TCT-733
Relation of Proton pump inhibitor and cytochrome P450 2C19 polymorphisms on platelet reactivity in patients with acute coronary syndromes

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Background: It remains unclear whether concomitant use of omeprazole attenuates platelet function in Asian patients with acute coronary syndromes (ACS) receiving clopidogrel according to cytochrome P450 (CYP) 2C19 phenotype.

Methods: Stent implantation was performed in 177 patients with ACS receiving aspirin 100mg/day and clopidogrel 75mg/day. The platelet reactivity index (PRI) was determined on admission and average 18 days of after stenting with VASP assay.

Results: On the basis of CYP2C19 genotype, 46 patients (26%) were classified as extensive metabolizers (EM), 103 (58%) as intermediate metabolizers(IM), and 28 (16%) as poor metabolizers (PM). There were no significant differences in baseline characteristics among 3 phenotypes. At baseline, PRI was similar in patients with PPIs and those without among 3 phenotypes. Among EM, patients with PPIs had higher PRI at 18 days (45±16 vs 38±13%; P=0.05) and the smaller PRI variation (-45±5% vs -9%; p < 0.01) compared with those without. In contrast, there were no significant differences in PRI (55±18 vs 53±15%) and the mean PRI variation (-39% vs-36%) in patients with PPIs and those without among IM. Similar trends were found in PRI (69±10 vs 73±8%) and the mean PRI variation (-18% vs 15%) among PM (p = NS, respectively).

Conclusions: In ACS patients treated with clopidogrel, co-administration of omeprazole attenuates platelet function in non-carriers, but not in CYP2C19 variant allele carriers.

TCT-734
Influence of Platelet Reactivity and Inflammation on Peri-procedural Myonecrosis in East Asian Patients Undergoing Elective Percutaneous Coronary Intervention

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Background: Compared with Caucasians, East Asians have shown relatively lower risk of ischemic events following percutaneous coronary intervention (PCI). The contribution of multiple risk factors to the occurrence of peri-procedural myocardial infarction (PMI) in East Asians remains controversial.

Methods: We sought to assess the influence of clinical or laboratory covariates on the occurrence of PMI in these patients undergoing elective PCI. Stable patients (n = 341) undergoing elective PCI were enrolled. Pre-PCI platelet reactivity was measured by light transmittance aggregometry (LTA) and the VerifyNow P2Y12 assay. Inflammation markers (WBC and C-reactive protein) and lipid profile were determined by standard methods. PMI was defined according to Universal definition [a post-procedural increase in cardiac biomarker (troponin I and CK-MB) 3 times the 99th percentile of the upper reference limit]. PMI (defined by troponin I and CK-MB) occurred in 47 (13.8%) and 30 (8.8%) patients, respectively.

Results: There was no significant difference in adenosine diphosphate (ADP)-induced platelet reactivity between patients with vs. without PMI. Patients with PMI (troponin I) had higher levels of 6 µg/mL collagen-induced platelet aggregation (PA) and VerifyNow BASE compared with those without PMI. In multivariate analysis, age, stent length, and low-density lipoprotein (LDL) cholesterol were independent determinants of PMI (troponin I). The combination of 6 µg/mL collagen-induced PA > 40% + BASE > 318 (odds ratio, 14.08; 95% confidence intervals, 1.68 to 111.11; P = 0.01) or 'WBC > 6550/mm3 + C-reactive protein > 2.3 mg/L' (odds ratio, 7.75; 95% confidence intervals, 2.49 to 24.39; P < 0.001) was associated with an increased risk of PMI (troponin I). The greatest likelihood ratio was observed when cholesterol, inflammation marker and platelet function were combined together.

Conclusions: This is the first study to demonstrate that heightened platelet responsiveness to collagen and thrombin may be a risk factor for myonecrosis in patients undergoing elective PCI. The utility of the combining measures of platelet function, inflammation and cholesterol to enhance risk stratification and thus facilitate person.

