Antiplatelet Agents and Anticoagulants (TCTAP A-027 to TCTAP A-036)

TCTAP A-027
Comparison of On-treatment Platelet Reactivity After One-month Use of Clopidogrel, Prasugrel or Ticagrelor in Koreans with Acute Coronary Syndromes

Ji Hyun Lee, Sung Gyun Ahn, Jun-Won Lee, Young Jin Youn, Min-Soo Ahn, Jung-Young Kim, Byung-Sa Yoo, Seung-Hwan Lee, Junghoon Youn
Wonju Severance Christian Hospital, Wonju, Korea (Republic of)

Background: Prasugrel and ticagrelor have greater anti-ischemic efficacy than clopidogrel, but they are not widely used in East Asia owing to their increased risk of bleeding. We compared on-treatment platelet reactivity (OPR) of these 3 drugs after 1 month in patients with acute coronary syndromes (ACS).

Methods: We assigned 95 patients undergoing percutaneous coronary intervention for ACS to clopidogrel, prasugrel, or ticagrelor treatment. We measured OPR using the VerifyNow P2Y12 assay. High OPR (OPR>420) was defined by P2Y12 reaction unit (PRU) >240; low OPR (OPR≤85) was defined by PRU ≤85. We compared the numbers of patients with HOPR and LOPR after 1 month of antplatelet treatment.

Results: OPR was lowest in the ticagrelor group (n=23), followed by the prasugrel (n=34) and clopidogrel groups (n=38). 49±30 vs 86±59 vs 179±77, p<0.001). OPR was not noted in the prasugrel or ticagrelor groups, but was noted in 5 clopidogrel-treated patients (13.9%, p=0.007). The ticagrelor group had the most number of patients with LOPR, followed by the prasugrel and clopidogrel groups (88% vs 52.9% vs 13.9%, p<0.001). The clopidogrel group had the highest number of patients in the therapeutic window of OPR (PRU 85–239) (Figure).

Conclusion: HOPR to clopidogrel can be overcome by using prasugrel or ticagrelor. However, prasugrel or ticagrelor increased LOPR, which may lead to excessive bleeding events in East Asians.

TCTAP A-028
Comparison of Platelet Aggregation Before & After Loading Dose of Prasugrel and Clopidogrel in Percutaneous Coronary Intervention in Adult Pakistani Coronary Artery Disease Patients

Ahmad Shahnaz1, Ahmad Noorani1, Khawar Mehti1, Muhammad Aze1
1PIC, Karachi, Pakistan, 2Getz Pharma, Karachi, Pakistan

Background: The use of dual antplatelet therapy with aspirin and a thienopyridine is an essential aspect of the supportive pharmacologic regimen administered to coronary artery disease (CAD) patients who are undergoing primary percutaneous coronary intervention (PCI). This study was carried out to compare the inhibition of platelet aggregation (IPA) between prasugrel and clopidogrel in adult Pakistani patients undergoing primary PCI.

Methods: A total of hundred subjects were randomly assigned to two groups A & B. Group A (n=50) received prasugrel (PRISA) 60 mg loading dose pre PCI and 10 mg QD maintenance dose, whereas group B (n=50) received clopidogrel 600 mg loading and 75 mg BID maintenance dose respectively. Adenosine diphosphate (ADP) was used as agonist before loading dose and post-PCI at 3-4 hours since it is the most commonly used agonist, particularly in systems that measure only platelet aggregation in whole blood.

Results: Male and female ratio was 4:1 in both groups. Mean age was insignificant between group A and group B (50.3±9.6 vs. 50.3±10.9; range: 29-68 and 23-71 years respectively). In Group A (Prasugrel) n=50; the respective occurrence of CAD was: LAD n=25 (50%), RCA n=14 (28%), Cx Distal n=5 (10%), MVOD n=3 (6%), Non-stent 1 (2%) & others n=2 (4%). In Group B (Clopidogrel) n=50; the respective occurrence of CAD was: LAD n=23 (46%), RCA n=11 (22%), MVOD n=8 (16%) & Cx Distal n=7 (14%) & others n=1 (2%). None of the patient experienced minor or major adverse cardiac events after taking loading dose in both groups. The before and after loading dose mean platelet aggregation (MPA) responses were statistically significant within the two treatment groups (Group A: 6.08±2.12 vs 1.56±2.11; p<0.001 and Group B: 4.27±2.06 vs 0.68±1.13; p<0.001). The mean reduction in platelet aggregation by Group A (Prasugrel) was 74.4% and by Group B (Clopidogrel) was 51.8%.

