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Research Article

Optimal Switching Antiplatelet Regimen in Patients with Ticagrelor to a Thienopyridine in Korean Patients (SWAPT-K Study)

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Abstract

Background: Dual antiplatelet therapy (DAPT) with aspirin and potent $P2Y_{12}$ inhibitors such as ticagrelor effectively reduces ischemic events but increases bleeding risk. In patients requiring long-term DAPT, switching from ticagrelor to a thienopyridine is often considered to reduce bleeding risk or address other clinical concerns. However, such switching may cause a transient reduction in platelet inhibition, raising concerns about thrombotic complications. In particular, evidence is limited regarding the optimal loading dose strategy for East Asian patients undergoing this transition.
Methods: In this randomized, open-label trial, 43 patients with acute coronary syndrome (ACS) who had received ticagrelor-based DAPT for > 6 months after stent implantation were randomized to clopidogrel 600 mg loading/75 mg maintenance, clopidogrel 300 mg loading/75 mg maintenance, or prasugrel 30 mg loading/5 mg maintenance. Platelet reactivity and inflammatory markers (MMP-2, MMP-9, TNF-α) were assessed at baseline, 48 h, and 5 days after switching. The primary endpoint was the proportion of patients achieving optimal platelet reactivity (OPR).
Results: The proportion of patients achieving OPR was similar among groups at baseline ($p = 0.483$), 48 h ($p = 0.699$), and 5 days ($p = 0.729$). No significant intergroup differences were observed in inflammatory marker levels at any time point. No major adverse cardiovascular events occurred during follow-up.
Conclusions: In stable ACS patients on long-term DAPT, switching from ticagrelor to either clopidogrel or prasugrel maintained consistent platelet inhibition and inflammatory profiles, indicating that these switching strategies produce comparable pharmacodynamic profiles in East Asian populations during the early post-switch period.
Trial Registration: This investigator-initiated pharmacodynamic study was not prospectively registered.

Keywords

invasive strategy, acute coronary syndrome, switching antiplatelet, platelet reactivity, $P2Y_{12}$ inhibitor

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Data Availability Statement included at the end of the article

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Introduction

Dual antiplatelet therapy (DAPT) with aspirin and a $P2Y_{12}$ inhibitor is the cornerstone of secondary prevention in patients with acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI).[1] Potent $P2Y_{12}$ inhibitors such as ticagrelor and prasugrel provide superior ischemic protection compared with clopidogrel, but their use is limited by higher bleeding risk, particularly during long-term maintenance therapy.[2–4] In clinical practice, discontinuation of ticagrelor before the guideline-recommended duration frequently leads to switching to a thienopyridine, either clopidogrel or prasugrel, as part of a de-escalation strategy.[5,6]

Ticagrelor and thienopyridines differ fundamentally in their pharmacologic profiles. Ticagrelor is a reversible, direct-acting $P2Y_{12}$ inhibitor with rapid onset and offset, resulting in a substantial decline in platelet inhibition within 48 h of discontinuation. Thienopyridines, in contrast, are prodrugs that irreversibly bind to the $P2Y_{12}$ receptor after hepatic activation, requiring several days to achieve maximal platelet inhibition.[6,7] This pharmacokinetic gap may expose patients to a transient period of heightened platelet reactivity, increasing the risk of thrombotic complications, especially early after ACS.[6] Administration of a loading dose during the switch has been proposed to minimize the risk of thromboembolic events.

Randomized pharmacodynamic trials in Western populations, including SWAP-2 and SWAP-4, have demonstrated that adequate loading doses—prasugrel 60 mg or clopidogrel 600 mg—achieve prompt platelet inhibition and minimize the pharmacodynamic gap when switching from ticagrelor.[8,9] Based on these data, contemporary European guidelines and expert consensus recommend administering a thienopyridine loading dose regardless of the timing of the last ticagrelor dose.[1,6] However, these studies were conducted predominantly in Caucasian patients and in the acute or subacute phase after ACS.

