervised PAD rehabilitation program is preferred over self-monitored home exercise. Key elements of a supervised exercise-training program can be found in Table 1. Exercise training, as a first-line claudication therapy, has several advantages, including that any primary care or vascular specialty clinician can prescribe it, it is effective in inducing clinical improvement in individuals with multiple causes of limb dysfunction, and it improves risk factors. Disadvantages are few but do include the current lack of reimbursed programs and the time required for participation. Both of these limitations could be easily reversed because health care payers and clinicians could emplace reimbursement via simple administrative decisions at the payer or hospital level, and motivation to participate is present for all other proven rehabilitative interventions and is only absent for PAD when clinicians do not encourage participation.

There is no evidence that functional gains achieved via an exercise program are lost once the supervised phase is completed. Even if this were true, every other claudication treatment also requires sustained intervention if long-term success is considered. Claudication medications require long-term adherence, endovascular procedures have limited patency, and open surgical procedures have both limited patency and an invariable short-term cardiovascular morbidity and mortality rate.

A baseline exercise treadmill test is valuable in identifying potential coronary ischemia, which may limit exercise ability, and in establishing a baseline from which to monitor progress during exercise training. Prescribed exercise therapy has been shown to be cost effective when compared to percutaneous transluminal angioplasty.[19] Furthermore, supervised exercise training has a specific current procedural terminology code (CPT 93668) for reimbursement. Even when not directly reimbursed by CMS, indirect costs from invasive procedures could be used to defray the cost of this program if clinicians demanded it. It is hard to imagine why all payers would not eagerly support primary use of this beneficial, safe, cost-effective, and science-based claudication treatment.

PHARMACOLOGICAL THERAPY OF CLAUDICATION

Similar to individuals with CAD, individuals with PAD sometimes believe that endovascular therapies might supplant the use of medications. In contrast, all individuals with PAD require a comprehensive medical management plan to lower their cardiovascular risk. As for CAD, there are effective medications that can also be used to diminish limb ischemic symptoms.

Two medications are FDA approved for the management of intermittent claudication: cilostazol and pentoxifylline. Cilostazol is a phosphodiesterase (PDE)-III inhibitor that increases tissue concentrations of cyclic adenosine monophosphate. Although the exact mechanism of benefit of cilostazol to improve claudication remains unclear, this medication's antiplatelet and vasodilatory effects are considered to be potentially important.[20] In multiple placebo-controlled, multicenter, randomized clinical trials, cilostazol improved walking distance by 40% to 60% after 3 to 6 months of therapy.[21,22] The recommended dose is 100 mg orally twice daily. Potential adverse events of cilostazol include headache, rapid heart rate or dizziness, nausea, loose stools, and diarrhea, but the impact of potential adverse effects can usually be moderated by careful dose titration. No cardiovascular morbidity or mortality has been described with cilostazol, either in clinical trials or via postmarketing surveillance. Nevertheless, this medication is contraindicated in patients with heart failure, as are all PDE-III inhibitors.

Pentoxifylline is a methylxanthine derivative with hemorrheologic properties, including a reduction in blood viscosity, increased blood cell deformability, and decreased neutrophil activation. It was the first drug approved for the treatment of intermittent claudication

TABLE 1. KEY ELEMENTS OF A THERAPEUTIC CLAUDICATION EXERCISE TRAINING PROGRAM (LOWER EXTREMITY PAD REHABILITATION)[1]

Primary clinician role

- Establish the PAD diagnosis using the ankle-brachial index measurement or other objective vascular laboratory evaluations.
- Determine that claudication is the major symptom limiting exercise.
- Discuss risk/benefit of claudication therapeutic alternatives, including pharmacological, percutaneous, and surgical interventions.
- Initiate systemic atherosclerosis risk modification.
- Perform treadmill stress testing.
- Provide formal referral to a claudication exercise rehabilitation program.

Exercise guidelines for claudication*

Warm-up and cool-down period of 5 to 10 minutes each.

- Types of exercise:
  - Treadmill and track walking are the most effective exercise for claudication.
  - Resistance training has conferred benefit to individuals with other forms of cardiovascular disease and its use, as tolerated, for general fitness is complementary to (but not a substitute for) walking.
- Intensity:
  - The initial workload of the treadmill is set to a speed and grade that elicit claudication symptoms within 3 to 5 minutes.
  - Patients walk at this workload until they achieve claudication of moderate severity, which is then followed by a brief period of standing or sitting rest to permit symptoms to resolve.
- Duration:
  - The exercise-rest-exercise pattern should be repeated throughout the exercise session.
  - The initial duration will usually include 35 minutes of intermittent walking and should be increased by 5 minutes each session until 50 minutes of intermittent walking can be accomplished.
- Frequency:
  - Treadmill or track walking 3 to 5 times per week.

