

# TOP Journal Club

## Vol 9: Number 3 March 2006

### The vascular effects of cilostazol.

*Can J Cardiol.* 2006 Feb;22 Suppl B:56B-60B.

Cilostazol is a phosphodiesterase III inhibitor with pharmacological effects that include vasodilation, inhibition of platelet activation and aggregation, inhibition of thrombosis, increased blood flow to the limbs, improvement in serum lipids with lowering of triglycerides and elevation of high density lipoprotein cholesterol, and inhibition of vascular smooth muscle cell growth. Cilostazol has been shown in multiple randomized clinical trials to result in decreased claudication and improved ability to walk in patients with peripheral arterial disease. In addition, cilostazol has been shown in multiple randomized clinical trials to decrease restenosis in the setting of coronary stent implantation. The purpose of the present paper was to review the vascular effects of cilostazol and to present results of the major clinical trials of the use of cilostazol in peripheral arterial disease and percutaneous coronary intervention with stent implantation.

### Drug treatment of peripheral arterial disease in the elderly.

*Drugs Aging.* 2006;23(1):1-12

Peripheral arterial disease (PAD) may be asymptomatic, may be associated with intermittent claudication or may be associated with critical limb ischaemia. Coronary artery disease (CAD) and other atherosclerotic vascular disorders may coexist with PAD. Persons with PAD are at increased risk for all-cause mortality, cardiovascular mortality and mortality from CAD. Smoking should be stopped and hypertension, diabetes mellitus, dyslipidaemia and hypothyroidism treated. HMG-CoA reductase inhibitors (statins) reduce the incidence of intermittent claudication and improve exercise duration until the onset of intermittent claudication in persons with PAD and hypercholesterolaemia. Antiplatelet drugs such as aspirin or clopidogrel

(especially the latter), ACE inhibitors and statins should be given to all persons with PAD. beta-Adrenoceptor antagonists should be given if CAD is present. The phosphodiesterase type 3 inhibitor cilostazol improves exercise time until intermittent claudication. Chelation therapy should be avoided. Correct implementation of medical therapy significantly reduces the excess mortality associated with PAD. In addition, medical therapy may result in significant improvements in walking ability that may obviate the need for lower extremity angioplasty with stenting and bypass surgery.

### Regional Differences in Incidence and Management of Stroke - Is There Any Difference between Western and Japanese Guidelines on Antiplatelet Therapy?

*Cerebrovasc Dis.* 2006;21 Suppl 1:17-24

Purpose: There have not been many discussions on the differences between the guidelines for the management of stroke used in eastern and western countries. The purpose of this paper was to examine whether or not there are substantial differences between western countries and Japan in the prevalence of stroke and the frequencies of stroke subtypes, as well as in the recommended therapy for secondary prevention of ischemic stroke. Results and Conclusions: Although there are racial differences and differences in approved drugs between the East and West, the prevalence of stroke and the frequencies of stroke subtypes tend to converge throughout the world. However, the ratio of stroke to ischemic heart disease is still different between the East and West. Comparison of various countries' guidelines shows that recommendations on antiplatelet therapy for secondary prevention of ischemic stroke are fundamentally similar in the East and West, but the recommended doses of antiplatelets, especially aspirin and ticlopidine, are smaller in Japan. Furthermore, Japanese guidelines only recommend the use of antiplatelets (particularly cilostazol) for patients with lacunar infarction with evidence.

## Antiplatelet therapy in stroke prevention: present and future.

*Cerebrovasc Dis.* 2006;21 Suppl 1:1-6

White platelet-fibrin thrombi often form on roughened endothelial surfaces and unstable arterial plaques. Agents that reduce the tendency of platelets to aggregate, agglutinate, and secrete and to attach to endothelial surfaces have been explored as agents that prevent brain and heart infarction. Aspirin, ticlopidine, clopidogrel, dipyridamole, cilostazol, and glycoprotein IIb/IIIa inhibitors are all used now and have various different modes of action and functions.

## Cilostazol: therapeutic potential against focal cerebral ischemic damage.

*Curr Pharm Des.* 2006;12(5):565-73.

Cilostazol was developed as a selective inhibitor of cyclic nucleotide phosphodiesterase 3 (PDE3). The anti-platelet and vasodilator properties of cilostazol have been extensively characterized and considered to contribute to the variety of clinical effects such as intermittent claudication and recurrent stroke. In this review, the novel action mechanism (s) of cilostazol are overviewed with the focus on the action of cilostazol in in vitro and in vivo studies as a maxi-K channel opener targeting anti-apoptotic signaling pathways. Under treatment with cilostazol (10 mg/kg intravenously or 30 mg/kg orally), a significant reduction in cerebral infarct area was evident in rats subjected to ischemia/reperfusion. Increase in cyclic AMP and decrease in TNF-alpha levels were identified in the ipsilateral cortex under treatment with cilostazol accompanied by decreased Bax formation and cytochrome c release with increased Bcl-2 production in the penumbral area as well as in the in vitro human umbilical endothelial cells. Cilostazol suppressed TNF-alpha-induced decrease in viability of SK-N-SH (human neuroblastoma) cells and HCN-1A (human cortical neuron) cells in association with decrease in PTEN phosphorylation and increase in Akt/CREB phosphorylation with suppression of DNA fragmentation, all of which were antagonized by iberiotoxin, a maxi-K(+) channel

blocker. Further, cilostazol prevented TNF-alpha-induced PTEN phosphorylation and apoptotic cell death via increased CK2 phosphorylation in the SK-N-SH cells. Cilostazol increased K(+) current in SK-N-SH cells by opening the maxi-K channels. Thus, it was suggested that the action of cilostazol to promote cell survival was ascribed to the maxi-K channel opening-coupled upregulation of CK2 phosphorylation and downregulation of PTEN phosphorylation with resultant increased phosphorylation of Akt and CREB. These in vitro data were confirmed in the in vivo results of rats subjected to focal transient ischemic damage.