In East Asian populations, balancing ischemic and bleeding risks is particularly challenging.[10,11] Ticagrelor use in this population is associated with a relatively greater bleeding hazard compared with Caucasians, often prompting earlier de-escalation.[12] Moreover, the high prevalence of CYP2C19 loss-of-function alleles complicates clopidogrel efficacy, and prasugrel use is frequently limited to reduced-dose regimens (20 mg loading, 3.75 mg maintenance) endorsed in Japanese guidelines.[13] Despite these unique clinical and pharmacogenetic considerations, data on the pharmacodynamic and anti-inflammatory effects of switching from ticagrelor to reduced-dose thienopyridines in East Asian patients are scarce.[14]

Against this background, we conducted the SWAPT-K trial to evaluate platelet reactivity and inflammatory biomarker changes following different switching strategies from ticagrelor to thienopyridines in Korean patients with ACS who had been on long-term ticagrelor-based DAPT. By assessing both pharmacodynamic and inflammatory responses, this study aimed to provide mechanistic and clinically relevant insights to inform switching protocols tailored to East Asian patients.

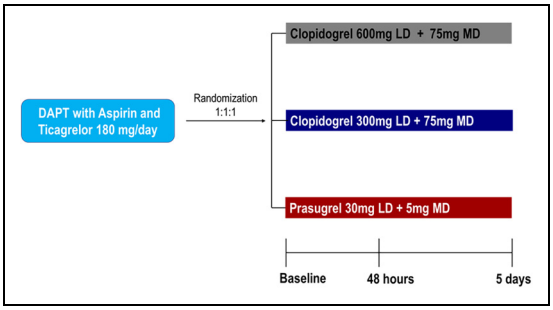

Figure 1. Study design schema.

Methods

Study Design and Population

The SWAPT-K (optimal SWitching Antiplatelet regimen in patients with Ticagrelor to a thienopyridine in Korean patients) trial is a prospective, open-label, two-center randomized controlled trial designed to evaluate the optimal strategy for transitioning from ticagrelor to a thienopyridine-based regimen in patients with ischemic heart disease (IHD) who have undergone drug-eluting stent (DES) implantation in a Korean population. Eligible participants were randomized (1:1:1) into one of three treatment groups: 1) Clopidogrel 600 mg loading dose followed by 75 mg maintenance (CLPD 600); 2) Clopidogrel 300 mg loading dose followed by 75 mg maintenance (CLPD 300); or 3) Prasugrel 30 mg loading dose followed by 5 mg maintenance (PRA). Following the initial loading dose, patients continued on their assigned maintenance antiplatelet regimen for a duration of 5 to 7 days (Figure 1). Throughout the study period, aspirin was maintained as part of the DAPT, and the use of additional antiplatelet agents or anticoagulants, including coumarin, was strictly prohibited. Standard treatment with other medications was administered as necessary for patient management in accordance with established guidelines for all enrolled patients.

Patients

Eligible patients were aged 20 to 75 years, weighed more than 60 kg, and had been receiving DAPT with aspirin and ticagrelor for at least 6 months following PCI with DES placement. Exclusion criteria included a history of stroke or transient ischemic attack, body weight less than 60 kg, age 75 years or older, a history of active bleeding or bleeding diatheses, use of oral anticoagulation therapy,

left ventricular ejection fraction below 30%, stroke within the previous 3 months or a life expectancy of less than 1 year. All participants provided written informed consent prior to enrollment.

The study protocol followed ethical guidelines, and approval was obtained from the institutional review boards (IRB number: 2018-05-006) of both participating centers prior to patient recruitment.

Assessment of Platelet Function and Inflammation Marker

Blood samples were collected at three specific time points: baseline, 48 h, and 5–7 days post-treatment, to simultaneously assess platelet reactivity and inflammatory cytokine levels (Fig 1). Platelet reactivity unit (PRU) was measured using the VerifyNow® system (Accumetrics, Inc., San Diego, CA, USA), which provides results as $P2Y_{12}$ reaction units. To ensure reliability, all samples were processed within 1 h of collection by trained operators who were blinded to the treatment assignments, minimizing potential bias in sample handling and analysis. Blood samples for the clinical trial were collected and processed at the Biomedical Research Laboratory of Jinju Gyeongsang National University Hospital.

