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ST. MICHAEL'S HOSPITAL, UNIVERSITY OF TORONTO
Scientific Update™

New Trends in Atherothrombosis Treatment

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Atherothrombosis is the consequence of an atherosclerotic plaque rupture with superimposed thrombosis. It is responsible for the clinical presentations of ischemic cerebrovascular, coronary artery, and peripheral vascular diseases. Platelets help to initiate the process of acute thrombosis and contribute to the growth of a stable plaque. The drug clopidogrel interferes with ADP-dependent platelet activation and also inhibits other mechanisms that are not affected by agents such as ASA. As demonstrated in the CAPRIE trial,[2] clopidogrel is superior to ASA in preventing recurrent atherothrombotic events, and it has high safety and efficacy profiles.

Atherothrombosis

The term atherothrombosis has been coined to refer to a sequence of events that produces an atherosclerotic plaque with superimposed thrombosis. This is a two-stage mechanism: first, formation of an atherosclerotic plaque in a process that takes many years or decades; second, thrombotic occlusion of the vessel, a process that takes a few minutes and usually is due to rupture of an unstable atherosclerotic plaque. Together, these processes are responsible for the clinical presentations of ischemic cerebrovascular disease, coronary artery disease, and peripheral vascular disease.

Platelet activation

Platelets have a major role in the process of thrombotic vascular occlusion. They help to initiate the process, and they contribute to the growth of a stable atherosclerotic plaque. Thrombotic vascular occlusion usually occurs after the rupture of an unstable plaque with subsequent release of many components, such as tissue factor, that lead to thrombin formation. Thrombin not only acts to convert fibrinogen to fibrin but is itself a powerful platelet activator.

Another aspect of the role of platelets in atherothrombosis, their contribution to the formation and growth of the atherosclerotic plaque, is less certain. However, immunohistochemical research has led to the identification of platelet-derived components within atherosclerotic plaques. These include, among others, platelet factor 4 and platelet derived growth factor (PDGF). Thus, the formation of intraplaque thrombi could play a role in the growth of the atherosclerotic lesion over the long term.

There is also the possibility that platelets are not alike in all individuals and that some patients with severe atherothrombosis actually have hyperreactive platelets that respond more easily to the activation process. For instance, it has been reported that abnormalities in glycoprotein (Gp)

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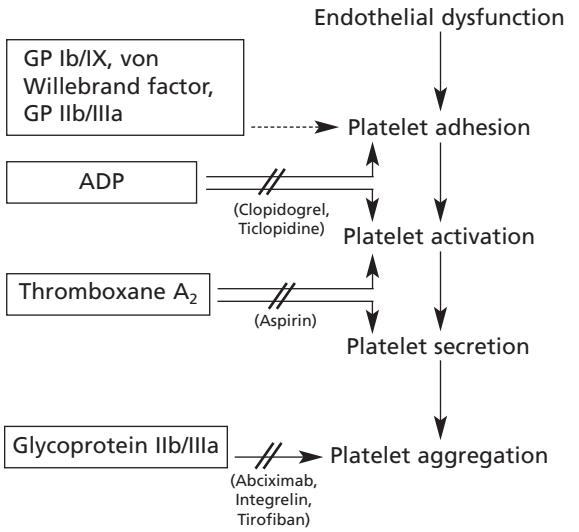
IIb/IIIa, a fibrinogen-binding receptor activated by ADP and thromboxane A_2, are associated with increased risk of coronary artery disease (CAD). It might be that platelet polymorphism is related to the risk of atherothrombosis.

The relationship between platelets and the vessel endothelium is likely important in the growth of atherosclerotic plaques as well as in acute vascular thrombosis. Therefore, and especially in view of the relatively weak antiplatelet effects of acetylsalicylic acid (ASA), clinical validation of newer and more effective antiplatelet agents is an important step in the evolution of the treatment of atherothrombosis (see figure 1).

Figure 1: Mechanisms of action of antiplatelet agents



Role of ADP antagonism

The normal surface of the endothelium is antithrombotic. However, after rupture of a plaque, there is stimulation of platelets by shear stress with the influence of secreted activators such as ADP, thromboxane A_2, thrombin, serotonin, and other mediators leading to platelet activation and aggregation. Many substances intervene in this pathway. ASA specifically interferes with thromboxane generation and all the thromboxane-dependent pathways of activation; compounds such as ticlopidine or clopidogrel act primarily as ADP antagonists.

