Rationale for antiplatelet therapy in patients with atherothrombotic disease

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Abstract: The most common cause of morbidity and mortality in developed countries results from atherosclerosis and superimposed thrombosis (atherothrombosis) leading to partial or complete vascular occlusion. Much evidence supports the idea that all atherothrombosis is similar, regardless of which vascular bed it occurs in. Thus, similar therapies may be used for patients with symptomatic cardiac, cerebral, or peripheral vascular disease. The types of agents that have shown efficacy in atherothrombosis include antihypertensives, lipid-lowering agents and antiplatelet agents. The focus of this article is on the antiplatelet agents, of which there are several subcategories, including ADP receptor antagonists, GpIIb/IIa antagonists, cyclooxygenase inhibitors and prostacyclin analogues. Clinical testing of these agents is ongoing and the efficacy and safety of the various agents are being defined. To date, the ADP receptor antagonist, clopidogrel, appears to provide the best antithrombotic result with the fewest side effects. Further testing may reveal that combinations of the various forms of antiplatelet agents may provide even further improvements on safety and efficacy.

Key words: antiplatelet agents; atherosclerosis; prophylaxis; thienopyridines; thrombosis

Introduction

Atherothrombotic diseases and complications are the commonest cause of morbidity and mortality in developed countries. Patients at greatest risk are those who already have symptoms of atherosclerosis with or without a history of thrombotic complications. Patients with symptoms of myocardial ischemia, cerebral ischemia and ischemia of the legs (peripheral arterial disease; PAD) make up over 95% of these patients. The underlying arterial atherosclerosis appears similar by histologic methods in these different regions of the vasculature and is associated with similar risk factors, although there is a suggestion that cigarette smoking and hyperlipidemia are more common in the PAD group.1 The clinical manifestations of atherosclerosis in these regions of the vasculature are different, of course, but superimposed thrombosis in either the cerebral or the coronary circulation will have similarly devastating effects. The clinical manifestations of atherothrombotic disease affecting circulation in the leg is somewhat different, being relatively benign. Only 2–3% of early symptomatic patients will ever be forced to undergo the serious handicap of an amputation, and death rarely occurs as a direct result of severe leg ischemia. Nevertheless, it has been shown in several series that approximately 4% of patients with intermittent claudication in the legs will sustain a fatal or non-fatal cardiac or cerebral event every year.2 There have also been a number of large, prospective, long-term studies comparing the fate of age- and sex-matched populations with and without symptomatic ischemia in the legs.3–6 These studies have shown that patients with claudication have a two- to fourfold increased risk of cardiovascular mortality compared with patients without claudication. In some studies, the relative risk of total mortality was also much greater in claudicants. Perhaps the most intriguing finding, however, is that the relative risk of cardiovascular and all-cause mortality is often unchanged, even after adjusting for differences in the traditional risk factors of hypertension, diabetes, hyperlipidemia and smoking.3,5,6 This finding suggests that symptomatic ischemia of the legs is not simply a marker of generalized atherosclerosis, but partly may be causally related to factors that precipitate ischemia 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 ischemic circulation in the legs during claudication.

There is no doubt that some lifestyle changes, in particular cessation of smoking, will decrease the progression of atherosclerosis and the risk of thrombotic complications. The control of coexisting diseases, particularly hypertension, will have similar general benefits. Specific, targeted therapy by surgical or endovascular intervention can deal with the most significant localized lesions, but is unlikely to have any direct effect on the generalized progression of the disease. However, the main concern should be with pharmacotherapeutic interventions that are not targeted at specific organs, such as beta-blockers in angina, but rather they should be aimed towards a more general effect on the progression and complications of atherothrombotic disease.

There are three principal groups of drugs that have proved to be of some benefit in modifying the progression of atherothrombotic disease: anticoagulants, lipid-lowering agents and antiplatelet agents. Anticoagulants are the oldest, but they are rarely used as a long-term therapy, except in some special circumstances. For instance, these agents may be used for patients with a hypercoagulable state or...
with an artificial thrombogenic prosthesis. The very definite long-term risk of serious bleeding has limited the use of anticoagulants for general antithrombotic prophylaxis.

