

# TOP Journal Club

## Vol: 6 No: 11 November 2003

### **Cilostazol as a unique antithrombotic agent.**

Reference: Curr Pharm Des. 2003;9(28):2289-302

Cilostazol (CLZ) was originally developed as a selective inhibitor of cyclic nucleotide phosphodiesterase 3 (PDE3). PDE3 inhibition in platelets and vascular smooth muscle cells (VSMC) was expected to provide an antiplatelet effect and vasodilation. Recent preclinical studies have demonstrated that CLZ also possesses the ability to inhibit adenosine uptake by various cells, a property that distinguishes CLZ from other PDE3 inhibitors, such as milrinone. After extensive preclinical and clinical studies, CLZ has been shown to have unique antithrombotic and vasodilatory properties based upon these novel mechanisms of action. CLZ was approved in 1988 for the treatment of symptoms related to peripheral arterial occlusive disease in Japan (Pletaal) and in 1999 in the U.S. and in 2001 in the U.K. (Pletal) for the treatment of intermittent claudication symptoms. Despite its remarkable antiplatelet properties, CLZ is not generally considered an antithrombotic agent in Western countries, perhaps due to the bulk of its antithrombotic preclinical and clinical development being conducted in Japan. In this review, the unique properties of CLZ are reviewed with the focus on CLZ as a unique antiplatelet agent targeting platelets and VSMC, demonstrating synergy with endogenous mediators and showing lowered risk of bleeding risk compared to other antiplatelet drugs.

### **Managing PAD with multiple platelet inhibitors: the effect of combination therapy on bleeding time.**

Reference: J Vasc Surg. 2003 Oct;38(4):710-3.

**PURPOSE:** Patients with lower-extremity peripheral arterial disease (PAD) face a high risk of cardiovascular morbidity and mortality. Platelet inhibition (PI) significantly reduces this risk. Combination PI is common and increasingly indicated in patients with PAD; however, the effect on platelet function has not been objectively evaluated. Aspirin (ASA), clopidogrel (Clop), and cilostazol (Cilo) are the three most commonly used PI drugs in patients with PAD. A prospective, sequential evaluation of platelet function using the template bleeding time (BT) was performed for PAD patients taking these medications singly and in combination. **METHODS:** Twenty-one patients with PAD, averaging 65.9 years of age, were studied.

Patients were placed on sequential two-week regimens of the following therapies: washout (no PI), ASA (325 mg daily), ASA + Cilo (100 mg twice daily), washout, Cilo, Cilo + Clop (75 mg each day), washout, Clop, Clop + ASA, and Clop + ASA + Cilo. At the end of each phase, trained personnel measured the BT. **RESULTS:** Baseline bleeding time for the group was 4.29 +/- 1.69 minutes. ASA (BT = 6.64 +/- 3.52) and Clop (BT = 10.17 +/- 5.4) significantly prolonged bleeding time ( $P < 0.01$ ); however, no significant effect was observed with Cilo alone (BT = 5.41 +/- 2.69). Combined treatment with ASA + Clop (BT = 17.39 +/- 4.59) had a more pronounced effect on BT compared with either agent alone ( $P < 0.01$ ). The addition of Cilo to either ASA (BT = 8.3 +/- 4.27) or Clop (BT = 12.7 +/- 7.46) or the combination of ASA + Clop (BT = 17.92 +/- 4.69) did not prolong BT. **CONCLUSION:** All patients with PAD require platelet inhibition, and many require pharmacotherapy for intermittent claudication. The platelet inhibitors aspirin and clopidogrel are used for the reduction of ischemic events. They significantly prolong bleeding time individually and to a greater extent in combination. Cilo is used to improve walking distance in patients with intermittent claudication. When Cilo is added to ASA, Clop, or the combination of the two, there is no additional increase in bleeding time. Therefore, Cilo can be used in combination with other platelet inhibitors without an additional effect on platelet function as reflected by the bleeding time.

### **Preoperative administration of rebamipide significantly lowers body temperature and circulating interleukin-6 in gastric cancer patients after gastrectomy.**

Reference: Dig Surg. 2003;20(6):500-5

**BACKGROUND/AIMS:** It has recently been reported that rebamipide (OPC-12759) inhibits inflammatory cytokines and activation of neutrophils. The aim of the present study was to investigate the effects of preoperative administration of rebamipide on parameters of systemic inflammatory response syndrome (SIRS) and serum levels of inflammatory cytokines in gastric cancer patients after gastrectomy. **PATIENTS AND METHODS:** We measured the parameters of SIRS, circulating cytokines and acute phase reactants in patients after (i) distal gastrectomy with D2 lymph node dissection (group 1, n = 10); (ii) distal gastrectomy with D2 lymph node dissection following administration of rebamipide (group 2, n = 10), and (iii) laparoscopy-assisted distal gastrectomy (LADG) with D1 lymph node dissection (group 3, n = 10). Group 2 was administered 100 mg of rebamipide 3 times/day after meals for 7 days before surgery. **RESULTS:** Among the parameters of SIRS, a difference