Clopidogrel interferes with ADP-dependent platelet activation and also inhibits other mechanisms that are not affected by ASA. Clopidogrel has greater activity in all situations in which ADP is an important agonist; it has a broad spectrum of activity and is potentially more effective than ASA. Clopidogrel also inhibits the activation of the GP IIb/IIIa receptor, although it is not an antagonist of the receptor itself in the traditional sense. Clopidogrel is qualitatively different from the IIb/IIIa antagonists because it does not directly interfere with the formation of complexes with fibrinogen receptors.

There are two types of ADP receptors. P2X1 is calcium-coupled and has little importance for the purpose of this discussion. The second receptor, P2Y1, is a G-protein-coupled receptor that leads to glycoprotein IIb/IIIa activation and platelet aggregation.

Another interesting mechanism of action of ADP is that it stimulates the synthesis of a G-protein that inhibits adenyl cyclase. Clopidogrel, acting at this level, prevents the decrease in cyclic AMP levels associated with ADP binding and platelet activation. Thus the three major pharmacologic targets of clopidogrel are:

- the ADP receptor itself,
- major regulatory pathways leading to IIb/IIIa activation,
- the maintenance of increased cylic AMP levels after stimulation of the ADP receptor.

In patients treated with a conventional dose of clopidogrel, there is a 60-70% decrease in the ADP binding sites. This is an irreversible response for the life of the platelet. The effects of clopidogrel are seen 2-4 hours after administration, and the full clinical effects occur between 3 and 7 days after the initial dose. An earlier peak effect could be achieved with a loading dose.

Clopidogrel is not an active compound, but the site of generation of the active metabolite is currently unknown; as is the site of action, since it is not clear whether it acts on mature platelets or in the megakaryocytes. Another aspect that is not presently clear is whether concomitant use of clopidogrel with ASA would provide additional benefits. In theory, since thromboxane pathways are independent of ADP pathways, the combination is an interesting alternative, espe-

cially in situations of acute platelet activation. Recent data with another ADP-antagonist, ticlopidine, in patients after coronary stent implantation supports this hypothesis.[1]

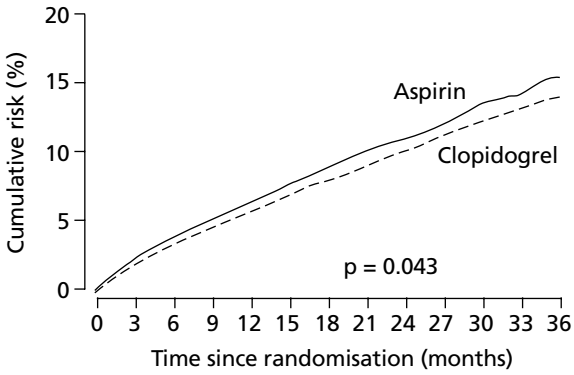
CAPRIE Results

In the CAPRIE trial[2] (Clopidogrel vs ASA in Patients at Risk of Ischemic Events), the effects of these two antiplatelet agents in patients who had presented previously with ischemic stroke, myocardial infarction, or peripheral vascular disease were compared. Clopidogrel is a thienopyridine derivative that inhibits thrombosis primarily by blocking the platelet ADP receptor. The assumption of the CAPRIE study was that atherothrombosis is a single disease with multiple clinical manifestations depending on the vascular territory involved. Support for this hypothesis was provided by the antiplatelet trialist's collaboration, which in 1994 published a meta-analysis of antiplatelet agents, predominantly ASA. A 25% risk reduction in events was observed regardless of whether the patients had suffered a stroke, a myocardial infarction, or peripheral vascular disease.[3]

Clopidogrel was derived from ticlopidine in an attempt to circumvent the small but troublesome incidence of problems with bone marrow toxicity associated with ticlopidine. In view of these problems, it appeared unlikely that ticlopidine would represent an alternative to ASA as a long-term antiplatelet drug.

A total of 19,885 patients were enroled in the CAPRIE study. About one-third of study subjects were randomized to treatment on the basis of a previous stroke, one-third because of a previous myocardial infarction, and one-third because of symptomatic peripheral vascular disease. The primary endpoint was the occurrence of ischemic stroke, myocardial infarction, or vascular death. Patients were randomly assigned to take either clopidogrel 75 mg once a day (n=9,599) or ASA 325 mg daily (n=9,586). Base-line characteristics of the patients in both groups were well matched. It is noteworthy that approximately 17% of the subjects who were included because they had a recent history of stroke or peripheral vascular disease, had also experienced a previous myocardial infarction.

