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Pharmacological Treatment of Patients with Peripheral Arterial Disease

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Contents

Abstract

Atherosclerosis is a disease process that affects the coronary, cerebral and peripheral arterial circulation. While great emphasis has been placed on the aggressive pharmacological management of coronary artery disease, less attention has been paid to the pharmacological management of peripheral vascular disease, despite its significant morbidity and mortality. The purpose of medical management in peripheral arterial disease is to relieve symptoms of claudication and to prevent thrombotic vascular events. These goals are best achieved through aggressive risk factor modification and pharmacotherapy. Risk factor modification includes smoking cessation, adequate control of blood pressure and cholesterol, as well as aggressive glycaemic control in patients with diabetes mellitus. Antiplatelet therapy and relief of claudication is also achieved through pharmacotherapy. With aggressive risk factor modification and adequate pharmacotherapy, patients with peripheral arterial disease can have an improved quality of life as well as prolonged survival.

Table I. Prevalence of symptoms in patients with proven peripheral arterial disease

Study	No. of participants	Classic claudication[a]	Atypical symptoms	No symptoms
Hirsch et al.[8]	726	63 (9%)	386 (53%)	277 (38%)
McDermott et al.[9]	460	150 (32%)	219 (48%)	91 (20%)

a Classic claudication defined as: exercise-induced calf pain, not present at rest, requires stopping and resolves in 10 minutes or less.

Peripheral arterial disease (PAD) is a major manifestation of systemic atherosclerosis and is frequently associated with other atherosclerotic diseases such as coronary artery disease (CAD) and cerebrovascular disease. Combined, this triad of systemic atherosclerosis is the principle cause of death and disability in persons aged 50 years and older.[1] It is estimated that 12% of the adult population in the US, approximately 8–10 million people, will be affected by PAD in their lifetime.[2,3]

The prevalence of PAD increases with age.[4,5] The Framingham Heart Study reported that the average annual incidence of PAD based on symptomatic intermittent claudication (IC) increased from 6 per 10 000 men aged 30–44 years to 61 per 10 000 men aged 65–74. Similar findings were reported in women as well.[6] It is estimated that 20% of the population over the age of 70 have PAD.[7]

The most common clinical symptoms of PAD are aching pain, cramping or numbness in the affected limb. They are induced by activities that increase blood and oxygen demand of the lower extremities such as exercise and walking, and are usually relieved by rest. However, the symptoms of classic claudication (exercise-induced calf-pain, not present at rest, which requires stopping and resolves within 10 minutes of rest) are rather uncommon among patients with PAD. Recently Hirsch et al. reported classic claudication in about 9% of 726 patients with proven PAD.[8] In another recent study McDermott et al.[9] found classic symptoms of IC only in 32%, atypical symptoms in 48% and no exertional leg pain in 20% of patients with noninvasively proven significant PAD (table I).

Because of the significant overlap between PAD, CAD and cerebrovascular disease, patients with PAD have significantly higher morbidity and mortality when compared with healthy controls. It has been reported that patients with IC, when compared with age-matched controls, have a 3-fold increase in cardiovascular mortality rate.[2,10-12] It is estimated that approximately 80% of mortality in PAD patients is from cardiovascular events. Sixty-three percent of deaths are from CAD, 9% are from cerebrovascular disease, and 8% are from other cardiovascular events such as a ruptured aneurysm.[13-15] In a retrospective analysis of 236 patients with PAD (mean age, 80 years), Ness and Aronow,[16] found that 68% of the patients had coexisting CAD and 42% had a history of ischemic stroke. However, the true prevalence of coexisting CAD and cerebrovascular disease in patients with PAD is highly dependent upon the diagnostic method used to identify the disease. The coexistence of CAD has been reported at 39% using clinical history and electrocardiogram, and as high as 90% when using angiography. Similar results have been reported with regard to cerebrovascular disease, with prevalence reported as low as 0.5–15% using clinical history, and as high as 44–52% using cervical bruit or abnormal Doppler testing.[2,14] This underscores the fact that PAD, CAD and cerebrovascular disease, are all inevitable manifestations of the same pathophysiological process: systemic atherosclerosis.

