

## Review Article

*Drug Therapy*ALASTAIR J.J. WOOD, M.D., *Editor***MEDICAL TREATMENT OF PERIPHERAL ARTERIAL DISEASE AND CLAUDICATION**

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**P**ERIPHERAL arterial disease, which is caused by atherosclerotic occlusion of the arteries to the legs, is an important manifestation of systemic atherosclerosis. The age-adjusted prevalence of peripheral arterial disease is approximately 12 percent, and the disorder affects men and women equally (Table 1).<sup>7,8</sup> Patients with peripheral arterial disease, even in the absence of a history of myocardial infarction or ischemic stroke, have approximately the same relative risk of death from cardiovascular causes as do patients with a history of coronary or cerebrovascular disease (Table 2).<sup>12,15</sup> In patients with peripheral arterial disease, the rate of death from all causes is approximately equal in men and women and is elevated even in asymptomatic patients. The severity of peripheral arterial disease is closely associated with the risk of myocardial infarction, ischemic stroke, and death from vascular causes. The lower the ankle-brachial index (Fig. 1), the greater the risk of cardiovascular events.<sup>17,18</sup> Patients with critical leg ischemia (the most severe clinical manifestation of peripheral arterial disease), who have the lowest ankle-brachial index values, have an annual mortality of 25 percent.<sup>19</sup>

The major risk factors for peripheral arterial disease are older age (over 40 years), cigarette smoking, and diabetes mellitus. Hyperlipidemia, hypertension, and hyperhomocysteinemia are also important risk factors.<sup>5,8,20</sup> Because of the presence of these risk factors, the systemic nature of atherosclerosis, and the high risk of ischemic events, patients with peripheral arterial disease should be considered candidates for secondary-prevention strategies that include aggressive risk-factor modification and antiplatelet-drug therapy.<sup>21,22</sup>

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Nevertheless, patients with peripheral arterial disease are undertreated with regard to the use of lipid-lowering and antiplatelet drugs, as compared with patients with coronary artery disease.<sup>23,24</sup>

**CLINICAL MANIFESTATIONS**

Approximately one third of patients with peripheral arterial disease have typical claudication (Table 1), defined as pain in one or both legs on walking, primarily affecting the calves, that does not go away with continued walking and is relieved by rest.<sup>25</sup> In patients with claudication, the severity of the condition increases slowly; 25 percent have worsening claudication, and 5 percent undergo an amputation within five years.<sup>26</sup> Less than 5 to 10 percent of patients have critical leg ischemia (ischemic pain in the distal foot, ischemic ulceration, or gangrene), but their risk of limb loss is substantial.<sup>19</sup> More than 50 percent of patients identified as having peripheral arterial disease on the basis of an abnormal ankle-brachial index value do not have typical claudication or limb ischemia at rest but, instead, have other types of leg pain on exertion, with reduced ambulatory activity and quality of life.<sup>27,28</sup> Thus, most patients with peripheral arterial disease have a reduced functional capacity that limits their ability to perform daily activities.

The goals of treatment for patients with claudication are to relieve their exertional symptoms, improve their walking capacity, and improve their quality of life. These goals are similar for patients with critical leg ischemia, with the additional goals of relieving ischemic pain at rest, healing ischemic ulceration, and preventing limb loss. The overall approach to the diagnosis and treatment of peripheral arterial disease was extensively reviewed in a recent consensus publication that provides a comprehensive discussion of the medical and surgical therapies for the disease.<sup>29</sup> This review will focus on risk-factor modification and antiplatelet therapies, as well as strategies for symptomatic relief in patients with peripheral arterial disease. Diagnosis and management are summarized in Figures 2 and 3.

**MODIFICATION OF RISK FACTORS****Smoking Cessation**

Smoking cessation slows the progression to critical leg ischemia and reduces the risks of myocardial infarction and death from vascular causes.<sup>30</sup> It is not certain whether smoking cessation reduces the severity of claudication. The authors of a meta-analysis of published data concluded that smoking cessation did not improve maximal treadmill walking distance.<sup>31</sup> Smoking-cessation programs, nicotine-replacement therapy,

**TABLE 1.** PREVALENCE OF PERIPHERAL ARTERIAL DISEASE, CLAUDICATION, AND ASSOCIATED CARDIOVASCULAR DISEASE.\*

STUDY	NO. OF SUBJECTS	AGE	SEX	PREVALENCE OF PERIPHERAL ARTERIAL DISEASE	PREVALENCE OF CLAUDICATION	PREVALENCE OF CLINICAL CARDIOVASCULAR DISEASE
				percent		
Schroll and Munck <sup>1</sup>	666	>60	M	16	6	—
			F	13	1	—
Meijer et al. <sup>2</sup>	7,715	>55	M	17	2	48
			F	21	1	33
Fowkes et al. <sup>3</sup>	1,592	55–74	Both	18	5	54
Newman et al. <sup>4</sup>	190	>60	Both	27	6	47
Newman et al. <sup>5</sup>	5,084	≥65	M	14	2	56
			F	11	2	40
Zheng et al. <sup>6</sup>	15,792	45–64	M	3	1	21
			F	3	1	5

\*An ankle-brachial index value of less than 0.90 was considered diagnostic of peripheral arterial disease in all the studies. Dashes indicate that no data were presented.

**TABLE 2.** RISKS OF DEATH FROM ALL CAUSES AND FROM CARDIOVASCULAR CAUSES IN PATIENTS WITH PERIPHERAL ARTERIAL DISEASE.\*

STUDY	AGE	SEX	NO. OF SUBJECTS	DEATH FROM ALL CAUSES			DEATH FROM CARDIOVASCULAR DISEASE		
				PATIENTS WITH PERIPHERAL ARTERIAL DISEASE		RR (95% CI)	PATIENTS WITHOUT CARDIOVASCULAR DISEASE AT ENTRY		
				CONTROLS	percent per year		ALL PATIENTS	RR (95% CI)	
Criqui et al. <sup>9</sup>	38–82	M	256	1.7	6.2	3.3 (1.9–6.0)	5.1 (2.4–10.8)	3.9 (1.5–10.6)	
				1.2	3.3	2.5 (1.2–5.3)	4.8 (1.6–14.7)	5.7 (1.4–23.2)	
Vogt et al. <sup>10</sup>	≥65	F	1492	1.1	5.4	3.1 (1.7–5.5)	4.0 (1.3–8.5)	4.5 (1.5–6.7)	
Leng et al. <sup>11</sup>	55–74	Both	1592	2.0	3.8	1.6 (0.9–2.8)	2.7 (1.3–5.3)	—	
					(with claudication)				
				2.0	6.1	2.4 (1.6–3.7)	2.1 (1.1–3.8)	—	
				(without symptoms)					
Newman et al. <sup>12</sup>	≥65	Both	5714	4.5	7.8	1.5 (1.2–1.9)	2.0 (1.1–2.8)	2.9 (1.8–4.6)	
Newman et al. <sup>13</sup>	≥60	M	669	1.5	5.3	3.0 (2.8–5.3)	—	3.4 (1.3–8.9)	
		F	868	1.3	3.8	2.7 (1.6–4.6)	—	3.3 (1.3–8.6)	
Kornitzer et al. <sup>14</sup>	40–55	M	2023	0.4	1.0	2.8 (1.4–5.5)	—	4.2 (1.7–10.5)	
					(without symptoms)				