For the analysis of inflammatory cytokines, blood samples were collected in heparinized vacutainers and centrifuged at 1200 rpm for 10 min. The plasma was immediately stored at −70 °C. Circulating cytokines, including tumor necrosis factor-α (TNF-α, BMS223-4, Invitrogen, Waltham, MA, USA), MMP-2 (MMP200, R&D Systems, Minneapolis, MN, USA), and MMP-9 (DMP200, R&D Systems, Minneapolis, MN, USA), were quantified using enzyme-linked immunosorbent assay (ELISA) kits, following the manufacturer's instructions. The color intensity generated in each assay was proportional to the concentration of the cytokines, and the results were calibrated using standard curves.

Clinical assessments included demographic data, medications, laboratory results, and the confirmation of major adverse cardiovascular events (MACE), as well as bleeding complications and adverse drug reactions. These assessments were documented throughout the trial period by the investigators.

Study Outcome

The primary endpoints in this study were the proportion of patients achieving optimal platelet reactivity (OPR, 85 < PRU < 208) in each group.[15] Secondary efficacy endpoints included platelet reactivity units and inflammatory cytokine levels at each time point post-randomization. The safety endpoints included the incidence of MACE, such as cardiovascular death, myocardial infarction, and stroke, the occurrence of bleeding complications classified by BARC score.

Statistical Analysis

A priori sample size estimation was performed during the study design phase. Based on previous studies,[16,17] the expected proportion of OPR at 48 h after clopidogrel 600 mg loading was assumed to be 60%. Assuming a 45% difference compared with the prasugrel group, a minimum of 17 patients per group was required to achieve 90% power with a two-sided α of 0.05. Considering a potential dropout rate of approximately 15%, the target sample size was set at 20 patients per group (total n = 60). Categorical variables were reported as frequencies and percentages and compared using the chi-square test or Fisher's exact test, as appropriate. Continuous variables were summarized as mean ± standard deviation and compared using Student's t-test or the Kruskal–Wallis test for variables that did not follow a normal distribution. For variables measured repeatedly over time, including PRU and inflammatory biomarkers, longitudinal analyses were performed using generalized estimating equations with group, time, and group-by-time interaction as fixed effects to account for within-subject correlations. An exchangeable working correlation structure was applied to model the within-subject repeated measurements. All statistical analyses were performed using Python 3.10 (Python Software Foundation; Delaware, USA) and R 4.2 (R Foundation; Vienna, Austria). A two-sided $p < 0.05$ was considered statistically significant.

Results

A total of 49 patients were enrolled, with 44 completing the study after five withdrew consent. The final analysis included 14 patients in the CLPD 600 group, 15 in the CLPD 300 group, and 14 in the PRA group. The mean ages of the groups were 58.9, 58.7, and 60.9 years, respectively, with no significant differences. The study population was predominantly male, with only two women in the PRA group. Baseline characteristics, including white blood cell count, platelet count, hemoglobin levels, lipid profiles, kidney function, liver function, medical history, and family history, showed no significant differences among the groups (Table 1).

Platelet Reactivity and Optimal Platelet Reactivity

PRU levels increased at 48 h and were maintained through day 5 in the overall study population (Figure 2A, Table 2). This trend was consistently observed across all three groups, without significant differences at baseline, 48 h, or day 5 (Figure 2B, Table 2). We assessed OPR defined as 85 < PRU < 208, among the three antiplatelet regimens at baseline, 48 h, and 5 days after the loading dose. Among the overall study population, 11.6% met OPR

Table 1. Baseline Characteristics.