Several recent, large studies have shown that lipid-lowering drugs, many of which are ‘‘statins’’, decrease cardiovascular mortality and morbidity, even in patients whose plasma lipid levels are within the ‘‘normal’’ range.2 This suggests that the so-called ‘‘normal’’ range is, in fact, not optimal and that, in biological terms, the present lower limit of the normal range is perhaps too high. The cardiovascular benefit of lipid lowering is directly related to the patient’s blood lipid levels; thus, the expected benefit from lipid-lowering drugs can be identified. In contrast, there are no laboratory measurements by which to identify high-platelet-risk patients.

**Clinical efficacy of antiplatelet therapy**

The rationale for antiplatelet treatment rests on the central roles of platelet activation, platelet adhesion to the endothelium, and platelet aggregation in the process of intravascular thrombosis. Since thrombosis has also been implicated in the early stages of atherosclerosis, long-term antiplatelet therapy may also have an effect on the progression of atherosclerotic lesions of the vasculature.

All the evidence from both published and unpublished controlled trials of antiplatelet therapy in patients with various manifestations of circulatory disease were summarized in the three key publications of the Antiplatelet Trialists’ Collaboration in the *British Medical Journal* in 1994.8–10 An update of that overview is currently underway. In the 1994 results, 145 randomized, controlled trials were analyzed, involving about 70,000 ‘‘high-risk’’ patients with symptomatic arterial disease. In the vast majority of these, aspirin, at various dosages, was compared with placebo. Overall, there was a 27% odds reduction in nonfatal or fatal vascular events, an 18% reduction in cardiovascular mortality, and a 17% reduction in risk for total mortality in patients treated with antiplatelet therapy. This benefit was not significantly different in the groups of patients who were enrolled with acute or old myocardial infarction, cerebrovascular accidents, or with symptomatic peripheral arterial disease. The benefit of antiplatelet therapy was statistically significant in each of these groups except the last. Only approximately 3000 patients in 22 trials had symptomatic arterial disease affecting the legs and, although the benefit was similar to that achieved in the other groups, it did not reach statistical significance on its own. Used as primary prophylaxis in patients who are asymptomatic, the benefit of antiplatelet drugs is in the order of 2–10%, depending on the endpoint. It is interesting that antiplatelet therapy was also shown to significantly improve vascular patency following any form of vascular intervention.8 Two other crucial findings of the collaboration were that the benefit of antiplatelet therapy, as a per cent odds reduction in events and irrespective of the absolute risk in a particular group, was the same; further, the benefit persisted and was consistent over at least 3 years. The equal benefit of antiplatelet therapy across all ischemic indications lends further support to the hypothesis that myocardial, cerebral and peripheral ischemia are essentially similar pathological processes that can be encompassed under the general term of ‘‘atherothrombotic disease’’.

**Use of antiplatelet therapy**

Given the evidence of efficacy summarized above, it might be expected that all patients with symptomatic ischemic disease in the coronary, cerebral, or peripheral circulation would be taking prophylactic antiplatelet therapy, particularly as the most commonly used antiplatelet drug, aspirin, is inexpensive. It is therefore surprising that a number of surveys have not found this to be the case. For instance, in an examination of primary care practitioners, it was found that only half the patients with a history of angina were receiving antiplatelet therapy.11 In the ASPIRE study, 2583 patients in 24 specialized cardiac centers in the UK were monitored for 6 months after they had experienced an acute myocardial infarction or cardiac surgery.12 Approximately 20% of the patients were not taking low-dose aspirin 6 months after discharge.

There are some side effects associated with aspirin, even with low doses, which could partially account for the low frequency of treatment. Aspirin is contraindicated in patients with a bleeding tendency, particularly in the gastrointestinal system. In addition, a significant number of patients develop gastric irritation; true allergy to aspirin, however, is exceedingly rare. There is no reliable data on the proportion of patients who would benefit from antiplatelet therapy but who, for some reason, cannot take aspirin. The general impression is that the figure lies somewhere between 10% and 15%. The concept of aspirin resistance has been applied recently to patients in whom aspirin cannot be shown to have affected platelet function; currently, it is not practical to screen all patients receiving low-dose aspirin for an antiplatelet effect.