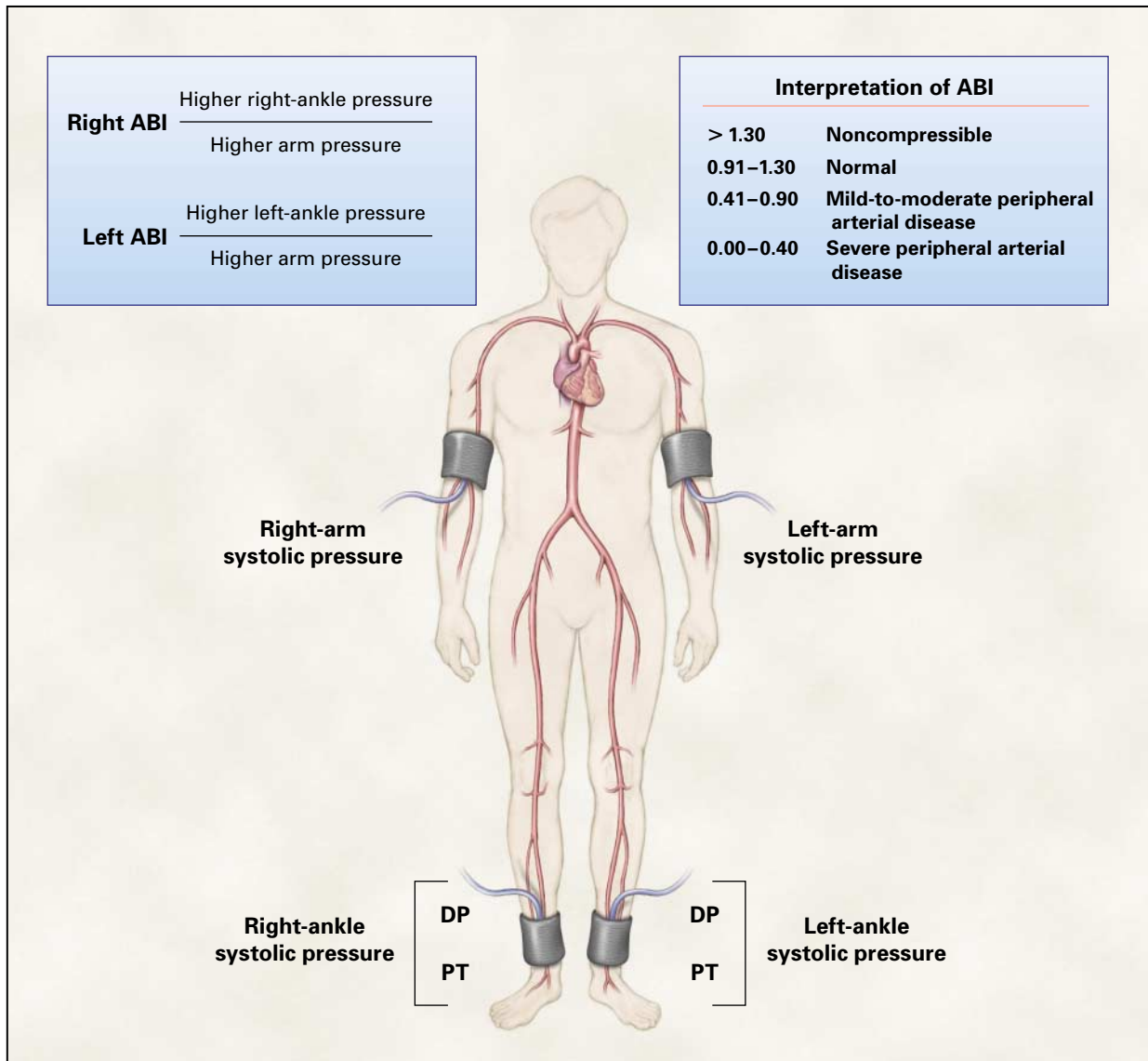
\*RR denotes relative risk, and CI confidence interval. Dashes indicate that no data were presented.

and the use of antidepressant drugs such as bupropion should be encouraged.<sup>32</sup>

**Treatment of Hyperlipidemia**

Several large clinical trials have determined the benefits of lowering cholesterol concentrations in patients with coronary artery disease.<sup>33</sup> In patients with peripheral arterial disease, therapy with a statin not only lowers serum cholesterol concentrations, but also improves endothelial function, as well as other markers

of atherosclerotic risk, such as serum P-selectin concentrations.<sup>34,35</sup> A meta-analysis was performed of randomized trials of lipid-lowering therapy in 698 patients with peripheral arterial disease who were treated with a variety of therapies, including diet, cholestyramine, probucol, and nicotinic acid, for four months to three years.<sup>36</sup> The total mortality was 0.7 percent in the treated patients, as compared with 2.9 percent in the patients given placebo — a nonsignificant difference. This analysis also demonstrated that lipid-



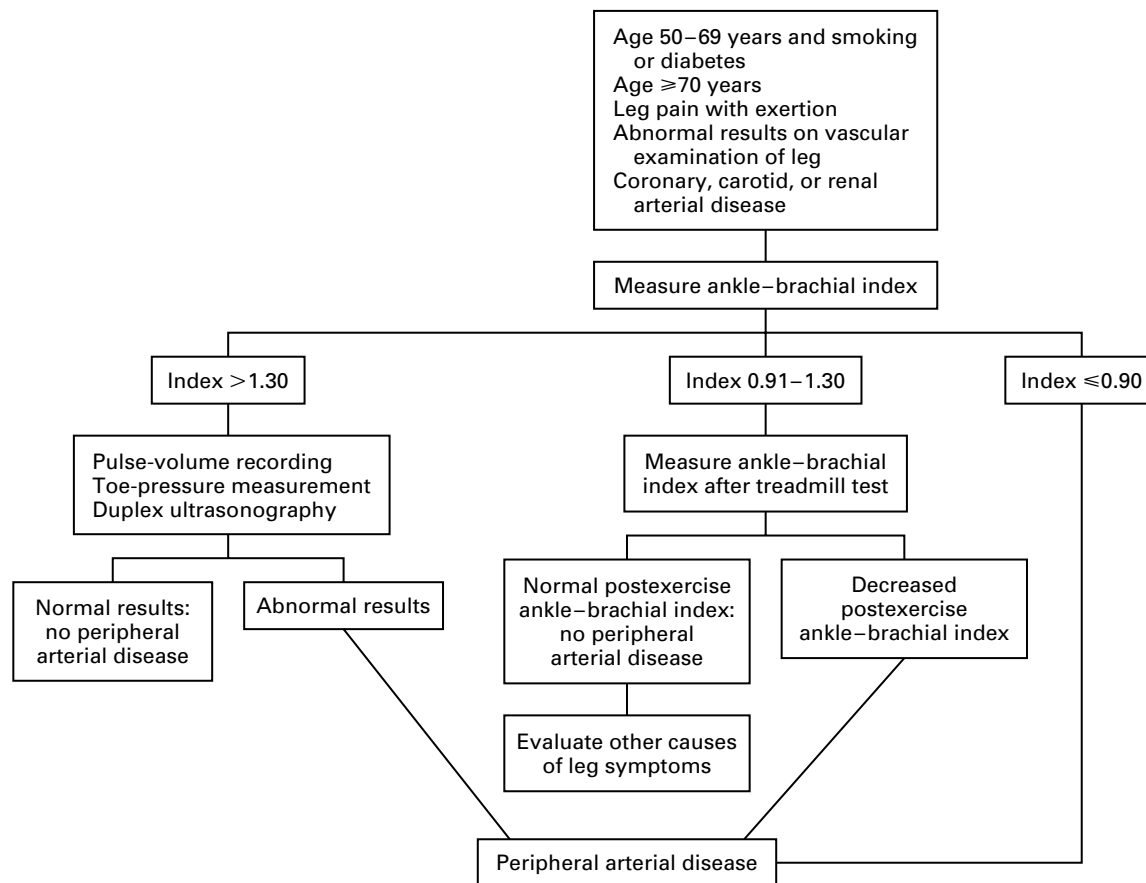
**Figure 1.** Measurement of the Ankle–Brachial Index (ABI).