Characteristic	Total	CLPD 600 (N=14)	CLPD 300 (N=15)	PRA (N=14)	p-Value
Age	59.5 ± 10.9	58.9 ± 13.9	58.7 ± 9.5	60.9 ± 9.3	0.839
Sex					
Female	2 (4.7%)	0 (0.0%)	0 (0.0%)	2 (14.3%)	0.114
Male	41 (95.3%)	14 (100.0%)	15 (100.0%)	12 (85.7%)	
Body Weight	73.5 ± 11.4	73.9 ± 13.2	73.3 ± 11.7	73.5 ± 9.9	0.991
Height	169.7 ± 7.6	169.2 ± 7.8	171.2 ± 6.4	168.4 ± 8.6	0.606
BMI	25.5 ± 4.4	26.1 ± 2.7	25.7 ± 2.5	24.7 ± 6.9	0.676
WBC	7.9 ± 2.4	7.6 ± 1.9	7.7 ± 2.2	8.3 ± 3.0	0.744
Hemoglobin	14.2 ± 1.4	13.8 ± 1.2	14.2 ± 1.6	14.5 ± 1.3	0.396
Platelets	243.7 ± 64.7	270.8 ± 67.1	234.1 ± 69.9	226.9 ± 50.7	0.156
Hematocrit	42.0 ± 3.8	41.2 ± 3.3	41.8 ± 4.2	43.1 ± 3.8	0.392
Total cholesterol	115.2 ± 30.4	109.1 ± 22.3	109.8 ± 31.9	129.1 ± 34.4	0.173
Triglyceride	144.5 ± 71.6	154.6 ± 72.7	164.7 ± 83.7	107.3 ± 36.0	0.093
LDL	59.2 ± 29.3	49.5 ± 19.5	65.7 ± 40.2	62.3 ± 20.9	0.307
HDL	44.4 ± 18.7	43.4 ± 11.9	38.2 ± 8.1	53.5 ± 29.6	0.101
AST	27.2 ± 8.8	26.4 ± 8.6	30.7 ± 10.5	24.1 ± 5.4	0.143
ALT	29.6 ± 13.4	27.4 ± 10.5	35.5 ± 18.5	25.2 ± 5.9	0.110
Creatinine	1.1 ± 1.1	1.0 ± 0.2	1.5 ± 1.8	0.9 ± 0.2	0.226
GFR	81.0 ± 23.7	84.0 ± 19.6	73.0 ± 30.4	86.9 ± 17.6	0.283
HbA1C	5.9 ± 0.8	5.8 ± 0.5	6.0 ± 1.1	5.8 ± 0.7	0.850
High sensitivity CRP	5.2 ± 18.1	1.0 ± 1.2	6.7 ± 20.1	8.2 ± 25.3	0.567
Smoking					0.792
Current-smoker	24 (55.8%)	7 (50.0%)	9 (60.0%)	8 (57.1%)	
Ex-smoker	17 (39.5%)	7 (50.0%)	5 (33.3%)	5 (35.7%)	
Hypertension	19 (44.2%)	8 (57.1%)	4 (26.7%)	7 (50.0%)	0.222
Diabetes	7 (16.3%)	2 (14.3%)	3 (20.0%)	2 (14.3%)	0.890
Dyslipidemia	13 (30.2%)	5 (35.7%)	3 (20.0%)	5 (35.7%)	0.565
CKD	1 (2.3%)	0 (0.0%)	1 (6.7%)	0 (0.0%)	0.385
Family history of CAD	2 (4.7%)	1 (7.1%)	0 (0.0%)	1 (7.1%)	0.570
Previous MI	3 (7.0%)	1 (7.1%)	0 (0.0%)	2 (14.3%)	0.320

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); WBC, white blood cell; LDL, low-density lipoprotein; HDL, high-density lipoprotein; AST, aspartate transaminase; ALT, alanine transaminase; GFR, glomerular filtration rate (calculated using modification of diet in renal disease study equation); CRP, C-reactive protein; CKD, chronic kidney disease; CAD, coronary artery disease; MI, myocardial infarction; PCI, percutaneous coronary intervention.

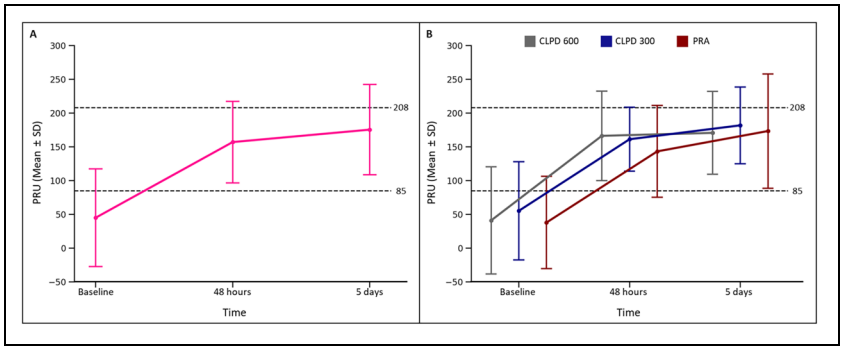

Figure 2. PRU over time. (A) PRU for overall patients, (B) PRU among CLPD 600, CLPD 300, and PRA groups over time. At 48 h, PRU levels increased in all groups compared to baseline. However, there were no significant differences in PRU between the three groups at baseline, 48 h, and on day 5.
PRU, platelet reactivity unit; CLPD, clopidogrel; PRA, Prasugrel.