was observed in body temperature on day 3. The mean body temperature of group 2 was significantly lower than group 1 ( $p = 0.006$ ), and was similar to group 3. In proinflammatory cytokines, a significant difference was observed in the serum levels of interleukin (IL)-6. On day 1 the IL-6 levels of group 2 were significantly lower than those of group 1 ( $p < 0.001$ ). The changes in the IL-6 level of group 2 were similar to group 3, except in the very early postoperative phase. However, other proinflammatory cytokines, such as IL-8 and IL-10, were not detected, and there was no difference in C-reactive protein between the 3 groups. **CONCLUSION:** Preoperative administration of rebamipide significantly decreased postoperative body temperatures and circulating IL-6 in gastric cancer patients after gastrectomy to levels similar to those of patients with LADG.

### **Pulse Wave Velocity in Lower-Limb Arteries among Diabetic Patients with Peripheral Arterial Disease.**

Reference: J Atheroscler Thromb. 2003;10(4):253-8.

**Objective:** Patients with type 2 diabetes mellitus are at an increased risk of atherosclerosis including peripheral arterial disease (PAD). The purpose of this study was to examine the possible alteration in pulse wave velocity (PWV) in lower-limb arteries among diabetic patients with PAD. **Methods:** We measured brachial-ankle PWV (baPWV) using an automatic device in 101 healthy control subjects and 102 type 2 diabetic patients including those with PAD. **Results:** Diabetic patients without PAD showed a higher baPWV than the healthy control subjects. There was no significant difference in baPWV between the right and left legs in these groups. In contrast, among diabetic patients with PAD, baPWV was significantly lower in the affected legs than in the non-affected legs, and the reduction in baPWV was greater in those with lower ankle-brachial pressure index (ABI). In the patients with PAD who received percutaneous transluminal angioplasty, both baPWV and ABI were increased following successful vessel dilatation. **Conclusions:** These results suggest that baPWV is increased in diabetic patients, whereas it is decreased in the affected legs in diabetic patients with PAD. Widening of the right-left difference in baPWV may be a novel marker of PAD.

### **Brachial-ankle pulse wave velocity as a marker of atherosclerotic vascular damage and cardiovascular risk.**

Reference: Hypertens Res. 2003 Aug;26(8):615-22.

The measurement of brachial-ankle pulse wave velocity (baPWV) is simple and applicable for general

population studies. The present study was conducted to evaluate the applicability of baPWV for screening cardiovascular risk as well as for use as a marker of the severity of atherosclerotic vascular damage in a general population. baPWV was measured in a cross-sectional study involving two cohorts constituting a total of 10,828 subjects who underwent annual health screening check up examinations (6,716 males and 4,112 females; age 30 to 74 years). The Framingham risk score and Pockock's score were obtained. Multivariate analysis demonstrated that baPWV was associated with both scores, independently from conventional atherosclerotic risk factors. The receiver-operator characteristic curve demonstrated that a baPWV of 14.0 m/s is useful for risk stratification by Framingham score and to discriminate patients with either stroke or coronary heart disease ( $n=143$ ), but the likelihood ratios were less than 5.0. Logistic regression analysis demonstrated that a baPWV $>14.0$  m/s is an independent variable for the risk stratification by Framingham score and for the discrimination of patients with atherosclerotic cardiovascular disease. Thus, baPWV has potential as a new marker of cardiovascular risk and may be more useful than other conventional markers; in addition, baPWV is easy to obtain and serves as an indicator of either atherosclerotic cardiovascular risk or severity of atherosclerotic vascular damage; thus it is useful to screen the general population. While the discriminating powers are not sufficiently high, a cutoff value of 14.0 m/s serves to screen subjects, especially in middle-aged ones, of either gender.

### **Brachial-ankle pulse wave velocity and symptomatic cerebral infarction in patients with type 2 diabetes: a cross-sectional study.**

Reference: Cardiovasc Diabetol. 2003 Aug 28;2(1):10.

**BACKGROUND:** Recently a new automatic device that measures brachial-ankle pulse wave velocity using an oscillometric method has been developed. However, the practical significance of brachial-ankle pulse wave velocity measurement remains uncertain. The purpose of this study was to examine the association between brachial-ankle pulse wave velocity and symptomatic cerebral infarction in patients with type 2 diabetes. **METHODS:** One thousand sixty six patients with type 2 diabetes were studied cross-sectionally. Measurements of brachial-ankle pulse wave velocity were made using the automatic device. Logistic regression analysis was used to calculate the odds ratio for cerebral infarction. **RESULTS:** The presence of symptomatic cerebral infarction was confirmed in 86 patients. In these patients brachial-ankle pulse wave velocity was found to be significantly higher than in patients without cerebral infarction (18.94 PlusMinus; 4.95 versus 16.46

PlusMinus; 3.62 m/s,  $p < 0.01$ ). The association between brachial-ankle pulse wave velocity and cerebral infarction remained significant after adjustment for traditional risk factors. There was an increasing odds ratio for each tertile of brachial-ankle pulse wave velocity, from the second tertile (odds ratio, 2.28; 95% confidence interval, 1.05 to 4.94), to the third (odds ratio, 2.53; 95% confidence interval, 1.09 to 5.86). CONCLUSION: Overall, we conclude that an increase in brachial-ankle pulse wave velocity is associated with symptomatic cerebral infarction in patients with type 2 diabetes.