Systolic blood pressure is measured by Doppler ultrasonography in each arm and in the dorsalis pedis (DP) and posterior tibial (PT) arteries in each ankle. The higher of the two arm pressures is selected, as is the higher of the two pressures in each ankle. The right and left ankle–brachial index values are determined by dividing the higher ankle pressure in each leg by the higher arm pressure.<sup>16</sup> The ranges of the ankle–brachial index values are shown, with a ratio greater than 1.30 suggesting a noncompressible, calcified vessel. In this condition, the true pressure at that location cannot be obtained, and additional tests are required to diagnose peripheral arterial disease. Patients with claudication typically have ankle–brachial index values ranging from 0.41 to 0.90, and those with critical leg ischemia have values of 0.40 or less.

lowering therapy reduced disease progression, as measured by angiography, and the severity of claudication.

Several trials have evaluated the effects of lipid-lowering therapy on atherosclerosis in the peripheral vessels. In the Cholesterol Lowering Atherosclerosis Study, 188 men with evidence of both coronary and peripheral arterial disease were treated with diet and

then randomly assigned to placebo or colestipol plus niacin. Lipid-lowering therapy was associated with stabilization or regression of femoral atherosclerosis.<sup>37</sup> The St. Thomas trial, in which 25 men were treated with diet, cholestyramine, nicotinic acid, or clofibrate for an average of 19 months, demonstrated a beneficial effect of therapy on femoral atherosclerosis.<sup>38</sup> In



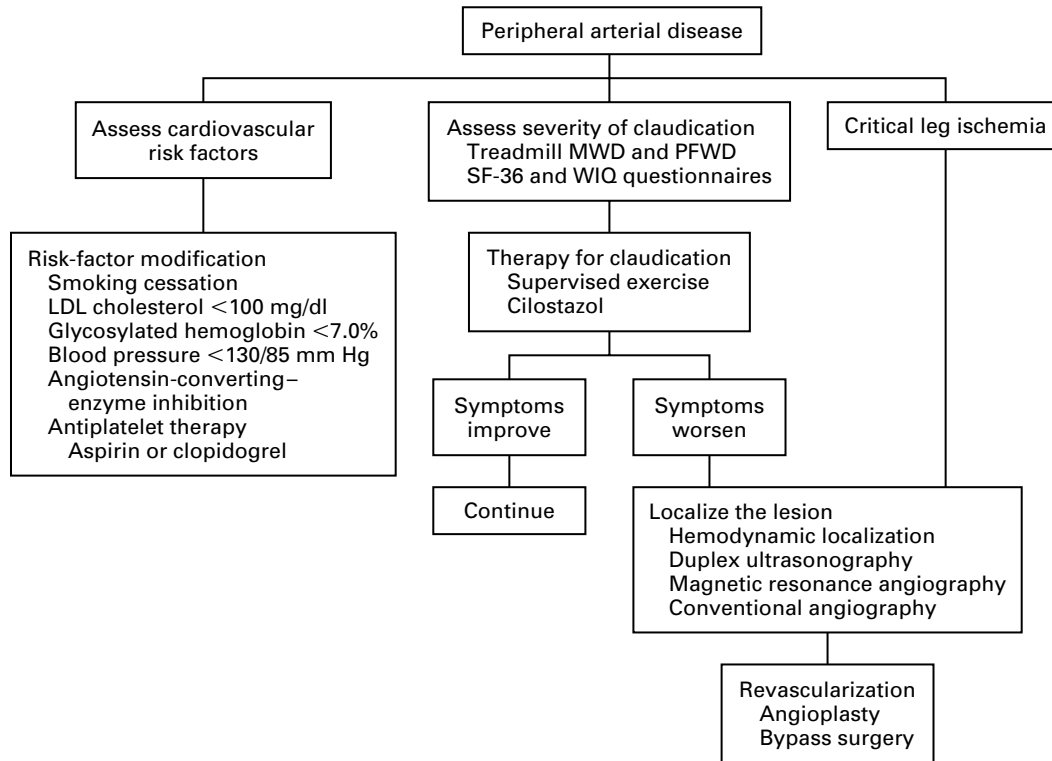
**Figure 2.** Evaluation of Patients in Whom Peripheral Arterial Disease Is Suspected.

Patients should be evaluated for peripheral arterial disease if they are at increased risk because of their age or the presence of atherosclerotic risk factors, have leg pain on exertion, or have distal limb ulceration for which the history and examination do not provide an obvious explanation. Additional vascular studies can be performed in patients with an ankle–brachial index value above 1.30, including pulse-volume recording, measurement of pressure in the first toe, or duplex ultrasonographic imaging of the peripheral vessels, to determine whether peripheral arterial disease is present. Patients with leg pain on exertion who have ankle–brachial index values of 0.91 to 1.30 should be considered for an exercise test. An ankle–brachial index value that is over 0.90 at rest but decreases by 20 percent after exercise is diagnostic of peripheral arterial disease.<sup>16</sup> If the initial ankle–brachial index value is 0.90 or less at rest, the patient probably has peripheral arterial disease, and no additional tests are necessary.

contrast, the Probucol Quantitative Regression Swedish Trial evaluated 303 patients with peripheral arterial disease who were treated with diet and cholestyramine and then randomly assigned to receive probucol or placebo for three years.<sup>39</sup> This study found no beneficial effect of probucol (a drug that lowers serum low-density lipoprotein [LDL] and high-density lipoprotein [HDL] cholesterol concentrations and has antioxidant properties) on femoral atherosclerosis or ankle–brachial index values.

