

TOP Journal Club

Vol: 6 No: 1 January 2003



Pharmacotherapy for peripheral arterial disease: emerging therapeutic options

Although endovascular therapy has revolutionized the management of patients with peripheral arterial disease (PAD), noninterventional regimens, such as structured exercise therapy, atherosclerotic risk factor modification, and pharmacotherapy, are effective in patients suffering from mild-to-moderate PAD and intermittent claudication (IC). For more than a decade, the only pharmacologic therapy for IC available in the United States was pentoxifylline, which had demonstrated superiority in improving walking distances but offered minimal clinical benefit. Recently, basic research into the pathophysiology of IC has led to the development of cilostazol, a new pharmacologic agent approved for treatment of this condition in 1999. Ongoing research in the use of angiogenic growth factors has further broadened the range of potential alternatives to treatment in patients with PAD. Revascularization procedures, including nonsurgical and surgical techniques, can thus be reserved to improve patency and reduce the risk of limb loss in patients with PAD and IC with more severe impairment.

Reference: *Angiology* 2002 Nov-Dec;53(6):627-33

Pharmacologic therapy for peripheral arterial disease and claudication

Peripheral arterial disease (PAD) is a common manifestation of systemic atherosclerosis that is associated with a high risk of cardiovascular mortality and significant limitation in function because of limb ischemia. Patients with PAD should be considered to have significant coronary and cerebral arterial disease that requires aggressive risk factor management, including the prescription of antiplatelet drugs, to lower the subsequent risk of myocardial infarction, stroke, and death. In the population with PAD, level 1 and level 2 evidence supports the use of statin drugs for lipid management, angiotensin-converting enzyme-1 inhibitors for blood pressure control, and aspirin or clopidogrel as antiplatelet agents. Once this is accomplished, the severity of limb symptoms should be assessed, and a structured exercise program or the selected use of drugs such as **cilostazol to treat claudication should be prescribed**. In patients primarily considered for surgical treatment, antiplatelet and anticoagulant drug therapy can be used as a means of promoting graft patency, and beta-adrenergic blockers can be used as a means of reducing the perioperative risks associated with vascular surgery.

Reference: *J Vasc Surg* 2002 Dec;36(6):1283-91

Effect of cilostazol on treadmill walking, community-based walking ability, and health-related quality of life in patients with intermittent claudication due to peripheral arterial disease: meta-analysis of six randomized controlled trials

OBJECTIVES: To assess whether cilostazol, a phosphodiesterase III inhibitor, improves treadmill and community-based walking ability and health-related quality of life (HQL) in patients with intermittent claudication resulting from peripheral arterial disease (PAD).

DESIGN: Retrospective meta-analysis of data pooled from six Phase 3, multicenter, double-blind, placebo-controlled, parallel-group, randomized studies.

SETTING: Patients were recruited from outpatient ambulatory medical care facilities.

PARTICIPANTS: Patients' (n = 1,751) mean age +/- standard deviation was 65 +/- 9, and they had a history of PAD for 6 months or longer and an ankle brachial index (ABI) of 0.90 or less.

INTERVENTION: Cilostazol 50 mg bid or 100 mg bid for 12, 16, or 24 weeks.

MEASUREMENTS: ABI; maximal walking distance (MWD); pain-free walking distance on a graded and constant-load treadmill; and HQL, measured using the Walking Impairment Questionnaire (WIQ) and the Medical Outcomes Study Short Form-36 (SF-36).

RESULTS: Maximal treadmill walking distance improved more in both cilostazol groups than in the placebo group (both P < .0001). WIQ and SF-36 physical summary scores improved significantly more with cilostazol than with placebo (for instance, WIQ distance score, P < .0001 and SF-36 physical summary score, P < .0001, comparing persons taking cilostazol with controls). Improved MWD correlated with improvements in WIQ (correlation with distance score, r = 0.34, P < .0001) and SF-36 physical summary scores (r = 0.29, P < .0001).

CONCLUSIONS: Treatment with cilostazol was associated with greater improvements in community-based walking ability and HQL in patients with intermittent claudication than treatment with placebo. These improvements correlated with increased MWD. This analysis of effects of cilostazol on improving walking ability in persons with claudication is the first cilostazol study focused on community-based measures of functional status and HQL. Questionnaires assessing walking ability and HQL provide important patient-based information about clinical outcomes of claudication therapy.

