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Randomized Comparisons of Double-Dose Clopidogrel or Adjunctive Cilostazol versus Standard Dual Anti-platelet in Patients with High Post-Treatment Platelet Reactivity: Results of the CREATIVE Trial (Clopidogrel Response Evaluation and AnTi-platelet InterVEntion in High Thrombotic Risk PCI Patients)

Running Title: *Tang et al.; Intensified Treatment in High Platelet Reactivity*

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Abstract

***Background*—**Patients undergoing percutaneous coronary intervention (PCI) react differently to antiplatelet drugs. Those with low responsiveness to clopidogrel have a higher risk of cardiac ischemic events. The goal of this study is to conduct a head-to-head comparison of the safety and effectiveness of intensified antiplatelet therapies (either double-dose clopidogrel [DOUBLE] or adjunctive cilostazol [TRIPLE]) and conventional strategy (STANDARD) in post-PCI patients.
***Methods*—**In this single-center, randomized, controlled trial, we used thromboelastography (TEG), a platelet function test, to select 1078 PCI patients at high thrombotic risk and compared the intensified antiplatelet therapies with standard antiplatelet therapy. The primary outcome was the incidence of major adverse cardiac and cerebrovascular events at 18 months post-PCI, defined as a composite of all-cause death, myocardial infarction, target vessel revascularization or stroke. Bleeding Academic Research Consortium (BARC) defined bleeding complications (types 1, 2, 3, or 5) were the safety endpoints.
***Results*—**The primary endpoint occurred in 52 patients (14.4%) in STANDARD group, 38 patients (10.6%) in DOUBLE group and 30 patients (8.5%) in TRIPLE group (HR: 0.720, 95%CI: 0.474-1.094, DOUBLE vs. STANDARD; HR: 0.550, 95%CI: 0.349-0.866, TRIPLE vs. STANDARD). No significant difference in the rates of major bleeding (BARC grade≥3) was found in DOUBLE group (3.34% vs. 1.93% in STANDARD, P=0.133) and TRIPLE group (2.53% vs 1.93% in STANDARD, P=0.240). The rate of BARC-defined minor bleeding increased in DOUBLE group (27.4% vs. 20.3% in STANDARD, P=0.031), but not in TRIPLE group (23.6% vs. 20.3% in STANDARD, P=0.146).
Conclusions—In patients with low responsiveness to clopidogrel, as measured by thromboelastography, the intensified antiplatelet strategies with adjunctive use of cilostazol significantly improved the clinical outcomes without increasing the risk of major bleeding. Decreased trend of negative outcomes could be observed in patients with double dosage of clopidogrel, but the difference was not significant.
***Clinical Trial Registration*—**URL: http://www.clinicaltrials.gov Unique Identifier: NCT01779401.

Key Words: anti-platelet, platelet function, high post-treatment platelet reactivity, cilostazol

Clinical Perspective

What is new?

- In PCI patients with low responsiveness to clopidogrel, defined by platelet function test, adjunctive use of cilostazol to dual anti-platelet therapy could significantly reduce ischemic adverse events without increasing the risk of major bleeding.
- Although both intensified anti-platelet strategies (double-dose clopidogrel and adjunctive cilostazol) achieved increased platelet inhibition, only the triple strategy with adjunctive use of cilostazol significantly reduced adverse events in long-term follow-up.
- No increased rate of major bleeding with intensified antiplatelet therapy (double-dose clopidogrel and adjunctive cilostazol) in patients with high post-treatment platelet reactivity was observed.

What are the clinical implications?

- Although high post-treatment platelet reactivity is associated with increases adverse events, simply intensified P2Y12 inhibitor treatment might not improve clinical outcomes.
- As a selective reversible phosphodiesterase type 3 inhibitor, cilostazol owns unique antithrombotic and vasodilatory properties, which contribute to the improvement of clinical outcomes.

Introduction

In the drug-eluting stent era, the prevention of ischemic events is a major challenge for the treatment of patients who have received percutaneous coronary intervention (PCI).[1, 2] Dual anti-platelet therapy (DAPT) with aspirin and a kind of P2Y12-inhibitor has been recommended by guidelines to prevent thrombotic complications.[3, 4] However, the anti-platelet effect of the most widely used P2Y12 receptor inhibitor, clopidogrel, is hampered by the slow and variable transformation of the prodrug to the active metabolite.[5] Clopidogrel needs to undergo a two-step metabolic transformation before binding to the platelet P2Y12 ADP receptor. This conversion procedure is regulated by the CYP450 system which presents genetic poly-morphisms in different populations, partly determining the extent to which clopidogrel inhibits ADP-induced platelet activation.[5-7] Post-PCI patients who have a low response, or are even nonresponsive to clopidogrel have an increased risk of ischemic events as compared to normal responders.[8-11]

Nowadays, low responsiveness to clopidogrel is mainly identified through the platelet function test. Previous cohort studies and meta-analyses have largely suggested that patients with high post-treatment platelet reactivity, as measured by platelet function tests, are at an increased risk of adverse events after PCI; despite this, the current post-PCI antiplatelet therapy remains a standardized DAPT strategy in most clinical settings. In recent years, pilot studies have explored new post-PCI antiplatelet strategies in patients with high post-treatment platelet reactivity, including the addition of cilostazol to dual antiplatelet therapy[12, 13] and doubling the dosage of clopidogrel.[14, 15] In addition, an increasing body of data suggests that East Asian patients have different risk profiles for both thrombophilia and bleeding compared with white patients, and that

a different 'therapeutic window' of post-treatment platelet reactivity might be appropriate in East Asian patients.[16, 17] Just as stated in the Word Heart Federation expert consensus on antiplatelet therapy in East Asian patients[18], at present, few randomized data on the efficacy and safety of P2Y12 receptor inhibitors for the treatment of East Asian patients with ACS or undergoing PCI, other than those from the COMMIT trial[19], have been published.

Several pilot trials have shown the salutary effects of double-dosage clopidogrel and triple antiplatelet therapies in East-Asian patients. However, head-to-head comparison of intensified anti-platelet strategies against standard DAPT on long-term outcomes still needs to be further investigated. The present study used thromboelastography (TEG), a method of platelet function testing, to select post-PCI patients with low responsiveness to clopidogrel, and compared the clinical outcomes of post-PCI patients who received intensified antiplatelet therapy versus standard DAPT.

Methods

The data, analytic methods, and study materials will not be made available immediately to other researchers for purposes of reproducing the results or replicating the procedure. The reason for the lack of availability is that we have signed an agreement with the sponsor to restrict approach to study data, and the access must be agreed by both investigator and sponsor. Request to get these materials can be sent to the corresponding author, and we will provide them to vetted and qualified applicants.

Study Design

The CREATIVE (Clopidogrel Response Evaluation and AnTi-platelet InterVEntion in High Thrombotic Risk PCI Patients) trial is a single-center, randomized, open-label trial conducted at Fuwai Hospital, the National Center for Cardiovascular Diseases of China. The details of the design have been registered on clinicaltrials.org. The study disposition is shown in Figure 1 and the screening process is shown in supplemental Figure 1. In brief, a total of 9741 post-PCI patients underwent TEG test to evaluate post-treatment platelet reactivity, and of them, 1078 PCI patients with low-responsiveness to clopidogrel were randomized into three groups utilizing different anti-platelet strategies after signing informed consent: standard antiplatelet therapy (clopidogrel 75mg daily plus aspirin 100mg daily, the STANDARD group), double-dose clopidogrel (clopidogrel 150mg daily plus aspirin 100mg daily, the DOUBLE group) and adjunctive use of cilostazol (cilostazol 100mg twice per day plus DAPT, the TRIPLE group). The data were independently managed by a contract research organization (PAREXEL International Corp., US). The primary data analysis was performed by the investigators with cooperation from the Medical Research & Biometrics Center of Fuwai Hospital. The corresponding author had full access to all data in the study and held final responsibility for the decision to submit for publication. The study was approved by the institutional ethics committee, and all participants provided written informed consent. All authors vouch for the accuracy and completeness of the data and analyses.

