

# TOP Journal Club

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## Antiplatelet and Antithrombotic Activity of Cilostazol is Potentiated by Dipyridamole in Rabbits and Dissociated from Bleeding Time Prolongation.

**Purpose:** To determine the antiplatelet effect of cilostazol (Pletal((R))) and its interaction with dipyridamole in in vitro and in vivo rabbit models, and to see if it can be dissociated from bleeding time prolongation. **Methods:** In vitro collagen-induced platelet aggregation was measured by an impedance-based aggregometer. The in vivo antithrombotic effect was evaluated in a rabbit carotid artery cyclic flow reduction (CFR) model, in which repetitive thrombosis was induced by mechanical injuries of the artery and stenosis. Template bleeding time was determined in rabbit ear arterioles and hindlimb nail cuticles. **Results:** In vitro platelet aggregation was slightly inhibited by 4 mu M cilostazol (22 +/- 6%), and modestly by 13 mu M (57 +/- 3% of aggregation). While dipyridamole itself up to 13 mu M had no significant inhibition, it potentiated the effect from cilostazol: in the presence of 4 mu M dipyridamole, 4 mu M cilostazol inhibited aggregation by 47 +/- 6%. Dipyridamole also potentiated the CFR reducing effect of cilostazol: combination of dipyridamole (no effect by itself) and cilostazol at 1 mu M decreased CFRs to levels achieved by 3-4 mu M cilostazol alone. Bleeding times were similar in controls and animals treated with cilostazol, or with cilostazol and dipyridamole. In contrast, aspirin (4 mg/kg), while reducing CFRs, significantly increased bleeding time. **Conclusion:** These results suggest that dipyridamole potentiates the antiplatelet effect of cilostazol without prolongation of the bleeding time, implying a potential novel combination antithrombotic therapy.

*Cardiovasc Drugs Ther. 2005 Jan;19(1):41-8.*

## Impaired health status and invasive treatment in peripheral arterial disease: a prospective 1-year follow-up study.

**OBJECTIVE:** It has been argued that health status and quality of life (QOL) should be taken into account in the

treatment policy of patients with peripheral arterial disease (PAD). In cardiac patients, it has been shown that poor perceived health status is an independent predictor of mortality and hospitalization. We therefore examined (1) the role of health status, QOL, and clinical indices of disease severity as determinants of invasive treatment in patients with PAD and (2) the effect of invasive treatment on health status and QOL. **METHODS:** At their first visit, patients completed the RAND 36-item Health Survey and World Health Organization Quality of Life assessment instrument questionnaires to assess health status and QOL, respectively. During the 1-year follow-up period, data concerning hospitalization were derived from the patients' medical files. Furthermore, patients completed the RAND 36 and the World Health Organization Quality of Life assessment instrument again at 1-year follow-up. The setting was a vascular outpatient clinic of a teaching hospital in Tilburg, The Netherlands; participants were 200 consecutive patients newly diagnosed with intermittent claudication, a common expression of PAD. Diagnosis was based on history, physical examination, treadmill walking distance, and ankle-brachial pressure indices. Main outcome measures were (1) invasive treatment of PAD that took place during the 1-year follow-up, derived from the patients' medical files, and (2) health status and QOL after 1 year of follow-up. **RESULTS:** After 1 year of follow-up, 107 patients (53.5%) were event free, whereas 77 patients (38.5%) had been hospitalized for invasive treatment of PAD. Sixteen patients (8%) were hospitalized for other cardiovascular reasons. In a multivariate logistic regression model, age (odds ratio [OR], 0.95; 95% confidence interval [CI], 0.91-0.99; P = .024), pain-free walking distance (OR, 2.74; 95% CI, 1.05-7.17; P = .04), and physical functioning (OR, 4.46; 95% CI, 1.79-11.12; P = .001) were independent predictors of invasive treatment of intermittent claudication. After 1 year of follow-up, patients who were treated invasively experienced a significant improvement in their physical functioning (P = .004), role limitations due to emotional problems (P = .018), and bodily pain (P = .026). **CONCLUSIONS:** Patients with poor self-reported physical functioning, limited walking distance, and a younger age were likely to be treated invasively. The physician's clinical judgment about when to intervene adequately reflects the patient's own opinion about his or her health status. Invasive treatment led to a significant improvement in patients' health status. These findings indicate the effectiveness of the strategy to include patients' perceived physical functioning into the process of clinical decision-making.