Role of direct supervision

- As patients improve their walking ability, the exercise workload should be increased by modifying the treadmill grade or speed (or both) to ensure that there is always the stimulus of claudication pain during the workout.
- As patients increase their walking ability, there is the possibility that cardiac signs and symptoms may appear, such as dysrhythmia, angina, or ST-segment depression. These events should prompt physician re-evaluation.

**These general guidelines should be individualized and based on the results of treadmill stress testing and the clinical status of the patient. A full discussion of the exercise precautions for persons with concomitant diseases can be found elsewhere. For diabetes, see Ruderman N, et al. Handbook of Exercise in Diabetes. Alexandria, VA: American Diabetes Association; 2002 (362a). For hypertension, see ACSMs guidelines for exercise testing and prescription. In: Franklin BA, ed. Baltimore, MD: Lippincott Williams & Wilkins; 2000 (3 62b). For coronary artery disease, see Guidelines for cardiac rehabilitation and secondary prevention/American Association of Cardiovascular and Pulmonary Rehabilitation. Champaign, IL: Human Kinetics; 1999 (362c).*

Adapted with permission from Hirsch AT, et al. Circulation. 2006;113:1474-1547.

because it showed a 20% to 30% improvement in walking distance in two randomized trials.[23,24] The dose of pentoxifylline is 400 mg orally three times daily, and potential adverse effects include sore throat, nausea, and diarrhea. Since approval, wide clinical experience has not supported the overt efficacy of pentoxifylline. More recent clinical trial data have compared the effectiveness of pentoxifylline with cilostazol and demonstrated that pentoxifylline's benefit was nearly that of placebo.[25]

The intersocietal PAD guidelines[1] recommend the use of cilostazol as a class 1 recommendation and first-line therapy for patients with intermittent claudication. In the absence of heart failure, a 3-month therapeutic trial is recommended for all such patients. In contrast, use of pentoxifylline is a class 2B recommendation with the recognition that its benefits are marginal and not well established.

Note that the role of these claudication medications for individuals with critical limb ischemia (eg, ischemic rest pain, nonhealing wounds, or gangrene) is not associated with any evidence base of efficacy. Parenteral administration of prostacyclin and/or iloprost has shown beneficial

(but inconsistent) clinical trial results and may be considered in patients to decrease ischemic pain and improve ulcer healing.[26,27] Revascularization remains the cornerstone of care for patients with critical limb ischemia.

MEDICAL TREATMENT IS MANDATORY AND IS NOT CONSERVATIVE TREATMENT

Endovascular clinicians, as central caregivers who establish PAD care standards, must be familiar with and use guideline-derived (evidence-based medicine) treatment of each risk factor (eg, smoking, diabetes mellitus, hypertension, and hyperlipidemia). A review of the treatment strategies for the atherosclerotic risk of PAD is beyond the scope of this article. However, two medication classes that deserve special attention by all vascular clinicians include the HMG-CoA reductase inhibitors (or statins) and the antiplatelet medications. Statins are extremely efficacious in reducing LDL levels and have been shown to reduce cardiovascular ischemic events, hospitalization, and mortality beyond their lipid-lowering effects.[1,28,29] Unless contraindicated or not tolerated, statin use is a class 1 recommendation for all patients with PAD.

The Antithrombotic Trialists' Collaboration provided a meta-analysis of 287 studies that showed a 22% odds reduction for adverse cardiovascular events in patients with PAD treated with aspirin compared to placebo.[30] The recommended daily dose is 75 to 325 mg for all patients with PAD unless specifically contraindicated. For patients who are unable to take aspirin, clopidogrel can be administered at a dose of 75 mg orally daily. The CAPRIE trial[31] randomized patients to aspirin and clopidogrel and, in patients with PAD, clopidogrel was found to be more efficacious than aspirin in reducing the risk of myocardial infarction, stroke, or vascular death. There is no proven role for dual antiplatelet therapy for any PAD clinical syndrome, and warfarin has no protective effect.[32]

THERAPEUTIC CHOICE IS THE FOUNDATION OF QUALITY CLAUDICATION CARE

Endovascular clinicians should note that exercise, pharmacotherapy, and invasive therapies are not competitive treatments, but they are always complementary. Each modality of claudication treatment (eg, cilostazol, supervised exercise, or percutaneous and open revascularization) can be combined and lead to even better exercise tolerance and functional status. Vascular clinicians, responsible for the overall quality of national claudication care, must support patient access to all proven interventions.