Conclusion: Pragrel 60 mg loading dose (PRISA) achieves significantly greater IPA as compared to clopidogrel 600 mg LD. Both drugs were well-tolerated and adverse drug reactions were comparable.

TCTAP A-029
Low Dose Proton Pump Inhibitors in Patients Treated with Dual-antplatelet Therapy After Acute Coronary Syndrome

Toshiki Nagata, Takaya Matumiy, Tomoya Harada, Masaki Kinoshita, Tsu0 Aburadani, Motoaki Horizawa, Michiro Maruyama, Kazuo Usuda Toyama Prefectural Central Hospital, Toyama, Japan

Background: The proton pump inhibitors (PPIs) with aspirin and clopidogrel are frequently concomitantly used to prevent adverse gastrointestinal effects. However, it has been reported that the antplatelet action becomes attenuated when a PPI is used in combination with clopidogrel. The Food and Drug Administration issued a warning against the concomitant use of high dose (40 mg) esomeprazole/omeprazole with clopidogrel. This warning has raised concerns that the addition of a PPI to clopidogrel in acute coronary syndrome (ACS) patients could actually increase the risk of recurrent cardiovascular adverse events. Methods: The effect of PPIs causing platelet aggregation during the administration of clopidogrel was investigated after primary percutaneous coronary intervention (PCI). The subjects consisted of 122 cases of ACS. Platelet aggregation function testing (light transmission intensity method) was conducted while aspirin and clopidogrel 75mg were orally taken before discharge. The minimum concentration of aggregation induction (Platelet aggregation threshold index; PATI) was measured. The PATI, measured with ADP as the inducing substance, was compared and investigated according to the type of concomitantly used PPIs.

Results: The result of the PATI were: non-PPI group: 3.73±0.93 (N=18) and PPI group: 3.33±0.94(MN=104). The difference of type of PPI were rabeprazole (10 mg) group: 3.63±0.63 (MN=20), esomeprazole (20 mg) group 3.11±0.93 (MN=39) and omeprazole (15 mg) group: 3.21±1.06 (MN=42). The omeprazole group was excluded, because the subjects were only 3 cases. The PATI of lansoprazole group was the lower than the other groups (p<0.05 compared with non-PPI group).

Conclusion: The effect of CYP2C19 differs depending on the type of PPI, with a dose of lansoprazole being caused in the interaction with clopidogrel. The concomitant use of low dose omeprazole reduced the antplatelet action of clopidogrel. The low dose esomeprazole reduced the antplatelet action, but the interaction effect was small. Rabeprazole was least in influence on the antplatelet action. When PPI is used in combination with dual-antplatelet therapy in ACS patients, low dose esomeprazole and rabeprazole should be considered.

TCTAP A-030
Safety and Efficacy of a Hybrid Dual Antplatelet Therapy Regimen for ST-elevation Myocardial Infarction Patients: A Single-centre Experience

Deanna Kho, Yee May Wong, Hee Hwa Ho, Yan Wei Ooi, Paul Jau, Lueng Ong, Fahim Haider Jafary, Kwok Kor Koh, Julian Tan, David Foo Tan Tock Seng Hospital, Singapore, Singapore

Background: Prasugrel, a third generation thienopyridine is recognised as one of the cornerstone treatment of contemporary dual antplatelet therapy (DAPT) in selected patients with ST-elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PCI). The incremental cost of prasugrel coupled
with a higher risk of bleeding have limited its widespread use. As the rates of early stent thrombosis are higher especially in the early stages of STEMI, the use of a more potent DAPT regimen in the initial period could potentially confer the most benefit. We therefore sought to evaluate the safety and efficacy of a hybrid DAPT regimen (involving a switch of prasugrel to clopidogrel at 1 month post MI) in STEMI patients and report on the clinical outcomes.

Methods: From January to August 2012, 141 STEMI patients (94% male, mean age 54 ± 9.2 years) were preloaded with 60 mg of prasugrel and 300 mg of aspirin in the emergency room of our institution prior to PCI. Patients aged > 75 years, body weight < 60 Kg and those with previous history of stroke were excluded. Upon hospitalization, patients received maintenance doses of 10 mg of prasugrel and 100 mg of aspirin for the first 30 days. At 30 days post MI prasugrel was stopped and patients were loaded with 300 mg of clopidogrel followed by 75 mg as maintenance dose (for the remaining 11 months in conjunction with aspirin). The primary endpoint was a composite of death from cardiovascular causes, nonfatal MI, or nonfatal stroke at 1 year follow-up. The key safety end point was Thrombolysis in Myocardial Infarction (TIMI) major bleeding at 1 year follow-up.

