

TOP Journal Club

Vol: 7 No: 9 September 2004

Cilostazol inhibits high glucose-mediated endothelial-neutrophil adhesion by decreasing adhesion molecule expression via NO production.

Reference: *Microvasc Res.* 2004 Sep;68(2):119.

Objective. Endothelial-neutrophil adhesion is crucial for vascular injury, the major cause of diabetic vascular complications. On the other hand, platelet aggregation inhibitors, frequently used for diabetic patients with intermittent claudication, have been shown to decrease the incidence of atherosclerosis-mediated diseases (acute myocardial infarction and stroke). However, whether these agents act directly on the endothelial reactions to hyperglycemia remains unclear. Therefore, we examined their direct effects on endothelial-neutrophil adhesion and expression of endothelial adhesion molecules induced by high glucose. **Methods and results.** After human endothelial cells were cultured in high glucose medium, neutrophils from healthy volunteers were added and allowed to adhere for 30 min. Adhered neutrophils were quantified by measuring their myeloperoxidase (MPO) activities, and surface expression of endothelial adhesion molecules was determined with an enzyme immunoassay. Of the platelet aggregation inhibitors tested, only cilostazol significantly attenuated the adhesion through decreasing expression of intercellular adhesion molecule-1 (ICAM-1) and P-selectin. In addition, nitric oxide (NO) synthase inhibitors reduced the inhibitory effects of cilostazol, but a protein kinase C (PKC) activator did not. **Conclusions.** Cilostazol may act directly on endothelial cells to inhibit expression of adhesion molecules and neutrophil adhesion induced by high glucose through increasing NO production.

Natural history of physical function in older men with intermittent claudication

Reference: *J Vasc Surg* 2004;40:73-8.

Purpose This study was undertaken to determine the natural history of physical function in older men limited by intermittent claudication.

Methods Forty-three men limited by intermittent claudication (mean age, 69 ± 7 years) were recruited and followed up for 18 months. At

baseline the patients reported a history of intermittent claudication for 6.1 ± 6.1 years, and were able to walk for 1.9 ± 1.6 blocks before experiencing claudication pain. Measurements during the 18-month study included ankle-brachial index (ABI), calf blood flow, 6-minute walk performance, monitored and self-reported physical activity, self-reported stability while walking, and summary performance score of physical function determined from a 4-m walk test, a chair stand test, and a tandem stand test.

Results Pain-free walking distance during the 6-minute walk test decreased by 22% ($P < .05$) from baseline (185 ± 96 m) to follow-up (144 ± 93 m), and the total 6-minute walk distance decreased by 9% ($P < .05$), from 368 ± 106 m to 334 ± 90 m. Furthermore, monitored physical activity decreased by 31% ($P < .05$), from 159 ± 151 kcal/d to 110 ± 137 kcal/d; self-reported physical activity declined by 27% ($P < .05$), from 1.5 ± 1.0 units to 1.1 ± 0.8 units; tandem stance time declined by 14% ($P < .05$), from 9.46 ± 1.83 seconds to 8.12 ± 2.10 seconds; summary performance score of physical function decreased by 12% ($P < .05$), from 6.8 ± 2.4 units to 6.0 ± 2.4 units; and the percentage of patients reporting ambulatory unsteadiness and stumbling increased from 28% to 43% ($P < .05$). Calf blood flow measured at rest declined by 18% ($P < .05$), from 3.72 ± 1.81 (mL/100 mL⁻¹/min⁻¹) to 3.04 ± 1.43 mL/100 mL⁻¹/min⁻¹, whereas ABI did not change ($P > .05$).

Conclusion Older men limited by intermittent claudication experienced decline in ambulatory function, physical activity, physical function, stability, and calf blood flow over 18 months of follow-up, despite no change in ABI.

Cilostazol prevents the progression of symptomatic intracranial arterial stenosis; the result of trial of cilostazol in symptomatic intracranial arterial stenosis (TOSS)

Presented at 5th World Stroke Congress, Vancouver, Canada on June 26, 2004.

