SMH ST. MICHAEL'S HOSPITAL Cardiology
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A REPORT BY THE DIVISION OF CARDIOLOGY
ST. MICHAEL'S HOSPITAL, UNIVERSITY OF TORONTO
Scientific Update™

Antiplatelet Agents in Cardiovascular Disease

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Satellite Symposium at the 70th Scientific Session of the American Heart Association
Orlando, Florida, November 8-12, 1997

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Presentations at this symposium focused on characteristics of atherosclerotic plaque, platelet activation and its role in thrombus formation, and the role of clopidogrel in managing cardiovascular disease. Since plaque rupture is mostly seen in lipid-rich lesions that have a thin, fibrous cap, presumably because of a low-grade inflammatory process, identifying particularly hot lesions or detecting temperature heterogeneity in plaque via a temperature probe or infrared imaging may allow local treatment. The distribution and extent of the lipid pool within plaque is also important, as is its thrombogenic characteristics. Six months after initiation of aggressive cholesterol therapy, endothelial dysfunction may be improved, and after two years, there is accrued benefit that may alter the physical and thrombogenic characteristics of plaque. Platelet activation and aggregation are pivotal steps in thrombus formation; intact endothelium plays a key role in preventing platelet activation via production of nitric oxide and prostacyclin. However, platelet-derived growth factor (PDGF) stimulates proliferation of smooth muscle cells which can lead to plaque formation and oxidized LDL inhibits nitric oxide release which augments atherosclerosis. Current anti-thrombotic agents use different pathways to inhibit platelet aggregation. ASA is effective in inhibiting the enzyme, cyclooxygenase, but is ineffective in inhibiting other mechanisms of platelet activation. Glycoprotein IIb/IIIa inhibition can be achieved with abciximab, tirofiban or integrilin. Clopidogrel, a new antiplatelet agent, blocks ADP-induced platelet activation. In the CAPRIE trial, which compared clopidogrel to ASA, consistent benefit was seen with clopidogrel across all three subgroups of patients with less side effects and no evidence of bone marrow toxicity.

The relationship of lipid-lowering agents and unstable plaque in thrombosis

Lipid metabolism is a key aspect in the development and progression of atherosclerotic plaques. In particular, oxidation of LDL cholesterol at endothelial and subendothelial surfaces not only potentiates endothelial damage, it also facilitates migration of monocytes and macrophages. In addition, endothelial dysfunction leads to platelet adhesion and the release of growth factors such as platelet-derived growth factor (PDGF). These factors can potentiate the growth of atherosclerotic plaque and contribute to the thrombosis which frequently follows rupture or plaque erosion.

The process of plaque rupture is the result of a number of complex events centered around macrophage and the

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release of metalloproteases (MMP), in particular, collagenase (MMP-1). Plaque rupture is seen mostly with lipid-rich lesions and in association with the thinning fibrous cap, presumably because of the low-grade inflammatory process that results in digestion of extracellular matrix. Thus, the extent of inflammation is an important component of plaque rupture, as well as the ongoing propensity for the acute ischemic syndrome. Important work has started on improving our ability to identify particularly hot lesions which may have a greater potential for instability.

Detecting vulnerable plaque

Vulnerable atherosclerotic plaques appear to have interesting physical properties, one of which is temperature heterogeneity. Excised atherosclerotic plaque specimens from carotid arteries have been shown to have measurable differences in temperature (temperature heterogeneity) with differences ranging between 0.5%°C and 3%°C, as measured by a hand-held, specially adapted, temperature probe. Close correlation has been demonstrated between temperature heterogeneity and inflammation in these human specimens. More recently, infrared imaging has been used to detect temperature heterogeneity with excellent correlation to measurements obtained with a temperature probe. It appears that infrared imaging may be used as a means to detect temperature heterogeneity to study sites of inflammation in human arteries and the potentially vulnerable plaque.

This early but exciting work suggests that detection of vulnerable atherosclerotic plaque is possible, thereby allowing a local treatment to be given with the hope of plaque stabilization and therefore prevention of acute ischemic syndromes.

Thrombogenicity following plaque rupture

Recent work has emphasized the importance of the lipid core in the thrombogenicity of a ruptured plaque. Since exposure of tissue factor from the lipid core is critical in thrombus formation, the distribution and extent of the lipid pool within the plaque is important (i.e. physical characteristics of the plaque), as is the amount of tissue factor expression (i.e. thrombogenic characteristics of the plaque).