Figure 2: Cumulative risk of ischaemic stroke, myocardial infarction, or vascular death



Patients at risk							
A: 9586	9190	8087	6139	3979	2143	542
C: 9599	9247	8131	6160	4053	2170	539

A=aspirin; C=clopidogrel

Adapted from CAPRIE Steering Committee. *Lancet* 1996; 348:1329-39

After the scheduled follow-up period, there were 1,960 primary end-point events. An intention-to-treat analysis showed that patients treated with clopidogrel had an annual risk for a primary event of 5.32% compared with 5.83% for patients treated with ASA. Thus, use of clopidogrel provides a statistically significant (p=0.043) relative risk reduction of 8.7% (see figure 2).

CAPRIE demonstrates that clopidogrel is at least as safe as ASA, a claim that cannot be made by many drugs. Indeed, the incidence of adverse events was very low in both the ASA and clopidogrel groups. There was a slight, but clinically significant increase in rash among patients treated with clopidogrel compared with ASA (0.26% vs 0.1%), but significantly fewer patients treated with clopidogrel experienced severe gastrointestinal hemorrhage (0.49% vs 0.72%). In terms of the important issue of hematologic toxicity, neutropenia (<1,200/mm^3) was extremely rare in both groups,

Table 1: Relative risks according to interventions

Drug	Relative Risk of Stroke	Intracranial Hemorrhage
Coumadin	-50% (at 3 years)	+3%
ASA	-25%	+0.5%
Clopidogrel	-32%	+0.3%

Table 2: Benefit of accepted prevention measurements

Intervention	Events Prevented per 1,000 patients/year	Source
Aspirin	19	Antiplatelet trialists[3]
Pravastatin	18	CARE[4]
Antihypertensive agents	13	MacMahon 1990[5]
Clopidogrel	24	CAPRIE[2]

occurring in 16 patients taking ASA and only 10 patients taking clopidogrel.

Clopidogrel caused no significant bone-marrow toxicity and was associated with significantly less gastrointestinal bleeding than ASA. Based on the results of CAPRIE, the new antiplatelet agent clopidogrel will improve on the effects of ASA by preventing an additional 5 events per 1,000 patients for each year of therapy. Based on a meta-analysis[3], it can be predicted that aspirin would prevent 19 events per 1000 patient-years in a population similar to that of the CAPRIE study. Based on the efficacy reported by the Antiplatelet Trialists' Collaboration[3] and the CAPRIE[2] study, ASA reduces the risk of a vascular event by one-quarter and clopidogrel by one-third.

Cerebrovascular disease in the cardiac patient

Several etiologies can cause stroke in the cardiac patient:

- direct embolization from the heart; patients with this problem do well with anticoagulant therapy
- disease of the small intracranial vessels (arteriolosclerosis), for which the main risk is hypertension, and
- disease in the large vessels, such as the carotids and the aortic arch; this encompasses 50–60% of all stroke patients.

However, this is a pathology-oriented and rather limited view of the process. The clinical view is much more complex, as most patients with stroke have multivascular disease, and the risk of stroke in cardiac patients is potentiated by the presence of additional risk factors, including age, a history of hypertension, heart failure, ventricular dysfunction, and previous atherothrombotic events.

Extrapolation from the CAPRIE results and comparison with previous trials suggest that the relative risk of a stroke after a myocardial infarction would vary with different interventions, as shown in table 1. Compared with other interventions, clopidogrel produces intermediate risk reduction with a low bleeding incidence, and it is superior to ASA in this respect.

The CAPRIE results can also be compared with those from other secondary prevention measures, as shown in table 2.

Conclusion

Antiplatelet therapy with clopidogrel is equivalent to or better than other accepted measures of secondary prevention. As demonstrated in the CAPRIE trial, clopidogrel is at least as safe as ASA and is more effective in preventing recurrent atherothrombotic events.

References:

1. Schomig A, Neuman FJ, Kastrati A, Schulen H et al. A randomized comparison of antiplatelet and anticoagulant therapy after the placement of coronary artery stents. *N Engl J Med* 1996;334:1084-1089.
2. CAPRIE Steering Committee. A randomised, blinded trial of clopidogrel versus aspirin in patients at risk of ischaemic events. *Lancet* 1996; 348:1329-39.
3. Antiplatelet Trialists Collaboration. Collaborative overview of randomized trials of antiplatelet therapy. *BMJ* 1994;308:81-106.
4. Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JO, Cole TG, Brown L, Warnica JW, Arnold JMO, Won C-C, Davis BR, Braunwald E, for the Cholesterol and Recurrent Events Trial Investigators. *N Engl J Med* 1996;335:1001-1009.
5. MacMahon S, Peto R et al. Blood pressure, stroke, and coronary heart disease. Part 1, Prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. *Lancet* 1990;335:765-74.