### Utility of automated brachial ankle pulse wave velocity measurements in hypertensive patients.

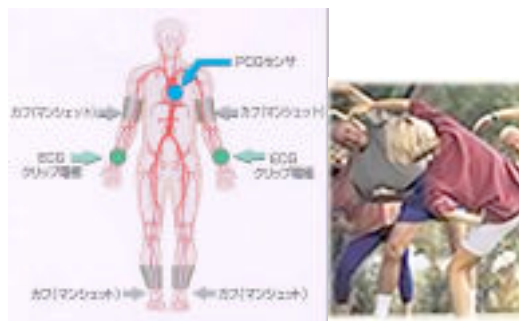
Reference: Am J Hypertens. 2003 Aug;16(8):653-7.

BACKGROUND: We examined whether pulse wave velocity (PWV), determined by brachial ankle arterial pressure wave measurements, using a newly developed, fully automated device could be a surrogate measure for carotid femoral PWV. METHODS & RESULTS: This device (AT-form PWV/ABI, Nippon Colin, Komaki, Japan) can simultaneously monitor bilateral brachial and ankle pressure wave forms using the volume plethysmographic method, with two optional tonometry sensors for carotid and femoral arterial wave measurements. We examined the right brachial-right ankle PWV and left carotid-left femoral PWV in 89 normotensive and untreated hypertensive patients. The brachial ankle PWV correlated well with carotid femoral PWV ( $r = 0.755$ ,  $P < .00001$ ). The Bland-Altman plots of the two variables, however, showed a significant difference exists between the two techniques over the range of measurement. The within-observer and between-observer coefficients of variation of the brachial ankle PWV were 6.5% +/- 4.1% and 3.6% +/- 3.9%, respectively. To determine the factors affecting brachial ankle PWV, we studied treated and untreated hypertensive patients with World Health Organization stage I ( $n = 146$ ), stage II ( $n = 74$ ), or stage III ( $n = 54$ ). In multiple regression analysis, age, brachial ankle PWV, and the presence of diabetes were significant predictors of the severity of hypertensive organ damage. Age, systolic blood pressure, and the stage of hypertensive organ damage were major determinants of brachial ankle PWV. CONCLUSIONS: Although the brachial ankle PWV does not agree with the carotid femoral PWV, this parameter may yet become a new, useful measure for arterial stiffness. Further longitudinal studies are necessary to confirm the clinical significance of the brachial ankle PWV.

### The aging of elastic and muscular arteries: a comparison of diabetic and nondiabetic subjects.

Reference: Diabetes Care. 2003 Jul;26(7):2133-8.

OBJECTIVE: To compare age-related changes in the mechanical properties of different arterial segments in normal volunteers and subjects with type 2 diabetes. RESEARCH DESIGN AND METHODS: In 169 subjects (diabetic  $n = 57$  and nondiabetic  $n = 112$ ), we assessed the mechanical properties of three arterial segments of differing wall composition. Pulse wave velocity (PWV) was measured noninvasively in a thoraco-abdominal segment (carotid femoral PWV [PWV(cf)], in an upper limb muscular artery (carotid radial PWV [PWV(cr)]), and from the aorta to the finger (PWV from the aorta to the finger [PWV(fin)]). Central aortic compliance (CAC) was also measured. RESULTS: Average CAC was lower (0.662 vs. 0.850,  $P < 0.05$ ) and all measures of PWV tended to be faster in diabetic subjects despite the fact that they were, on average, 10 years younger. However, these measures were not related to age in diabetic subjects. After correcting for blood pressure, only PWV(cf) was associated with age in nondiabetic subjects ( $P < 0.001$ ). Expressing results as ratios of nonelastic to elastic arterial segments (i.e., PWV(cr)-to-PWV(cf) and PWV(fin)-to-PWV(cf)) improved the relationship with age. Both PWV(cr)-to-PWV(cf) and PWV(fin)-to-PWV(cf) were significantly associated with age in nondiabetic subjects ( $r = -0.59$ ,  $P < 0.001$ ;  $r = -0.57$ ,  $P < 0.001$ ) but not in diabetic subjects ( $r = -0.15$ ,  $P = 0.302$ ;  $r = -0.24$ ,  $P = 0.129$ ). Multivariate analysis showed that the ratios were not associated with systolic blood pressure. CONCLUSIONS: There are significant differences in the rate of age-related decline in vascular stiffness in elastic arteries of nondiabetic compared with diabetic arteries. Diabetic arteries appear to age at an accelerated rate at an earlier age and then reach a functional plateau.



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