Study Patients

Participants were 18 years of age or older and had at least one clinically significant stenotic

lesion amenable to PCI. All index PCI patients received loading doses of 300 to 600 mg clopidogrel or maintaining clopidogrel treatment ≥ 5 days before the TEG screening to discover (1) if ADP-induced platelet-fibrin clot strength (MA_{ADP}) was > 47 mm, and (2) if ADP-induced platelet inhibition rate (IR) was < 50% (which would indicate low responsiveness to clopidogrel and a high risk for ischemic events)[20]. Major exclusion criteria include: symptoms of severe heart failure (NYHA Class III and above) or left ventricular ejection fraction < 40% (ultrasound or left ventricle angiography); severely impaired renal function before procedure (serum creatinine > 2.0mg/dl); bleeding tendency, a history of active peptic ulcers, a history of cerebral hemorrhage or cavum subarachnoidale bleeding; patients with antiplatelet agent and anticoagulant treatment contraindications (who hence are unable to undergo antithrombotic therapy); patients who are unable to withstand dual antiplatelet therapy due to allergies to aspirin, clopidogrel or cilostazol, heparin, contrast agents, paclitaxel and metals; patients who plan to undergo coronary artery bypass grafting or other surgery within 1.5 years.

Platelet function test and CYP2C19 genotyping

Blood samples for platelet function test were obtained at 18-24 hours post-PCI and were handled in 2 hours since blood draw according to standard operating procedure. Reexamination of platelet function was performed at 3-6 month after PCI during the maintenance of antiplatelet therapy. The median time interval between the last-dose administration of anti-platelet drugs and blood sampling was 168 minutes (interquartile range, 97 to 230) during hospitalization, and was 275 minutes (interquartile range, 148 to 327) at 3-6 months follow-up. Thromboelastography technology is described elsewhere.[8] In brief, blood was collected in an evacuated vacuum tube

containing 3.2% trisodium citrate and lithium heparin at least six hours after the patient had taken the clopidogrel dose. Modified TEG uses 4 channels to detect the effects of antiplatelet therapy action via the arachidonic acid (AA) and ADP pathways. The TEG Hemostasis Analyzer (Haemonetics Corp, Braintree, MA, USA) and automated analytical software were used to measure the physical properties. Low responsiveness to clopidogrel was defined as an ADP-induced platelet-fibrin clot strength (MA_{ADP}) > 47 mm plus an ADP-induced platelet inhibition rate (IR) < 50%. The criteria of MA_{ADP} > 47 mm were derived from previously published long-term observational studies.[20, 21] The criteria of ADP-induced platelet IR < 50% was defined in the product manual of TEG mapping and was tested in our pilot trial.

CYP2C19*2 and *3 were genotyped by sequencing in central laboratory of Fuwai Hospital. The operating procedure was according to the CYP2C19*2 and *3 Gene Detection Kit instructions (Beijing SinoMDgene Technology Co., Ltd), which was performed on an ABI 3500xL Dx DNA Analyzer (Applied Biosystems, Foster City, CA, USA). Genotypes were called independently by two professionals, 5% of which were verified by resequencing. CYP2C19*2 and *3 alleles were defined as "LOF" alleles. Patients without allele of *2 or *3 (i.e. *1/*1) were defined as "extensive metabolizers (EM)", those with single *2 or *3 allele (i.e. *1/*2 or *1/*3) were defined as "intermediate metabolizers (IM)", and those with two *2 or *3 alleles (i.e. *2/*2, *2/*3 or *3/*3) were defined as "poor metabolizers (PM)".

Study treatment and follow-up.

Eligible post-PCI patients with low-responsiveness to clopidogrel were randomly assigned to a strategy of anti-platelet therapy. The randomization was conducted centrally with the use of an

interactive voice-response system. Participants received different anti-platelet therapies for 1 year: standard antiplatelet therapy (clopidogrel 75mg daily plus aspirin 100mg daily, the STANDARD group), double-dose clopidogrel (clopidogrel 150mg daily plus aspirin 100mg daily, the DOUBLE group) and adjunctive use of cilostazol (cilostazol 100mg twice per day plus DAPT, the TRIPLE group). Clinical and telephone follow-up was conducted on Day 30 and Months 3, 6, 9, 12 and 18 to monitor the primary and secondary endpoints.

Study endpoints

The primary endpoint was major adverse cardiovascular and cerebrovascular events (MACCE, a composite of all-cause death, myocardial infarction, target vessel revascularization and cerebrovascular events). The secondary endpoints were major adverse cardiovascular events (MACE, a composite of all-cause death, myocardial infarction, and target vessel revascularization) and net adverse clinical and cerebral events (NACCE, a composite of all-cause death, all MI, stroke, and major bleeding). Other efficacy endpoints include Academic Research Consortium (ARC) defined stent thrombosis[22], platelet function, and quality of life (Seattle Angina Questionnaire). Major bleeding was defined as Bleeding Academic Research Consortium (BARC) type≥3 bleeding.[23] Myocardial infarction was defined in accordance with the universal definition proposed in 2007. Evaluation for stent thrombosis was performed according to the ARC criteria. Stroke was defined as focal loss of neurologic function caused by an ischemic or hemorrhagic event, with residual symptoms lasting at least 24 hours or leading to death.

Statistical analysis

The research hypothesis for this study is that the MACCE incidence rate can be significantly

reduced in the trial group as compared to the control group. At the initiation of study design, no exact evidence comparing the effectiveness of TRIPLE and DOUBLE was available. Both intensified strategies showed potential effects to reduce high post-treatment platelet reactivity after PCI,[24, 25] so we assumed that they had same capability to reduce MACCE. The MACCE incidence rate of the control group in this study was forecasted at 15%,[7] and the intensified antiplatelet therapies applied in the trial group were forecasted to reduce the MACCE incidence in the 18 month follow-up period to 8% (the two strategies were both capable of reaching this level separately).[24, 25] The sample size was calculated with the minimum meaningful effect size. At a two-sided alpha level of 5% and a beta error of 20%, each group is required to recruit 325 patients based on superiority assumption. Assuming an attrition rate of about 5%, 350 patients would be needed in each group in the study.

In this study, analysis was conducted based on ITT principles, and all patients who participated in the randomized study and received treatment will be included in the analysis. All continuous variables are presented as mean ± SD, and analysis of variance was used to compare means across multiple groups. Non-continuous and categorical variables are presented as frequencies or percentages and were compared using the Chi-square test. The continuity-adjusted Chi-square test was used for the comparison of primary endpoint. The absolute differences on MACCE between groups and the corresponding 95% confidence intervals would be reported. The Kaplan–Meier curve method was used to calculate time to clinical endpoints, and the log-rank test was used to compare the survival curves. The Cox proportional hazards model was further applied to estimate the hazard ratios, and the proportional hazards assumptions were

tested by log minus log plot. Data from all patients were censored at the date of the last available information. Unless otherwise specified, a 2-sided P value <0.05 was considered to indicate statistical significance. Statistical analysis was performed using SAS software version 9.1.3 (SAS Institute, Cary, NC).

Results

Baseline characteristics of study patients.

From December 2012 to through March 2015, we recruited 1078 patients, of whom 362 were assigned to the STANDARD group, 359 to the DOUBLE group and 355 to the TRIPLE group. The follow-up period ended in September 2016, when information on vital status was available for all patients except six. Baseline characteristics of the ITT-analysis population were well balanced among the three groups (Table 1). Most of the non-study medications and PCI procedures were also well matched except for the use of proton pump inhibitors (11.3% in STANDARD, 8.1% in DOUBLE, and 9.9% in TRIPLE, P=0.028; Table 2). The transradial approach was used in 94.4%, 94.2% and 93.5% of patients in the three groups, respectively (P=0.635); total stent lengths per patient were 31.86±16.89mm, 32.79±18.66mm and 31.71±17.16mm, respectively, (P=0.672).

Clinical outcomes.

The primary endpoint of MACCE events at 18 month post-PCI (defined as a composite of all-cause death, myocardial infarction, target vessel revascularization or stroke) occurred in 52 patients (14.4%) in the STANDARD group, 38 patients (10.6%) in the DOUBLE group, and 30

patients (8.5%) in the TRIPLE group (Table 3). Absolute difference in 18-month MACCE rates between the TRIPLE and STANDARD groups was -5.9% (95% confidence interval [CI]: -8.8% to -1.4%), demonstrating the superiority of the TRIPLE strategy over standard DAPT. Regarding the DOUBLE group, there was no significant difference compared with the STANDARD group (absolute difference = -3.8%; 95%CI, -7.2 to 1.3). Figure 2 shows the cumulative Kaplan-Meier estimates of MACCE and BARC-defined major bleeding. The risks of cardiac death, nonfatal MI, target vessel revascularization, and stroke did not differ significantly among the three groups (see Figure 3, Table 3). Significantly decreased risk of secondary endpoints, include MACE (hazard ratio [HR]: 0.506, 95%CI: 0.306-0.836) and NACCE (HR: 0.584, 95%CI: 0.353-0.967), could also be detected in the TRIPLE group as compared to the STANDARD group (see Figure 3, Table 3). Again, the DOUBLE strategy did not show significant difference with respect to MACE or NACCE.

