Introduction

The clinical manifestations of atherothrombotic disease that affects the circulation to the legs are deceptively benign. The prognosis for the leg is relatively good. Only 2–3% of early symptomatic patients will ever progress to the point that amputation is required, and death is rarely directly due to severe ischaemia of the legs.

Nevertheless, it has been shown in several studies that every year approximately 4% of patients with intermittent claudication in the legs will sustain a fatal or non-fatal cardiac or cerebral event\[1\]. There have also been a number of large, prospective, long-term studies\[1–3\] that have compared the fate of two populations – those with and those without symptomatic ischaemia in the legs, matched for age and sex. Those studies have shown that a population with claudication has a twofold to fourfold increased risk for cardiovascular mortality as compared with a non-claudicant population. In some studies the relative risk of total mortality was also much greater in claudicant patients. Perhaps the most intriguing finding is that the relative risk for cardiovascular and all-cause mortality is often unchanged even after adjusting for differences in the traditional risk factors of hypertension, diabetes, hyperlipidaemia and smoking\[1\]. This latter finding suggests that symptomatic ischaemia of the legs is not simply a marker of generalized atherosclerosis, but rather may in part be causally related to ischaemia in other territories. A number of possible mechanisms have been suggested for such an effect, including the release of activated white cells and cytokines from the ischaemic circulation in the legs during claudication.

Pharmacological therapies

There is no doubt that some lifestyle changes, in particular cessation of smoking, will decrease progression of atherosclerosis and risk for clinical deterioration. The control of coexisting diseases, particularly hypertension and diabetes, will have similar general benefit. Specific targeted surgical or endovascular interventions can deal with the most significant localized lesions, but are unlikely to have any direct effect on the generalized progression of the disease. However, pharmacotherapeutic intervention that is not targeted at specific organs (e.g. beta-blockers in angina) but rather are aimed at a more general effect on the progression and complications of atherothrombotic disease must be an essential component of medical treatment for intermittent claudication.

There are three principal groups of drugs that have been shown to be of some benefit in modifying the progression of antiplatelet therapy the future probably lies in a combination of these two drugs, which affect platelet function through different pathways.

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atherothrombotic disease: anticoagulants, lipid-lowering agents and antiplatelet drugs. The oldest of these is anticoagulants, but they are rarely used long-term except in some special circumstances, for instance in patients with hypercoagulable states or with an artificial exceptionally thrombogenic prosthesis. The very definite long-term risk for serious bleeding has limited the use of anticoagulants for general antithrombotic prophylaxis. Several large recent studies[6-8] have shown that lipid-lowering drugs, usually a statin, decrease cardiovascular mortality and morbidity, even in patients whose plasma lipid levels are within the ‘normal’ range. This rather suggests that the so-called ‘normal’ range is in fact not optimal, and that in biological terms virtually the whole population has abnormal lipids. The cardiovascular benefit of lipid lowering is directly related to the initial levels, and therefore the expected benefit from lipid-lowering drugs can be reasonably accurately identified. With regard to this latter aspect, lipid-lowering therapy differs radically from the last group of drugs, the antiplatelet agents, in that no laboratory measure has yet been developed that can easily identify those patients who are particularly likely to benefit from antiplatelet therapy.

**Antiplatelet therapy: results of clinical trials**

The rationale for antiplatelet treatment rests essentially on the central role of platelet adhesion to endothelium, platelet aggregation, platelet activation and release reaction in the process of intra-vascular thrombosis. Because thrombosis has also been implicated in the early stages of atherosclerosis, long-term antiplatelet therapy may also have an effect on the progression of the lesion in the wall. Much of the evidence from published controlled trials of antiplatelet therapy in patients with various manifestations of circulatory disease was summarized in three key reports of the Antiplatelet Trialists’ Collaboration published in the *British Medical Journal*[6-8], which were discussed by Underwood and Moore[9]. This series was last published in 1994, but an updated analysis is currently underway. In the last published results 145 randomized controlled trials were analyzed that involved approximately 70,000 patients with symptomatic arterial disease.

**Aspirin and the thienopyridines**

In the vast majority of the trials analyzed by the Antiplatelet Trialists’ Collaboration[6-8], aspirin, at various dosages, was compared with placebo. Overall there was a 27% odds reduction in non-fatal or fatal vascular events, an 18% reduction in cardiovascular mortality and a 17% odds reduction in total mortality in the patients treated with antiplatelet therapy. This benefit was not significantly different in the subgroups of patients who were entered following acute or old myocardial infarction, cerebrovascular accidents, or with symptomatic peripheral vascular disease. The benefit of antiplatelet therapy was statistically significant in all of these subgroups except the latter. Only approximately 3000 patients in 22 trials had symptomatic arterial disease that affected the legs; although the benefit in this group was similar to that in the other groups, it did not reach statistical significance on its own.