The science base documents true equipoise between available claudication treatments, which have never been evaluated simultaneously in one population. The CLEVER study is an NHLBI-funded trial designed to assess the relative efficacy, safety, and health economic impact of the three current claudication treatments that might be offered to individuals with atherosclerotic aortoiliac PAD. Subjects are randomly assigned to one of four treatment groups: (1) optimal medical care (home exercise and cilostazol), (2) supervised exercise rehabilitation for 6 months, (3) primary aortoiliac stenting, or (4) stenting with supervised exercise. The study will recruit 252 subjects and continues active recruitment. The "CLEVER Design Paper" will be published in the *Journal of Vascular Surgery*.[33] The 20 national CLEVER study sites have created a novel system in which PAD exercise rehabilitation—previously unavailable in the US despite the PAD guideline class 1A efficacy recommendation—can be conveniently offered to subjects at no cost, provides all subjects with supervised achievement of all current atherosclerotic risk reductions goals, carefully evaluates clinical benefit and safety, monitors rates of both cardiovascular and peripheral adverse events, and prospectively measures associated health economic costs. All patients who are potential CLEVER study candidates who reside near CLEVER study sites should be offered information about the trial and thereby should be able to consider study participation. All endovascular therapists should support "best science" as represented by NHLBI clinical investigations.

CONCLUSION

PAD is a major national cause of cardiovascular morbidity and mortality. Temporal increases in population-based atherosclerotic risk factor exposure (eg, obesity and diabetes) suggest that the societal costs of PAD are likely to increase. As all clinicians become familiar with this PAD burden, this disease will not remain underrecognized and undertreated. As additional patients seek and receive medical care, all vascular clinicians must support, prescribe, and utilize all effective therapeutic claudication options. Supervised exercise therapy and claudication medications are proven to be as effective as currently available revascularization treatments. As for any important illness, clinicians should inform each PAD patient of their treatment options. Patients with PAD deserve, no less than individuals with any important illness, access to therapeutic choice. ■

Mudassar Ahmed, MD, is with the Cardiovascular Division, University of Minnesota Medical School, in Minneapolis, Minnesota. Dr. Ahmed will be assuming a position at St. Mary's-Duluth Clinic Health System in Duluth, Minnesota. He has disclosed that he holds no financial interest in any product or manufacturer mentioned

herein. Dr. Ahmed may be reached at (612) 626-2451; ahmed097@umn.edu.

Sara Murray, MD, is with the Cardiovascular Division, University of Minnesota Medical School, in Minneapolis, Minnesota. Dr. Murray will be assuming a position at St. Paul Heart Clinic in St. Paul, Minnesota. She has disclosed that she holds no financial interest in any product or manufacturer mentioned herein. Dr. Murray may be reached at (612) 626-2451; smurray@umn.edu.

Alan T. Hirsch, MD, is with The Minneapolis Heart Institute Foundation and Division of Epidemiology and Community Health, University of Minnesota School of Public Health, in Minneapolis, Minnesota. He has disclosed that he receives research funding from Bristol-Myers Squibb/Sanofi Aventis Partnership. Dr. Hirsch may be reached at (612) 863-3900; hirsc005@umn.edu.