criteria prior to switching, which increased to 72.1% at 48 h and was maintained at 55.8% at 5 days post-switching (Figure 3A). Prior to switching, 7.1% of patients in the CLPD 600 group, 20.0% in the CLPD 300 group, and 7.1% in the PRA group met OPR criteria, with no significant differences between groups (p = 0.483). After 48 h,

Table 2. PRU Values among CLPD 600, CLPD 300, and PRA Groups.

	Total (N=43)	CLPD 600 (N=14)	CLPD 300 (N=15)	PRA (N=14)	p-Value
Baseline	44.95±72.29	41.00±79.40	55.20±72.81	37.93±68.41	0.406
48 h	157.07±60.32	166.36±66.37	161.27±47.38	143.29±67.93	0.827
5 days	175.49±66.97	170.71±61.42	181.87±56.78	173.43±84.68	0.954

Values are mean ± SD.
PRU, platelet reactivity unit; CLPD, clopidogrel; PRA, Prasugrel.

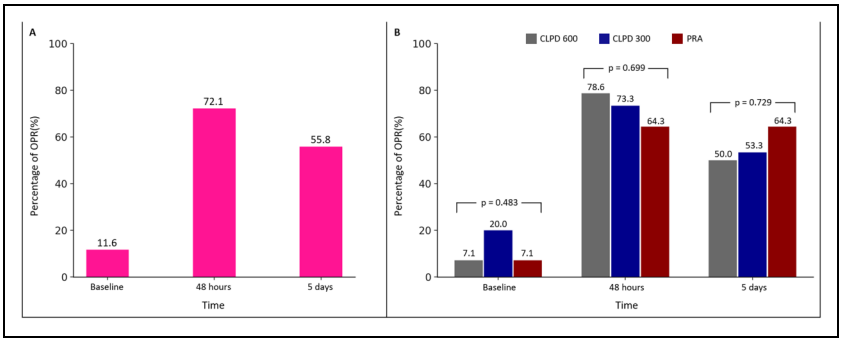

Figure 3. Proportion of patients achieving optimal platelet reactivity. (A) OPR rate for overall patients, (B) OPR rate among CLPD 600, CLPD 300, and PRA groups over time.
Bar graph showing the proportion of patients achieving OPR (85 < PRU < 208) at baseline, 48 h, and 5 days post-loading dose. At 48 h, the majority of patients in all three groups achieved OPR, with no significant differences. By day 5, OPR rates decreased compared with 48 h but remained comparable across the three groups.
OPR, optimal platelet reactivity; CLPD, clopidogrel; PRA, Prasugrel.

the proportions increased to 78.6% for CLPD 600, 73.3% for CLPD 300, and 64.3% for PRA, again with no significant differences observed (p = 0.699). At 5 days, 50.0% of the CLPD 600 group, 53.3% of the CLPD 300 group, and 64.3% of the PRA group met OPR criteria, with no significant group differences (p = 0.729) (Figure 3B).

Inflammatory Cytokine Levels Across Groups

The levels of inflammatory cytokines, including MMP-2, MMP-9, and TNF-α, were measured at baseline, 48 h, and 5 days across the different treatment groups of CLPD 600, CLPD 300, and PRA.

