$P2Y_{12}$ inhibitor monotherapy combined with colchicine following PCI in ACS patients: the MACT pilot study

Seung-Yul Lee, MD[1,2], Young-Hoon Jeong, MD[3], Kyeong Ho Yun, MD[4], Jae Young Cho, MD[4], Diana A Gorog, MD[5], Dominick J. Angiolillo, MD, PhD[6], Jin Won Kim, MD[2], Yangsoo Jang, MD[1]

[1]CHA Bundang Medical Center, CHA University, Seongnam, Korea;
[2]Multimodal Imaging and Theranostic Laboratory, Cardiovascular Center, Korea University Guro Hospital, Seoul, Korea;
[3]CAU Thrombosis and Biomarker Center, Heart and Brain Hospital, Chung-Ang University Gwangmyeong Hospital, Gwangmyeong and Department of Internal Medicine, Chung-Ang University College of Medicine, Seoul, Korea;
[4]Regional Cardiocerebrovascular Center, Wonkwang University Hospital, Iksan, Korea;
[5]Faculty of Medicine, National Heart and Lung Institute, Imperial College, London, United Kingdom and Centre for Health Services Research, School of Life and Medical Sciences, University of Hertfordshire, Hatfield, Hertfordshire, United Kingdom;
[6]Division of Cardiology, University of Florida College of Medicine, Jacksonville, FL, USA.

Funding: This study was supported by the Cardiovascular Research Center, Seoul, Korea.

Conflicts of interest: Jeong YH has received honoraria for lectures from AstraZeneca, Daiichi Sankyo, Sanofi-Aventis, and Han-mi Pharmaceuticals; and research grants or support from Yuhan Pharmaceuticals, Han-mi Pharmaceuticals, Sam-jin Pharmaceuticals, Biotronik, and U&I Corporation. Gorog DA reports institutional research grants from AstraZeenca, Werfen, Medtronic, Bayer and Alpha MD, and speaker frees from AstraZeneca. Angiolillo DJ declares that he has received consulting fees or honoraria from Abbott, Amgen, AstraZeneca, Bayer, Biosensors, Boehringer Ingelheim, BristolMyers Squibb, Chiesi, Daiichi Sankyo, Eli Lilly, Haemonetics, Janssen, Merck, Novartis, PhaseBio, PLx Pharma, Pfizer, Sanofi, and Vectura; he also declares that his institution has received research grants from Amgen, AstraZeneca, Bayer, Biosensors, CeloNova, CSL Behring, Daiichi Sankyo, Eisai, Eli Lilly, Gilead, Idorsia, Janssen, Matsutani Chemical Industry Co., Merck, Novartis, and the Scott R. MacKenzie Foundation. The other authors report no conflicts of interest.

Running title: Mono Antiplatelet and Colchicine Therapy in ACS

Word count: 4,476

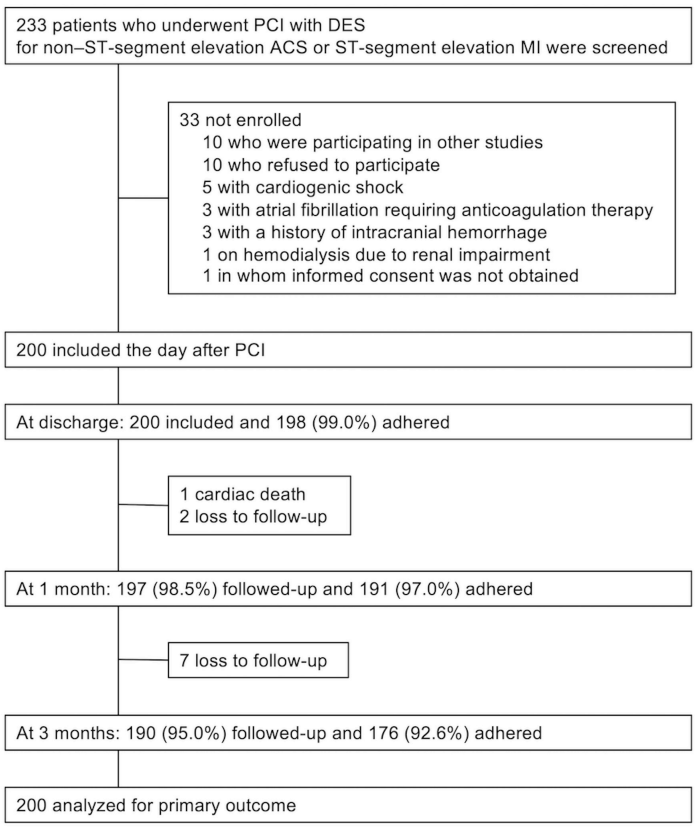
Address for correspondence: Seung-Yul Lee, MD.
Associate Professor, Department of Internal Medicine, CHA Bundang Medical Center, 59, Yatap-ro, Bundang-gu, Seongnam-si, Gyeonggi-do, Republic of Korea (13496). e-mail: seungyul79@gmail.com