In a recent study of plasma apheresis to reduce serum Lp(a) lipoprotein concentrations, 42 patients with coronary artery disease were randomly assigned to simvastatin plus apheresis or simvastatin alone and followed for two years.<sup>40</sup> There was a 19 percent re-

duction in serum Lp(a) lipoprotein concentrations in patients receiving combined therapy, as compared with a 15 percent increase in patients receiving simvastatin alone ( $P < 0.001$ ). Peripheral arterial end points were assessed with duplex ultrasonographic imaging of the femoral and tibial vessels. At the end of the study, the number of patients in the simvastatin-only group with hemodynamically important new stenoses in their peripheral vessels had increased from 6 to 13, as compared with a decrease from 9 to 7 patients in the simvastatin-plus-apheresis group ( $P = 0.002$ ). Although apheresis is not a practical means of treating hyperlipidemia, this study suggests that high serum Lp(a) lipoprotein concentrations are important in the development of peripheral arterial disease.



**Figure 3.** Evaluation and Treatment of Patients with Proved Peripheral Arterial Disease.

All patients with peripheral arterial disease, regardless of the severity of symptoms, should undergo risk-factor modification to achieve the listed treatment goals and should receive antiplatelet therapy with aspirin or clopidogrel. Angiotensin-converting-enzyme inhibitors may be considered because of the potential for prevention of ischemic events that is independent of blood-pressure lowering.

A treadmill test to define the maximal walking distance (MWD) and the pain-free walking distance (PFW) can provide an objective assessment of the severity of claudication and the response to therapy. The functional limitations of claudication and response to therapy can also be quantified by the physical-function scales of the non-disease-specific Medical Outcomes Short Form 36 questionnaire (SF-36) and the disease-specific Walking Impairment Questionnaire (WIQ). Treatment of claudication should begin with exercise therapy or drugs such as cilostazol. In patients whose condition does not improve and who remain disabled, or who have worsening symptoms, the location of the occlusive lesions should be determined to plan endovascular or surgical intervention.

Noninvasive localization can be performed with hemodynamic tests, such as segmental-limb-pressure and pulse-volume recording. Duplex ultrasonographic imaging and magnetic resonance angiography both have high sensitivity and specificity for the localization of lesions (with magnetic resonance angiography having the higher sensitivity), but conventional angiography is still required in most patients before surgery or angioplasty. Patients with critical leg ischemia typically have ankle-brachial index values of less than 0.40 and should initially be considered for localization of their occlusive disease in anticipation of the need for revascularization. LDL denotes low-density lipoprotein.

Two studies evaluated the effects of lipid-lowering therapy on clinical end points in the leg. The Program on the Surgical Control of the Hyperlipidemias was a randomized trial of ileal-bypass surgery for the treatment of hyperlipidemia in 838 patients.<sup>41</sup> After five years, the relative risk of an abnormal ankle-brachial index value was 0.6 (95 percent confidence interval, 0.4 to 0.9; absolute risk reduction, 15 percentage points;  $P < 0.01$ ), and the relative risk of claudication or limb-threatening ischemia was 0.7 (95 percent confidence interval, 0.2 to 0.9; absolute risk reduction, 7 percentage points;  $P < 0.01$ ), as compared with the

control group. In a subgroup of patients treated with simvastatin in the Scandinavian Simvastatin Survival Study, the relative risk of new claudication or worsening of preexisting claudication was 0.6 (95 percent confidence interval, 0.4 to 0.9; absolute risk reduction, 1.3 percentage points), as compared with patients randomly assigned to placebo.<sup>42</sup>

In summary, lipid-lowering therapy has benefit in patients with peripheral arterial disease, who often have coexisting coronary and cerebral arterial disease. The current recommendation for patients with peripheral arterial disease is to achieve a serum LDL cho-

lesterol concentration of less than 100 mg per deciliter (2.6 mmol per liter) and a serum triglyceride concentration of less than 150 mg per deciliter (1.7 mmol per liter).<sup>43</sup> A statin should be given as initial therapy, but niacin is an important drug because it increases serum HDL concentrations and lowers serum triglyceride concentrations without worsening glucose metabolism in these patients.<sup>44</sup>

#### Treatment of Diabetes Mellitus

Intensive control of blood glucose prevents the microvascular complications of diabetes, but its effect on macrovascular complications is less certain. The Diabetes Control and Complications Trial compared intensive and conventional insulin therapy in 1441 patients with type 1 diabetes. Intensive therapy was associated with a trend toward a reduction in cardiovascular events ( $P=0.08$ ) but had no effect on the risk of peripheral arterial disease.<sup>45</sup> The results were similar in 3867 patients with type 2 diabetes in the United Kingdom Prospective Diabetes Study, which compared intensive drug treatment using sulfonylurea or insulin with dietary therapy. Intensive drug therapy was associated with a trend toward a reduction in myocardial infarction ( $P=0.05$ ) but had no effect on the risk of death or amputation due to peripheral arterial disease (relative risk 0.6; 95 percent confidence interval, 0.4 to 1.2).<sup>46</sup> These data suggest that intensive blood glucose control in patients with either type 1 or type 2 diabetes may not favorably affect peripheral arterial disease.

#### Treatment of Hypertension

Hypertension is a major risk factor for peripheral arterial disease (as recognized by the Joint National Committee<sup>22</sup>), but data are not available to clarify whether treatment will alter the progression of the disease or the risk of claudication.

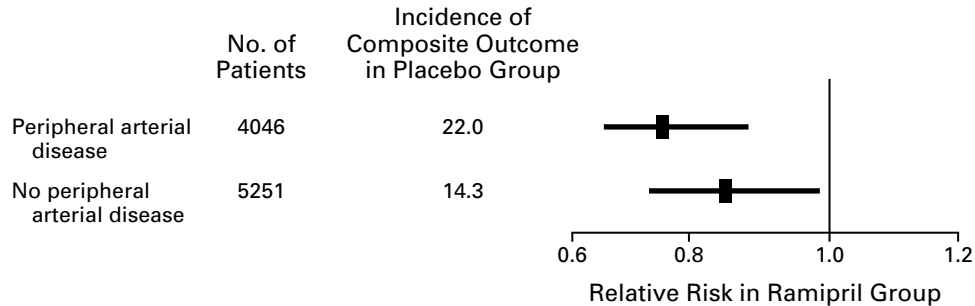
Beta-adrenergic-antagonist drugs have been thought to have unfavorable effects on symptoms in patients with peripheral arterial disease.<sup>22</sup> This concern arose from several early case reports of worsening claudication and decreases in blood flow in the legs in patients taking these drugs.<sup>47</sup> In one study, either atenolol or the calcium-channel-blocking drug nifedipine, given alone, did not adversely affect skin temperature in the extremities or maximal treadmill walking distance, but the combination of the two drugs reduced maximal treadmill walking distance by 9 percent.<sup>48</sup> In other studies, both selective and non-selective beta-adrenergic-antagonist drugs had no adverse effects on the peripheral circulation in patients with peripheral arterial disease.<sup>49</sup> A meta-analysis and a critical review of these studies concluded that beta-adrenergic antagonists are safe in patients with peripheral arterial disease, except in the most severely affected patients, in whom the drugs should be administered with caution.<sup>50,51</sup>

