

**ANTIPLATELET AGENTS AND ANTICOAGULANTS
(TCTAP A-137)****TCTAP A-137****Impact of Diabetes Mellitus as well as History of Cerebral Infarction on Clopidogrel Response Variability in Patients with Chronic Coronary Artery Disease**Keishi Ichikawa¹¹Iwakuni Clinical Center, Japan

BACKGROUND Dual antiplatelet therapy with aspirin and clopidogrel is standard for prevention of coronary stent thrombosis. Response variability of these medications is well-known; however, factors associated with this variability have not been fully elucidated.

METHODS 46 patients scheduled for elective PCI were enrolled (73 ± 8 years, 38 males). Platelet aggregability was assessed by light transmission aggregometry after stimulation with ADP and collagen. All patients were received aspirin (100 mg) and clopidogrel (75 mg) for at least 7 days before the blood test. Platelet aggregability grade was calculated (1 to 9), and patients with grade 7 to 9 were defined as non-responder.

RESULTS 10 patients (22%) were determined as non-responder to clopidogrel, whereas all patients were responders to aspirin. Non-responders to clopidogrel had higher ratio of female (40% vs. 11%, $p=0.033$), higher prevalence of hypertension (90% vs. 56%, $p=0.047$), diabetes mellitus (70% vs. 31%, $p=0.024$) and history of cerebral infarction (30% vs. 3%, $p=0.006$). By logistic regression analysis, female gender, prevalence of diabetes mellitus and history of cerebral infarction were independent determinants of non-responder to clopidogrel.

CONCLUSION Female gender, prevalence of diabetes mellitus and cerebral infarction was risk for clopidogrel resistance. Evaluation of platelet aggregation after administration of antiplatelet therapy should be done, especially in patients with diabetes mellitus and history of cerebral infarction.

**BASIC SCIENCE, ANIMAL MODELS AND PRECLINICAL
STUDIES (TCTAP A-138 TO TCTAP A-142)****TCTAP A-138****Insulin Enhances Dendritic Cells Scavenger Receptor-Mediated Endocytic Uptake of oxLDL**Hao Lu,¹ Dong Huang,¹ Jianying Ma,¹ Juying Qian,¹ Junbo Ge¹¹Zhongshan Hospital, Fudan University, Shanghai, China

BACKGROUND The prevalence of atherosclerotic cardiovascular disease is higher in patients with type 2 diabetes, a disorder characterized by hyperinsulinemia and insulin resistance. The role of hyperinsulinemia as an independent participant in the atherogenic process has been controversial. Therefore, we examined whether insulin could regulate the expression of scavenger receptors responsible for oxidized low-density lipoprotein (oxLDL) uptake in DCs, a critical step in atherogenesis. In addition, we investigated the impact of insulin on DC maturation regarding changes in phenotype and cytokine secretion.

METHODS Immature DCs were cultured with different concentrations of insulin (1nmol/L, 10nmol/L, 100nmol/L) in the absence or presence of LY294002 or wortmannin for 24 hours. The expression of the scavenger receptors SR-A and CD36 was determined by real-time PCR and western blot analysis. Furthermore, DCs were incubated with DiI-labelled oxLDL. The DiI-oxLDL-incorporated fraction was investigated by flow cytometry analysis. Finally, flow cytometry analysis was used to investigate immunophenotypic protein expression (CD83 and CD11a). DC-differentiation was evaluated using the expression of BDCTCTAP A-1/-2 by flow cytometer analysis. Supernatant cytokine measurements were used for immune function assays.

RESULTS The incubation of DCs with insulin enhanced, in a dose-dependent manner, the gene and protein expression of SR-A and CD36. This effect was partially abolished by wortmannin, a phosphatidylinositol-3-OH kinase (PI3 kinase) inhibitor. But LY294002 did not inhibit the effect of insulin on scavenger receptors' expression. High concentration of insulin increased the oxLDL-uptake capacity of DCs. Blockage of the scavenger receptors SR-A and CD36 significantly reduced oxLDL uptake. Furthermore, high concentration of insulin induced DC-maturation and triggered differentiation of DCs in myeloid and plasmacytoid DCs. Finally, high concentration of insulin decreased IL-10 secretion and increased IL-6 release.