Structured Abstract
Objectives: To investigate the feasibility of ticagrelor or prasugrel $P2Y_{12}$ inhibitor monotherapy combined with colchicine immediately after percutaneous coronary intervention (PCI) in patients with acute coronary syndrome (ACS).
Background: After a brief period of dual antiplatelet therapy, $P2Y_{12}$ inhibitor monotherapy, in the absence of aspirin, effectively reduces bleeding without increasing recurrent ischemia in patients undergoing PCI. In addition, early anti-inflammatory therapies may have clinical benefits in ACS patients.
Methods: This was a proof-of-concept pilot trial. ACS patients treated with drug-eluting stents were included. On the day after PCI, low-dose colchicine (0.6 mg daily) was administered in addition to ticagrelor or prasugrel maintenance therapy, while aspirin therapy was discontinued. The primary outcome was any stent thrombosis at three months. Key secondary outcomes were platelet reactivity measured by VerifyNow assay before discharge and reduction in high-sensitivity C-reactive protein (hs-CRP) over 1 month.
Results: We enrolled 200 patients, of whom 190 (95.0%) completed the three months' follow-up. The primary outcome occurred in two patients (1.0%): one definite and one probable stent thrombosis. The level of platelet reactivity overall was 27±42 $P2Y_{12}$ reaction unit (PRU) and only one patient had high platelet reactivity (>208 PRU). The hs-CRP levels decreased from 6.1 (2.6-15.9) mg/L at 24 hours after PCI to 0.6 (0.4-1.2) mg/L at 1 month ($p<0.001$), and the prevalence of high-inflammation criteria (hs-CRP ≥2 mg/L) decreased from 81.8% to 11.8% ($p<0.001$).
Conclusions: In ACS patients undergoing PCI, it is feasible to discontinue aspirin therapy and administer low-dose colchicine on the day after PCI in addition to ticagrelor or prasugrel P2Y12 inhibitors. This approach is associated with favorable platelet function and inflammatory profiles.

Clinical Trial Registration: ClinicalTrials.gov identifier: NCT04949516.

Key words: Acute coronary syndrome; Aspirin; Ticagrelor; Prasugrel; Colchicine.

Condensed Abstract
This proof-of-concept pilot trial investigated the feasibility of ticagrelor or prasugrel $P2Y_{12}$ inhibitor monotherapy combined with colchicine immediately after PCI in ACS patients. The day after PCI, aspirin was replaced with low-dose colchicine (0.6 mg daily) on ticagrelor or prasugrel maintenance. Among 200 ACS patients enrolled, stent thrombosis occurred in two patients for 3 months. High platelet reactivity assessed by VerifyNow assay was low at discharge and hs-CRP levels decreased significantly within 1 month after PCI. Accordingly, $P2Y_{12}$ inhibitor mono antiplatelet and colchicine therapy is feasible in ACS patients undergoing PCI and associated with favorable platelet function and inflammatory profiles.