The 12-month landmark analysis of clinical outcomes is shown in supplemental Table 1. The incidence rates of MACCE at 12 month were 13.0% in the STANDARD group, 9.7% in the DOUBLE group and 6.8% in the TRIPLE group. Absolute difference in 12-month MACCE rates between TRIPLE and STANDARD was -6.2% (95%CI: -8.8% to -2.2%). The DOUBLE group did not show significant difference compared with the STANDARD group (absolute difference = -3.3%; 95%CI, -6.5 to 1.7). The risks of cardiac death, nonfatal MI, target vessel revascularization, stroke and BARC-defined major bleeding did not differ significantly among the three groups. Significant decreased risk of MACE and NACCE could be detected in TRIPLE group, but not in DOUBLE group.

Definite or probable stent thrombosis≤12 months occurred in 6 patients (1.66%) in the STANDARD group, 2 patients (0.56%) in the DOUBLE group, and 4 patients (1.13%) in the TRIPLE group (log-rank P=0.32), as shown in supplemental Table 2 and Table 4. All stent thrombosis cases occurred within 8 months from the index procedure while the patients were taking clopidogrel; 7 cases occurred within 30 days of PCI. There were no new definite or probable stent thrombosis between the 12 to 18 month period of the follow-up (see Table 4). All the above results were consistent in the "as treated" analysis.

Bleeding

The rates of BARC-defined major bleeding were similar in the three groups (3.34% vs. 1.93%, P=0.133, DOUBLE vs. STANDARD; 2.53% vs 1.93%, P=0.240, TRIPLE vs. STANDARD; see Figure 2). The rate of BARC-defined minor bleeding increased in the DOUBLE group (27.4% vs. 20.3% in STANDARD, P=0.031), but not in the TRIPLE group (23.6% vs. 20.3% in STANDARD, P=0.146). The absence of a significant difference in BARC-defined major bleeding was consistent at the 12 month landmark analysis (supplemental Table 1).

Compliance with study regimen

Premature discontinuation of the study drugs was more common in the DOUBLE group and the TRIPLE group than in the STANDARD group (22.5% vs. 14.5%, P=0.018; 26.1% vs. 14.5%, P=0.007). The median duration of exposure to double-dosage of clopidogrel was 281 days (interquartile range, 149 to 365); the median duration of exposure to cilostazol was 246 days (interquartile range, 109 to 365). Drug-related adverse events were the major reason for discontinuation of medication in TRIPLE group, including namely headache (n=29), followed by

easy bruisability or bleeding (n=27), tachycardia (n=18), and gastrointestinal side effects (n=14). In the DOUBLE group, the major reasons for discontinuation were easy bruisability or bleeding (n=35), gastrointestinal side effects (n=19) and drug expenditure (n=16).

Platelet function test and genotype test.

As shown in Figure 4, the changes of MA_{ADP} and platelet IR between the baseline and the 3-6 month follow-up were significant in the DOUBLE group (11.33±10.53 vs 18.14±18.53, P=0.018; 57.2±5.9 vs 49.9±11.0, P=0.015) and the TRIPLE group (14.08±11.06 vs 21.65±25.23, P=0.006; 54.8±6.3 vs 48.2±12.4, P=0.033), but not in the STANDARD group (14.72±10.62 vs 15.32±17.43, P=0.325; 53.6±4.1 vs 51.8±8.5, P=0.472). Changes between the DOUBLE and TRIPLE groups were similar (P=0.308). The clopidogrel metabolism enzyme CYP2C19 genotype was tested in about 65% of all participants (total number is 700; 216 in the STANDARD group, 245 in the DOUBLE group, and 239 in TRIPLE group). There were 112 patients (16%) without allele of *2 or *3 (i.e. *1/*1). The defined intermediate metabolizers (i.e. *1/*2 or *1/*3) were 329 patients (47%) and the defined poor metabolizers (i.e. *2/*2, *2/*3 or *3/*3) were 259 patients (37%). The distributions of different genotypes in the three groups were similar (see Figure 4C).

Discussion

The CREATIVE trial demonstrated that the adjunctive use of cilostazol as compared to standard DAPT in patients with low-responsiveness to clopidogrel can significantly reduce the rate of MACCE, a composite of all-cause death, myocardial infarction, target vessel revascularization or

stroke. A similar benefit was also seen for the reduction of MACE and NACCE. In addition, the beneficial effects of the triple anti-platelet strategy were achieved without a significantly increased risk of major bleeding. Although the double-dosage clopidogrel strategy showed a trend of reduced MACCE rates, it did not achieve significant improvement of clinical outcomes. In dual antiplatelet therapy with aspirin and P2Y12 inhibitor, the evaluation of antiplatelet therapies has been largely focused on reducing ischemic event occurrence (efficacy). However, bleeding (safety) has also been a heightened risk with the emergence of more potent antiplatelet drugs and strategies. The balance between the risk reduction in ischemic events and the risk increase in bleeding events has attracted much attention in recent years, leading to the introduction of the novel clinical composite endpoint "net adverse clinical events". Accordingly, the present study did not only focus on the efficacy of intensive antiplatelet therapy, but also paid attention to the safety.

Low responsiveness to clopidogrel is mainly identified through platelet function testing[11, 21] Platelet aggregation analysis using light transmittance aggregometry (LTA) and thromboelastography (TEG) are the two main platelet function testing methods used in clinical settings in China. Although LTA platelet aggregation measurement is presently the most popular clinical test method, it requires a larger blood sample and is time consuming and complicated[26]; moreover, the agonist type and concentration differ from laboratory to laboratory, making it difficult to compare test results. [27] TEG has gained popularity in recent years; it is able to measure the quantitative platelet inhibition rate to determine low responsiveness to clopidogrel and aspirin[8]. Nowadays there is no "gold standard" for platelet function testing. Aside from

TEG, there are also other methods of platelet function testing, such as VerifyNow, vasodilator-stimulated phosphoprotein (VASP) phosphorylation analysis, and Multiplate measurement. VerifyNow evaluates the combination of both platelet activation and aggregation, while VASP measurements only reflect the potential for platelet activation. The Multiplate measurement is based on the combination of platelet activation and adhesion of activated platelets to a foreign surface. Despite these differences and the lack of standardization, each method correlates significantly with P2Y12 inhibitor active metabolite concentrations, with the highest correlations reported for VerifyNow PRU, TEG and VASP; weaker correlations were reported for LTA and Multiplate. High on-treatment platelet reactivity (HOPR) as defined by each method has been significantly associated with an increased occurrence of thrombotic and ischemic events after PCI in high-risk patients.

Patients with low responsiveness to clopidogrel suffer at a high rate from stent thrombosis and cardiac ischemic events after PCI procedures than normal responders.[10, 11] So far, the ADAPT-DES trial has been the largest scale registry examining the relationship between platelet reactivity and stent thrombosis after drug-eluting stent implantation. In this prospective, multicenter population, those with high on-treatment platelet reactivity had a 3-fold adjusted hazard for the occurrence of 30-day stent thrombosis.[10] In 2010, Gurbel PA et al. published a long-term observational study and reported that ADP inhibition rate (borderline value of 50.9%) and MA_{ADP} (borderline value of 46.6mm) are excellent indicators of platelet dysfunction and low responsiveness to clopidogrel.[20] In our study, we combined these two indicators, defining a patient with an ADP inhibition rate of < 50% and a MA_{ADP} of > 47mm to be at high thrombotic

risk. Previous studies have reported that 20-25% of PCI patients have low responsiveness to clopidogrel.[18, 28, 29] Several factors (e.g., age, BMI, diabetes, chronic kidney disease, congestive heart failure, drug-drug interaction, the CYP2C19 variant) have been suggested to determine clopidogrel response.[30-32]

Remarkably, the Asian population has almost twice the prevalence of the CYP2C19 loss of function (LOF) genotype as compared to the Caucasian population, thus contributing to the high prevalence of low-responsiveness to clopidogrel in Asians.[29] In our study, more than 60% of patients (low responsiveness to clopidogrel) had the mutant allele of CYP2C19. However, few East Asian patients have been included in the trials to assess the use of CYP2C19 receptor inhibitor agents, particularly the potent agents prasugrel and ticagrelor. Additionally, an increasing body of data suggests that East Asian patients have differing risk profiles for both thrombophilia and bleeding compared with white patients, and that a different 'therapeutic window' of on-treatment platelet reactivity might be appropriate in East Asian patients. Deficient data specific to East Asian patients are available to demonstrate the superiority of intensified antiplatelet therapy over conventional strategy, which is the initial aim of CREATIVE study.

