

# TOP Journal Club

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## **Platelet activation markers, microparticles and soluble adhesion molecules are elevated in patients with arteriosclerosis obliterans: therapeutic effects by cilostazol and potentiation by dipyridamole.**

Reference: Platelets. 2004 May;15(3):167-72.

We evaluated the plasma concentrations of platelet activation markers, microparticles and soluble adhesion molecules in patients with arteriosclerosis obliterans (ASO) and compared the beneficial effects of cilostazol alone and combination therapy of cilostazol and dipyridamole in these patients. There was a significant elevation of CD62P, CD63, PAC-1, annexin V, platelet-derived microparticles (PDMPs), sP-selectin, sE-selectin, sICAM-1 and sVCAM-1 in the ASO patients compared with the controls. Platelet aggregation was decreased by 2 weeks of cilostazol monotherapy in the ASO patients. Adding dipyridamole to the cilostazol therapy for 2 weeks further reduced platelet aggregation. While treatment with cilostazol alone reduced levels of CD62P, CD63, PAC-1, annexin V, PDMP, and sP-selectin, the combination therapy reduced these parameters further. While sE-selectin and cell adhesion molecules did not change significantly after 2 weeks of combination therapy, they exhibited a remarkable decrease after 16 weeks of combination treatment. These findings suggest that platelets are activated in ASO patients, and cilostazol is effective to reduce platelet activation. Furthermore, dipyridamole may potentiate the beneficial effect of cilostazol in ASO patients. Combination use of both drugs may help to prevent the onset of cardiovascular complications in patients with ASO by activated platelets and PDMP.

## **Studies on the effectiveness and safety of cilostazol, beraprost sodium, prostaglandin E1 for the treatment of intermittent claudication.**

Reference: Yakugaku Zasshi. 2004 Jun;124(6):321-32.

To study the effectiveness for the treatment of intermittent claudication (IC) of three drugs with antiplatelet effects, cilostazol, beraprost sodium, and prostaglandin E(1) (PGE(1)), by using a

systemic review of literature and a meta-analysis. A search was undertaken for studies reported between 1966-2002 in the MEDLINE database, and references in published articles and reviews were obtained. Data for maximum walking distance (MWD), pain-free walking distance (PFWD), and adverse clinical events were extracted from the articles that met the inclusion criteria. The pooled estimates of the weighted mean differences (WMD) of MWD and PFWD for cilostazol were 52.19 m [95% confidence interval (CI) 32.08, 72.31] and 39.75 m [95% CI 23.39, 56.10], and those for PGE(1) were 100.27 m [95% CI 15.76, 184.78] and 55.73 [95% CI 21.54, 89.92], respectively. These differences were statistically significant between the test drugs and placebo. However there was no statistical significance difference between beraprost sodium and placebo, even though there was one study that showed a tendency for improvement in walking distance. The total rate of adverse clinical events in cilostazol and beraprost sodium was higher than that for placebo, while there was no statistical significant difference between PGE(1) and placebo, although PGE(1) had a higher tendency for adverse clinical events. The literature evaluation results and the meta-analysis suggest that these two drugs (cilostazol and PGE(1)) can be considered to be effective drugs for the treatment of IC. Due to current availability of only a few clinical reports, further studies are needed to clarify the efficacy of beraprost sodium in the treatment of IC.

## **Platelet inhibition by aspirin is diminished in patients during carotid surgery: a form of transient aspirin resistance?**

Reference: Thromb Haemost. 2004;92(1):89-96.