233 patients who underwent PCI with DES
for non–ST-segment elevation ACS or ST-segment elevation MI were screened
33 not enrolled
10 who were participating in other studies
10 who refused to participate
5 with cardiogenic shock
3 with atrial fibrillation requiring anticoagulation therapy
3 with a history of intracranial hemorrhage
1 on hemodialysis due to renal impairment
1 in whom informed consent was not obtained
200 included the day after PCI
At discharge: 200 included and 198 (99.0%) adhered
1 cardiac death
2 loss to follow-up
At 1 month: 197 (98.5%) followed-up and 191 (97.0%) adhered
7 loss to follow-up
At 3 months: 190 (95.0%) followed-up and 176 (92.6%) adhered
200 analyzed for primary outcome

Abbreviations List
ACS, acute coronary syndrome
BARC, Bleeding Academic Research Consortium
DAPT, dual antiplatelet therapy
DES, drug-eluting stent(s)
HPR, high platelet reactivity
hs-CRP, high-sensitivity C-reactive protein
LPR, low platelet reactivity
MI, myocardial infarction
PCI, percutaneous coronary intervention
PRU, P2Y12 reaction unit

Introduction

Dual antiplatelet therapy (DAPT) with aspirin and a $P2Y_{12}$ inhibitor has represented the standard of care for the prevention of thrombotic events in high-risk patients with coronary artery disease, such as patients with an acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI) (1,2). However, this strategy comes at the expense of an increased bleeding particularly when used long term, underscoring the need to identify strategies associated with a more favorable safety profile without compromising efficacy (3). Studies have shown that discontinuation of aspirin therapy after a brief period of DAPT (e.g., 1-3 months) and maintaining P2Y12 inhibitor monotherapy reduces the risk of major bleeding without increasing the rate of ischemic events (4–9). However, more recent studied have shown that the risk of ischemic events may depend on the potency of the $P2Y_{12}$ inhibitor (ticagrelor or prasugrel versus clopidogrel), clinical presentation (ACS versus stable ischemic heart disease), and the complexity of coronary artery disease or PCI (9,10).

In addition to antiplatelet therapy, anti-inflammatory agents may reduce recurrent ischemia in high-risk patients (11–14). Among them, colchicine has been effective in a randomized clinical trial of patients with ACS (12). The benefits of colchicine may be more beneficial with early (i.e., in-hospital) initiation (15). These considerations support the rationale for testing a strategy that substitutes aspirin with colchicine during the acute phase to maximize the treatment effect of reducing recurrent ischemia and bleeding.

This study aimed to evaluate the feasibility of ticagrelor or prasugrel $P2Y_{12}$ inhibitor monotherapy, in the absence of aspirin, combined with colchicine in patients with ACS immediately after PCI.

Methods

Study design

The Mono Antiplatelet and Colchicine Therapy (MACT) study was an investigator-initiated, single-center, single-arm, open-label, proof-of-concept pilot trial (NCT04949516). The present study had a similar design to the Acetyl Salicylic Elimination Trial (ASET) study, which investigated the feasibility and safety of aspirin-free prasugrel maintenance immediately after PCI in patients with stable ischemic heart disease: a sample of 200 patients and a safety termination rule (16). There is no formal sample size rationale for the study due to the exploratory nature, however If more than three cases of definite stent thrombosis occurred during three months' follow-up, patient recruitment was planned to be terminated (16). The study protocol was approved by the institutional review board including ethics committee of Wonkwang University Hospital.

Study population

Patients with non-ST-segment elevation ACS or ST-segment elevation myocardial infarction (MI) who underwent PCI with drug-eluting stents (DES) were eligible (**Supplemental Methods**). Patients with the following conditions were excluded from the study: 1) cardiac arrest or cardiogenic shock; 2) age <19 or >90 years; 3) severe liver (Child-Pugh class C) or renal impairment (creatinine clearance less than 30 mL/min by Cockcroft-Gault formula); 4) atrial fibrillation requiring anticoagulation therapy; 5) intolerance to prasugrel, ticagrelor, or colchicine; 6) history of intracranial hemorrhage; 7), or active bleeding. Written informed consent was obtained from all enrolled patients.

Study procedures

PCI with DES implantation was performed according to standard of care. All patients received a loading dose of aspirin (300 mg) and ticagrelor (180 mg) or prasugrel (60 mg).