The current post-PCI antiplatelet therapy remains a standardized strategy, although clinical evidence has indicated that MACCE incidence is higher in patients with low responsiveness to clopidogrel. Our study indicated that the adjunctive use of cilostazol could significantly reduce the rate of MACCE in patients with low-responsiveness to clopidogrel, without a significant increased risk of major bleeding.

Previous efforts have explored new post-PCI antiplatelet strategies, including double-dosage clopidogrel, triple antiplatelet therapy with the addition of cilostazol/warfarin, or replacing clopidogrel with potent P1Y12 inhibitors (prasugrel or ticagrelor). [12, 13, 24, 25, 33] The triple antiplatelet strategy with warfarin significantly increased the risk of bleeding, so this strategy is mainly used for atrial fibrillation coronary patients after PCI procedure.[34-37] Although meta-analysis of pilot studies showed that a double dosage of clopidogrel lowered the incidence of post-PCI adverse events, its effect is controversial.[14, 15] The GRAVITAS trial was the first large-scale investigation of personalized antiplatelet therapy (guided by VerifyNow) in elective PCI patients.[38] In this study, a high dosage of clopidogrel was ineffective in reducing 6-month composite ischemic event occurrence. A possible explanation for the neutral results is that high-dose clopidogrel reduced the prevalence of high on-treatment platelet reactivity at 30 days in only 60% of patients, indicating that clopidogrel was not an optimal remedy to overcome high on-treatment platelet reactivity. The findings from our study is partly consistent with GRAVITAS study, but significant improvement is observed in the TRIPLE group. Different from GRAVITAS study and the present study, ARCTIC and ANTARCTIC study take a strategy of monitoring platelet-function to adjust antiplatelet drug, instead of continuous intensified strategy. Both of them showed no significant improvements in clinical outcomes with platelet-function monitoring and treatment adjustment. These evidence, together with our findings, indicates that although HOPR is associated with increases adverse events, simply intensified P2Y12 inhibitor treatment might not improve clinical outcomes. But it is worth noting that, up to now, no data related to ticagrelor is available.

A clinical trial conducted in Korea showed that the triple antiplatelet strategy with cilostazol could significantly inhibit platelet reactivity.[39] The KAMIR study retrospectively analyzed 4203 PCI patients who were divided into the dual antiplatelet group (aspirin + clopidogrel) and triple antiplatelet group (aspirin + clopidogrel + cilostazol).[33] In this study, the hospital readmission rates were 3.4% vs. 2.2% (P = 0.022), and the mortality rates at 8 months were 4.9% vs. 3.1% in the double strategy and the triple strategy, respectively (P=0.007). An interesting trial conducted in the type 2 diabetes population showed that adding cilostazol could achieve greater platelet inhibition as compared to double-dosage clopidogrel, which is not influenced by genetic polymorphisms.[39, 40] In 2009, the ACCEL-RESISTANCE study[39] firstly reported that adjunctive cilostazol could reduce the rate of HOPR and intensify platelet inhibition. In 2013, the HOST-ASSURE study[41] indicated that adjunctive use of cilostazol was non-inferior to doubling the dose of clopidogrel for 1 month. The present study, to our knowledge, is the first randomized trial to demonstrate that adjunctive cilostazol could improve the long-term clinical outcomes in in patients with low-responsiveness to clopidogrel.

In the present study, although both intensified anti-platelet strategies achieved increased platelet inhibition, only the triple strategy significantly reduced adverse events (all-cause death, myocardial infarction, target vessel revascularization or stroke) in long-term follow-up. The rate of ischemic adverse events in the DOUBLE group was lower than in the STANDARD group, but the difference was not significant. In 2013, the HOST-ASSURE trial reported that the adjunctive use of cilostazol was non-inferior to doubling the dose of clopidogrel in 1 month post-PCI period. In fact, even the 1-month rate of adverse events was lower in TRIPLE group (1.2% vs.

1.4%).[41] Our study further strengthens the evidence of the adjunctive use of cilostazol in high on-treatment platelet reactivity.

Several previous efforts exploring the adjunctive use of cilostazol found that TRIPLE strategy could reduce the rate of high on-treatment platelet reactivity. However, results of TEG test at 3-6 month post PCI did not show significant difference between TRIPLE and DOUBLE groups in the present study. Possible explanation for the neutral results is that: first, previous studies (ACCEL-RESISTANCE study and HOST-ASSURE study) reexamined platelet function at 1-month post PCI, while we did the reexamination at 3-6 month post PCI, this time difference might lead to changes in the pharmacodynamics of cilostazol; second, drug discontinuation was more common in TRIPLE group than that in DOUBLE group (22.5% vs. 26.1%), partly influencing the results; third, as antiplatelet effect of cilostazol is dependent on its plasma level, the prolonged time interval between TEG sampling and cilostazol administration at 3-6 month follow-up (presented in Methods) could also contribute to relatively low inhibitory level in TRIPLE. Despite similar effects on platelet function, the adjunctive use of cilostazol still provides clinical benefits in the present study. Multiple functions of cilostazol may contribute to the improvement of outcomes. As a selective reversible phosphodiesterase type 3 inhibitor, cilostazol owns unique antithrombotic and vasodilatory properties. Cilostazol inhibits platelet aggregation induced by ADP, arachidonic acid, collagen, and epinephrine. TRIPLE strategy could bring additive elevation of intracellular cAMP through both increase of cAMP production by clopidogrel and inhibition of cAMP degradation by cilostazol.

Prevalence of high on-treatment reactivity in our original cohort was relatively low. Based

on the criteria of MA_{ADP} > 47 mm, prevalence of HOPR was 31.3% (3046/9741, see supplementary Figure 1). Previous data has shown that HOPR prevalence was over 50% in East Asian patient, if criteria derived from Western population were used.[16, 18] As mentioned above, this observation might be primarily caused by a higher frequency of the CYP2C19 loss-of-function alleles in East Asians. Possible explanation for the relatively low prevalence of HOPR in the present study cohort is that: as cutoffs of platelet function testing methods (TEG, VerifyNow and VASP) were derived from different clinical evidence, the HOPR populations defined by different methods could also be inconsistent. In the future, appropriate cut-off points for HOPR should be established in large-scale cohort in East Asian patients.

In the present study, no increased rate of major bleeding with intensified antiplatelet therapy in patients with high on-treatment platelet reactivity was observed. This phenomenon could be also found in GRAVITAS, ARCTIC and ANTARCTIC.[38, 42, 43] Moreover, a recent meta-analysis published by Aradi et al further strengthened intensifying antiplatelet therapy on the basis of platelet function testing did not expose patients to higher risk for bleeding.[44] Contrary to this, in the TRITON–TIMI 38 study[45], prasugrel increased the risk for TIMI major bleeding events by 32%, while ticagrelor was also associated with a 25% increase in this endpoint in the study of PLATO trial[46]. As bleeding complications are as serious as thrombotic events after PCI, platelet function testing is a potentially effective tool to guide antiplatelet treatment and prevent bleeding events in those receiving intensified antiplatelet therapy.

Study limitations

Despite the encouraging findings, our study has some limitations. First, this is a single center

trial. Although single center design helps maintaining standard procedures (TEG/gene testing, PCI, and medication), a multi-center design could provide more convincing data, especially for this head-to-head comparison trial on intensified strategies. Second, premature discontinuation of the study drug was more common in the DOUBLE and TRIPLE groups than in the STANDARD group, which may have affected the outcomes. However, our results were identical whether analyzed by the intention to treat or per protocol. Third, this study included only East Asian PCI patients. Because the strength of platelet reactivity and anti-platelet therapy on clinical events can be different, which is influenced by gene variation or environment, the mechanistic popularization from the result of the present study may be inappropriate. Finally, a decreased trend of major primary endpoint could be found in the DOUBLE group, although the p value did not reach a significant level. At the initial of study design, no exact evidence was available for the superiority of TRIPLE strategy over DOUBLE, so we assumed that the two intensified antiplatelet strategies had same capability to reduce MACCE. This might lead to the insufficient power to test the effectiveness of DOUBLE strategy.