CONCLUSION This study suggests that hyperinsulinemia could promote DC activation and oxLDL uptake and thus may contribute to atherosclerosis in patients with type 2 diabetes.

TCTAP A-139**Tongxinluo Treatment Protects Infarcted Rat Hearts by Increasing Autophagy and Decreasing Apoptosis via AMPK/mTOR Pathway**Qing Li,¹ Yue-Jin Yang¹¹Fuwai Hospital, CAMS&PUMC, China

BACKGROUND Our previous studies have demonstrated the pro-survival role of Tongxinluo (TXL) on cardiomyocytes after acute myocardial infarction (AMI), but the underlying mechanisms are still unknown. The present study was to investigate whether TXL could have an effect on autophagy of cardiomyocytes via the AMPK/mTOR pathway, and to investigate the interaction of autophagy and apoptosis.

METHODS In vitro, H9C2 cardiomyocytes were exposed to TXL (800 mg/ml) and Compound C (10 mg/ml) treatments and subjected to hypoxia each for 3 hours, were then moved to normal conditions for 1 hours of reoxygenation. After the treatment, cells were harvested and analyzed at 1h, 2h, 4h, 12h, 24h. In vivo, Male Sprague-Dawley rats (n=100) were randomly assigned to sham, control, TXL (4 mg/kg/d), TXL + Compound C (intraperitoneal injection at 20 mg/kg per week) groups. TXL and Compound C were given from 1 week before rat coronary artery ligation model were established. Transthoracic echocardiography and pathological studies were performed to investigate the cardiac function and the extent of fibrosis, infarct size. The expression of apoptotic proteins, autophagy proteins and AMPK pathway proteins were detected by western blotting analysis.

RESULTS In vitro, TXL enhanced autophagy and decreased apoptosis in a dose-dependent manner. Inhibition of autophagy by knocking down of Atg7 attenuated cell death. TXL upregulated AMPK and mTOR phosphorylation. However, Compound C abrogated AMPK phosphorylation and decreased autophagy and increased apoptosis. In vivo, compared with the control group, the TXL group increased ejection fraction by 10% four weeks after the operation and substantially decreased the fibrosis, infarcted area ($p<0.05$). TXL treatment increased the AMPK activity and the expression of autophagy protein LC3 in the reflow and no-reflow myocardium ($p<0.05$) and inhibited the elevation of apoptotic protein as bax, caspase-3. Addition of the AMPK inhibitor Compound C counteracted these beneficial effects.

CONCLUSION AMP-mediated cardioprotection of TXL against no-reflow and reperfusion injury relates to the inhibition of apoptosis and promotion of autophagy in myocardium in rats.

TCTAP A-140**Evaluation of Radial Strength and Stiffness in Coronary Stents**Takashi Sasou¹¹Mie University Hospital, Japan

BACKGROUND Acute stent recoil has been radial strength and stiffness are important determinants of the mechanical performance of coronary stents. In this study, we quantitatively evaluated the radial strength and stiffness of four types of stent.

METHODS The test involved compression of the expanded stent at a specified pressure in the radial direction with a uniform 25% load. Radial strength and rigidity were calculated from the displacement curves for the radial strength of each stent as follows.

RESULTS Resolute Integrity (a), 0.280 ± 0.001 ; Endeavor Sprint (B), 0.263 ± 0.001 ; Promus Element (C), 0.283 ± 0.001 ; and Nobori (D), 0.245 ± 0.001 N/mm. Radial stiffness was also calculated: a, 0.567 ± 0.001 ; B, 0.517 ± 0.001 ; C, 0.541 ± 0.001 ; and D, 0.494 ± 0.001 .

CONCLUSION The radial strength and stiffness of different stents was evaluated quantitatively under the same conditions. It is possible that selection of stents based on these parameters might contribute to risk reduction in both in animal experiments and clinical evaluation.