## Medical treatment of peripheral arterial disease.

*JAMA.* 2006 Feb 1;295(5):547-53.

CONTEXT: Peripheral arterial disease (PAD) affects approximately 20% of adults older than 55 years and is a powerful predictor of myocardial infarction, stroke, and death due to vascular causes. The goals of treatment are to prevent future major coronary and cerebrovascular events and improve leg symptoms. OBJECTIVE: To review the best evidence for medical treatment of PAD. EVIDENCE ACQUISITION: MEDLINE and the Cochrane database were searched from 1990 to November 2005 for randomized trials and meta-analyses of medical treatments for PAD. References from these articles were also searched. Search terms included, singly and in combination: peripheral arterial disease, peripheral artery disease, PAD, randomized controlled trial, controlled trial, randomized, and meta-analysis. Particular attention was directed toward randomized controlled trials and meta-analyses of clinically relevant medical treatments for PAD. Outcome measures included leg symptoms (intermittent claudication and walking distance), death, and major coronary and cerebrovascular events. EVIDENCE SYNTHESIS: Symptoms of leg claudication, walking distance, and quality of life can be improved by smoking cessation (physician advice, nicotine replacement therapy, and bupropion), a structured exercise program, statin drugs, cilostazol, and angiotensin-converting

enzyme inhibitors. The risk of major coronary and cerebrovascular events can be reduced through lowering blood pressure with angiotensin-converting enzyme inhibitors and other antihypertensive drugs, use of statin drugs, antiplatelet therapy with aspirin or clopidogrel, and probably by stopping smoking. CONCLUSION: The substantial and increasing burden of PAD, and its local and systemic complications, can be reduced by lifestyle modification (smoking cessation, exercise) and medical therapies (nicotine replacement therapy, bupropion, antihypertensive drugs, statins, and antiplatelet drugs).

### Medical management of peripheral arterial disease: a therapeutic algorithm.

*J Endovasc Ther.* 2006 Feb;13 Suppl 2:III9.

Over half of the people with peripheral arterial disease (PAD) may be asymptomatic. The most common symptom of mild-to-moderate PAD is intermittent claudication, present in about one third of symptomatic patients. Patients with intermittent claudication often have severely impaired functional status. Despite the high prevalence of the disease and the strong association with cardiovascular morbidity and mortality, patients with PAD are less likely to receive appropriate treatment for their atherosclerotic risk factors than are those being treated for coronary artery disease. The goals of treatment are to prevent progression of systemic atherosclerosis and its associated morbidity and mortality, to prevent limb loss, and to improve functional capacity for symptomatic patients. For claudicating patients, medical management includes symptomatic treatment with cilostazol or pentoxifylline. For all patients, it is equally important to pursue risk reduction through exercise programs and promotion of smoking cessation, as well as with the use of statins, antiplatelet therapies, antithrombotic strategies, angiotensin-converting-enzyme inhibitors, beta-blockers, and attention to homocysteine levels. Because not all patients are symptomatic, medical management of peripheral arterial disease may proceed along an algorithmic pathway that recognizes 3 types of patients: those requiring risk reduction only, symptomatic patients

with minimal lifestyle limitation, and symptomatic patients with significant lifestyle impairment.

### Peripheral arterial disease and risk of cardiac death in type 2 diabetes: the fremantle diabetes study.

*Diabetes Care.* 2006 Mar;29(3):575-80

OBJECTIVE: The purpose of this study was to examine the natural history of peripheral arterial disease (PAD) complicating type 2 diabetes, in particular the influence of PAD on the risk of cardiac death and the adequacy of PAD risk factor management. RESEARCH DESIGN AND METHODS: The Fremantle Diabetes Study (FDS) was a prospective community-based observational study of diabetic patients recruited between 1993 and 1996. The present sample comprised the 1,294 FDS type 2 diabetic patients and a subgroup of 531 of these who had valid data at baseline and five or more subsequent consecutive annual reviews. Assessments consisted of a range of clinical and biochemical variables including the ankle/brachial index (ABI). PAD was defined as an ABI  $\leq 0.90$  at two consecutive reviews or any PAD-related lower-extremity amputation. RESULTS: The prevalence of PAD at study entry was 13.6% and the incidence of new PAD was 3.7 per 100 patient-years. Both prevalent and incident PAD was strongly and independently associated with increasing age, systolic blood pressure, total serum cholesterol, and especially smoking. Risk factor management improved but remained suboptimal during follow-up. An ABI of  $\leq 0.90$  was independently associated with an increased risk of cardiac death of 67%. CONCLUSIONS: Measurement of the ABI is a simple means of identifying PAD in diabetic patients. PAD is common in diabetic patients and predicts cardiac death. These data further support the role of regular screening for PAD in diabetes so that intensive management of vascular risk factors can be pursued.

<http://www.thai-otsuka.co.th/pxnews/index.html>  
Dr. Shwe Win: [shwewin@thai-otsuka.co.th](mailto:shwewin@thai-otsuka.co.th)