Despite the high prevalence of PAD in the general population, and its strong association with cardiovascular morbidity and mortality, PAD has not received sufficient attention with regard to aggressive treatment and risk factor modification, especially when compared with CAD.[8,17]

The medical management of PAD consists of two primary goals: (i) relief of IC and, hence, improve-

ment of functional status and quality of life (section 3); and (ii) prevention of thrombotic events in the peripheral, coronary and cerebrovascular circulation, which prolongs overall survival. Aggressive risk factor modification (table II) and pharmacological therapy (table III) are the cornerstones through which these goals may be achieved.

1. Risk Factor Modifications

1.1 Cigarette Smoking

Tobacco use is the single most important risk factor for the development and progression of PAD. In patients with PAD, tobacco use is associated with decreased survival; with patients who quit smoking having approximately twice the 5-year survival rate of those who continue to smoke.[18] Smoking is associated with increased progression of atherosclerosis and increased risk of surgical amputation.[19] Tobacco use is also associated with increased risk of developing IC and life-threatening ischaemia.[20,21] Furthermore, smokers have lower patency and survival rates after revascularization than non-smokers.[22]

Spontaneous quit rates even for motivated persons are low (<5% per year). Psychological support and counselling improves quit rates. However, the most effective method of smoking cessation is using nicotine replacement therapy (NRT), either alone or in combination with the oral antidepressant bupropion.[23,24]

Table II. Risk factors for peripheral arterial disease and treatment goals

Smoking	Cessation (nicotine replacement therapy, bupropion)
Hypertension	Blood pressure <130/85mm Hg
Diabetes mellitus	Glycosylated haemoglobin <7%
Dyslipidaemia	Low-density lipoprotein <100 mg/dL (2.59 mol/L)

Table III. Pharmacological treatment of peripheral arterial disease

Drug class	Drug[a]
Antiplatelet	Clopidogrel 75 mg/day or aspirin 81–325 mg/day
ACE inhibition	Ramipril 10 mg/day[b]
Statin	Simvastatin 40 mg/day[b]
Anti-claudication	Cilostazol 100mg twice daily

a Recommendations are made on the basis of the most solid data available to date.

b The effects seen may be a group effect; further studies are needed to evaluate this.

1.2 Hypertension

Epidemiological studies have shown hypertension to be associated with the development of CAD and cerebrovascular disease, as well as with a 2- to 3-fold increased risk of claudication.[25-28] Antihypertensive therapy reduces the risk of stroke, CAD and vascular death.[28] Solomon et al. found neither adverse nor beneficial effects with the β-blocker atenolol or the calcium channel antagonist nifedipine on PAD when given as single therapy. However, the combination of both decreased walking ability by 9% (pain-free walking distance measured by treadmill).[29] Another group of investigators found no adverse effects of selective or non-selective β-blockers on the lower extremity circulation in patients with PAD (assessed by pletysmographic measurement of calf blood flow and symptoms of claudication before and after exercise).[30] The current consensus regarding the use of β-blockers in patients with PAD is that they can be safely used for the treatment of hypertension in all but those with the most severe PAD.[31] The large interventional hypertension trials have not specifically targeted patients with PAD. Therefore, it is unclear what effect antihypertensive therapy has on the development or progression of PAD. However, consensus recommends treatment of hypertension in patients with PAD to a blood pressure of less than 130/85mm Hg.[32]

ACE inhibitors may be ideal agents for hypertension control in patients with PAD because of their

vascular protective effects.[33,34] In the Heart Outcomes Prevention Evaluation (HOPE) study,[35] ramipril was found to significantly reduce cardiovascular death, MI and stroke in a broad range of patients at risk for cardiovascular death (relative risk = 0.78; 95% CI, 0.7–0.86; $p < 0.001$). Secondary outcomes such as revascularization, either cardiac or peripheral, were also significantly reduced in patients treated with ramipril. Patients with PAD (4051/9297) receiving ramipril had similar reductions in events as patients without PAD (figure 1). Therefore, in patients with PAD, ramipril reduces the risk of fatal and nonfatal ischemic events. Interestingly, the beneficial results could not be explained by blood pressure lowering as most patients did not have hypertension and the mean decrease in systolic blood pressure was only 2mm Hg.