The use of angiotensin-converting-enzyme inhibitors in patients with peripheral arterial disease may confer protection against cardiovascular events beyond that expected from blood-pressure lowering. In the Heart Outcomes Prevention Evaluation Study, 4051 of the 9297 patients (44 percent) had evidence of peripheral arterial disease (ankle-brachial index values of  $<0.90$ ).<sup>52</sup> In the entire study population, the primary end point of death from vascular causes, nonfatal myocardial infarction, or stroke occurred in 17.7 percent of the placebo group, as compared with 14.1 percent of the ramipril group. The efficacy of ramipril did not differ significantly between patients with peripheral arterial disease and those without it (Fig. 4). This study not only underscores the importance of including patients with peripheral arterial disease in trials of the secondary prevention of cardiovascular disease, but also suggests that angiotensin-converting-enzyme inhibitors reduce the risk of ischemic events in these patients.

#### Additional Approaches to Risk Modification

A high serum homocysteine concentration is an independent risk factor for peripheral arterial disease and also increases the risk of death from cardiovascular causes.<sup>20</sup> Homocysteine facilitates the oxidation of LDL cholesterol. Furthermore, by causing the formation of reactive oxygen species, homocysteine can promote endothelial dysfunction and the proliferation of vascular smooth-muscle cells, leading to acceleration of atherosclerosis.<sup>53</sup> The causes of high serum homocysteine concentrations include genetic defects in homocysteine metabolism, alterations in vitamin B<sub>12</sub> metabolism, and dietary folate deficiency. Supplementing the diet with B vitamins and fortification of food with folate lower serum homocysteine concentrations.<sup>54</sup> Despite the ease of therapy with vitamin supplements, there are no clinical trials demonstrating that reducing serum homocysteine concentration is beneficial in patients with peripheral arterial disease.

Estrogen therapy reduces several cardiovascular risk factors in postmenopausal women. In a population-based study of 2196 women who had undergone natural menopause, estrogen treatment for one year or more was associated with a decrease in the incidence of peripheral arterial disease, defined by an ankle-brachial index value of  $<0.90$  (odds ratio, 0.5; 95 percent confidence interval, 0.2 to 0.8).<sup>55</sup> The Heart and Estrogen/Progestin Replacement Study evaluated the effects of estrogen therapy in 2763 postmenopausal women with coronary artery disease.<sup>56</sup> The incidence of peripheral arterial events (defined as aortic or carotid surgery or revascularization or amputation of the foot or leg) was unaffected by therapy. In addition, estrogen therapy has been associated with reduced graft patency in women undergoing femoropopliteal bypass surgery, possibly as a result of the prothrombotic effects of the therapy.<sup>57</sup> Thus, at present, estro-



**Figure 4.** Results of Ramipril Therapy in Patients with and Patients without Peripheral Arterial Disease from the Heart Outcomes Prevention Evaluation Study.

The rate of the composite outcome of death from vascular causes, nonfatal myocardial infarction, and stroke was reduced in patients treated with ramipril; the outcomes did not differ significantly between patients with and patients without peripheral arterial disease.<sup>52</sup> Horizontal bars denote 95 percent confidence intervals. In the graph, values below unity favor ramipril treatment.

gen has no role in the treatment of peripheral arterial disease in postmenopausal women; however, the presence of peripheral arterial disease is not a contraindication to estrogen therapy in women with indications for such therapy.

#### Antiplatelet-Drug Therapy

In patients with cardiovascular disease, antiplatelet drugs reduce the risks of nonfatal myocardial infarction, ischemic stroke, and death from vascular causes. These conclusions are based primarily on meta-analyses of studies of antiplatelet-drug therapy (primarily aspirin) conducted by the Antiplatelet Trialists' Collaboration, which included 102,459 patients who had clinical evidence of cardiovascular disease (acute or prior myocardial infarction, ischemic stroke, or other vascular diseases, including peripheral arterial disease).<sup>58</sup> The principal conclusion was that antiplatelet-drug therapy reduced the risk of fatal or nonfatal cardiovascular events from 11.9 percent in the control group to 9.5 percent in the treatment group. Thus, aspirin is recommended for secondary disease prevention in patients with cardiovascular disease. The data supporting the use of antiplatelet drugs in patients with peripheral arterial disease are described below.

##### Aspirin

The analysis by the Antiplatelet Trialists' Collaboration included a subgroup of 3295 patients with claudication. In these patients, the risk of myocardial infarction, stroke, or death from vascular causes after a mean of 27 months of follow-up was 9.7 percent in patients who received antiplatelet therapy, as compared with 11.8 percent in control patients — a reduction of 18 percent. However, the reduction was not statistically significant. Similar nonsignificant results were obtained in a subgroup of 1928 patients

who had received peripheral arterial grafts or had undergone peripheral angioplasty. The interpretation of these results has varied. The American College of Chest Physicians recommends aspirin at doses of 81 to 325 mg per day for patients with peripheral arterial disease.<sup>59</sup> In contrast, a Food and Drug Administration (FDA) expert panel found insufficient evidence to approve the labeling of aspirin as indicated for patients with peripheral arterial disease.<sup>60</sup>

Despite the lack of a statistically significant effect of aspirin in reducing the overall risk of ischemic events in patients with peripheral arterial disease, aspirin may favorably affect the peripheral circulation. For example, in the Physicians' Health Study, a primary-prevention trial, aspirin reduced the subsequent need for peripheral arterial surgery.<sup>61</sup> The Antiplatelet Trialists' Collaboration found that aspirin therapy significantly improved vascular-graft patency in 3226 patients with peripheral arterial disease who were treated with bypass surgery (with a saphenous-vein or prosthetic graft) or peripheral angioplasty and followed for an average of 19 months.<sup>62</sup> Overall, there was a 43 percent reduction in the rate of vascular-graft occlusion: 25 percent in the control group as compared with 16 percent in the aspirin group. All the antiplatelet regimens contained aspirin. Aspirin alone was as effective as the combination of aspirin and dipyridamole, sulfapyrazone, or ticlopidine in preventing graft occlusion, and high-dose aspirin (600 to 1500 mg per day) was as effective as low-dose aspirin (75 to 325 mg per day).

##### Ticlopidine

Ticlopidine is a thienopyridine drug that inhibits platelet activation by blocking platelet adenosine diphosphate receptors. In patients with peripheral arterial disease, ticlopidine was more effective than placebo in reducing the risk of fatal or nonfatal myocardial

infarction or stroke.<sup>63</sup> Ticlopidine may reduce the severity of claudication and the need for vascular surgery.<sup>64,65</sup> However, enthusiasm for this drug is tempered by the substantial risk of thrombocytopenia, neutropenia (which occurs in 2.3 percent of treated patients), and thrombotic thrombocytopenic purpura (which occurs in 1 in 2000 to 4000 patients), for which extensive hematologic monitoring is required.<sup>66,67</sup> This concern has led to the development of other drugs in the thienopyridine class.