*J Vasc Surg. 2005 Mar;41(3):436-42.*

## **A dose-effect study of beraprost sodium in intermittent claudication.**

We compared the efficacy and safety of three doses of beraprost sodium, an epoprostenol analogue, with placebo in the treatment of intermittent claudication (Fontaine's stage II). One hundred sixty-four patients were randomized to receive either placebo, 20 micrograms beraprost sodium (BPS60 group), 40 micrograms beraprost sodium (BPS120 group), or 60 micrograms beraprost sodium (BPS180 group) three times daily administered orally in a double-blind manner for 12 weeks. Treadmill exercise tests were performed twice during an initial selection phase (D-28 and D0) at week 10 (at trough beraprost concentration) and week 12 (at peak beraprost concentration) of the treatment phase. At week 10, all groups showed an increase in pain-free walking distance, and this distance was greatest in the BPS60 and BPS120 groups ( $p = 0.055$ ). At week 12, a similar pattern was observed, and the difference was significant between the groups ( $p = 0.023$ ). The most frequent adverse events reported were gastrointestinal disorders, headaches, skin disorders, and flushes. Patients who received either 60 or 120 micrograms of beraprost sodium daily had an increased pain-free walking distance. Further studies are required to investigate why the highest dose used (180 micrograms daily) showed lower efficacy. Having both vasodilating and antiplatelet properties and being able to increase pain-free walking distance in the short term, beraprost sodium is a promising drug for the treatment of intermittent claudication.

*J Cardiovasc Pharmacol. 1996 Jun;27(6):788-93.*

## **Oral Beraprost sodium, a prostaglandin I<sub>2</sub> analogue, for intermittent claudication: a double-blind, randomized, multicenter controlled trial. Beraprost et Claudication Intermittente (BERCI) Research Group.**

**BACKGROUND:** Beraprost sodium (BPS) is a new stable, orally active prostaglandin I<sub>2</sub> analogue with antiplatelet and vasodilating properties. We report the results of a phase III clinical trial of BPS in patients with intermittent claudication. **METHODS AND RESULTS:** Patients ( $n=549$ ) with a pain-free walking distance of between 50 and 300 m were entered into a 4-week single-blind placebo run-in phase. Patients whose pain-free walking distance had changed by  $<25\%$  were then

randomized to receive either BPS (40 microg TID,  $n=209$ ) or placebo ( $n=213$ ) in a double-blind manner for 6 months. Pain-free and maximum walking distances were measured on the occasion of treadmill exercise tests performed at baseline and 1.5, 3, 4.5, and 6 months after randomization. Success was defined as an improvement of  $>50\%$  in pain-free walking distance at month 6 and in  $>$  or  $=1$  earlier treadmill exercise test in the absence of critical cardiovascular events. Success was observed more frequently in the BPS group (43.5%) than in the placebo group (33.3%,  $P=0.036$ ). Pain-free walking distances increased by 81.5% and 52.5%, respectively, in the BPS and placebo groups ( $P=0.001$ ) and maximum walking distances by 60.1% and 35.0%, respectively ( $P=0.004$ ). The incidence of critical cardiovascular events was 4.8% in the BPS group and 8.9% in the placebo group. **CONCLUSIONS:** These results show that BPS is an effective symptomatic treatment of patients with intermittent claudication. The beneficial effects of BPS on critical cardiovascular events should be confirmed in appropriate clinical trials.

*Circulation. 2000 Jul 25;102(4):426-31.*

## **Studies on the effectiveness and safety of cilostazol, beraprost sodium, prostaglandin E<sub>1</sub> for the treatment of intermittent claudication.**

The literature evaluation results and the meta-analysis suggest that these two drugs (cilostazol and PGE<sub>1</sub>) 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.

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

## **Usefulness of granular BCAA after hepatectomy for liver cancer complicated with liver cirrhosis.**

**CONCLUSIONS:** BCAA supplementation after hepatectomy promotes rapid improvement in protein metabolism and inhibits progression to liver cirrhosis. Administration of BCAA after hepatectomy is considered beneficial to a patient's nutritional state.

*Nutrition. 2005 Apr;21(4):480-6.*

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