

## **TOP Journal Club**

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### **Cilostazol reduces target lesion revascularization after percutaneous transluminal angioplasty in the femoropopliteal artery.**

**BACKGROUND:** Although percutaneous transluminal angioplasty (PTA) is being widely used for the treatment of stenosis of peripheral arteries, the high in-stent restenosis rate (50-60%) in the femoropopliteal artery still remains an unsolved issue. Cilostazol is a unique antiplatelet drug that has vasodilatory effects and inhibits smooth muscle cell proliferation. **METHODS AND RESULTS:** A total of 141 consecutive patients scheduled for PTA in the femoropopliteal artery between September 1999 and April 2004 were retrospectively analyzed for the use of cilostazol. Target lesion revascularization (TLR) was defined as repeated PTA in patients who had a recurrence of symptoms with diameter stenosis >50% by angiography. Patient and lesion characteristics were similar between the cilostazol (+) and cilostazol (-) groups. Use of other medications was similar between the groups, except for ticlopidine, which was more frequently used in the cilostazol (-) than in the cilostazol (+) group (15% vs 61%,  $p < 0.01$ ). TLR was significantly reduced in the cilostazol (+) group (12% [8/68] vs 32% [23/73],  $p < 0.01$ ). **CONCLUSIONS:** Although this study was retrospective and nonrandomized, the results suggest that cilostazol reduces TLR after PTA in the femoropopliteal artery.

*Circ J. 2005 Oct;69(10):1256-9.*

### **Coronary Stent Restenosis in Patients Treated With Cilostazol.**

**BACKGROUND:** Restenosis after implantation of coronary artery stents remains a significant clinical problem. We undertook a randomized, double-blind, placebo-controlled trial to determine whether cilostazol, a drug that suppresses intimal proliferation, would reduce renarrowing in

patients after stent implantation in native coronary arteries. **METHODS AND RESULTS:** We assigned 705 patients who had successful coronary stent implantation to receive, in addition to aspirin, cilostazol 100 mg BID or placebo for 6 months; clopidogrel 75 mg daily was administered to all patients for 30 days. Restenosis was determined by quantitative coronary angiography at 6 months. The minimal luminal diameter at 6 months for cilostazol-treated patients was 1.77 mm for the analysis segment (stent plus 5-mm borders) compared with 1.62 mm in the placebo group ( $P = 0.01$ ). Restenosis, defined as  $\geq 50\%$  narrowing, occurred in 22.0% of patients in the cilostazol group and in 34.5% of the placebo group ( $P = 0.002$ ), a 36% relative risk reduction. Restenosis was significantly lower in cilostazol-treated diabetics (17.7% versus 37.7%,  $P = 0.01$ ) and in those with small vessels (23.6% versus 35.2%,  $P = 0.02$ ), long lesions (29.9% versus 46.6%,  $P = 0.04$ ), and left anterior descending coronary artery site (19.3% versus 39.8%,  $P = 0.001$ ). There was no difference in bleeding, rehospitalization, target-vessel revascularization, myocardial infarction, or death. **CONCLUSIONS:** Treatment with the drug cilostazol resulted in a significantly larger minimal luminal diameter and a significantly lower binary restenosis rate compared with placebo-treated patients. These favorable effects were apparent in patients at high risk for restenosis.

*Circulation. 2005 Oct 24*

### **Resistance to antiplatelet therapy.**

Cardiovascular mortality continues to be high and events continue to occur in patients taking antiplatelet medications. Aspirin and clopidogrel have become integral parts of management in patients with coronary artery disease and after percutaneous angioplasty. However, the platelet responses to aspirin and clopidogrel are not uniform. Diminished or lack of response to these agents has been termed aspirin resistance and clopidogrel resistance. These phenomena have tremendous clinical significance as together they may occur in more than 50% of all patients on

chronic therapy with aspirin or clopidogrel. Postulated mechanisms of aspirin and clopidogrel resistance include alterations in genetic, pharmacokinetic, and platelet properties. There is a dearth of information in regard to their clinical significance, methods to test them, and strategies to treat them. Further research is necessary in these areas to identify these patients and treat them appropriately.

*Curr Cardiol Rep. 2005 Jul;7(4):242-8.*

### **Variable extent of platelet responsiveness to clopidogrel inhibition: "clopidogrel resistance"?**

During percutaneous coronary angioplasty, platelet inhibition by clopidogrel and aspirin has drastically decreased the risk of thrombotic occlusion of the stented vessels. However, despite the widespread use of these drugs, the incidence of acute or subacute stent thrombosis remains elevated, concerning 1 to 2% of the treated patients. Considerable differences in the responsiveness to clopidogrel could be observed, suggesting a possible underlying biological resistance. "Clopidogrel resistance" has recently been associated to an increased risk of thrombotic events following coronary angioplasty. Variations in enteric absorption, biotransformation in the liver by the CYP3A4, changes in the ADP receptor P2Y12, abnormalities of intraplatelet signal transduction, extent of platelet activation, class angina, diabetes mellitus may account for the considerable interindividual response variability widely reported. In this view, laboratory tests evaluating "clopidogrel resistance" might be useful tools for the identification and follow-up of patients at higher thrombotic risk. Indeed, in these patients, further platelet inhibition can be achieved by higher doses of clopidogrel.

*Ann Cardiol Angeiol (Paris). 2005 Aug;54(4):194-200.*

### **Relation of aspirin resistance to coronary flow reserve in patients undergoing elective percutaneous coronary intervention.**

Previous studies have shown that more complete platelet inhibition improves the coronary flow reserve (CFR), a measure of microvascular integrity, in patients undergoing percutaneous coronary intervention (PCI). We hypothesized that patients with aspirin resistance would have impaired CFR after elective PCI. We used VerifyNow Aspirin to determine the response to aspirin in 117 consecutive patients who underwent elective single-lesion PCI. The assay results are expressed quantitatively in Aspirin Reaction Units based on the degree of platelet aggregation. All patients received a 300-mg loading dose of clopidogrel >12 hours before and a 75-mg maintenance dose the morning of PCI. CFR was estimated using the Thrombolysis In Myocardial Infarction frame count method. Of the 117 patients, 22 (18.8%) were aspirin resistant. The clinical, angiographic, and procedural characteristics of the aspirin-sensitive and -resistant patients were balanced. All patients underwent successful PCI with <50% residual diameter stenosis and Thrombolysis In Myocardial Infarction grade 3 flow after PCI. Aspirin-resistant patients had a lower CFR than the aspirin-sensitive patients (1.42 +/- 0.35 vs 1.80 +/- 0.64, p = 0.018). Univariate correlates of CFR included the Aspirin Reaction Unit (r = -0.227, p = 0.014) and post-PCI creatine kinase-MB elevation (p = 0.048). Multivariate linear regression analysis revealed the Aspirin Reaction Unit to be the only independent determinant of CFR after PCI (r<sup>2</sup> = 0.051, p = 0.014). Thus, aspirin resistance was associated with impaired CFR in patients who underwent elective PCI, implicating insufficient aspirin-induced platelet inhibition as a cause of microvascular dysfunction by distal atherothrombotic embolization and/or spasm.

*Am J Cardiol. 2005 Sep 15;96(6):760-3.*

### **Resistance to antiplatelet drugs: current status and future research**

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