Introduction: Cilostazol, a phosphodiesterase III inhibitor, reduced restenosis rate after coronary angioplasty and stenting in clinical studies. However, little information is available for the effect of cilostazol on intracranial arterial stenosis (IAS). **Objective:** To evaluate of the effect of cilostazol on symptomatic IAS **Methods:** In this multicenter double-blind study, we randomized 135 patients with acute symptomatic stenosis in M1 segment of middle cerebral artery or basilar

artery to either Cilostazol 200mg a day or matching placebo for 6 months. All patients additionally received 100mg of aspirin per day during this period. We excluded the patients with potential embolic sources in the extracranial arteries or heart. The stenosis was defined and evaluated by MR angiogram (MRA) and transcranial Doppler (TCD). The main outcome measures were cerebrovascular events and the change of the symptomatic stenosis evaluated by MRA and TCD at six months later. Results: Finally 38 patients were dropped out. Recurrent ischemic stroke developed none, but sudden death one in each group. No serious adverse events were related with trial drugs. The symptomatic stenosis in cilostazol group had significantly ($p=0.018$) better outcome (progressed in 3 and regressed in 11 of 45 arteries) than in placebo group (15 and 8 of 52 arteries). Asymptomatic stenosis was worsened in 1 of 39 in cilostazol and 4 of 51 in placebo group. Conclusion: We revealed that symptomatic IAS is a dynamic lesion and cilostazol prevents its progression. Cilostazol add-on with aspirin is safe and may be effective to prevent the recurrent stroke with IAS.

Anticoagulants for acute ischaemic stroke.

Reference: Cochrane Database Syst Rev. 2004;(3):CD000024

BACKGROUND: Most ischaemic strokes are caused by blood clots blocking an artery in the brain. Clot prevention with anticoagulant therapy could have a significant impact on patient survival, disability and stroke recurrence. **OBJECTIVES:** The objective of this review was to assess the effect of anticoagulant therapy versus control in the early treatment of patients with acute ischaemic stroke. **SEARCH STRATEGY:** We searched the Cochrane Stroke Group trials register (last searched 30 October 2003). For previous updates of this review, we searched the register of the Antithrombotic Trialists' (ATT) Collaboration, consulted MedStrategy (1995), and contacted relevant drug companies. **SELECTION CRITERIA:** Randomised trials comparing early anticoagulant therapy (started within two weeks of stroke onset) with control in patients with acute presumed or confirmed ischaemic stroke. **DATA COLLECTION AND ANALYSIS:** Two reviewers independently selected trials for inclusion, assessed trial quality and extracted the data. **MAIN RESULTS:** Twenty-two trials involving 23,547 patients were included. The quality of the trials varied considerably. The

anticoagulants tested were standard unfractionated heparin, low-molecular-weight heparins, heparinoids, oral anticoagulants, and thrombin inhibitors. Based on nine trials (22,570 patients) there was no evidence that anticoagulant therapy reduced the odds of death from all causes (odds ratio (OR) = 1.05, 95% confidence interval (CI) 0.98 to 1.12) at the end of follow-up. Similarly, based on six trials (21,966 patients), there was no evidence that anticoagulants reduced the odds of being dead or dependent at the end of follow-up (OR = 0.99; 95% CI 0.93 to 1.04). Although anticoagulant therapy was associated with about 9 fewer recurrent ischaemic strokes per 1000 patients treated (OR = 0.76; 95% CI 0.65 to 0.88), it was also associated with a similar sized 9 per 1000 increase in symptomatic intracranial haemorrhages (OR = 2.52; 95% CI 1.92 to 3.30). Similarly, anticoagulants avoided about 4 pulmonary emboli per 1000 (OR = 0.60, 95% CI 0.44 to 0.81), but this benefit was offset by an extra 9 major extracranial haemorrhages per 1000 (OR = 2.99; 95% CI 2.24 to 3.99). Sensitivity analyses did not identify a particular type of anticoagulant regimen or patient characteristic associated with net benefit. **REVIEWERS' CONCLUSIONS:** Immediate anticoagulant therapy in patients with acute ischaemic stroke is not associated with net short- or long-term benefit. The data from this review do not support the routine use of any type of anticoagulant in acute ischaemic stroke. People treated with anticoagulants had less chance of developing deep vein thrombosis (DVT) and pulmonary embolism (PE) following their stroke, but these sorts of blood clots are not very common, and may be prevented in other ways.

Omega-3 fatty acids for intermittent claudication

Reference: Cochrane Database Syst Rev. 2004;3:CD003833.

Omega-3 fatty acids appear to have some beneficial biochemical and haemodynamic effects in people with intermittent claudication but there is no evidence of improved clinical outcomes. It should be noted that no consistent effect on primary outcome measures was detected. Further research is needed in this area, to evaluate short- and long-term effects on more clinically relevant outcomes.

<http://www.thai-otsuka.co.th/pxnews/index.html> Opinions and suggestions are welcomed Dr. Shwe Win, shwewin@thai-otsuka.co.th