The choice of ticagrelor or prasugrel was at the discretion of the treating physicians. The day after PCI, aspirin was discontinued, and colchicine (0.6 mg once daily) was administered with ticagrelor (90 mg twice daily) or prasugrel (10 mg once daily). In patients who received DES implantation with a loading dose of aspirin and clopidogrel, both were discontinued the day after PCI, with colchicine and a loading dose of ticagrelor or prasugrel started, followed by maintenance doses. Staged PCI was performed under the maintenance of colchicine and ticagrelor or prasugrel. The concomitant use of other antiplatelet agents or anticoagulants was not permitted. However, re-administration of aspirin was allowed for patient safety, based on the results of platelet function testing (e.g., cases of high platelet reactivity [HPR]) before discharge.

All patients underwent platelet function testing using the VerifyNow $P2Y_{12}$ assay (Accriva, San Diego, CA, USA) before discharge, and levels of high-sensitivity C-reactive protein (hs-CRP) were measured at admission, 24 and 48 hours after PCI, and at the 1-month follow-up.

Clinical follow-up was performed at one and three months. Patient symptoms, treatment adherence, and clinical events were assessed using medical records. If an in-person visit was not possible, telephone interviews were performed. The institutional review board monitored the study to identify potential adverse events that were not reported.

Study outcomes

The primary outcome was stent thrombosis within three months of follow-up. Stent thrombosis was classified into definite, probable, or possible according to the Academic Research Consortium definition (17). The secondary outcomes were all-cause mortality, all MI, all revascularization, major bleeding (18), a composite of cardiac death, target vessel-MI, or target lesion revascularization, $P2Y_{12}$ reaction unit (PRU) using VerifyNow $P2Y_{12}$ assay

(Accriva, San Diego, CA, USA), and the change in hs-CRP levels between 24 hours after PCI and 1-month follow-up. HPR (>208 PRU) and low-platelet reactivity (LPR: <85 PRU) were defined based on a prior consensus document (19), and elevated hs-CRP level (≥2 mg/L) related to the risk of adverse cardiac events were defined based on prior studies (11,20). All clinical outcomes were independently adjudicated by the clinical event committee. The definition of clinical outcomes and the members of the clinical event committee are provided in **Supplemental Methods**.

In a post hoc analyses, the risk of bleeding and ischemia in the study population was assessed based on the Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy (PRECISE-DAPT) score and the presence of complex PCI. The PRECISE-DAPT score of each patient was calculated using an online calculator (http://www.precisedaptscore.com). A PRECISE-DAPT score ≥ 25 was defined as high bleeding risk (21). Complex PCI was defined as having at least one of the following features: three-vessel treatment, ≥ 3 stents implanted, ≥ 3 lesions treated, bifurcation with two stents implanted, total stent length >60 mm, and chronic total occlusion (10).

Statistical analysis

All analyses were performed based on the intention-to-treat principle. Continuous variables are reported as mean ± SD or median (interquartile range [IQR]) and were compared using t-test or Wilcoxon signed-rank test. Categorical variables were reported as numbers (percentages) and compared using McNemar's test. Kaplan-Meier estimates were used to determine the cumulative incidence of clinical events at three months. If a case was censored, the last available data were used for survival analysis. Statistical analyses were performed

using SAS (version 9.2; SAS Institute, Cary, NC, USA). All tests were two-sided, and statistical significance was set at $p<0.05$.

Results

Patient screening and enrollment

From June 2021 to September 2022, 233 patients with non–ST-segment elevation ACS or ST-segment elevation MI who underwent PCI with DES were screened (**Figure 1**). Thirty-three patients were excluded for the following reasons: participation in another study (n=10), patient refusal (n=10), cardiogenic shock (n=5), use of anticoagulation therapy (n=3), prior intracranial hemorrhage (n=3), hemodialysis (n=1), and informed consent was not obtained (n=1). Overall, 200 patients were included after the index PCI.