In a large, double-blind, randomised study the angiotensin II (ATII) receptor antagonist losartan was also found to significantly reduce the composite endpoint of cardiovascular death, MI or stroke in patients with hypertension compared with atenolol (508/4605 [11%] vs 588/4588 [13%]; $p = 0.021$).[36] Although the results seem to be very comparable to the HOPE data, there are several important differences between the two studies. The mean decrease in systolic blood pressure compared with baseline was 30.2mm Hg and 29.1mm Hg in the losartan and atenolol groups, respectively. When primary endpoints were examined individually only the reduction of stroke in the losartan group was found to be significant (232/4605 [5%] vs 309/4588 [7%]; $p = 0.001$). The prevalence of coronary or peripheral revascularization procedures, a prespecified secondary endpoint, did not differ between the two treatment groups. The total number of participants with a history of PAD included in the study was low (520/9193 [6%]). On the basis of the current data, the use of losartan for the treatment of hypertension in patients with PAD can be recommended. However, possible protective vascular effects of losartan and other ATII receptor antagonists on PAD are still to be determined.

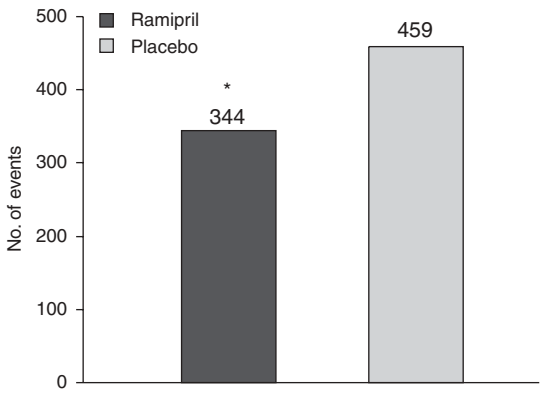

Fig. 1. Results from the Heart Outcomes Prevention Evaluation study (HOPE). Number of events (myocardial infarction, stroke or death from cardiovascular cause) in patients with peripheral arterial disease treated with either ramipril 10 mg/day (n = 1966) or placebo (n = 2085) for an average of 5 years.[35] * $p < 0.001$.

1.3 Dyslipidaemia

Several large randomised trials have looked at lipid lowering therapy with HMG-CoA reductase inhibitors (statins) in patients with CAD. The Scandinavian Simvastatin Survival Study (4S),[37] and Cholesterol and Recurrent Events (CARE)[38] both showed major reductions in cardiac morbidity and mortality in patients receiving statin therapy. Stroke was also reduced in both trials by approximately 20%, suggesting statin therapy has an effect on atherosclerosis throughout the peripheral circulation. In the 4S study, only 4% of participants had IC at baseline. However, a post hoc analysis of the 4S trial found that simvastatin reduced the risk of new or worsening claudication by 38% compared with placebo.[39]

The recently published Heart Protection Study reported effects of cholesterol lowering in individuals with CAD, other arterial disease or diabetes mellitus over a period of 5 years.[40] A total of 20 536 patients were randomised to either simvastatin 40 mg/day or matching placebo. All-cause mor-

tality was significantly reduced from 14.7 to 12.9%, mainly as a result of a reduction in coronary death. MI and stroke were also significantly reduced in the simvastatin group compared with placebo (8.7 vs 11.8% and 4.3 vs 5.7%, respectively). Simvastatin reduced the need for revascularization procedures from 11.7 to 9.1%; this finding was also highly significant. For the first occurrence of any of these major vascular events there was a significant 24% reduction in the event rate (2033 [19.8%] vs 2585 [25.2%] patients, $p < 0.0001$). In the subgroup of patients with PAD only, the reduction in major vascular events was similar (24.7 vs 30.5%, $p < 0.0001$) [figure 2]. This very large, randomised treatment trial supports the use of statin drugs in patients without CAD but other arterial disease or diabetes. Even before the release of this compelling data the National Cholesterol Education Program (NCEP) considered peripheral vascular disease a coronary heart disease (CHD) risk equivalent and recommended a target LDL of less than 100 mg/dL (2.59 mmol/L) in these patients.[41]