Conclusions

In East Asian PCI patients with low responsiveness to clopidogrel, as measured by thromboelastography, the intensified antiplatelet strategies with adjunctive use of cilostazol significantly reduced platelet reactivity and the MACCE rate without increasing the risk of major bleeding. Decreased trend of negative outcomes could be observed in patients with double dosage of clopidogrel, but the difference was not significant.

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Table 1. Baseline characteristics of the patients according to treatment group.

	STANDARD N=362	DOUBLE N=359	TRIPLE N=355	P value
Gender (male)	214 (59.1%)	219 (61.0%)	211 (59.4%)	0.136
Age (year)	58.64±8.75	58.12±8.97	58.39±9.03	0.201
BMI (kg/m^2)	25.78±3.12	26.02±3.16	25.69±3.04	0.073
SBP (mmHg)	128.1±17.5	127.2±16.4	126.9±15.4	0.599
DBP (mmHg)	77.6±10.7	78.6±10.5	77.3±9.3	0.197
Diabetes mellitus	121 (33.4%)	115 (32.0%)	121 (34.1%)	0.838
Hypertension	243 (67.1%)	219 (61.0%)	229 (64.5%)	0.228
Dyslipidemia	233 (64.4%)	246 (68.5%)	229 (64.5%)	0.408
Previous stroke	39 (10.8%)	37 (10.3%)	46 (13.0%)	0.503
Smoking	124 (34.3%)	137 (38.2%)	137 (38.6%)	0.320
Previous MI	57 (15.7%)	59 (16.4%)	44 (12.4%)	0.260
Previous CABG	8 (2.2%)	7 (1.9%)	4 (1.1%)	0.495
Previous PCI	72 (19.9%)	77 (21.4%)	67 (18.9%)	0.688
Atrial fibrillation	9 (2.5%)	4 (1.1%)	7 (2.0%)	0.367
Presentation				0.9931
NSTEMI	43 (11.9%)	48 (13.4%)	46 (13.0%)	
STEMI	25 (6.9%)	24 (6.7%)	26 (7.3%)	
Unstable angina	148 (40.9%)	148 (41.2%)	140 (39.4%)	
Stable angina	146 (40.3%)	139 (38.7%)	143 (40.3%)	

Values are mean±SD or n (%). BMI, body mass index; BP, blood pressure; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; NSTEMI, non-ST segment elevation MI; STEMI, ST-segment elevation MI.
Continuous variables were compared using analysis of variance. Categorical variables were compared using the Chi-square test.

Table 2. Baseline treatments and procedure characteristics according to treatment group.

	STANDARD N=362	DOUBLE N=359	TRIPLE N=355	P value
Procedure time (minute)	26.34±16.10	29.77±21.05	28.55±20.85	0.061
No. of stents	1.65±0.75	1.73±0.85	1.73±0.84	0.215
Length of stents (mm)	31.86±16.89	32.79±18.66	31.71±17.16	0.672
Transradial approach	339 (94.4%)	338 (94.2%)	330 (93.5%)	0.635
Pre-dilatation	254 (70.2%)	264 (73.5%)	258 (72.7%)	0.578
B2/C type lesions	282 (78.8%)	297 (83.9%)	277 (78.7%)	0.128
No. of target lesions				0.064
1	274 (75.7%)	242 (67.4%)	235 (66.2%)	
≥2	88 (24.3%)	117 (32.6%)	120 (33.8%)	
Chronic total occlusion lesions	48 (13.4%)	56 (15.6%)	47 (13.3%)	0.741
Left main lesions	15 (4.1%)	14 (3.9%)	16 (4.5%)	0.582
Bifurcation lesions	114 (31.5%)	109 (30.4%)	105 (29.6%)	0.855
Clopidogrel exposure at time of enrollment				0.579
Loading dose, 300 mg	85 (23.5%)	92 (25.6%)	84 (23.7%)	
Loading dose, 600 mg	50 (13.8%)	54 (15.0%)	49 (13.8%)	
Maintenance, 75 mg＞5d	227 (62.7%)	213 (59.3%)	222 (62.5%)	
Perioperative anticoagulation				
Low-molecular-weight heparin	197 (54.4%)	192 (53.5%)	195 (54.9%)	0.925
Fondaparinux	111 (30.7%)	118 (32.9%)	107 (30.1%)	0.706
Unfractionated heparin	138 (38.1%)	134 (37.3%)	140 (39.4%)	0.843
IIb/IIIa inhibitors	44 (12.2%)	52 (14.5%)	44 (12.4%)	0.598
Statin	1818 (86.7%)	1895 (89.2%)	1761 (90.6%)	0.625
Calcium-channel blocker	480 (22.9%)	514 (24.2%)	418 (21.5%)	0.081
Proton pump inhibitor	41 (11.3%)	29 (8.1%)	35 (9.9%)	0.028

Values are mean±SD or n (%).
Continuous variables were compared using analysis of variance. Categorical variables were compared using the Chi-square test.

Table 3. Primary and secondary endpoints

Endpoints	STANDARD	DOUBLE	TRIPLE	Hazard Ratio (95%CI) DOUBLE vs STANDARD	Hazard Ratio (95%CI) TRIPLE vs STANDARD
Primary endpoint: all-cause death, MI, TVR or stroke	52 (14.4%)	38 (10.6%)	30 (8.5%)	0.720 (0.474,1.094)	0.550 (0.349,0.866)
Secondary endpoints:					
All-cause death	6 (1.7%)	2 (0.6%)	0 (0.0%)	0.334 (0.067,1.655)	0
Cardiac death	5 (1.4%)	1 (0.3%)	0 (0.0%)		
Myocardial Infarction	23 (6.4%)	15 (4.2%)	12 (3.4%)	0.652 (0.340,1.249)	0.525 (0.261,1.055)
Target vessel revascularization	20 (5.5%)	13 (3.6%)	14 (3.9%)	0.644 (0.321,1.296)	0.705 (0.356,1.395)
Stroke	9 (2.5%)	10 (2.8%)	7 (2.0%)	1.117 (0.454,2.750)	0.674 (0.240,1.893)
Stent thrombosis	6 (1.7%)	2 (0.6%)	4 (1.1%)		
Major Bleeding	7 (1.93%)	12 (3.34%)	9 (2.53%)	1.734 (0.683,4.405)	1.310 (0.488,3.518)
MACE: all-cause death, MI or TVR	45 (12.4%)	30 (8.4%)	23 (6.5%)	0.656 (0.414,1.042)	0.506 (0.306,0.836)
NACCE: all-cause death, MI, stroke or major bleeding	41 (11.3%)	35 (9.7%)	25 (7.0%)	0.854 (0.544,1.340)	0.584 (0.353,0.967)

The percentages are Kaplan–Meier estimates of the rate of endpoints at 18 month. Patients could have had more than one type of endpoint.
P values were calculated by means of Cox regression analysis.

Table 4. Cases of stent thrombosis in three groups.

	Time to event, day	Classification	Asprin	Clopidogrel	Cilostazol	Outcomes
STANDARD	0	Definite	Continued	Continued		MI, TVR
	0	Definite	Continued	Continued		MI, TVR
	21	Definite	Continued	Continued		MI, TVR
	67	Probable	Continued	Continued		MI, cardiac death
	93	Probable	Continued	0		MI, TVR
	242	Probable	Continued	Continued		MI, cardiac death
DOUBLE	18	Probable	Continued	75mg		MI
	146	Probable	0	Continued		MI, cardiac death
TRIPLE	0	Definite	Continued	Continued	Continued	MI, TVR
	5	Probable	Continued	Continued	0	MI
	27	Probable	Continued	Continued	0	MI, TVR
	62	Definite	Continued	Continued	Continued	MI

Classification of stent thrombosis is according to the Academic Research Consortium criteria.
MI, myocardial infarction; TVR, target vessel revascularization.