1. Hirsch AT, Haskal ZJ, Hertzer NR, et al. ACC/AHA Guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to develop guidelines for the management of patients with peripheral arterial disease [lower extremity, renal, mesenteric, and abdominal aortic]). Circulation. 2006;113:1474-1547.
2. Newman AB, Siskovick DS, Manolio TA, et al. Ankle-arm index as a marker of atherosclerosis in the Cardiovascular Health Study. Circulation. 1993; 88:837-845.
3. Hirsch AT, Criqui MH, Teat-Jacobson D, et al. Peripheral arterial disease detection, awareness, and treatment in primary care. JAMA. 2001;286:1317-1324.
4. McDermott MM, Greenland P, Liu K, et al. Leg symptoms in peripheral arterial disease: associated clinical characteristics and functional impairment. JAMA. 2001;286:1599-1606.
5. Hirsch AT, Hartman L, Town RJ, et al. National healthcare costs of peripheral arterial disease in the usa medicare population. Vascular Medicine. In press.
6. McDermott MM, Mehta S, Greenland P. Exertional leg symptoms other than intermittent claudication are common in peripheral arterial disease. Arch Intern Med. 1999;159:387-392.
7. McDermott MM, Liu K, Greenland P, et al. Functional decline in peripheral arterial disease: associations with the ankle brachial index and leg symptoms. JAMA. 2004;292:453-461.
8. McDermott MM, Greenland P, Liu K, et al. The ankle-brachial index is associated with leg function and physical activity: the Walking and Leg Circulation Study. Ann Intern Med. 2002;136:I-32.
9. Resnick HE, Lindsay RS, McDermott MM, et al. Relationship of high and low ankle brachial index to all-cause and cardiovascular mortality. The Strong Heart Study. Circulation. 2004;109:733-739.
10. Criqui MH, Langer RD, Fronek A, et al. Mortality over a period of 10 years in patients with peripheral arterial disease. N Engl J Med. 1992;326:381-386.
11. Steg G, Bhatt D, Wilson PWF et al. One-year cardiovascular event rates in outpatients with atherothrombosis. JAMA. 2007;297:1197-1206.
12. Hirsch AT. The treatment of peripheral arterial disease—extending "intervention" to "therapeutic choice." N Engl J Med. 2006;354:1944-1947.
13. Stewart KJ, Hiatt WR, Regensteiner JG, et al. Exercise training for claudication. N Engl J Med. 2002;347:1941-1951.
14. Gardner AW, Poehlman ET. Exercise rehabilitation programs for the treatment of claudication pain. A meta-analysis. JAMA. 1995;274:975-980.
15. Bulmer AC, Coombes JS. Optimising exercise training in peripheral arterial disease. Sports Med. 2004;34:983-1003.
16. Gardner AW, Katzel LI, Sorkin JD, et al. Improved functional outcomes following exercise rehabilitation in patients with intermittent claudication. J Gerontol A Biol Sci Med Sci. 2000;55:M570-577.
17. Regenstenier JG, Steiner JF, Hiatt WR. Exercise training improves functional status in patients with peripheral arterial disease. J Vasc Surg. 1996;23:104-115.
18. Hobbs SD, Marshall T, Fegan C, et al. The effect of supervised exercise and cilostazol on coagulation and fibrinolysis in intermittent claudication: a randomized controlled trial. J Vasc Surg. 2007;45:65-70.
19. Treesak C, Kasemsup V, Treat-Jacobson D, et al. Cost-effectiveness of exercise training to improve claudication symptoms in patients with peripheral arterial disease. Vasc Med. 2004;9:279-285.
20. Igawa T, Tani T, Chijiwa T, et al. Potentiation of anti-platelet aggregating activity of cilostazol with vascular endothelial cells. Thromb Res. 1990;57:617-623.
21. Dawson DL, Cutler BS, Meissner MH, et al. Cilostazol has beneficial effects in treatment of intermittent claudication. Circulation. 1998;98:678-686.
22. Money SR, Herd JA, Isaacsohn JL, et al. Effect of cilostazol on walking distances in patients with intermittent claudication caused by peripheral vascular disease. J Vasc Surg. 1998;27:267-274.
23. Lindgarde F, Jelnes R, Bjorkman H, et al. Conservative drug treatment in patients with moderately severe chronic occlusive peripheral arterial disease. Scandinavian study group. Circulation. 1989;80:1549-1556.
24. Porter JM, Cutler BS, Lee BY, et al. Pentoxifylline efficacy in the treatment of intermittent claudication: multicenter controlled double-blind trial with objective assessment of chronic occlusive arterial disease patients. Am Heart J. 1982;104:66-72.
25. 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.
26. U.K. Severe Limb Ischaemia Study Group. Treatment of limb threatening ischaemia with intravenous iloprost: a randomised double-blind placebo controlled study. Eur J Vasc Surg. 1991;5:511-516.
27. Balzer K, Bechara G, Bisler H, et al. Reduction of ischaemic rest pain in advanced peripheral arterial occlusive disease: a double blind placebo controlled trial with iloprost. Int Angiol. 1991;10:229-232.
28. The Scandinavian Simvastatin Survival Study. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease. Lancet. 1994;344:1383-1389.
29. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet. 2002;360:7-22.
30. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ. 2002;324:71-86.
31. CAPRIE Steering Committee. A randomized, blinded, trial of clopidogrel versus aspirin in patients at risk of ischemic events. Lancet. 1996;348:1329-1339.
32. The Warfarin Antiplatelet Vascular Evaluation Trial Investigators. Oral anticoagulant and antiplatelet therapy and peripheral arterial disease. N Engl J Med. 2007;357:217-227.
33. Murphy TP, Hirsch AT, Cutlip DE, et al. The National Institutes of Health CLEVER Study (Claudication: Exercise Vs. Endoluminal Revascularization): rationale and methods. J Vasc Surg. In press.