Nicotinic acid has previously been shown to reduce cardiovascular morbidity and mortality.[42-45] It increases high-density lipoprotein (HDL) as well as lowering triglyceride levels. However, its use has been limited because of previously published reports discouraging its use among patients with diabetes because of a possible effect on blood glucose levels.[42-45] However, the Arterial Disease Multiple Intervention Trial (ADMIT) performed in patients with PAD[46] showed no difference in glycosylated haemoglobin (HgA_{1c}) levels from baseline among those receiving nicotinic acid. Nicotinic acid raised HDL by 29% and lowered triglycerides by approximately 25%.[46] Nicotinic acid also had an anticoagulant effect lowering levels of fibrinogen and F1.2, both markers for thrombin generation.[47] These findings suggest that nicotinic acid may safely be used in patients with diabetes as an alternative to a statin and/or a fibric acid derivative in those who cannot tolerate these agents, or fail previous therapy to correct hypertriglyceridaemia or low HDL.

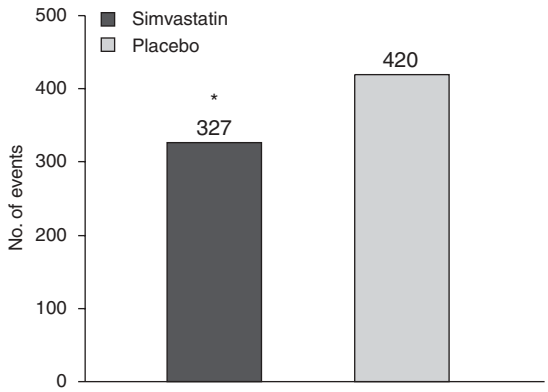

Fig. 2. Results from the Medical Research Council/British Heart Foundation (MRC/BHF) Heart Protection Study. Number of events (major coronary events, strokes or revascularization) in patients with peripheral arterial disease treated with either simvastatin 40 mg/day (n = 1325) or placebo (n = 1376) for an average of 5 years.[40] * $p < 0.0001$.

1.4 Diabetes Mellitus

Diabetic patients have a 2- to 4-fold increased risk of developing IC compared with those without diabetes.[7,48,49] They also tend to have more severe, diffuse multivessel PAD that is less amenable to revascularization, and are also more prone to restenosis. They are at high risk of developing microangiopathy, such as retinopathy, nephropathy and neuropathy.[50] Aggressive glycaemic control decreases the risk of microvascular complications. However, limited data exist to support aggressive glycaemic control to prevent the clinical manifestations of systemic atherosclerosis, especially PAD.

In the United Kingdom Prospective Diabetes Study (UKPDS),[51] intensive versus conventional glycaemic control was evaluated. The study found that aggressive glycaemic control reduced the overall microvascular complication rate by 25%. However, there was no significant difference found in reducing risk of amputation as a result of PAD (relative risk = 0.51; 99% CI, 0.01–19.64). Further-

more, no significant effect on cardiovascular complications was found (16% reduction, p = 0.052). Despite this, the UKPDS did show a continuous association between cardiovascular events and hyperglycaemia. However, it did not definitively show that aggressive management of hyperglycaemia would reduce the risk of these events.[51] Unfortunately, the prevalence of PAD was not defined in this patient population. Therefore, it is difficult to make any conclusions as to the effect of aggressive glycaemic control on PAD. Current guidelines recommend a target HbA_{1c} level of <7% in patients with diabetes.[52]

