

# TOP Journal Club

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## **Peripheral arterial disease: pathophysiology, risk factors, and role of antithrombotic therapy.**

Ref: J Am Pharm Assoc. 2004;44(2 Suppl 1):S37

**OBJECTIVE:** To provide an overview of the impact of peripheral arterial disease (PAD) and the steps that can be taken to reduce its burden through greater awareness of the disease, improved diagnosis, and better treatment, with emphasis on the use of antiplatelet agents. **DATA SOURCES:** Recent (1990-2003) published scientific literature, as identified by the author through Medline searches, using the terms peripheral arterial disease, atherothrombosis, pathophysiology, risk factors, treatment, clinical trials, and reviews on treatment. **STUDY SELECTION:** Recent systematic English-language review articles and reports of controlled randomized clinical trials were screened for inclusion. **DATA SYNTHESIS:** PAD is a distinct atherothrombotic syndrome marked by stenosis and occlusion of peripheral arterial beds, typically those in the lower extremities. Symptoms range from intermittent claudication (IC) during exercise to peripheral limb ischemia requiring limb amputation. IC, the most common symptom, is experienced by 2% to 3% of men and 1% to 2% of women aged 60 years and older. Despite its recognition as a major atherothrombotic risk factor, PAD is not widely appreciated by clinicians, and most cases remain undiagnosed. Asymptomatic PAD, as indicated by a reduced ankle brachial systolic pressure index, should alert the health care provider to the presence of diffuse atherothrombotic disease and need for treatment. Risk factors for development and progression of PAD include smoking, hypertension, diabetes, hyperlipidemia, and physical inactivity. The aim of pharmacotherapy is to improve the symptoms of PAD (especially IC), defer onset of limb-threatening ischemia, and improve long-term survival. Successful treatment strategies include risk factor modification, particularly smoking cessation; initiation of regular exercise; control of hypertension, diabetes, and hyperlipidemia; and use of antiplatelet agents to reduce the risk of atherothrombotic events. Available data suggest that aspirin reduces morbidity and mortality in PAD, while clopidogrel reduces the risk of atherothrombotic events such as myocardial infarction and stroke in these patients. **CONCLUSION:** Increased awareness among members of the health care community about the prevalence of PAD and benefits

associated with risk-factor reduction and antiplatelet therapy could produce substantial decreases in the burden of this disease.

## **Conservative regimen for chronic critical limb ischemia.**

Ref: J Med Assoc Thai. 2004 Mar;87(3):310-8.

**OBJECTIVE:** The objective of this study was to determine the effectiveness of the treatment of chronic critical limb ischemia by conservative regimen. **METHOD:** Data for all patients who underwent a conservative regimen at a single institution from January 1997 to December 2001 were entered into the registry. Conservative regimen consisted of cilostazol (Pletaal) 200 mg/day, a vegetarian diet, had completely stopped smoking and had progressive walking training. **RESULTS:** A total of 53 patients (59 limbs) with chronic critical limb ischemia were treated with a conservative regimen. The conservative regimen failed in 19 limbs (32.2%). In the failed limbs, infrainguinal bypass was performed on 8 limbs, aortoiliac endarterectomy was performed on 1 limb and 6 had primary amputation. The other four limbs were treated conservatively until death because of very poor cardiac function. Post-operatively, 2 grafts had thrombosis and led to amputation. **CONCLUSION:** These early results appear to be promising with 67.8 per cent limb saving. This conservative regimen may be appropriately performed in selected chronic critical limb ischemia, especially those who presented with clinical severe claudication, rest pain or nonhealed ulcer. Cilostazol administration may play a positive role in gangrenous limbs.

## **Methods for the economic and quality of life supplement to the cilostazol for RESTenosis (CREST) trial.**

Ref: J Invasive Cardiol. 2004 May;16(5):257-9.