Baseline characteristics

Clinical and angiographic characteristics of the patients are shown in **Table 1**. The mean PRECISE-DAPT score was 14 ± 8, and 11.5% of patients had a score ≥25. Approximately 30% of the patients had multi-vessel disease, and the culprit lesion was detected in the left anterior descending artery in 54.5% of the patients. Procedural characteristics are shown in **Table 2**. PCI through radial access was performed in 60.9% of the patients, and sirolimus-eluting stents were used in 51.6% of the patients. After PCI, 95.3% of the treated lesions had Thrombolysis in Myocardial Infarction grade 3 flow. Complex PCI was performed in 15.5% of enrolled patients, and nine patients (4.5%) underwent staged PCI. In addition, baseline characteristics of patients with ST-segment elevation MI were reported in **Supplemental Results**.

Adherence to study medications and serious adverse events

Adherence to study medications is shown in **Table 3**. At discharge, 198 (99.0%) of the 200 patients followed the study procedure. At one month, 197 (98.5%) patients attended clinical follow-up and 191 (97.0%) followed the study procedure. At three months, 190 (95.0%) patients completed clinical follow-up, and 176 (92.6%) followed the study procedure. Details regarding the adherence to study medications were described in **Supplemental Results**. Other than the study outcomes, no other procedure-related serious adverse events were reported.

Clinical outcomes

Clinical outcomes during the three months' follow-up are shown in **Table 4**. The primary outcome occurred in two patients (incidence 1.0%). The first case occurred five days after the index procedure in which a 2.75 × 38 mm amphilimus-eluting stent (Cre8; CID SpA, member of Alvimedica, Saluggia, Italy) was implanted in left anterior descending artery due to ST-segment elevation MI (**Supplemental Figure 1**). The patient received both aspirin and ticagrelor due to HPR at discharge (242 PRU). This definite subacute stent thrombosis was successfully treated with balloon angioplasty (**Supplemental Figure 2**). After repeated PCIs, we were able to confirm that the patient was not compliant to antiplatelet medications. Platelet reactivity level decreased to 88 PRU after supervised ticagrelor intake. The second case occurred eight days after the index procedure in which a 2.75 × 30 mm sirolimus-eluting stent (Orsiro; Biotronik AG, Buelach, Switzerland) was implanted in left anterior descending artery due to ST-segment elevation MI (**Supplemental Figure 3**). The patient received ticagrelor and had LPR at discharge (1 PRU). This probable subacute stent thrombosis was diagnosed based on the clinical criteria of unexplained death. Neither patient underwent complex PCI.

Although bleeding occurred in 36 patients, major bleeding (BARC type 3 or 5) occurred in only one patient (incidence 0.5%) with a PRECISE-DAPT score of 10. Gastrointestinal bleeding developed the day after PCI and was successfully treated with endoscopic hemostasis and transfusion. The patient was discharged with ticagrelor monotherapy (26 PRU at discharge). No further clinical events occurred after discharge.

Laboratory measurements

The level of platelet reactivity at discharge was 27 ± 42 PRU (from the 191 analyzed patients). Most patients (n=174; 91.1%) met the criteria for LPR, whereas only one patient (0.5 %) met the criteria for HPR (**Figure 2A**). Platelet reactivity was similar in patients taking ticagrelor and prasugrel treatment (29 ± 44 PRU versus 26 ± 40 PRU, p=0.65) (**Figure 2B**). The level of inflammation was reduced considerably over time. After 1 month on study treatment, the hs-CRP level decreased from 6.1 (2.6-15.9) mg/L at 24 hours after PCI to 0.6 (0.4-1.2) mg/L (p<0.001) (**Figure 3A**). Accordingly, the prevalence of high-inflammation criteria (hs-CRP ≥2 mg/L) decreased significantly (81.8% at 24 hours after PCI versus 11.8% at 1 month, p<0.001) (**Figure 3B**). The data on platelet reactivity and inflammation in patients at high bleeding risk were reported in **Supplemental Results**.