2. Antiplatelet Therapy

2.1 Aspirin

The Antiplatelet Trialists' Collaboration (APTC) is a meta-analysis that investigated the efficacy of prolonged (at least 1 month) antiplatelet therapy (mainly aspirin [acetylsalicylic acid]) in preventing vascular events, including nonfatal myocardial infarction (MI), stroke and vascular death. Data were evaluated from 145 randomised studies that included approximately 100 000 patients. Approximately 70 000 of these patients were high-risk patients with evidence of cardiovascular disease such as previous MI, cerebrovascular disease and also peripheral vascular disease. Results showed that there was a 27% reduction in the odds ratio for subsequent vascular death, MI or stroke in patients taking aspirin compared with controls.[53] The APTC also found that in patients who had bypass surgery or peripheral angioplasty, aspirin significantly improved vessel patency. There was a reduction of vascular graft occlusion from 25% in the control group to 16% in the aspirin group ($p < 0.0001$).[54] These results suggest efficacy of aspirin to reduce morbidity and mortality in patients with PAD but it should be noted that to date no prospective, randomised study has been performed to confirm these findings.

2.2 Dipyridamole, Ticlopidine and Clopidogrel

The use of dipyridamole as monotherapy has not been shown to have significant antithrombotic effects in patients with PAD.[55] However, its efficacy as combination therapy with aspirin has had mixed results. In the APTC, no significant difference was found between the use of dipyridamole and aspirin versus aspirin alone with regards to preventing vascular events.[53] However, McCollum et al.[56] found that in patients undergoing femoropopliteal bypass surgery, the incidence of cardiovascular events was significantly lower in patients receiving aspirin and dipyridamole (35 events) than in patients who received placebo (53 events) [p = 0.004].

Ticlopidine and clopidogrel are both adenosine diphosphate receptor antagonists that have potent antiplatelet activity. In the Swedish Ticlopidine Multicenter Study (STIMS), ticlopidine was compared with placebo in preventing cardiovascular events in 687 patients with IC. Ticlopidine was found to significantly reduce cardiovascular events and was also found to reduce mortality by 30% (p = 0.015).[57] The findings from the Estudio Multicentrico Argentino de la Ticlopidine en las Arteriopatias Perifericas (EMATAP) trial showed ticlopidine to significantly reduce thrombotic events and revascularization in patients with IC (5/304 vs 20/311 patients treated with ticlopidine and placebo, respectively, p = 0.002).[58] Furthermore, ticlopidine has been found to relieve symptoms, increase walking distance and improve lower extremity ankle pressure indices.[59,60] However, these trials were rather small and their results never confirmed in a larger trial. Therefore, use of ticlopidine in PAD can be recommended for its antiplatelet action only.

Unfortunately, the use of ticlopidine has been limited because of potential adverse effects, most importantly, bone marrow suppression. Neutropenia has been reported to occur in approximately 2.4% of patients taking ticlopidine. Thrombotic thrombo-

cytopenia purpura occurs at a rate of about 1 in every 2000–4000.[61] Therefore, haematological monitoring is recommended during the first 3 months of therapy. More common adverse effects include nausea, diarrhoea, vomiting and GI bleeding, which also limit its clinical use.[57,58,61]

The Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial looked at the use of clopidogrel versus aspirin in preventing vascular events in patients with systemic atherosclerosis (recent stoke, MI or symptomatic PAD).[62] The study enrolled 19 185 patients and followed them for an average of approximately 2 years. Patients treated with clopidogrel had an annual 5.32% risk of stroke, MI or vascular death compared with 5.83% with aspirin. This represents a statistically significant 8.7% relative risk reduction ($p = 0.043$; 95% CI 0.3–16.5).[62] In a subset analysis of 6452 patients with PAD, clopidogrel recipients had a 23.8% relative risk reduction ($p = 0.0028$; 95% CI = 8.9–36.2) compared with aspirin recipients with an annual event rate of 3.71% compared with 4.86% (figure 3). Safety was also evaluated. Clopidogrel could be as safely used as medium-dose aspirin (325mg) with no significant difference in frequency of neutropenia or thrombocytopenia. As a result, no haematological monitoring is recommended.