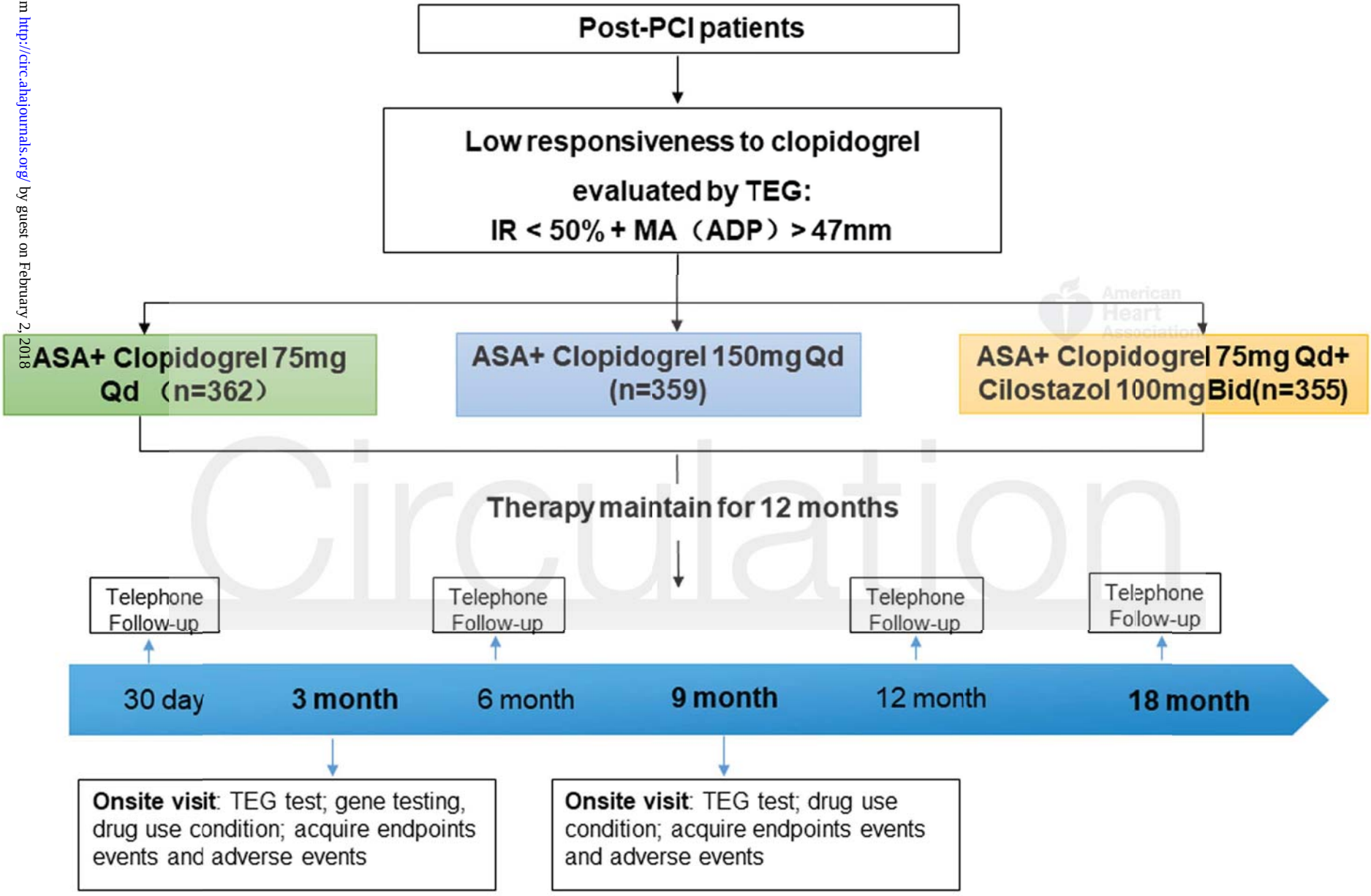
Figure Legends

Figure 1. Flow Diagram of the CREATIVE Study.

Figure 2. Cumulative Kaplan-Meier Estimates of the Time to the First Adjudicated Occurrence of Primary Endpoints (MACCE) and Major Bleeding Endpoint. MACCE = major adverse cardiac and cerebrovascular events.

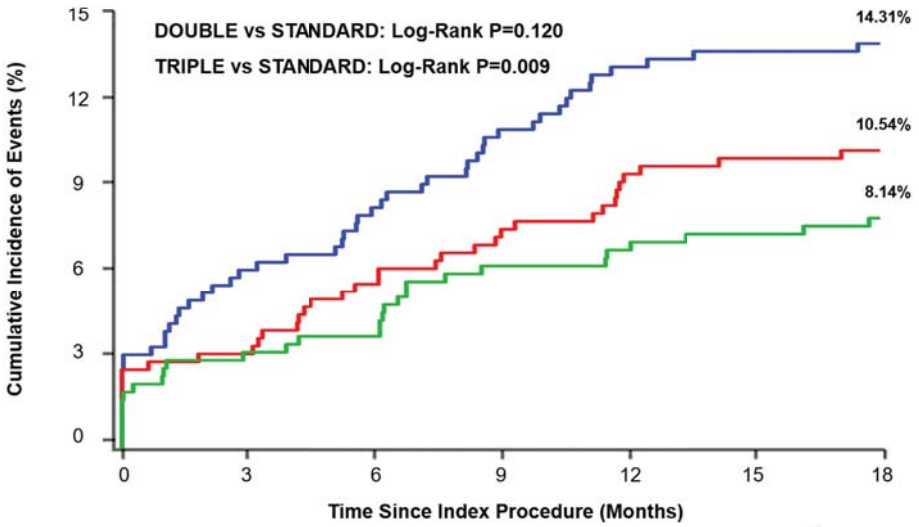
Figure 3. Cumulative Kaplan-Meier Estimates of the Time to the First Adjudicated Occurrence of Adverse Events. Cumulative event curves through 18 months of NACCE (A), MACE (B), all-cause death (C), myocardial infarction (D), stroke (E), and target lesion revascularization (F). NACCE = net adverse clinical and cerebral events; MACE = major adverse cardiac events.

Figure 4. Change of Platelet Function and Distribution of CYP2C19 Genotype. (A) Changes of ADP-induced platelet-fibrin clot strength (MA_{ADP}). (B) Changes of ADP-induced platelet inhibition rate. (C) Distribution of CYP2C19 Genotype in 700 subjects. Extensive Metabolizer: CYP2C19 *1/*1; Intermediate Metabolizer: CYP2C19 *1/*2 or *1/*3; Poor Metabolizer: CYP2C19 *2/*2, *2/*3, *3/*3.



Standard Treatment Group — Double Dose Group — Cilostazol + DAPT Group

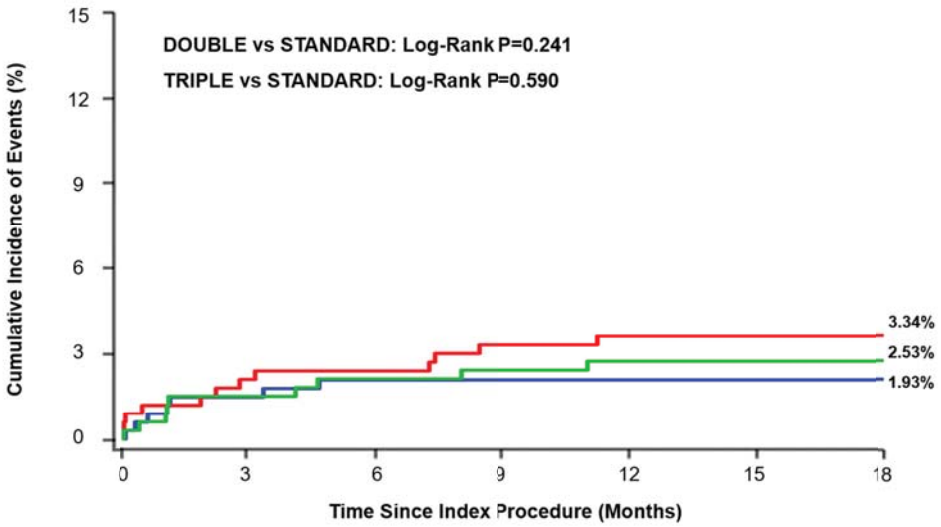
MACCE



Patients at Risk:

Months	0	3	6	9	12	15	18
STANDARD	362	337	331	319	313	311	310
DOUBLE	359	344	338	330	324	322	321
TRIPLE	355	342	341	332	330	328	326

Major Bleeding

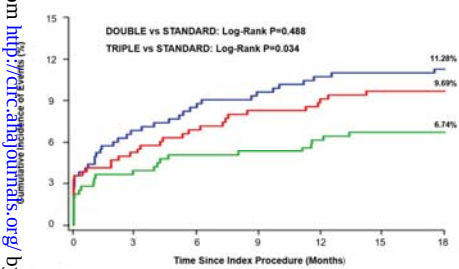


Patients at Risk:

Months	0	3	6	9	12	15	18
STANDARD	362	356	354	352	350	350	350
DOUBLE	359	351	351	347	345	345	345
TRIPLE	355	350	348	347	346	346	346

Standard Treatment Group — Double Dose Group — Cilostazol + DAPT Group

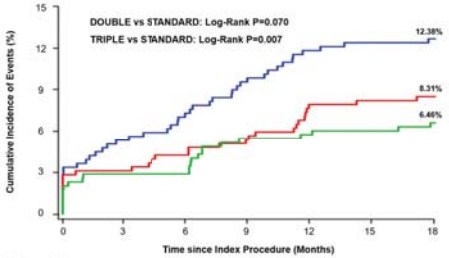
A MACCE



Patients at Risk:

Months	0	3	6	9	12	15	18
STANDARD	362	335	330	325	323	322	321
DOUBLE	359	338	334	329	326	324	324
TRIPLE	355	340	337	336	333	331	331

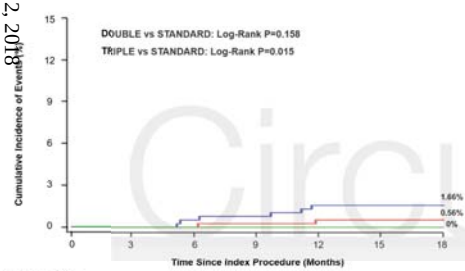
B MACE



Patients at Risk:

Months	0	3	6	9	12	15	18
STANDARD	362	341	336	325	320	318	317
DOUBLE	359	347	344	338	331	330	329
TRIPLE	355	345	345	336	335	334	332

C All-Cause Death



Patients at Risk:

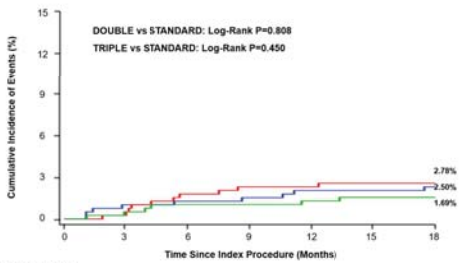
Months	0	3	6	9	12	15	18
STANDARD	362	362	360	358	356	356	356
DOUBLE	359	359	359	358	357	357	357
TRIPLE	355	355	355	355	355	355	355

D Myocardial Infarction

Patients at Risk:

Months	0	3	6	9	12	15	18
STANDARD	362	344	340	336	334	333	333
DOUBLE	359	348	347	346	343	342	342
TRIPLE	355	346	346	346	344	343	343

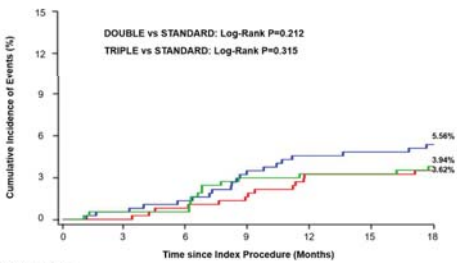
E Stroke



Patients at Risk:

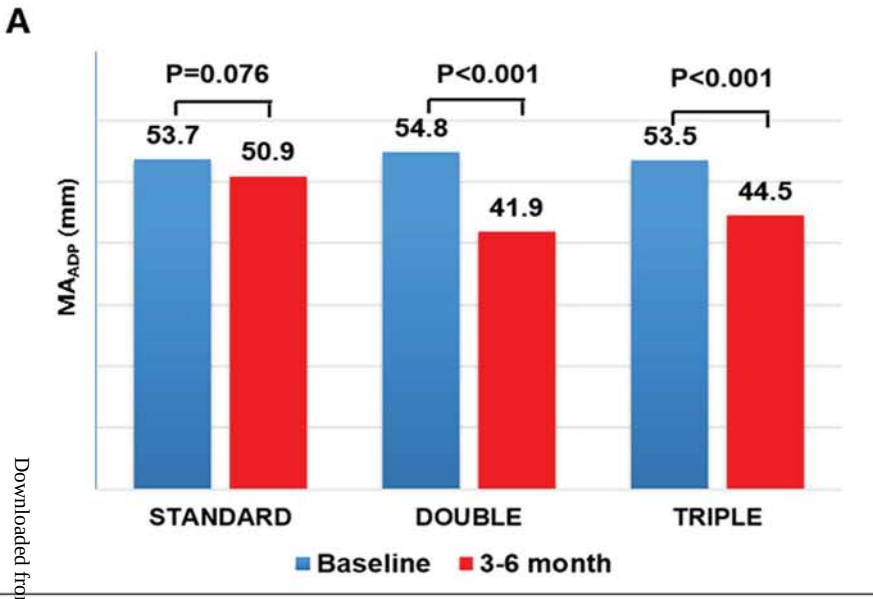
Months	0	3	6	9	12	15	18
STANDARD	362	358	355	352	349	349	348
DOUBLE	359	355	352	349	348	347	347
TRIPLE	355	352	351	351	350	349	349

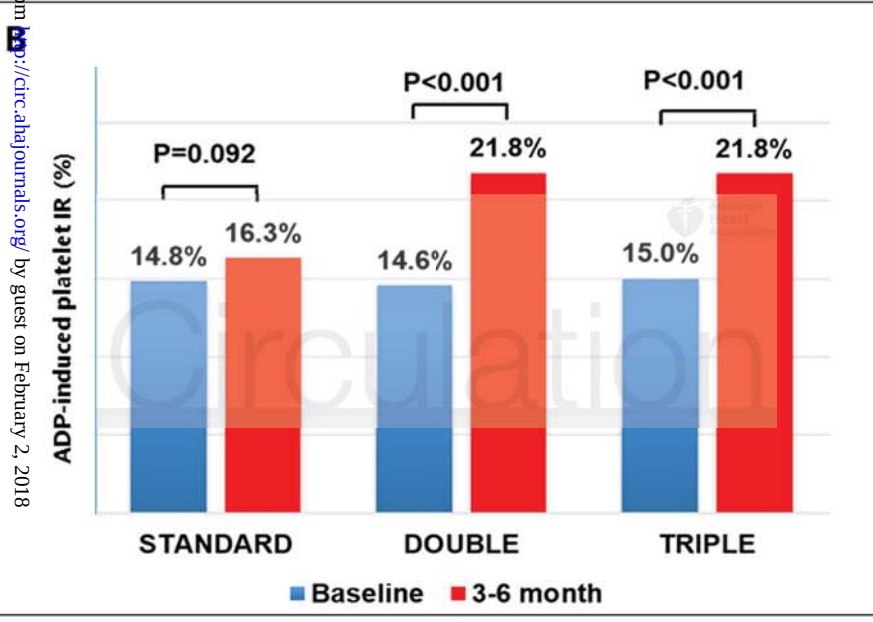
F Target Vessel Revascularization

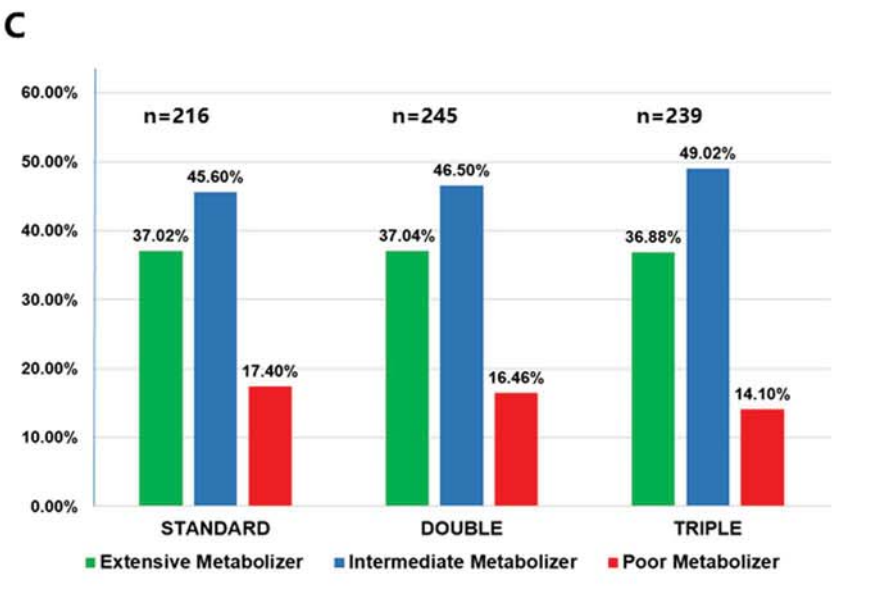


Patients at Risk:

Months	0	3	6	9	12	15	18
STANDARD	362	358	355	345	340	339	337
DOUBLE	359	358	356	350	345	345	344
TRIPLE	355	353	353	344	343	343	341







Randomized Comparisons of Double-Dose Clopidogrel or Adjunctive Cilostazol versus Standard Dual Anti-platelet in Patients with High Post-Treatment Platelet Reactivity: Results of the CREATIVE Trial (Clopidogrel Response Evaluation and AnTi-platelet InterVEntion in High Thrombotic Risk PCI Patients)

Yi-Da Tang, Wenyao Wang, Min Yang, Kuo Zhang, Jing Chen, Shubin Qiao, Hongbing Yan, Yongjian Wu, Xiaohong Huang, Bo Xu, Runlin Gao and Yuejin Yang
on behalf of the CREATIVE investigators

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SUPPLEMENTAL MATERIAL

Supplemental Table 1. Primary and secondary endpoints at 12 month.

Endpoints	STANDARD	DOUBLE	TRIPLE	Hazard Ratio (95%CI) DOUBLE vs STANDARD	Hazard Ratio (95%CI) TRIPLE vs STANDARD
Primary endpoint: all-cause death, MI, TVR or stroke	47 (13.0%)	35 (9.7%)	24 (6.8%)	0.736 (0.475-1.140)	0.506 (0.309-0.827)
Secondary endpoints:					
All-cause death	6 (1.7%)	2 (0.6%)	0 (0.0%)	0.309 (0.062-1.540)	0
Myocardial Infarction	21 (6.0%)	14 (3.9%)	11 (3.0%)	0.702 (0.357-1.378)	0.547 (0.264-1.131)
Target vessel revascularization	16 (4.4%)	12 (3.3%)	12 (3.4%)	0.701 (0.330-1.488)	0.734 (0.346-1.558)
Stroke	7 (1.9%)	9 (2.5%)	4 (1.1%)	1.294 (0.482-3.473)	0.579 (0.170-1.978)
Stent thrombosis	6 (1.7%)	2 (0.6%)	4 (1.1%)		
Major Bleeding	7 (1.9%)	12 (3.3%)	9 (2.5%)	1.734 (0.683-4.405)	1.310 (0.488-3.518)
MACE: all-cause death, MI or TVR	41 (11.3%)	28 (7.8%)	20 (5.6%)	0.683 (0.421-1.108)	0.496 (0.290-0.849)
NACCE: all-cause death, MI, stroke or major bleeding	38 (10.5%)	32 (9.1%)	21 (5.9%)	0.869 (0.545-1.385)	0.553 (0.324-0.942)

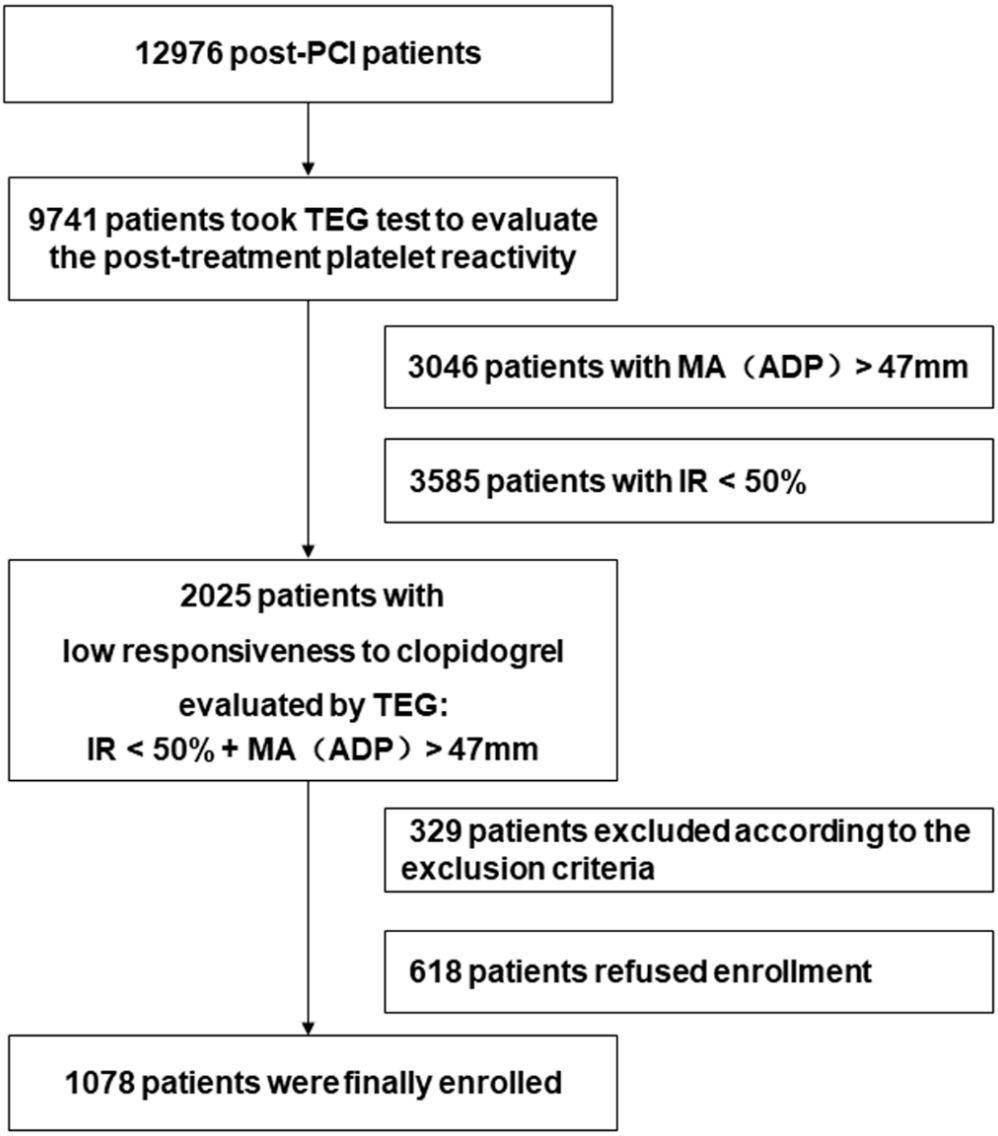
The percentages are Kaplan–Meier estimates of the rate of endpoints at 12 month. Patients could have had more than one type of endpoint.
P values were calculated by means of Cox regression analysis.

Supplemental Table 2. Cases of stent thrombosis in three groups at 12 month.

	Time to event, day	Classification	Asprin	Clopidogrel	Cilostazol	Outcomes
STANDARD	0	Definite	Continued	Continued		MI, TVR
	0	Definite	Continued	Continued		MI, TVR
	21	Definite	Continued	Continued		MI, TVR
	67	Probable	Continued	Continued		MI, cardiac death
	93	Probable	Continued	0		MI, TVR
	242	Probable	Continued	Continued		MI, cardiac death
DOUBLE	18	Probable	Continued	75mg		MI
	146	Probable	0	Continued		MI, cardiac death
TRIPLE	0	Definite	Continued	Continued	Continued	MI, TVR
	5	Probable	Continued	Continued	0	MI
	27	Probable	Continued	Continued	0	MI, TVR
	62	Definite	Continued	Continued	Continued	MI

Classification of stent thrombosis is according to the Academic Research Consortium criteria.
MI, myocardial infarction; TVR, target vessel revascularization.

Supplemental Figure 1. Study Diagram Showing Screening and Selection of Participants.



Appendix

CREATIVE Investigators

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