In the overall population, MMP-2 levels were 233.68 ± 73.42 ng/ml at baseline, 241.40 ± 83.20 ng/ml at 48 h, and 246.19 ± 79.90 ng/ml at 5 days, showing no substantial change over time (Figure 4A, Table 3). At baseline, MMP-2 levels were similar across all groups: CLPD 600 (239.13 ± 57.80 ng/ml), CLPD 300 (248.87 ± 102.22 ng/ml), and PRA (212.33 ± 43.36 ng/ml). MMP-2 levels remained relatively stable across all time points without notable fluctuations in any group. No statistically significant differences were observed in MMP-2 levels between groups at any time point (Baseline: p = 0.431, 48 h: p = 0.724, 5 days: p = 0.592) (Figure 4B, Table 3). In the overall population, MMP-9 levels were 343.62 ± 260.57 ng/ml at baseline, 503.56 ± 439.66 ng/ml at 48 h, and 542.92 ± 334.47 ng/ml at 5 days, showing no meaningful changes over time (Supplementary Figure S1A, Supplementary Table S1). Similarly, baseline MMP-9 levels were consistent across groups: CLPD 600 (298.47 ± 138.82 ng/ml), CLPD 300 (377.90 ± 379.54 ng/ml), and PRA (348.81 ± 194.39 ng/ml). No statistically significant differences were observed in MMP-9 levels between groups over time (Baseline: p = 0.595, 48 h: p = 0.094, 5 days: p = 0.565) (Supplementary Figure S1B, Supplementary Table S1). In the overall population, TNF-α levels were 33.23 ± 2.03 pg/ml at baseline, 35.32 ± 7.13 pg/ml at 48 h, and 40.89 ± 27.73 pg/ml at 5 days, also showing no substantial changes (Supplementary Figure S2A, Supplementary Table S2). TNF-α levels followed a similar trend across groups, with no significant variation between groups at baseline, 48 h, and 5 days. The TNF-α values were as follows: CLPD 600 group (32.92 ± 2.88, 34.06 ± 3.48, 48.52 ± 45.40 pg/ml); CLPD 300 group (33.28 ± 1.87, 33.83 ± 3.33, 33.64 ± 3.43 pg/ml); PRA group (33.48 ± 1.17, 38.08 ± 11.17, 41.58 ± 19.76 pg/ml), and no statistically significant differences were observed (baseline: p = 0.775, 48 h: p = 0.364, 5 days: p = 0.147) (Supplementary Figure S2B, Supplementary

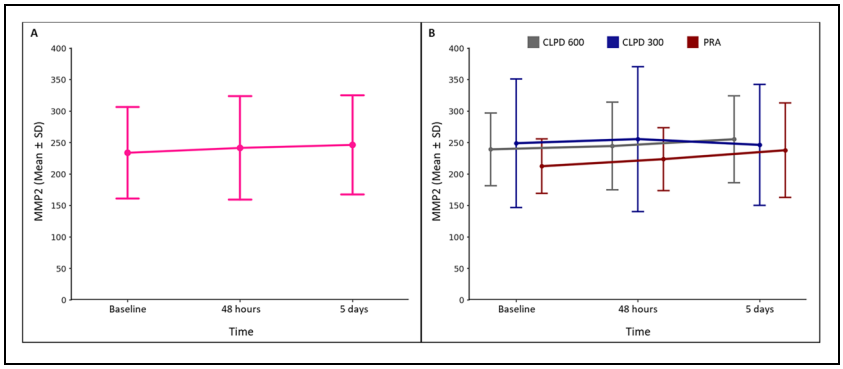

Figure 4. Point plot of MMP-2 levels. (A) MMP-2 levels for all patients, (B) MMP-2 levels across CLPD 600, CLPD 300, and PRA groups.
Point plot showing MMP-2 levels with mean and standard deviation. No significant differences were observed among groups at any time points.
CLPD, clopidogrel; PRA, Prasugrel.

Table 3. MMP-2 Levels among CLPD 600, CLPD 300, and PRA Groups Over Time.

	Total (N=43)	CLPD 600 (N=13)	CLPD 300 (N=15)	PRA (N=14)	p-Value
Baseline	233.68±73.42	239.13±57.80	248.87±102.22	212.33±43.36	0.431
48 h	241.40±83.20	244.39±69.68	255.48±115.15	223.55±49.92	0.724
5 days	246.19±79.90	255.23±68.98	246.26±96.05	237.73±75.17	0.592

Values are mean ± SD. MMP-2 concentrations are expressed in ng/mL.
CLPD, clopidogrel; PRA, Prasugrel.

Table S2). These findings suggest that the switching regimens had no significant impact on inflammatory cytokine levels at any of the time points measured.

Safety Assessment

No serious adverse events were reported across the groups during the treatment switching period. While one patient in the PRA group experienced a gastrointestinal bleeding event, there were no significant differences in bleeding incidents between the treatment groups. Additionally, no major cardiovascular events occurred among the participants throughout the trial.