It is difficult to explain why a substantial proportion of patients who would benefit from antiplatelet therapy are not, in fact, receiving it. Presumably, this may result from a combination of factors: physicians who do not provide sufficient incentive; patient reluctance to comply with any long-term therapy; and possibly disbelief in the efficacy of a treatment that is so easily and cheaply available.

**Recent antiplatelet drugs**

The thiienopyridines are a group of antiplatelet agents that act through a mechanism totally different from that of aspirin. The latter reduces cyclo-oxygenase activity, thereby reducing thromboxane-induced platelet aggregation. Thienopyridines, on the other hand, block ADP-induced activation of platelets. Ticlopidine was the first agent in this group to be widely tested. Approximately 6500 patients in the ‘‘Antiplatelet Trialists’ Collaboration meta-analysis participated in trials testing ticlopidine. The analysis found a 33% odds reduction for the occurrence of stroke, MI, or vascular death in patients treated with ticlopidine compared with controls.8 Direct and indirect comparisons with aspirin suggest that ticlopidine may be about 10% relatively more effective than aspirin in preventing thromboembolic complications. However, ticlopidine has not
been widely accepted for long-term use because of a low incidence of neutropenia.

Clopidogrel has been tested in the largest randomized study of a new drug in development – the recently completed ‘clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE)’ study. In CAPRIE, clopidogrel was found to be significantly more effective and at least as safe as aspirin without the serious side effect of neutropenia associated with ticlopidine. A more detailed analysis of the CAPRIE study is given in Mark Creager’s article on pages 257–260. The most recent group of antiplatelet agents to undergo clinical testing are the oral platelet glycoprotein IIb/IIIa antagonists, but the precise efficacy and role of these agents has yet to be defined.

Prostacyclin and prostacyclin analogues have powerful antiplatelet effects; they are probably the most powerful naturally occurring in vivo antiplatelet agents. At the moment, however, antiplatelet drugs have not been tested for secondary prophylaxis in thromboembolic disease. Further, many of these agents are only formulated for intravenous administration.

### Conclusion

The story of antiplatelet agents in the secondary prophylaxis of patients with atherothrombotic disease is far from complete, and the role of oral GpIIb/IIIa antagonists remains to be defined. The combined use of antiplatelet agents that work through different mechanisms, such as dual therapy with clopidogrel and aspirin, remains to be tested; however, early experience suggests that the benefits may be at least additive. Direct comparisons of antiplatelet drugs with other groups of pharmacologic agents used in the secondary prophylaxis of high-risk patients are 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 Trialists’ Collaboration showed that aspirin prevents about 19 fatal and non-fatal cardiovascular events per year for every 1000 patients treated compared with placebo. Extrapolating from this to the CAPRIE study, clopidogrel prevents 24 similar events per year per 1000 patients, a 26% increase in the number of events prevented. A figure for ‘statins’ that may be comparable comes from the study of simvastatin for secondary prevention of mortality and morbidity in patients with coronary heart disease that enrolled over 4000 patients; treatment prevented approximately 20 events per year per 1000 patients. Similarly, a recent meta-analysis of antihypertensive therapy in the elderly showed that it prevented 14 events per year per 1000 patients treated. The magnitude of the benefit of these very different approaches seems to be in the same order; however, there is a likelihood that the benefits of combination therapy with these different agents would be additive.

In conclusion, antiplatelet therapy is effective in decreasing the incidence of serious non-fatal and fatal complications in patients with symptomatic atherothrombotic disease. This is a prevalent disease and its complications are the commonest cause of morbidity and mortality in the elderly. It remains to be seen whether combinations of different classes of antiplatelet drugs will be even more effective without significantly increasing the risk of side effects such as bleeding. Meanwhile, clinicians should ensure that all patients who would benefit from this type of treatment are indeed receiving it.

### References