TCT-735
Pharmacodynamic Effect of Adjunctive Cilostazol vs. High-dose Clopidogrel in Acute Coronary Syndrome Patients According to the CYP2C19 Genotype

ACC/CEL-GENOTYPE study

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Background: Cilostazol use in ACS patients reduces the risks of ischemic events and restenosis in East Asians. Compared with Caucasians, East Asians have higher frequency of CYP2C19 loss-of-function allele (*2 and *3). We compared the pharmacodynamic effect of adjunctive cilostazol vs. high-dose clopidogrel in PCI-treated East Asians with ACS according to CYP2C19 genotype.

Methods: ACS patients were assigned to either clopidogrel 150 mg/d (DOUBLE; n = 139) or cilostazol 100 mg twice a day + clopidogrel 75 mg/d (TRIPLE; n = 136) on top of aspirin. Platelet aggregation (PA) was measured at baseline and follow-up (± 30 days) with conventional aggregometry and adjusted with known clinical covariates. Primary endpoint was the level of 20 µM ADP-induced PA at follow-up. HPR was defined as 20 µM ADP-induced PA > 59%.

Results: During standard-dose clopidogrel, platelet measurements did not differ according to individual CYP2C19 genotype between the groups (Fig A). PA levels and the risk of HPR increased across CYP2C19 genotype (p = 0.174). At follow-up, TRIPLE vs. DOUBLE showed significantly lower level of PAs irrespective of CYP2C19 genotype (Fig B). DOUBLE showed 27.3% of HPR risk, which was increased across CYP2C19 genotype (adjusted p = 0.042), whereas TRIPLE effect was not significantly influenced with CYP2C19 genotype (adjusted p = 0.289). Similar trend was observed for collagen-induced PA.

TCT-736
Markedly Reduced Platelet Inhibition with Clopidogrel Given To Patients Undergoing Therapeutic Hypothermia Post Cardiac Arrest

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Background: Current guidelines recommend that pts undergoing coronary stenting receive dual-antiplatelet therapy to prevent acute stent thrombosis. There is limited data on platelet inhibition in pts presenting with cardiac arrest who require both acute coronary stenting and therapeutic hypothermia (TH). We sought to determine the extent of platelet inhibition in pts requiring TH who were treated with clopidogrel.

Methods: We prospectively recruited pts who presented with a cardiac arrest who required TH and acute coronary stenting. The loading dose of clopidogrel was 600mg followed by a maintenance dose of 75mg daily administered via a nasogastric tube. Platelet function was tested at baseline, and at 4, 8, 24, 48, 72, 96 and 120 hrs from the loading dose of clopidogrel. Platelet activity was analyzed with the VerifyNow point-of-care rapid platelet function analyzer. Primary endpoint was the extent of platelet inhibition as a function of time.

Results: We evaluated 8 consecutive patients who received coronary stents and subsequently required TH. The results of the platelet testing are depicted in the figure.
below. During the period of TH, there was essentially minimal response as 7 out of 8 pts had 0% of platelet inhibition and 1 patient had marginal response of 7%. Platelet inhibition became apparent during the re-warming phase but appeared to be relatively delayed.

Conclusions: In this pilot trial, we found that platelet inhibition with clopidogrel was minimal during the period of TH. These results raise concerns regarding the potential risks of stent thrombosis in pts receiving stents and managed with TH.

TCT-737

Relationship between post treatment platelet reactivity and ischemic and bleeding events at one year follow-up in acute coronary syndrome patients receiving prasugrel

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Background: Post-treatment platelet reactivity (PR) is associated with ischemic and bleeding events in patients receiving P2Y12-ADP receptor antagonists. We aimed to investigate the relationship between post-treatment PR after a 60 mg loading dose of prasugrel and ischemic and bleeding events (TIMI) at one year follow-up at one year of follow-up. The rates of thrombotic and bleeding events at one year were 7.5% (9.7%, 5.3%) in a native coronary artery. Prior CABG patients had more high-risk characteristics.