#### **Clopidogrel**

Clopidogrel is a thienopyridine drug that has fewer hematologic side effects than ticlopidine. The primary data that support the use of clopidogrel were derived from the Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) trial. This trial compared 75 mg of clopidogrel per day with 325 mg of aspirin per day in more than 19,000 patients with recent myocardial infarction, recent ischemic stroke, or peripheral arterial disease (6452 patients).<sup>15</sup> The patients with peripheral arterial disease either had claudication with an ankle-brachial index value of 0.85 or less or a history of claudication with previous peripheral bypass surgery, angioplasty, or amputation. Thus, these patients were symptomatic and had moderately severe peripheral arterial disease. Clopidogrel was associated with an overall reduction of 8.7 percent in the primary end point of fatal or nonfatal ischemic stroke, fatal or nonfatal myocardial infarction, or death from other vascular causes ( $P=0.04$ ) (Fig. 5). This result led to FDA approval of clopidogrel for the secondary prevention of atherosclerotic events in patients with atherosclerosis, including those with peripheral arterial disease. In the CAPRIE trial, both clopidogrel and aspirin were well tolerated. However, a recent report described the occurrence of thrombotic thrombocytopenic purpura early in the course of treatment with clopidogrel.<sup>68</sup> The estimated risk of thrombotic thrombocytopenic purpura is 4 per million patients, a level that does not warrant routine hematologic monitoring.

In the CAPRIE trial, there were differences in the treatment effect among patients with stroke, myocardial infarction, and peripheral arterial disease. In the 6452 patients with peripheral arterial disease, the primary end point occurred at an annual rate of 4.9 percent in patients given aspirin and 3.7 percent in patients given clopidogrel, an adjusted risk reduction of 23.8 percent. This treatment effect was greater than that in patients with myocardial infarction or stroke, but the differences could also have occurred by chance (Fig. 5).

#### **Other Antiplatelet Drugs**

Picotamide inhibits thromboxane  $A_2$  synthase and blocks thromboxane  $A_2$  receptors. In an 18-month trial in 2304 patients with peripheral arterial disease,

there was a nonsignificant 19 percent reduction in fatal and nonfatal ischemic events in the picotamide group, as compared with the placebo group.<sup>69</sup> No further studies have been performed with this drug. Ketanserin is an antagonist of  $S_2$  serotonin receptors that has antiplatelet effects. In a large trial of ketanserin in 3899 patients with peripheral arterial disease, the mortality rate was slightly, but not significantly, higher in the ketanserin group (perhaps in relation to prolongation of the QT interval), and the drug did not relieve claudication.<sup>70,71</sup>

In summary, patients with peripheral arterial disease have systemic atherosclerosis and are at high risk for cardiovascular disease and death. Although the data are not conclusive, aspirin should be considered the primary antiplatelet drug for preventing ischemic events in patients with peripheral arterial disease. Aspirin is also effective in maintaining vascular-graft patency and may prevent thrombotic complications of peripheral arterial disease. Clopidogrel has FDA approval for the prevention of ischemic events in patients with peripheral arterial disease and may be more effective than aspirin in these patients.

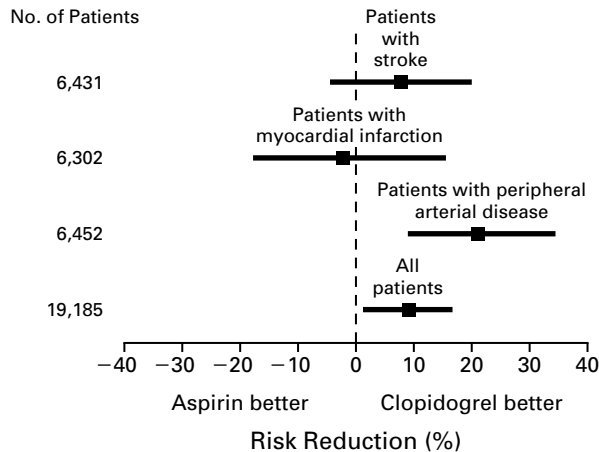
### **NONPHARMACOLOGIC THERAPY FOR CLAUDICATION**

#### **Goals of Therapy**

Patients with claudication have marked impairment in exercise performance and overall functional capacity. Their peak oxygen consumption measured during graded treadmill exercise is 50 percent of that in age-matched normal subjects, indicating a level of impairment similar to that among patients with New York Heart Association class III heart failure.<sup>72</sup> In addition, patients with claudication typically report great difficulty in walking short distances, even at a slow speed. Reduced walking capacity is associated with impairment in the performance of activities of daily living and in the quality of life.<sup>28,73</sup> Improving mobility and improving the quality of life are important treatment goals for patients with peripheral arterial disease.

#### **Exercise Therapy**

The primary nonpharmacologic treatment for claudication is a formal exercise-training program, as demonstrated in over 20 randomized trials (albeit many with small samples).<sup>74</sup> Exercise improves not only maximal treadmill walking distance, but also the quality of life and community-based functional capacity (i.e., the ability to walk at defined speeds and for defined distances).<sup>75</sup> A rigorous exercise-training program may be as beneficial as bypass surgery and may be more beneficial than angioplasty.<sup>76,77</sup> A meta-analysis of randomized trials found that exercise training increased maximal treadmill walking distance by 179 m (95 percent confidence interval, 60 to 298).<sup>31</sup> This degree of



**Figure 5.** Results of the Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) Trial.

In the subgroup of patients with peripheral arterial disease, the primary end point of fatal or nonfatal myocardial infarction, fatal or nonfatal stroke, or death from other vascular causes occurred at an annual rate of 4.9 percent in those taking aspirin and 3.7 percent in those taking clopidogrel, a reduction of 23.8 percent. This reduction was greater than that in the subgroups of patients with myocardial infarction or stroke.<sup>15</sup> Horizontal bars denote 95 percent confidence intervals.

improvement should translate into longer walking distances on level ground.

Although exercise therapy is clearly effective, it has several limitations. The best results require a motivated patient in a supervised setting, typically modeled after cardiac rehabilitation.<sup>78</sup> However, supervised exercise-training programs are not covered by medical insurance, which prevents their widespread use. Exercise training must also be maintained on a regular basis, or the benefits will be lost. Thus, although exercise is recommended as the initial treatment for patients with claudication (Fig. 3), lack of availability and insurance coverage limit the overall effectiveness of exercise therapy.