The majority of patients who suffer peri-operative thromboembolic complication while undergoing vascular procedures do so despite taking aspirin. This study examined the antiplatelet effect of aspirin during surgery in patients undergoing carotid endarterectomy (CEA). Fifty patients undergoing CEA were standardised to 150 mg aspirin daily for  $\geq 2$  weeks. Platelet aggregation in response to arachidonic acid (AA) was measured in platelet rich plasma prepared from blood taken prior to, during, and at the end of surgery. Spontaneous platelet aggregation was also studied, as was the role of physiological agonists (ADP, collagen, thrombin, and epinephrine) in mediating the in vivo and in vitro responses to AA. Eighteen patients undergoing leg

angioplasty, also on 150 mg aspirin, without general anaesthesia, served as a control group. In the CEA patients aggregation induced by AA (5 mM) increased significantly from 7.6 +/- 5.5% pre-surgery to 50.8 +/- 29.5% at the end of surgery (p <0.0001). Aggregation to AA was even greater in samples taken mid-surgery from a sub-set of patients (73.8 +/- 7.2%; p = 0.0001), but fell to 45.9 +/- 7.4% by the end of surgery. The increased aggregation in response to AA was not due to intra-operative release of physiological platelet agonists since addition of agents that block/neutralise the effects of ADP (apyrase; 4 micro g/ml), thrombin (hirudin; 10 units/ml), or epinephrine (yohimbine; 10 micro M/l) to the samples taken at the end of surgery did not block the increased aggregation. The patients undergoing angioplasty also showed a significant rise in the response to AA (5 mM), from 5.6 +/- 5.5% pre-angioplasty to 32.4 +/- 24.9% at the end of the procedure (p <0.0001), which fell significantly to 11.0 +/- 8.1% 4 hours later. The antiplatelet activity of aspirin, mediated by blockade of platelet arachidonic acid metabolism, diminished significantly during surgery, but was partially restored by the end of the procedure without additional aspirin treatment. This rapidly inducible and transient effect may explain why some patients undergoing cardiovascular surgery remain at risk of peri-operative stroke and myocardial infarction.

### **Almost Half of Stroke Patients May Be Aspirin Resistant**

Reference: Reuters Health: June 25, 2004

The results of a small study suggest that almost half of patients hospitalized after a stroke or transient ischemic attack (TIA) that are caused by a blocked blood vessel do not develop anti-clotting effects with aspirin therapy.

Dr. Mark Alberts, of Northwestern University Medical School, Chicago, reported at the 5th World Stroke Congress that 47 percent of stroke or TIA patients showed "aspirin resistance," which was defined as a clotting time of 171 seconds or less.

The study involved 59 patients (average age 64 years) who had been taking aspirin for at least three days before they had a stroke or TIA. The patients were tested at the time of hospital diagnosis, before treatment with additional anticlotting therapy.

The researchers used a machine that measures the clotting time of a blood sample that is pumped through a membrane, a test design that mimics the behavior of circulating blood. The results, Alberts said, are available in "about 5 minutes -- and the test costs only \$15 to \$20."

Sixty-three percent of patients were taking 325 mg/day of aspirin, and 37 percent were using 81 mg. Aspirin resistance was more common in patients taking low-dose aspirin. The results were normal in 73 percent of patients on the low-dose aspirin versus 32 percent of patients taking high-dose aspirin.

There also was a trend toward more resistance in patients taking enteric-coated aspirin compared with those taking uncoated aspirin (73 percent versus 39 percent).

The results suggest that "dose-adjusted antiplatelet therapy is where the field is heading," Alberts concluded. "One size fits all therapy doesn't work for aspirin."

## **NUTRITIONAL SUPPLEMENTATION IN ADVANCED CIRRHOSIS**

In patients with advanced cirrhosis, long-term nutritional supplementation with oral branched-chain amino acids helps prevent progressive hepatic failure, find researchers from Italy.

Researchers performed a multicenter, randomized study to compare 1-yr BCAA supplementation with either lactalbumin or maltodextrins.

Average hospital admission rate was lower in the branched-chain amino acid group. They also determined that the average hospital admission rate was lower in the BCAA group, compared with other groups. The team also found that nutritional parameters and liver function tests were stable or showed improvement during treatment with BCAA. In addition, the Child-pugh score decreased.

Furthermore, improvements were found in anorexia and health-related quality of life.

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