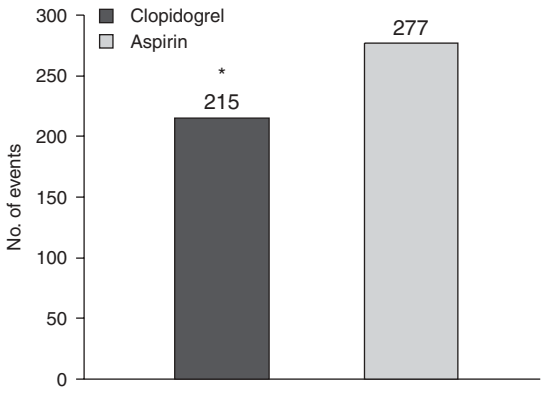

Fig. 3. Results of the clopidogrel versus aspirin in patients at risk of ischemic events (CAPRIE) trial. Number of events (ischemic stroke, myocardial infarction or vascular death) in patients with peripheral arterial disease treated with either clopidogrel 75 mg/day (n = 3223) or aspirin (acetylsalicylic acid) 325 mg/day (n = 3229) for an average of 2 years.[62] * $p = 0.0028$.

2.3 Warfarin

The utility of warfarin as secondary prevention in patients with PAD has yet to be fully established. Limited studies have shown that systemic anticoagulation with warfarin slows the progression of PAD, as well as reduces stroke and recurrent MI in patients after an MI.[63,64] Long-term anticoagulation with warfarin in addition to aspirin is recommended after thrombolytic therapy for acute arterial occlusion in PAD.[65] In the Post Coronary Artery Bypass Graft Trial (Post CABG),[66] low-dose warfarin was not found to have any significant benefit on cardiovascular morbidity and mortality during the 3 years of follow up. However, after extended follow-up of approximately 7.5 years mortality was reduced by 35% ($p = 0.008$), and death or nonfatal MI by 31% ($p = 0.003$). Nonetheless, there was no reduction in peripheral vascular procedures in patients treated with warfarin. It has been shown that patients with PAD have altered coagulation markers, which are associated with increased risk of vascular complications.[67,68]

However, as a result of bleeding complications from full anticoagulation (International Normalised Ratio [INR] 2–3), warfarin use in this population has been limited. The ADMIT trial looked at the efficacy and safety of low-dose warfarin (INR 1.5–2.0 or maximum dose of 4mg). There was a 3% rate of bleeding complications in patients receiving warfarin compared with a 4% rate for placebo.[69] However, given in combination with nicotinic acid (niacin), warfarin therapy had an increased rate of bleeding complications compared with warfarin alone. Low-dose warfarin was found to have a significant anticoagulation effect compared with placebo.

Therefore, low-dose warfarin can be used safely and is also effective as an anticoagulant in patients

with PAD. However, further study is needed to determine if low-dose warfarin can decrease vascular events in patients with PAD.

3. Pharmacotherapy for Claudication

3.1 Pentoxifylline

Pentoxifylline is a xanthine derivative used to treat IC in patients with PAD. It is a haemorrheological agent that decreases blood viscosity and improves erythrocyte flexibility.[70] It has been found to increase absolute claudication distance after 24 weeks of treatment by approximately 20%.[71-73] However, in a recent study, Dawson et al.[74] reported similar effects of pentoxifylline and placebo on increasing maximal walking distance. Two meta-analyses of randomised, placebo-controlled trials found that pentoxifylline increased initial claudication distance by approximately 20–30 metres and absolute claudication distance by approximately 45–50 metres.[75,76] Both analyses concluded that while pentoxifylline may have a small positive effect on claudication, there is currently insufficient data to justify generalised use in patients with symptomatic PAD.