Several studies have examined the mechanisms by which exercise training exerts its benefits. Exercise training is not associated with substantial changes in blood flow to the legs, and the changes that occur do not predict the clinical response.<sup>79</sup> Despite the absence of a hemodynamic effect, exercise training improves oxygen extraction in the legs.<sup>80</sup> The intermediary metabolism of skeletal muscle is also favorably affected by training, as evidenced by an improvement in muscle carnitine metabolism.<sup>81</sup> Finally, alterations in gait and walking efficiency may contribute to the training response. At submaximal workloads, training results in a decrease in oxygen consumption and thus improved walking efficiency.<sup>82</sup>

## DRUG THERAPY FOR CLAUDICATION

### Vasodilator Drugs

Vasodilator drugs, such as papaverine, were the first medications studied for the treatment of claudication, but several controlled trials have found no evidence of clinical efficacy of drugs of this class.<sup>83</sup> There are several pathophysiologic explanations for this finding. During exercise, the portion of a resistance vessel located distally to a stenosis or occlusion dilates in response to ischemia. Vasodilators do not affect these vessels, whose dilation is due to endogenous factors, but they may decrease resistance in other vessels, leading to a “steal” of blood flow away from the under-perfused muscle. Vasodilators can also lower systemic pressure, leading to a reduction in perfusion pressure. Thus, current data do not support the use of vasodilators for claudication.

### Pentoxifylline

Pentoxifylline is a methylxanthine derivative that improves the deformability of red cells and white cells, lowers plasma fibrinogen concentrations, and has antiplatelet effects.<sup>84</sup> The drug was approved in 1984 for the treatment of claudication. In one of the first randomized trials, pentoxifylline increased maximal treadmill walking distance by 12 percent as compared with placebo, but there was no difference between the two groups in the increase in maximal treadmill walking distance as compared with base-line values (Table 3).<sup>85</sup> Another study found a nonsignificant increase of 21 percent in maximal treadmill walking distance in patients treated with pentoxifylline as compared with placebo.<sup>86</sup> Similarly, in a recent study pentoxifylline was no more effective than placebo in increasing maximal treadmill walking distance or functional status as assessed by questionnaires.<sup>87</sup> A meta-analysis of the pentoxifylline studies found a net benefit of 44 m in the maximal distance walked on a treadmill (95 percent confidence interval, 14 to 74).<sup>31</sup> This and another meta-analysis and two systematic reviews of pentoxifylline concluded that the drug may have a small effect on walking ability, but that the data are insufficient to support its widespread use.<sup>31,88,101,102</sup>

### Cilostazol

Cilostazol was approved in 1999 by the FDA for the treatment of claudication. The primary action of cilostazol is to inhibit phosphodiesterase type 3, thereby increasing intracellular concentrations of cyclic AMP. Cilostazol undergoes extensive hepatic metabolism by the 3A4 isoform of cytochrome P450 (CYP3A4) and to a lesser extent by the 2C19 and 1A2 isoforms. Although the drug does not inhibit the cytochrome CYP450 enzyme system, other drugs that inhibit CYP3A4 may increase serum cilostazol concentrations.<sup>103</sup> Cilostazol inhibits platelet aggregation, the formation of arterial thrombi, and vascular

smooth-muscle proliferation and causes vasodilatation.<sup>104-106</sup> However, as discussed above, vasodilator and antiplatelet drugs do not improve claudication-limited exercise performance, and therefore the mechanism of effect of cilostazol in peripheral arterial disease is unknown.

Type 3 phosphodiesterase inhibitors such as milrinone were developed as inotropic agents for the treatment of heart failure. In patients with chronic heart failure, milrinone treatment was associated with an increase in mortality.<sup>107</sup> In comparison with milrinone, cilostazol has fewer cardiac inotropic effects but equivalent vasodilating and platelet-inhibiting properties.<sup>108</sup>

Four randomized, placebo-controlled trials of cilostazol enrolling 1534 patients with claudication have been published (Table 3 and Fig. 6).<sup>87,89-91</sup> In all four trials, cilostazol (100 mg twice daily) improved both pain-free and maximal treadmill walking distance, as compared with placebo. Cilostazol (50 mg twice daily) also increased maximal treadmill walking distance.<sup>91</sup> In one trial, cilostazol (100 mg twice daily) was su-

perior to both placebo and pentoxifylline.<sup>87</sup> In three of the trials, cilostazol also improved several aspects of physical functioning and the quality of life, as assessed by questionnaires.<sup>89-91</sup> The drug also causes small increases in ankle-brachial index values and raises serum HDL cholesterol concentrations.<sup>90</sup>

The predominant side effect of cilostazol is headache, which affects 34 percent of patients taking 100 mg twice daily, as compared with 14 percent of patients taking placebo (data presented to the FDA Cardiovascular and Renal Drugs Advisory Committee on July 9, 1998). In addition, transient diarrhea, palpitations, and dizziness have been described. Cilostazol can be administered with aspirin, but there are no data on the safety of coadministration of cilostazol with clopidogrel. Because of concern about the risk of death with this class of drugs, data from more than 2000 patients who were followed for up to six months were presented to the FDA. Death from cardiovascular causes occurred in 0.6 percent of cilostazol-treated patients and 0.5 percent of placebo-treat-

TABLE 3. DRUG THERAPIES FOR PATIENTS WITH CLAUDICATION.

DRUG AND STUDY	NO. OF SUBJECTS	DOSAGE	MONTHS OF THERAPY	NET MWD*	P VALUE†	RESULTS OF FUNCTIONAL ASSESSMENT‡
%						
Pentoxifylline						
Porter et al. <sup>85</sup>	128	1.2 g/day orally	6	12	0.19	ND
Lindgarde et al. <sup>86</sup>	150	1.2 g/day orally	6	21	0.09	ND
Dawson et al. <sup>87</sup>	698	1.2 g/day orally	6	0	0.82	Negative
Hood et al. <sup>88</sup>	511	Various oral doses	Varied	30	<0.05	ND
Cilostazol						
Dawson et al. <sup>89</sup>	81	200 mg/day orally	3	73	<0.01	Positive
Money et al. <sup>90</sup>	239	200 mg/day orally	4	32	<0.001	Positive
Beebe et al. <sup>91</sup>	516	200 mg/day orally	6	82	<0.001	Positive
Dawson et al. <sup>87</sup>	698	200 mg/day orally	6	33	<0.001	Positive
Naftidrofuryl						
Moody et al. <sup>92</sup>	188	600 mg/day orally	6	11	0.27	ND
Trubestein et al. <sup>93</sup>	104	600 mg/day orally	3	16	NS	ND
Adhoute et al. <sup>94</sup>	94	633 mg/day orally	6	32	<0.001	Positive
Propionyl levocarnitine						
Brevetti et al. <sup>95</sup>	245	1-3 g/day orally	6	27	0.049	ND
Brevetti et al. <sup>96</sup>	114	2 g/day orally	12	41	<0.01	Positive
Prostaglandins						
Belch et al. <sup>97</sup>	80	Prostaglandin E <sub>1</sub> , multi-dose parenterally	2	70	<0.01	Positive
Diehm et al. <sup>98</sup>	213	Prostaglandin E <sub>1</sub> , 60 µg/day parenterally	2	41	<0.05	ND
Lievre et al. <sup>99</sup>	83	Beraprost, 120 µg/day orally	3	50	NS	ND
Lievre et al. <sup>100</sup>	424	Beraprost, 120 µg/day orally	6	25	0.004	Positive
Ticlopidine						
Balsano et al. <sup>64</sup>	121	500 mg/day orally	21	33	<0.01	ND

\*Net MWD is the net improvement in maximal treadmill walking distance with the drug as compared with placebo.