Reference: *J Am Geriatr Soc* 2002 Dec;50(12):1939-46



PLEETAL

Meta-analysis of results from eight randomized, placebo-controlled trials on the effect of cilostazol on patients with intermittent claudication

We examined the effect of cilostazol, a type III phosphodiesterase inhibitor, on pain-free and maximal walking distance and quality of life measures. The present study examined adverse effects in 2,702 patients with stable, moderate to severe claudication enrolled in 8 randomized, double-blind, placebo-controlled trials. Treatment duration ranged from 12 to 24 weeks. **Cilostazol therapy increased maximal and pain-free walking distances by 50% and 67%, respectively.** In subgroup analysis, cilostazol increased pain-free and maximal walking distance similarly in men and women, in older (>=65 years) and younger patients, and in patients with and without diabetes. Quality-of-life assessments revealed enhanced scores for physical well-being. Cilostazol-treated patients reported a higher incidence of headache, bowel complaints, and palpitations than patients given placebos. **Cilostazol decreased triglycerides by 15.8% and increased high-density lipoprotein cholesterol by 12.8%**, but there were no deleterious effects on any hematologic or serum markers. We conclude that cilostazol significantly increases walking distance and quality-of-life measures in patients with claudication without major adverse effects.

Reference: *Am J Cardiol* 2002 Dec 15;90(12):1314-9

Amino acid dysbalance in liver failure is favourably influenced by recirculating albumin dialysis (MARS)

INTRODUCTION: Dysbalance between branched chain (BCAA) and aromatic amino acids (AAA), which can be quantified by a low Fischer's Index (SigmaBCAA/SigmaAAA), as well as elevated levels of free tryptophan in plasma are common in hepatic failure and may contribute to the development of hepatic encephalopathy.

AIM: To evaluate the influence of a new extracorporeal detoxification system for liver failure (Molecular Adsorbents Recirculating System, MARS(R), i.e. dialysis against a recirculating albumin solution cleaned online by charcoal and an anion exchange resin) on plasma tryptophan and Fischer's Index.

METHODS: Plasma samples were taken before, during and after MARS treatments (n = 11, mean blood flow 135 ml/min, mean dialysate flow 120 ml/min, high flux polysulfone membrane). Simultaneous to blood sampling, aliquots of the albumin dialysate were taken between the elements of the dialysate circuit.

RESULTS: Fischer's Index in systemic blood increased during MARS by 24% (from 1.44 to 1.79, P < 0.001; mean treatment duration, 5.5 h). Systemic tryptophan level was significantly reduced at the same time (-25%, n = 8). Amino acid removal rates from plasma during a single

dialyser passage ranged from 10 to 53%. In particular, AAA were preferentially removed (42-44% throughout treatment), while BCAA removal was 28-46% initially and later declined to 24-28%. A maximum concentration gradient between plasma and dialysate was maintained for the AAA throughout treatment through their apparently complete removal by the charcoal adsorber. Conversely, BCAA removal at both adsorbers was only minor. As a result, **Fischer's Index showed a significant increase in the processed plasma**, which became even more pronounced with increasing treatment duration.

CONCLUSIONS: MARS enables an elevation of a pathologically decreased Fischer's Index as well as a reduction of systemic tryptophan levels in patients with liver failure. The effects of MARS on plasma amino acid dysbalance may contribute to an improvement of hepatic encephalopathy.

Reference: *Liver* 2002;22 Suppl 2:35-9

Cocarcinogenic effects of alcohol in hepatocarcinogenesis.

Alcohol is a major aetiological factor in hepatocarcinogenesis but our understanding of its importance as a modulating factor is just beginning to emerge. Alcohol may enhance the development of hepatoma. These include dietary or environmental carcinogens ingested along with alcoholic beverages, alcoholic cirrhosis as a precancerous condition, and the effects of alcohol metabolism.

Reference: *Gut* 2002 Jul;51(1):132-9

Quality of life and objective disease criteria in patients with intermittent claudication in general practice

BACKGROUND: The quality of life (QoL) of patients with chronic diseases is an important decision criterion for medical treatment, especially in primary care settings. It is known that subjective sickness feelings often cannot be correlated with objective disease criteria.

OBJECTIVE: The aim of the study was to determine the QoL of patients with intermittent claudication with the arterial morphology, haemodynamic parameters and functional disability of peripheral arterial occlusive disease (PAOD). **METHODS:** In 150 patients with stable intermittent claudication, the health-related QoL was compared with the angiogram score, the resting Doppler pressure values, and the initial claudication distance (ICD) and absolute claudication distance (ACD) with treadmill exercise. **RESULTS:** The QoL did not correlate significantly with either the angiogram score or the ankle systolic blood pressure and ankle brachial index. ICD and ACD correlated significantly with the QoL activity subscales of pain, complaints and functional status (P < 0.001). In a multiple regression analysis, ACD and body mass index were the most predictive variables for the QoL. **CONCLUSION:** The QoL of PAOD patients is independent of the peripheral Doppler pressure and the angiographic severity of the disease. The most important criterion for the QoL is the patient's functional disability.

Reference: *Fam Pract* 2003 Jan;20(1):36-40

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