3.2 Cilostazol

Cilostazol inhibits the action of phosphodiesterase and increases the amount of intracellular cyclic adenosine monophosphate. This results in significant antiplatelet and vasodilatory activity, as well as antiproliferative properties.[77-79] As antiplatelet and vasodilatory drugs were shown to have no positive effect on claudication-limited walking distance, the mechanism by which cilostazol achieves improvement in PAD patients remains speculative.[80]

Several randomised, placebo-controlled studies using cilostazol 100mg twice daily have shown improved maximal walking distance of 40–50% compared with placebo.[74,81,82] There is evidence for a dose-response effect of cilostazol. Maximal walking distance was less comparing 50mg with 100mg twice daily but still significantly greater than with placebo[83] (figure 4). In a direct comparison mean maximal walking distance of cilostazol-recipients was significantly greater compared with that of patients who received pentoxifylline or placebo[74] (figure 5). Furthermore, cilostazol has been shown to improve functional status and quality of life.[81,83]

The most common adverse effect is headache in 34% of patients compared with 14% of placebo recipients. Palpitations, dizziness and diarrhoea have also been described.

Other phosphodiesterase inhibitors such as milrinone possess more positive inotropic effects than cilostazol, and are used in the treatment of acute and chronic heart failure. One study using oral milrinone long-term in patients with chronic heart failure found increased mortality in the milrinone arm.[84] On the basis of these findings the use of cilostazol is contraindicated in patients with heart failure.

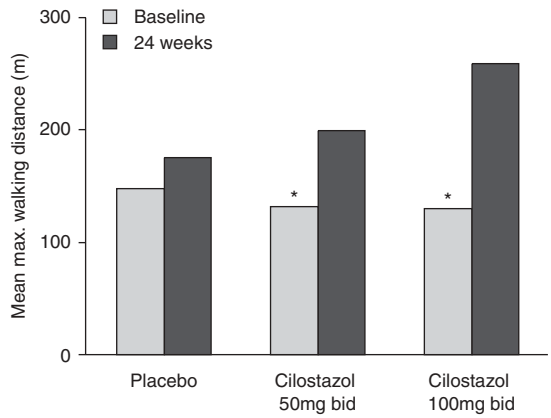

Fig. 4. Results from a new pharmacological treatment for intermittent claudication. The mean maximal (max.) walking distance in patients with peripheral arterial disease treated with placebo (n = 140), cilostazol 50mg bid (n = 139) or cilostazol 100mg bid (n = 140) at baseline and after 24 weeks of treatment. In both cilostazol groups maximal walking distance improved significantly from baseline (* $p < 0.001$) compared with placebo. Cilostazol 100mg bid was more effective then 50mg bid.[83] **bid** = twice daily.

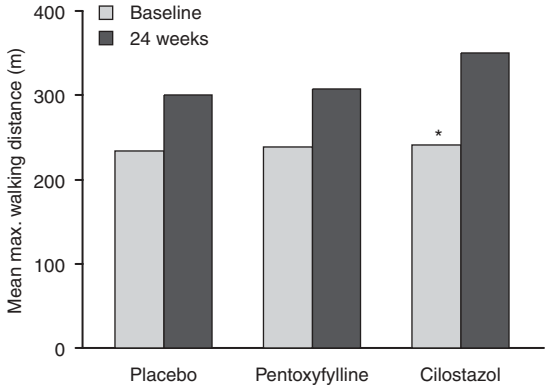

Fig. 5. Results from a comparative study of cilostazol and pentoxifylline in patients with intermittent claudication. The mean maximal (max.) walking distance in patients with peripheral arterial disease treated with placebo (n = 226), pentoxifylline 400mg po tid (n = 212) or cilostazol 100mg bid (n = 205) at baseline and after 24 weeks of treatment. The treatment results for placebo and pentoxifylline were similar (p = 0.82). Treatment with cilostazol lead to a significant improvement in maximal walking distance (* p < 0.0005) compared with placebo.[74] **bid** = twice daily; **po** = orally; **tid** = three times daily.

4. Conclusion

Peripheral vascular disease is just one manifestation of the general disease process of atherosclerosis. There is growing evidence that atherosclerosis in the peripheral circulation should be considered in the same manner as atherosclerosis in the coronary circulation. Until evidence to the contrary is reported, patients with PAD should be treated as aggressively with respect to risk factor modification (table II) and additional pharmacological therapy (table III) as patients with CAD.

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