†NS indicates a result reported as not significant but with no P value provided.

‡Functional assessment involved the use of questionnaires to assess the effect of treatment on the quality of life. ND denotes not done.

ed patients. Myocardial infarction occurred in 1.5 percent of cilostazol-treated patients and 1.1 percent of placebo-treated patients. Because of the experience with milrinone, the cilostazol label includes a black-box warning that cilostazol should not be given to patients with claudication who also have heart failure.

**Naftidrofuryl**

Naftidrofuryl has been available for several decades in Europe for treating claudication. Several mechanisms of action have been proposed, including antagonism of 5-hydroxytryptamine receptors. A critical review of five placebo-controlled trials concluded that naftidrofuryl improved pain-free treadmill walking distance, but not maximal walking distance (Table 3), and was associated with fewer cardiovascular events than placebo.<sup>109</sup> This drug is not available in the United States.

**Levocarnitine and Propionyl Levocarnitine**

In patients with peripheral arterial disease, metabolic abnormalities develop in the skeletal muscles of the lower extremities.<sup>110</sup> These abnormalities include impairment of the activity of the mitochondrial electron-transport chain in the ischemic muscles and accumulation of intermediates of oxidative metabolism (acylcarnitines).<sup>111,112</sup> Exercise performance is most impaired in patients with the greatest accumulation of acylcarnitines in muscle. Thus, claudication is caused not just by reduced blood flow, but also by alterations in skeletal-muscle metabolism.

Levocarnitine and propionyl levocarnitine may improve metabolism and exercise performance of ischemic muscles. Levocarnitine, 2 g twice daily, improved maximal treadmill walking distance, but propionyl levocarnitine (an acyl form of carnitine) was more effec-

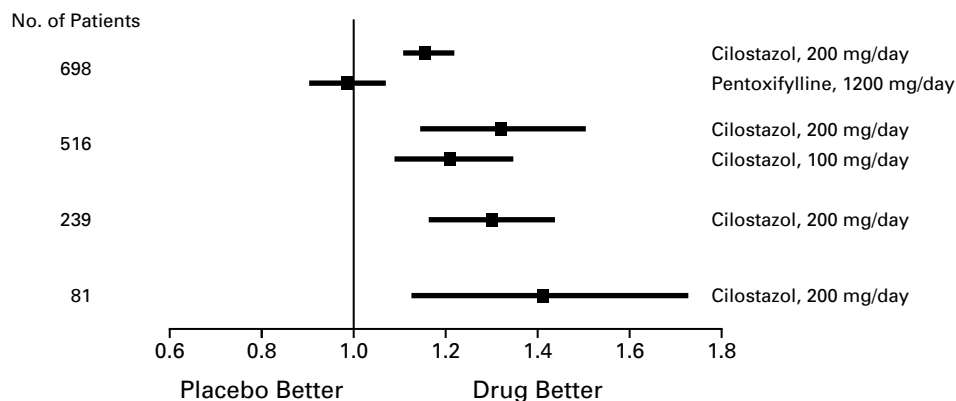
tive than levocarnitine in improving maximal treadmill walking distance.<sup>113</sup> In two multicenter trials enrolling 730 patients, the pain-free and maximal treadmill walking distance improved more in patients receiving propionyl levocarnitine than in those receiving placebo.<sup>95,96</sup> The drug also improved the quality of life more than placebo and had fewer side effects.<sup>96</sup> Propionyl levocarnitine has not been approved for use in the United States.

**Prostaglandins**

Prostaglandins have been evaluated primarily for the treatment of patients with critical leg ischemia. The primary end points of these trials were relief of ischemic pain, healing of ischemic ulcers, and reduction in the rate of amputation.<sup>114,115</sup> Fewer studies have been performed in patients with claudication. A study of 90 such patients found that parenteral administration of prostaglandin E<sub>1</sub> in a formulation of lipid microspheres improved maximal treadmill walking distance and quality of life.<sup>97</sup> Oral analogues of prostaglandins have not been as well studied. A small trial found that beraprost was moderately efficacious, but at higher doses it had substantial side effects, such as headache, flushing, and gastrointestinal intolerance.<sup>99</sup> A recent study found that beraprost had positive effects on maximal treadmill walking distance and the quality of life (Table 3) and reduced the rate of critical cardiovascular events.<sup>100</sup> The use of prostaglandins in patients with peripheral arterial disease needs further evaluation.

**Other Drugs**

Treatment with chelation, vitamin E, or testosterone has no effect on claudication.<sup>116-118</sup> Treatments that have had promising results in preliminary studies in-



**Figure 6.** Results of Four Randomized, Placebo-Controlled Trials of Cilostazol for the Treatment of Claudication.

The data are shown as the geometric mean ratios of the maximal treadmill walking distance (on the horizontal axis) and 95 percent confidence intervals for cilostazol as compared with placebo.<sup>87,89-91</sup>

clude buflomedil, *Ginkgo biloba*, inositol niacinate, defibrotide, verapamil, anticoagulants, and arginine, but none of these have been evaluated in large clinical trials.<sup>119-125</sup>

### CONCLUSIONS

Peripheral arterial disease is a highly prevalent manifestation of atherosclerosis that is associated with a substantial risk of illness and death and a marked reduction in ambulatory capacity and quality of life. Unfortunately, peripheral arterial disease is undertreated with regard to risk-factor modification, use of antiplatelet drugs, and treatment of symptoms. Clinical trials specifically directed to patients with peripheral arterial disease are needed to address the benefits of the treatment of hyperlipidemia, diabetes, hyperhomocysteinemia, and other prevalent risk factors. Despite these limitations, patients with peripheral arterial disease should be considered candidates for secondary-prevention strategies, just as are patients with coronary artery disease. Angiotensin-converting-enzyme inhibitors may decrease the risk of ischemic events. However, antiplatelet drugs are effective at reducing the risk of fatal and nonfatal ischemic events in patients with peripheral arterial disease. The data supporting the use of antiplatelet drugs are stronger than those supporting the use of angiotensin-converting-enzyme inhibitors. Aspirin should be considered in all patients, with clopidogrel an alternative (and potentially more effective) drug.

Medical therapies to treat the symptoms of claudication and limited mobility are now well established. A supervised walking-based exercise program should be considered first for all patients because of the low risk and the likelihood of marked improvement in functional capacity that is associated with exercise. Drugs that improve functional status are also available. Pentoxifylline has limited efficacy, but cilostazol improves both pain-free and maximal treadmill walking distance and the quality of life. Several other compounds, such as propionyl levocarnitine, are under investigation for the treatment of claudication and critical leg ischemia.

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