Thrombogenicity of the eroded plaques, which may represent up to one-third of the plaque pathology among patients presenting with acute ischemic syndromes, has also been linked to cholesterol levels.

Cholesterol reduction and plaque stabilization

Aggressive cholesterol reduction, in particular reduction of LDL, has been associated with a more favorable outcome, especially with respect to cardiovascular morbidity and mortality, in patients with established cardiovascular disease or in those at high risk for disease. While the degree of luminal narrowing improves only minimally with LDL cholesterol reduction, there is evidence that endothelial function may be improved as early as six months after initiation of treatment. Thereafter, improvement in clinical outcome is seen with continued divergence of the curves, suggesting accruing benefit from cholesterol reduction. Based on our current understanding of pathophysiology,[1,2,3] it is clear that reduction of LDL cholesterol may result not only in improved endothelial function, but also in alteration of the physical and thrombogenic characteristics of the plaque, leading to plaque stabilization.

The role of platelets in cardiovascular disease

Platelet activation is a pivotal step in intracoronary thrombus formation. Nitric oxide and prostacyclin produced by endothelial cells inhibit platelet activation and aggregation in response to mechanical forces (such as sheer stress), receptor-mediated agonists (ADP, serotonin, thrombin, epinephrine, thromboxane A_2), and exposure to collagen.

When prostacyclin and nitric oxide are released, they produce vasodilatation and inhibit proliferation and migration of smooth muscle cells in the subendothelial space. While in the lumen, they interact with platelets, resulting in inactivation via the formation of cyclic GMP (in the case of nitric oxide) and cyclic AMP as a second messenger (in the case of prostacyclin). Thus, endothelium plays a key role in the regulation of platelet and vessel wall interaction with prevention of platelet activation even under conditions of high sheer stress.

When the endothelium is intact, platelets also modulate vascular tone via endothelium-dependent relaxation due to the release of ADP and ATP following platelet aggregation, which stimulates formation of nitric oxide. In contrast, in endothelium denuded preparations, platelet aggregation causes vasoconstriction mediated by thromboxane A_2 and serotonin.

Finally, thrombin is an important modulator of platelet activation and aggregation and, therefore, in endothelium denuded preparations, the addition of thrombin potentiates the vasoconstrictor effect of aggregating platelets through the additional release of thromboxane A_2.

The role of platelets in atherogenesis

Under normal conditions of preserved endothelial function, platelets do not adhere to the vessel wall because of the release of nitric oxide and prostacyclin. However, with endothelial dysfunction, platelets can adhere to the vessel wall, resulting in platelet aggregation and secretion of platelet-derived growth factor (PDGF). PDGF stimulates proliferation of smooth muscle cells which, under pathological conditions, can lead to plaque formation.

Oxidized LDL is a potent inhibitor of nitric oxide release and this process contributes to the initiation and potentiation of atherosclerosis through augmentation of vasoconstriction, adhesion of monocytes and subsequent release of growth factors (such as PDGF), and platelet adhesion, as discussed above.

Activated platelets in acute coronary syndromes

Understanding how platelet activation occurs in response to a number of factors has lead to the development of therapeutic options. Cyclooxygenase, a major enzyme that controls production of thromboxane A_2, can be inhibited by ASA, resulting in a therapeutic benefit. However, platelet activation via other mechanisms such as ADP, thrombin, or serotonin is unaffected by ASA, indicating that ASA efficacy could be improved upon.

Glycoprotein IIb/IIIa is expressed on platelet surfaces when platelets are activated. Since the interaction of glycoprotein IIb/IIIa receptor with fibrin represents the final common pathway for platelet aggregation, its inhibition also offers an important therapeutic option. Benefit has been demonstrated in an angioplasty model using abciximab, and more recently with tirofiban and integrilin in patients with non-ST elevation acute ischemic syndromes.[4,5]

Managing cardiovascular disease with clopidogrel

Clopidogrel blocks ADP-induced platelet activation and is similar in action to the already marketed compound, ticlopidine. The difference between clopidogrel and ticlopidine is a one point change from a hydrogen group to CO_2CH_3, which prevents bone marrow suppression.

