

## TOP JOURNAL CLUB

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### Therapeutic potential of oral antiproliferative agents in the prevention of coronary restenosis.

Reference: Drugs 2004; 64(21):2379.

The treatment of coronary artery disease has reached many milestones - from balloon angioplasty to drug-eluting stents. The last decade witnessed the revolution of bare metal stents with new designs, alloys and strut thicknesses. Yet restenosis, the aphorismic 'Achilles heel', remains to be conquered. The restenosis rates with balloon angioplasty alone are 30-40% and are reduced to 20-30% with stents. Although intravascular brachytherapy proved to be a durable and safely used technique to treat in-stent restenosis, clinical event rates were not reduced to single digits. Drug-eluting stents are showing positive results in this direction, but it is too early to predict their efficacy in various subsets of lesions. With the increased usage of these stents, there are reports of problems such as late stent malapposition, subacute and late thromboses, and aneurysm formations due to the vessel toxicity associated with this method of treatment. Furthermore, when multivessel stenting is considered, the cost of drug-eluting stents is a significant problem given the fact that these are no longer 'zero restenosis' devices. There is a definite need for a simple, safe and durable solution to restenosis. Oral agents are an alternative delivery strategy that can target multiple coronary lesions, which are targets for catheter-based revascularisation with any approved metal stent and with potentially lower cost. Although oral agents have been an interesting option to treat restenosis and several agents have been tested in trials since the 1980s, the results were disappointing. The development of devices such as intravascular ultrasound has led to a greater understanding of restenosis mechanisms, and the focus on pathophysiological mechanisms, which centred mainly on platelets, growth factors and lipids, has changed to inflammation, endothelium and smooth muscle cell proliferation. Accordingly, the targets of pharmaceutical agents have shifted from platelets to cell cycle inhibition, smooth muscle cell proliferation and migration, synthesis of extra cellular

matrix, and inflammatory mediators. Initial encouraging results with oral drugs such as cilostazol, sirolimus (rapamycin) and thiazolidinediones indicate a definite place for this strategy to reduce restenosis. A desirable oral agent would be anti-inflammatory, inhibit smooth muscle cell migration and proliferation, promote endothelial growth, and be well tolerated and free from significant adverse effects. It may be useful to start with a high loading dose before stent implantation and then follow with a short-term lower maintenance dose. Future trials should be aimed at finding an ideal agent, effective loading dose, maintenance dose and optimum duration of therapy.

### The role of cilostazol in the treatment of intermittent claudication.

Reference: Curr Med Res Opin. 2004;20(10):1661

This paper represents a review, by experts, of current opinion and information on intermittent claudication (IC) and the role that cilostazol plays in its treatment. IC is a common and debilitating condition that has a significant adverse impact on health-related quality of life (HR-QoL). It is currently under-recognised as a powerful marker of increased cardiovascular (CV) risk. The clinical priority is secondary prevention - sometimes referred to as best medical therapy aimed at reducing CV risk. However, the priority for most patients (often overlooked by clinicians) is symptom relief: an increase in walking distance leading to an improvement in HR-QoL. The symptoms of IC may be improved by exercise, pharmacotherapy, and when these are unsuitable or unsuccessful, endovascular or surgical intervention. Cilostazol is indicated for the improvement of maximal and pain-free walking distance in patients with IC who do not have rest pain or tissue necrosis. In clinical trials, cilostazol improved symptoms both objectively and subjectively, and also improved HR-QoL. Cilostazol is usually well tolerated, with adverse events being generally mild to moderate in intensity, and transient or resolved after symptomatic treatment (e.g. non-prescription analgesics). Such events only infrequently require permanent drug withdrawal. There are no interactions with other drugs commonly prescribed in patients with IC, such as statins and anti-platelet agents. Cilostazol also has a range of potentially beneficial effects that may in the future be proven to decrease CV risk and modify the underlying process of atherosclerosis.

Cilostazol represents the best evidence-based pharmacological therapy available for the symptoms of IC and should be the first-line treatment for symptom improvement in appropriate patients. Based on the available treatment strategies, the paper presents a suggested algorithm for the management of IC highlighting the role of cilostazol.

### **Cilostazol inhibits leukocyte integrin Mac-1, leading to a potential reduction in restenosis after coronary stent implantation.**

Reference: J Am Coll Cardiol. 2004;6;44(7):1408.

**OBJECTIVES:** The aim of this study was to confirm clinically a hypothesis that cilostazol inhibits leukocyte Mac-1, leading to prevention of post-stent restenosis. **BACKGROUND:** The platelet phosphodiesterase III inhibitor called cilostazol also inhibits alpha-granule release of P-selectin in platelets. The P-selectin-mediated platelet-leukocyte interaction promotes activation and upregulation of leukocyte Mac-1 after coronary stenting, which plays a key role on the mechanism of restenosis. Thus, cilostazol's potential inhibition of this process may lead to prevention of restenosis. **METHODS:** Using flow cytometric analysis of whole blood obtained from the coronary sinus, the expression of platelet membrane glycoproteins and neutrophil adhesion molecules was observed in 70 consecutive patients undergoing coronary stenting. The patients were randomly assigned to either a cilostazol or ticlopidine group before stent placement. **RESULTS:** The restenosis rate was lower (15% vs. 31%,  $p < 0.05$ ) in the cilostazol group ( $n = 34$ ) than in the ticlopidine group ( $n = 32$ ). A stent-induced increase in platelet P-selectin (CD62P) expression and an increase in neutrophil Mac-1 (CD11b) expression were suppressed in the cilostazol group compared with the ticlopidine group. Angiographic late lumen loss was correlated with the relative changes in platelet P-selectin and neutrophil Mac-1 at 48 h after coronary stenting. **CONCLUSIONS:** Cilostazol may have effects on suppression of P-selectin-mediated platelet activation, platelet-leukocyte interaction, and subsequent Mac-1-mediated leukocyte activation, which might lead to a reduced restenosis rate after coronary stent implantation.

### **Type 2 Diabetes Mellitus and Insulin Resistance: Stroke Prevention and Management.**

Reference: Curr Treat Options Neurol. 2004;6(6):443

Clinically recognized disorders of glucose metabolism include impaired fasting glucose, impaired glucose tolerance (both termed prediabetes), and diabetes mellitus. Type 2 diabetes mellitus affects 6% to 13% of adults in the United States. Among patients with recent stroke, 70% will have known diabetes, occult diabetes (detectable on an oral glucose tolerance test), or prediabetes. Type 2 diabetes mellitus is associated with a two- to six-fold increased risk for first or recurrent ischemic stroke. The mechanisms for the association are myriad and include the effects of hyperglycemia on vascular tissues and coagulation, and aberrations in blood pressure regulation, lipid metabolism, endothelial function, vascular inflammation, lipid metabolism, smooth muscle cell proliferation, and fibrinolysis. The most effective strategies to prevent stroke among people with diabetes include blood pressure control, antiplatelet therapy, and statin therapy. Tight glycemic control is recommended to prevent microvascular disease, but the effect on macrovascular disease, including stroke, has not been proven. Target blood pressure should be less than 130/80. Statins should be given in dosages effective to reduce low-density lipoprotein cholesterol to less than 100 mg/dL. For glycemic control, first line therapy for most patients is metformin, starting at 500 mg daily. Treatment of insulin resistance with weight loss, exercise, or medication can correct these derangements, and represents a promising approach to stroke prevention.

<http://www.thai-otsuka.co.th/pxnews/>

E-mail: [shwewin@thai-otsuka.co.th](mailto:shwewin@thai-otsuka.co.th)