Discussion

In this randomized trial, we compared three de-escalation strategies from ticagrelor to thienopyridines—clopidogrel 600 mg loading, clopidogrel 300 mg loading, and prasugrel 30 mg loading—in Korean ACS patients who had been maintained on ticagrelor-based DAPT for more than 6 months after PCI. Across all groups, OPR was achieved and maintained without significant differences in PRU levels or inflammatory biomarkers, and no major ischemic or bleeding events occurred in the early switching period. To our knowledge, this is the first randomized study in an East Asian population to directly compare multiple switching regimens with simultaneous assessment of platelet function and inflammatory responses, addressing a gap in evidence for a population with distinct bleeding and pharmacogenetic profiles.

Ticagrelor and thienopyridines differ fundamentally in pharmacology. Ticagrelor's reversible binding and short half-life lead to a substantial loss of platelet inhibition within 48 h after discontinuation. Thienopyridines, such as clopidogrel and prasugrel, irreversibly bind to the $P2Y_{12}$ receptor after hepatic activation, requiring several days to achieve maximal inhibition.[6,7] This pharmacokinetic mismatch creates a transient period of increased platelet reactivity-especially within the first 48 h-during which thrombotic risk, including stent thrombosis, is heightened.[6] While prolonged ticagrelor use reduces ischemic events, it carries a sustained bleeding hazard,[3,4] a risk magnified in East Asian patients[10]; hence the clinical need for de-escalation strategies that preserve platelet inhibition while mitigating bleeding.

Evidence from Western pharmacodynamic trials largely informs guideline recommendations. SWAP-4 showed that a 600 mg clopidogrel loading dose given immediately after ticagrelor discontinuation minimized the rebound in platelet reactivity seen with maintenance dosing alone.[9] SWAP-2

demonstrated that a 60 mg prasugrel loading dose achieved rapid and sustained inhibition, albeit with low on-treatment platelet reactivity in a subset of patients.[8] These trials-conducted primarily in Caucasian cohorts in the acute or subacute post-ACS phase-support the use of full loading doses when switching from ticagrelor to a thienopyridine.

East Asian data add crucial context. In Korean AMI patients, TALOS-AMI showed that unguided de-escalation from ticagrelor to clopidogrel 1 month after PCI reduced bleeding without increasing ischemic events.[18] Yet the high prevalence of CYP2C19 loss-of-function alleles in East Asians complicates clopidogrel responsiveness and invites interest in prasugrel.[11,19] In addition to loss-of-function alleles, multiple genetic and clinical factors may influence the pharmacodynamic response to thienopyridines. For example, the CYP2C19*17 gain-of-function variant has been associated with enhanced conversion of clopidogrel and prasugrel to their active metabolites and may increase bleeding risk.[20] Moreover, treatment response to clopidogrel can be affected by drug–drug interactions, particularly with proton pump inhibitors such as omeprazole, which may reduce clopidogrel responsiveness in patients with ACS.[21,22] These observations highlight that multiple pharmacogenetic and clinical variables can interact to influence antiplatelet efficacy. Accordingly, recent pharmacogenetic studies emphasize the importance of integrating genetic, clinical, and pharmacological information to optimize antithrombotic therapy and personalize treatment strategies.[23] In Japan, PRASFIT-ACS found that reduced-dose prasugrel (20 mg loading, 3.75 mg maintenance) offered similar ischemic protection with lower bleeding risk compared with clopidogrel.[24] Together, these observations argue for region-specific switching strategies attentive to pharmacogenetics and bleeding propensity.