The safety and efficacy of clopidogrel was studied in the CAPRIE (Clopidogrel vs ASA in Patients at Risk for Ischemic Events) trial, a large-scale, multicenter study of patients with manifestations of thrombotic vascular disease in either coronary, cerebrovascular, or peripheral arterial systems.[6] A total of 19,185 patients were included in the study with about one-third of the enrollment based on previous myocardial infarction, one-third on ischemic stroke, and one-third on symptomatic peripheral artery disease. The primary outcome cluster consisted of myocardial infarction, ischemic stroke, or vascular death.

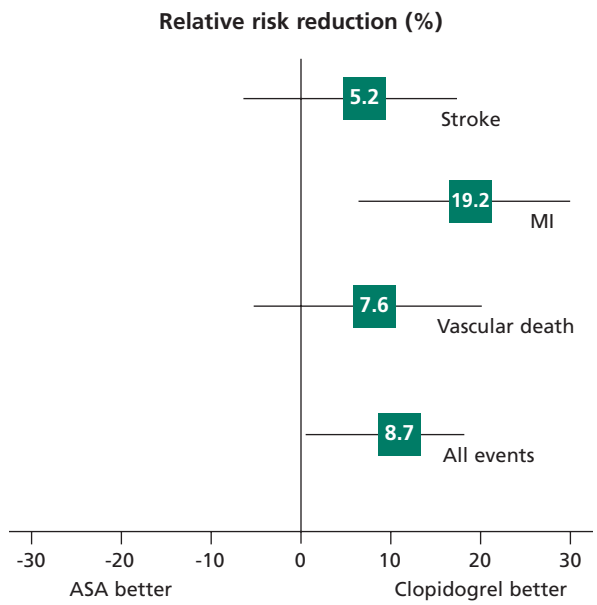
The results of the CAPRIE trial showed clopidogrel to be more advantageous than ASA in preventing major vascular events in high risk patients (table 1). In an intention-to-treat analysis, clopidogrel provided an overall relative risk reduction of 8.7% compared to ASA, and on treatment analysis, resulted in a relative risk reduction of 9.4% in favor of clopidogrel.

A post hoc analysis based on outcome events is shown in figure 1. A significant reduction in myocardial infarction as an end point was particularly interesting, given the fact that clopidogrel benefit was least obvious in the subgroup of patients who were enrolled following myocardial infarction.

Table 1: Number of primary outcome events recorded in CAPRIE

Outcome	Clopidogrel	ASA
Stroke		
Nonfatal	405	430
Fatal	33	32
Myocardial infarction		
Nonfatal	226	270
Fatal	49	63
Other vascular death	226	226
Total	939	1021
Event rate/year	5.32%	5.83%
Relative risk reduction (95% CI)	8.7% (0.3 to 16.5)	
p Value	$p = 0.043$	

Figure 1: Relative risk reduction for each component of the outcome cluster in the entire CAPRIE population. Note that the benefit of clopidogrel was seen in each subgroup.



It is important to note, however, that the results of CAPRIE trial overall indicated consistent benefit across all three subgroups of patients enrolled, as well as across the three end points of the primary end point cluster: stroke, myocardial infarction, vascular death.

To put these findings into perspective in a patient population similar to that enrolled in the CAPRIE trial, clopidogrel would be expected to prevent about 24 major vascular events for 1,000 patients treated per year, compared to 19 such events being prevented with ASA. Thus, treatment with clopidogrel provides a 26% reduction in major vascular events compared to ASA.

Most importantly, clopidogrel therapy resulted in significantly less upper gastrointestinal distress and less GI bleeding, as well as less abnormal liver function compared to ASA. However, ASA caused less rash and diarrhea than clopidogrel. There was no evidence of bone marrow toxicity with clopidogrel, suggesting that prolonged treatment is safe.

The results of the CAPRIE trial indicate, on one hand, significant benefit from clopidogrel treatment in reducing cardiovascular events vs. ASA, and on the other, an excellent safety profile with significant improvement as compared to ASA with respect to serious bleeding. Since clopidogrel, unlike ticlopidine, avoids the problem of bone marrow toxicity, it is likely that clopidogrel will be a significant addition to our armamentarium in the treatment of atherothrombosis and for achieving secondary prevention.

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