Results: PPCI was performed predominantly via the radial approach (86%) with Clexane used as procedural anti-coagulant in 60% of patients (40% received heparin). Glycoprotein Ib/IIa inhibitors were administered in 82% of patients with the majority (64%) receiving drug eluting stent implantation during PPCI.

The primary end point occurred in 6 patients (4.3%) with 4 events (2.8%) occurring within the first 30 days. Death due to multivisceral causes occurred in 3 patients (2.1%). Non-fatal MI occurred in 2 patients (1.4%) with a patient (0.7%) developing a non-fatal stroke. Stent thrombosis occurred in 3 (2.1%) patients with 1 case of probable stent thrombosis (0.7%) occurring within 30 days of MI. Bleeding events were observed in 10 patients (7.6%) with TIMI major bleeding episode occurring in 3 patients (2.1%). There was 1 bleeding episode occurring in the setting of coronary artery bypass surgery.

Conclusion: Our preliminary experience showed that a hybrid DAPT regimen in a selected group of STEMI patients is feasible, efficacious and safe. The long term clinical outcomes were good with a low incidence of ischaemic and bleeding events.

TCTAP A-031
Platelet Function Test and Bleeding Risk in Patients with Coronary Artery Disease: A Case-control Study
Ho Fai Daniel Fong
Princess Margaret Hospital, HK, Hong Kong, China

Background: Management of coronary heart disease remains a challenge even with modern advances. New anti-platelet agents which reduce thromboembolic events in patients with coronary heart disease were introduced. However, there are concerns about an increased bleeding risk for patients taking these new anti-platelet agents. Platelet function test, such as VerifyNow, claimed to be able to predict bleeding risk. However, the evidence was limited, especially among the Asian population. This study aimed to evaluate the use of VerifyNow to assess bleeding risk. Subjects with low residual platelet reactivity, i.e. low PRU value, were hypothesized to have an increased bleeding risk.

Methods: This was a case control study performed in the Princess Margaret Hospital of Hong Kong. A total of 120 subjects who were taking a P2Y12 inhibitor and had a VerifyNow test were recruited. The cases were defined as subjects with a PRU value of less than 250. In order to avoid bias, only patients taking same type of anti-platelet agents were included in this study. The controls were age matched to the cases. The primary endpoint was defined as the increase in bleeding risk associated with a low PRU value at 30 days. The secondary outcome was the increase in bleeding risk associated with a low PRU value at 1 year. The usual PRU threshold of platelet inhibition was also evaluated as a secondary outcome. Multivariable logistic regression was used to obtain the odds ratio of the low PRU group.

Results: Bleeding events occurred more frequently in the low PRU group. At 30 days, 31.7% of subjects among the case had a bleeding event while 43.3% of the cases had a bleeding event at 1 year. The majority of these bleeding events were minor bleeding, such as easy bruising. After adjusting for confounders, there was no statistically significant increase in bleeding risk among those in the low PRU group at 30 days or 1 year. Subjects with a high percentage of platelet inhibition (>50%) was also not associated with a statistically significant increase in bleeding risk.

Conclusion: A low PRU value was not associated with an increased bleeding risk at 30 days. Thus the VerifyNow test was not shown to be useful in assessing the bleeding risk of patients in an Asian population, contrary to the findings from Western literature. A possible explanation was that the VerifyNow threshold for predicting bleeding might be higher among Asian population. The definition for low residual platelet reactivity might be different in our locality. A larger sample size might also be needed. Further studies are needed to evaluate whether a different cut off is more optimal for the Asian population.

TCTAP A-032
Reappraisal of Pharmacodynamic Effect of Adjunctive Cilostazol and High-dose Clopidogrel in East Asian ACS Patients
Young-Haon Jeong
Yongwhi Park, Jin Sin Koh, Jin-Yong Hwang
Gyeongsang National, Jinju, Korea (Republic of)

Background: Compared with Westerners, East Asians have shown different thera- peutic level of platelet reactivity (HPR) during PCI, raising concerns about the safety of dual anti-platelet therapy (DAPT). We aimed to reappraise the pharmacodynamic effect of cilostazol and high-dose clopidogrel in East Asian patients based on these criteria.

Methods: PCI-treated ACS patients were assigned to either clopidogrel 150 mg/d (DOUBLE; n=139) or cilostazol 100 mg bid + clopidogrel 75 mg/d (TRIPLE; n=240) on top of aspirin. PR was measured at least 30-day follow-up with light transmission aggregometry. Primary endpoint was the prevalence of HPR at follow-up.

