CILOSTAZOL ENHANCES MOBILIZATION AND PROLIFERATION OF CIRCULATING ENDOTHELIAL PROGENITOR CELLS AND COLLATERAL FORMATION MEDIATED BY MODIFYING VASCULO-ANGIOGENIC BIOMarkers IN PATIENTS WITH PERIPHERAL ARTERIAL OCCLUSIVE DISEASE

Moderated Poster Contributions
Poster Sessions, Expo North
Saturday, March 09, 2013, 3:45 p.m.-4:30 p.m.

Session Title: Classic and Novel Cardiovascular Risk Predictors and Impact
Abstract Category: 35. Vascular Medicine: Non Coronary Arterial Disease
Presentation Number: 1167M-171

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Background: Cilostazol is an antiplatelet agent with vasodilating effect. We have reported that it could promote angiogenesis and enhance endothelial progenitor cells (EPCs) functions. In this study, we investigated the vasculo-angiogenic effect of cilostazol on EPCs in patients with peripheral arterial occlusive disease (PAOD).

Methods: Forty-four eligible patients with PAOD were consecutively enrolled in this double-blinded and placebo-controlled study. Twenty-five participants received 200 mg cilostazol and 19 participants took placebo per day for 12 weeks. The number and functions of circulating early EPCs and plasma biomarkers were measured. Collateral formation was assessed by a 128-row dual source computed tomography.

Results: Baseline characteristics and parameters did not significantly differ between both groups. Cilostazol, but not placebo, significantly increased circulating EPCs (KDR+CD34+) count and viability (XTT) (404.2 ± 234.6 vs -75.4 ± 7.1 %, p=0.05; 94.1 ± 34.1 vs -19.4 ± 13.0 %, p=0.02) without influence on apoptotic endothelial cells (CD146+Annexin V+). Cilostazol also improved hemoglobin A1C and triglyceride levels (both p<0.05). Plasma levels of vascular endothelial growth factor A165, stromal cell-derived factor (SDF)-1, and adiponectin were significantly increased [33.1 ± 18.1 vs -23.7 ± 9.5 %; 27.4 (-8.5-52.3) vs -5.1 (-34.9-9.3) %; 101.7 ± 43.9 vs -23.2 ± 10.6 %, respectively; all p<0.05] and soluble thrombomodulin level was decreased in participants treated with cilostazol (-9.4 ± 5.2 vs 11.0 ± 6.1 %, p=0.02). Changes of plasma SDF-1 were significantly correlated to the changes of circulating EPCs counts (r=0.603, p=0.001), whereas, changes of adiponectin levels were significantly correlated to the changes of XTT (r=0.518, p=0.005), respectively. Collateral vessels were tended to be more in cilostazol-treated participants.

Conclusions: Cilostazol has significantly beneficial effects on mobilization and proliferation of EPCs partly mediated by modifying vasculo-angiogenic biomarkers. Further clinical studies of cilostazol in cardiovascular high-risk patients without pre-existing atherosclerotic disease will be justified.