Beyond regional considerations, de-escalation strategies have gained increasing attention in patients at high bleeding risk (HBR). A recent meta-analysis evaluating $P2Y_{12}$ inhibitor monotherapy after short-duration DAPT in ACS demonstrated that reducing antiplatelet intensity may maintain ischemic protection while significantly lowering bleeding complications.[25] In addition, contemporary reviews of antiplatelet therapy have highlighted that carefully selected monotherapy or de-intensification strategies can help achieve a more favorable balance between ischemic and bleeding risks in patients with atherosclerotic cardiovascular disease.[26] Furthermore, risk stratification tools such as the PRECISE-HBR score have been developed to identify patients at increased bleeding risk after PCI, supporting individualized antiplatelet strategies, including potential de-escalation approaches in appropriately selected patients.[27]

Given these pharmacodynamic and population-specific considerations, our data suggest that in stable East Asian patients over 6 months post-PCI, reduced loading doses – clopidogrel 300 mg or prasugrel 30 mg – can maintain OPR and PRU at levels comparable to those reported with full-dose loading in SWAP-2 and SWAP-4, without early safety signals. The preservation of OPR despite reduced loading implies that in long-term ticagrelor users, the pharmacodynamic gap may be less pronounced than in acute or subacute settings, allowing simpler and potentially safer protocols.

Because $P2Y_{12}$ inhibitors may also modulate inflammatory pathways, we profiled MMP-2, MMP-9, and TNF-α. Levels remained stable across groups and time points, indicating no systemic inflammatory activation during the early switch. Prior studies have yielded mixed results regarding anti-inflammatory effects—ticagrelor's adenosine-mediated mechanisms have been proposed,[28,29] while several trials reported no meaningful between-drug differences.[30–32] Our findings align with the latter and reinforce the biological safety of de-escalation, as switching did not generate a pro-inflammatory milieu that could predispose to thrombotic events.[33,34]

Clinically, these results support reduced-dose switching from ticagrelor to either clopidogrel or prasugrel in stable East Asian ACS patients on long-term DAPT. Such approaches may preserve ischemic protection while lowering bleeding risk and could inform region-specific practice patterns. Future multicenter studies with longer follow-up should confirm these findings and test whether platelet function– or genotype-guided switching further improves outcomes.

Limitations

Our study has several limitations. First, although the study was designed with a planned sample size based on pharmacodynamic assumptions, the final number of enrolled patients was smaller than originally planned, which limits the statistical power to detect potentially meaningful differences between treatment groups. Second, the follow-up period was limited to 5–7 days and the study relied primarily on pharmacodynamic and biomarker measurements rather than hard clinical endpoints, restricting the evaluation to early pharmacodynamic responses and limiting the ability to assess longer-term ischemic or bleeding outcomes. Third, the study population consisted of relatively stable ACS patients who were more than 6 months post-PCI, and the trial was conducted at only two centers in South Korea. Therefore, the findings may not be fully generalizable to patients in the acute phase after ACS, to different clinical settings, or to populations with different ethnic or genetic backgrounds. Finally, the trial was not registered in a public clinical trial registry because prospective trial registration was not routinely required in Korea at the time the study was initiated.

Conclusion

In summary, among Korean patients with ACS receiving long-term ticagrelor therapy, reduced-dose loading regimens of clopidogrel or prasugrel preserved platelet inhibition

and maintained stable inflammatory profiles over the early post-switch period without emergent safety concerns. These findings provide population-specific pharmacodynamic evidence supporting potential DAPT de-escalation strategies in East Asian clinical practice, although larger studies with longer follow-up and clinical endpoints are required to confirm safety and efficacy.

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Ethical Considerations

This study was approved by the Institutional Review Board of Gyeongsang National University Hospital and Gyeongsang National University Changwon Hospital (IRB No. 2018-05-006). All procedures were conducted in accordance with the Declaration of Helsinki.

Consent to Participate

Written informed consent was obtained from all individual participants included in the study.

Author Contributions

Koh JS and Park YH conceived and designed the study.
Koh JS, Park YH, Hwang JY, Hwang SJ, Park JR, Kang MG, Kim K, Kim HR, Noh HW and Kim M contributed to data acquisition and patient enrollment.
Koh JS, Park YH, Hwang JY, Hwang SJ, Park JR, Kang MG, Kim K, Kim H, Kim YL, Noh HW and Seo CO assisted with data curation and interpretation.
Noh HW, Kim YL and Seo SH conducted statistical analysis and visualization.
Noh HW, Koh JS and Park YH drafted the manuscript.
Park YH and Koh JS critically revised the manuscript and supervised the project.
All authors reviewed and approved the final version of the manuscript.

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Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Data Availability Statement

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request, in accordance with the SAGE Research Data Sharing Policy.[35]

Supplemental Material

Supplemental material for this article is available online.

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