Results: DOUBLE and TRIPLE together showed low prevalences of HPR (9.4% and 2.2%, respectively). Although the level of PR in TRIPLE increased according to the number of CYP2C19 loss-of-function (LoF) allele (p=0.015), HPR risk was almost overcome irrespective of CYP2C19 phenotype (p=0.633). The level of PR and HPR risk in DOUBLE increased proportionally depending on CYP2C19 phenotype (p<0.001 and p=0.006, respectively). In multivariate analysis, carriage of 2 CYP2C19 LoF alleles only increased HPR risk by 8.5-fold in DOUBLE.

Conclusion: Our results support clinical usefulness of TRIPLE in East Asians based on pharmacodynamic data. Clinical efficacy and safety of more potent P2Y12 inhib- itor, prasugrel and ticagrelor, must be reevaluated separately in this unique race.

Methods: We recruited A total of 878 consecutive clopidogrel-treated patients undergoing emergent or elective PCI. The main outcome measures were cardiovascular (CV) death, definite/probable stent thrombosis (ST), nonfatal myocardial infarction (MI), coronary revascularization and a composite end point of ischemic events. We assessed Platelet reactivity 12 hours later by measuring P2Y12 reactivity unit (PRU) with VerifyNow P2Y12 assay (Accumetrics, San Diego, California). High platelet reactivity (HPR) was defined as PRU value > 240.

Results: In total, 877 consecutive patients were enrolled. Patients with HPR were 454 (Male, 284). In all patients, coronary stent was implanted. All patients received clopi- dogrel pretreatment (500mg loading dose), received a maintenance dose of 75 mg daily. The composite end point of the study at follow-up of 12 months were CV death, nonfatal MI, and coronary revascularization. At a 12-month follow-up, we found 85 ischemic events (26 CV deaths [3.4%], 11 nonfatal MIs [1.4%] and 56 target-vessel revascularizations [7.1%]). The composite event rate of patients with HPR (PRU > 240) was significantly higher (7.5% vs 4.3% (p = 0.047)) than the patient population with normal value. In survival analysis, there was no significant difference between patient with HPR (PRU > 240) and normal reactivity. But between patient with HPR (PRU > 240) and normal reactivity, the survival rate free from the primary end point was significantly lower in patients with HPR (p = 0.014, Generalized Wilcoxon test).

Conclusion: High on-clopidogrel platelet reactivity tested by VerifyNow predict coronary adverse event in patients after PCI. In Korean, we seem to have to raise the optimal cutoff value of PRU to predict future coronary event.

Reappraisal of Pharmacodynamic Effect of Adjunctive Cilostazol and High-dose Clopidogrel in East Asian ACS Patients
TCTAP A-033

Observational Studies of Bleeding and Thrombotic Events in Acute Coronary Syndrome Patients Between Different Metabolizer of Clopidogrel
Wen Duong Zhang, Fu Sai Jr
Beijing Hospital, Beijing, China

Background: Compared with CYP2C19*1 carriers CYP2C19*2/3 carriers have a higher risk of stent thrombosis in clopidogrel-treated patients. Therefore

Compartment of Platelet Reactivity and Clinical Outcomes in Patients Treated with Clopidogrel and Coronary Intervention
Sang Yeub Lee, Ju-Hye Lee, Sang Min Kim, Jang-Whan Bae, Kyung-Kuk Whang, Yongwhi Park, Jin Sin Koh, Jin-Yong Hwang
Beijing Hospital, Beijing, China

Background: Platelets are associated with vascular occlusive event. High on-clopi- dogrel platelet reactivity (HPR) is associated with recurrent thrombotic events after percutaneous coronary intervention (PCI). We evaluated platelet reactivity measured by the VerifyNow P2Y12 assay and clinical outcomes in patients receiving clopi- dogrel and PCI of real world practice.

Comparison of Platelet Reactivity and Clinical Outcomes in Patients Treated with Clopidogrel and Coronary Intervention
TCTAP A-032

ORALS

TCTAP A-034

Comparison of Platelet Reactivity and Clinical Outcomes in Patients Treated with Clopidogrel and Coronary Intervention
Reappraisal of Pharmacodynamic Effect of Adjunctive Cilostazol and High-dose Clopidogrel in East Asian ACS Patients
Reappraisal of Pharmacodynamic Effect of Adjunctive Cilostazol and High-dose Clopidogrel in East Asian ACS Patients