**OBJECTIVE:** To determine economic and quality of life outcomes for the Cilostazol for RESTenosis (CREST) trial, which is investigating the efficacy of cilostazol vs. placebo in preventing post-stent restenosis. **DESIGN:** CREST is a prospective, multicenter, randomized, placebo-controlled, double-blind trial. **SETTING:** 20 clinical sites; the Emory Center for Outcomes Research (ECOR) will serve as the economic and data coordinating center. **PATIENTS:** 705 patients (>18 years) who have undergone successful, uncomplicated

placement of an intracoronary stent in a native coronary artery. INTERVENTION: Cilostazol (100 mg twice daily) or placebo for 6 months. OUTCOME MEASURES: Costs: Primary endpoint, total direct medical costs at 6 months; secondary endpoints, initial hospital costs and follow-up costs. QOL: Health-related quality of life (QOL) will be assessed using the EQ-5D and the Seattle Angina Questionnaire at baseline and at 1, 3, and 6 months. Cost-effectiveness analysis: Preliminary data show that cilostazol is clinically superior to placebo and if the mean cost for the cilostazol arm is higher than that for placebo, cost-effectiveness analysis will be determined for the cost per episode of restenosis prevented, the cost per episode of major clinical and angiographic endpoints averted, and the cost per quality-adjusted life-years gained.

### **Rebamipide activates genes encoding angiogenic growth factors and Cox2 and stimulates angiogenesis: a key to its ulcer healing action?**

Ref: Dig Dis Sci. 2004 Feb;49(2):202-9.

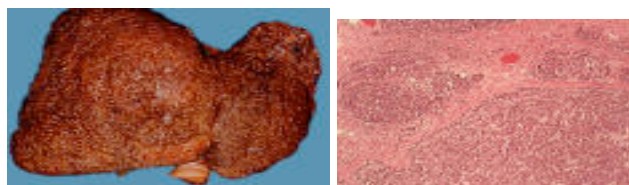
Clinical and experimental data indicate that rebamipide accelerates ulcer healing, improves scar quality, and prevents ulcer recurrence. However, the mechanisms responsible for these rebamipides' actions are not fully elucidated. We studied, using gene expression microarray analysis, which of the ulcer healing genes are activated by rebamipide treatment. Normal rat gastric epithelial cells (RGM1) were treated with either vehicle or rebamipide. Gene expression was determined using Affymetrix rat genome U34A gene chip arrays and data were analyzed using the GeneSpring program. Activation of some of the genes and protein translation were also examined by RT/PCR and Western blotting. Rebamipide significantly upregulated the proangiogenic genes encoding vascular endothelial growth factor (VEGF), by 7.5-fold, heparin binding epidermal growth-like factor (HB-EGF), by approximately 5-fold, fibroblast growth factor receptor-2 (FGFR2), by 4.4-fold, and cyclooxygenase-2 (Cox2), by 9.3-fold, as well as growth promoting genes, e.g., insulin growth factor-1 (IGF-1), by 5-fold. RT/PCR and Western blotting demonstrated that Cox2 mRNA and protein were upregulated; the latter, approximately 6-fold. Treatment of rat gastric mucosal endothelial cells with rebamipide

stimulated in vitro angiogenesis by approximately 240% (vs. controls,  $P < 0.001$ ). Conclusions are as follows. (1) Rebamipide activates in gastric epithelial RGM-1 cells a genetic program that promotes angiogenesis and signals cell growth and tissue regeneration. (2) In addition, rebamipide treatment directly stimulates angiogenesis in gastric microvascular endothelial cells. Thus rebamipide has two separate and distinct mechanisms of proangiogenic action: one through activation in gastric epithelial cells of proangiogenic growth factor genes and the second a direct angiogenic action on microvascular endothelial cells.

*Chem Pharm Bull (Tokyo). 2004 Apr;52(4):490-3.*

### **Suppression of the bitterness of enteral nutrients using increased particle sizes of branched-chain amino acids (BCAAs) and various flavours: a taste sensor study.**

An improved formulation of the enteral nutrient Aminoleban EN (Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan), has been commercially available since Spring 2004. Like the previous formulation, the improved product contains branched-chain amino acids (BCAAs) L-isoleucine (L-Ile), L-leucine (L-Leu), and L-valine (L-Val), but the average particle size of these amino acids has been increased to 180 to 250 microm in the improved formulation, compared with 40 to 90 microm in the old product. The improved formulation has a significantly lower bitterness intensity score than the older formulation, as evaluated both in human gustatory tests and using the artificial taste sensor. We propose that this improved taste masking is due to the larger particle size of the BCAA crystals, due to which their release rates are reduced. The addition of improved flavours has also helped to reduce the bitterness of the improved Aminoleban EN formulation significantly. Analysis of the taste sensor data suggests that the sourness and sweetness of the added flavours were critical in diminishing the bitterness of Aminoleban EN.



<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)