Used as primary prophylaxis in patients who are asymptomatic, the benefit from antiplatelet drugs was of the order of 2–10%, depending on the end-point. It is interesting that antiplatelet therapy was also shown to significantly improve patency following any form of vascular intervention. Two other crucial findings were that the benefit in terms of percentage reduction in events was the same irrespective of the absolute risk in a particular group, and that the benefit persisted and was consistent over at least 3 years. The equal benefit of antiplatelet therapy across all ischaemic indications lends further support to the hypothesis that myocardial, cerebral and peripheral ischaemia are essentially similar pathological processes that can be encompassed under the general term ‘atherothrombotic disease’.

Another group of antiplatelet agents are the thienopyridines[10]. These act by a totally different mechanism from that of aspirin, which blocks the cyclo-oxygenase pathway and reduces thromboxane-induced platelet aggregation. Thienopyridines block the activation of platelets by adenosine diphosphate.

Ticlopidine is the first agent of this group to have been widely tested. Only approximately 6500 patients included in the Antiplatelet Trialists’ Collaboration analyses[6-8] participated in trials that tested ticlopidine. Direct and indirect comparison with aspirin suggests that ticlopidine may be approximately 10% more effective in preventing thromboembolic complications. However, ticlopidine has not been widely accepted for long-term use because of a very low incidence of severe agranulocytosis (0.5–0.9%). In a meta-analysis of seven placebo-controlled studies that evaluated administration of ticlopidine to patients with peripheral arterial disease (2073 patients randomized)[11], long-term follow-up revealed a 29% odds reduction in total mortality.

A newer thienopyridine, clopidogrel, was evaluated in probably the largest prospective study of any drug in development for this indication – the recently completed Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) study[12]. In that study, clopidogrel was compared with aspirin and found to be significantly more effective and at least as safe, with none of the side effects previously found with ticlopidine. Almost 20,000 patients were randomized and approximately one-third were entered on the basis of their leg ischaemia, usually intermittent claudication. In a post hoc analysis, patients with leg ischaemia appeared to derive greater benefit from clopidogrel, with a 23.8% relative risk reduction.

Therefore, looking at all of the antiplatelet trials, including CAPRIE, there is definite evidence that this type of treatment in patients with intermittent claudication reduces cardiovascular morbidity and mortality. Although clopidogrel is more effective than aspirin, there is a very
considerable difference in cost. However, clopidogrel is certainly indicated in the 10–15% of patients who cannot take aspirin because of gastrointestinal side effects or possibly even a true allergy. It is also indicated in patients who appear to be aspirin resistant. This can be a clinical impression in patients who develop thrombotic events, such as transient ischaemic attack, while on aspirin. Aspirin resistance can also be shown to be present by direct testing of platelet function in those taking aspirin, but at the moment this is not a practical proposition for all patients who should be receiving low-dose aspirin for a platelet effect.

Despite the availability of aspirin and clopidogrel, and the overwhelming evidence of their efficacy in patients with intermittent claudication, a very substantial proportion of these patients still do not receive any antiplatelet therapy. This is presumably due to an educational deficit both in doctors and in the patients.

**Glycoprotein IIb/IIIa blockers**

The most recent group of antiplatelet agents are the platelet glycoprotein IIb/IIIa blockers[13]. Several studies have failed to show a benefit for the orally active glycoprotein IIb/IIIa blockers.

**Combination therapy**

The combined use of antiplatelet drugs that act through different pathways, such as a combination of clopidogrel and aspirin, remains to be tested in claudicant patients, although early experience in other atherothrombotic conditions suggests that the benefit may be additive. Direct comparisons of antiplatelet drugs with other groups of pharmacological agents used for secondary prophylaxis in claudicant patients are not available. Direct comparison with other therapies such as antihypertensive treatment and statins in other circulatory diseases is difficult because the benefit of these agents depends on the magnitude of the initial risk in terms of hypertension or abnormal lipid levels. Some attempt at comparison can be made by considering the number of cardiovascular events avoided every year for every 1000 patients treated. The Antiplatelet Triallists’ Collaboration[6–8] showed that low-dose aspirin prevents 19 fatal and non-fatal cardiovascular events per year for 1000 patients treated as compared with placebo. Extrapolating from this to the CAPRIE study[12], clopidogrel prevents 24 similar events per year per 1000 patients. A possibly comparable figure for statins could come from a study of simvastatin for secondary prevention conducted in more than 4000 patients[4], in which treatment would prevent approximately 20 events per year per 1000 patients on therapy. Similarly, a recent meta-analysis of antihypertensive therapy in the elderly[14] showed that this avoided 14 events per year per 1000 patients treated. The magnitude of the benefit of these very different approaches appears to be of the same order; the benefits are also probably additive.

**References**