Results: Three hundred and one patients were enrolled. Nine patients (5%) were lost to follow-up at one year. The rates of thrombotic and bleeding events at one year were 7.5% and 6.8% respectively. The mean VASP index after a 60 mg LD of prasugrel was 22.4 ± 22.7% in patients with normal-dose prasugrel and double-dose clopidogrel, however with a more pronounced effect with prasugrel. Increased PR was associated with ischemic and bleeding events.

Conclusions: Platelet reactivity measurement after prasugrel LD predicts both ischemic and bleeding events at one year follow-up for ACS patients undergoing PCI.

TCT-738

Thrombocytes And Individualization Of ORAL Antiplatelet Treatment After Percutaneous Coronary Intervention (TAILOR)

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Background: Stent thrombosis is a feared complication following stent implantation. The multi-factorial causes include low anti-platelet response (LR) to the routinely used drug, clopidogrel. Newer anti-platelet drugs such as prasugrel and ticagrelor have higher potency with less inter-individual variability in platelet response, however with an increased bleeding risk. We sought to evaluate the safety and anti-platelet effect of double-dose clopidogrel as compared with normal-dose prasugrel in patients with clopidogrel LR undergoing non-urgent PCI.

Methods: "TAILOR" is a randomized, open-label, single-centre trial. All patients pre-treated with clopidogrel and undergoing PCI were screened for clopidogrel LR by whole-blood aggregometry, using the Multiplate analyzer® (Dynabyte, Germany) where low response to clopidogrel was defined as Multiplate ADP > 70 units. Patients demonstrating LR were randomized to either 150 mg clopidogrel or 10 mg prasugrel (5 mg for patients > 75 years or < 60 kg).

Results: Of 990 patients screened, 246 (24.9%) exhibited LR to clopidogrel. Of these, 100 (40.5%) were randomized to one of the two regimens (n=50 in each group); the remaining served as controls.

Conclusions: Tailoring of anti-platelet treatment in patients with clopidogrel LR undergoing non-urgent PCI translates into improved platelet inhibition with both normal-dose prasugrel and double-dose clopidogrel, however with a more pronounced effect with prasugrel.

TCT-739

Effect of Ticagrelor on the Outcomes of Patients With Prior Coronary Artery Bypass Graft Surgery: Insights From The PLATelet inhibition and patient Outcomes (PLATO) trial

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Background: Patients with prior coronary artery bypass graft surgery (CABG) who present with an acute coronary syndrome have high risk for recurrent events. Whether more intense anti-platelet therapy with ticagrelor might be beneficial compared to clopidogrel is unknown. In this substudy of the PLATO trial we studied the effects of randomized treatment dependence on history of CABG.

Methods: Patients participating in PLATO were classified according to whether they had prior CABG. The trial’s primary and secondary end points were compared using Cox proportional hazards regression.

Results: Of the 18,613 study patients, 1,133 (6.5%) had prior CABG, of whom 353 (31%) underwent percutaneous coronary intervention in a saphenous vein graft and 190 (17%) in a native coronary artery. Prior CABG patients had more high-risk characteristics at study entry, experienced more clinical events during follow-up, but had less major bleeding (Table). The primary endpoint (composite of cardiovascular death, myocardial infarction, and stroke) was reduced to a similar extent by ticagrelor among patients with [19.6% vs. 21.4%; hazard ratio (HR), 0.90 (0.69, 1.17)] and without [9.2% vs. 11.0%; HR, 0.84 (0.76, 0.93), Pinteraction=0.66] prior CABG. Major bleeding was similar with ticagrelor vs. clopidogrel among patients with [8.1% vs. 8.7%; HR, 0.93 (0.61, 1.43)] and without [11.8% vs. 11.4%; HR, 1.04 (0.95, 1.14), Pinteraction=0.61] prior CABG.

Table: Outcomes in patients with and without prior coronary artery bypass graft surgery (CABG).

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