Discussion

The present study is the first trial to evaluate the feasibility of $P2Y_{12}$ inhibitor monotherapy with ticagrelor or prasugrel, in the absence of aspirin, with colchicine therapy in patients with ACS immediately after PCI. The main findings of this study are as follows: 1) in ACS patients undergoing PCI, discontinuing aspirin therapy and administering low-dose colchicine (0.6 mg daily) on the day after PCI in addition to ticagrelor or prasugrel P2Y12

inhibitors is associated with a low incidence of stent thrombosis (1.0%) at three months; 2) major bleeding is rare, with a three-month incidence of 0.5%; 3) high platelet reactivity at discharge is low (0.5%); and 4) inflammatory levels were rapidly reduced within one month as shown by a significant decrease in hs-CRP levels. The low incidence of stent thrombosis reflects that reported by prior studies of patients undergoing PCI with DES (22).

Over the last decade, a strategy of $P2Y_{12}$ inhibitor monotherapy after a brief period of DAPT has been assessed in a number of randomized trials, including GLOBAL LEADERS, STOPDAPT-2, STOPDAPT-2 ACS, SMART-CHOICE, TWILIGHT, and TICO (4–9,16). Among these, TICO and STOPDAPT-2 ACS were the only trials specifically conducted in patients with ACS (8,9). The TICO study was the first randomized study to be conducted in patients with ACS. Its design was similar to that of the TWILIGHT study (6); aspirin was discontinued three months after PCI and patients continues on ticagrelor maintenance therapy. The trial showed a significant reduction in the composite outcome of major bleeding and cardiovascular events at one year (8). However, the STOPDAPT-2 ACS study showed that aspirin discontinuation 1–2 months after PCI followed by clopidogrel maintenance therapy failed to achieve a net clinical benefit; additionally, there was an increase in cardiovascular events despite a reduction in bleeding (9). These contradictory findings suggest that aspirin has minimal additional efficacy in the presence of effective $P2Y_{12}$ inhibition. A potent $P2Y_{12}$ inhibitor alone inhibits platelet aggregation, which is marginally enhanced by aspirin (23,24). Potent $P2Y_{12}$ inhibitors reportedly downregulate other markers of platelet reactivity, including arachidonic acid- and collagen-induced aggregation (25,26). Nevertheless, aspirin is still recommended immediately after PCI for its additive effect of preventing thrombosis that may be partly induced by stenting injury and subsequent subendothelial collagen exposure (2,27). Moreover, thrombogenicity is enhanced with myocardial injury during the acute to subacute phase in ACS patients, making post-PCI

DAPT a necessity. However, the immediate aspirin withdrawal after PCI has been extensively studied in patients with concomitant use of oral anticoagulation (28). In this setting, it has been highlighted as the best strategy.

In addition to the ASET study (16), the OPTICA study recently showed that ticagrelor or prasugrel mono antiplatelet therapy directly following PCI was feasible in patients with non-ST-segment elevation ACS (29). The present results extend its possibility into all ACS patients including ST-segment elevation MI. In our study, aspirin was discontinued without checking platelet reactivity to consider its potential application in clinical practice, as platelet function testing is not routinely recommended after PCI (1,2). Most patients had LPR at discharge, and definite stent thrombosis occurred only in the patient with HPR. Therefore, potent inhibition of the $P2Y_{12}$ signaling pathway by ticagrelor or prasugrel may enable immediate aspirin discontinuation due to its limited additional antiplatelet effects. The present results suggest that the potential benefits of the immediate discontinuation of aspirin are primarily due to the reduction in major bleeding, which frequently occurs before discharge or within one month after PCI. In the TICO sub-study, half of major bleeds occurred within one month of DES implantation (30). About 90% of enrolled patients showed excessive platelet inhibition (< 85 PRU), and direct discontinuation of aspirin may have a potential to reduce the risk of major bleeding.

Inflammation plays a fundamental role in the development and progression of the atherothrombotic process (31). Thus, anti-inflammatory agents are beneficial in a range of cardiovascular conditions. Leukocytes uptake colchicine. Its ability to bind to tubulin and interfere with microtubular function affects the expression of cytokines and interleukins and neutrophils' ability to marginate, ingress, aggregate, express superoxide, release neutrophil extracellular traps, and interact with platelets (32). Colchicine's efficacy has been well established by the COLCOT and LoDoCo2 randomized clinical trials in which low-dose

colchicine significantly reduced the risk of ischemic cardiovascular events (12,13). In a sub-analysis of the COLCOT study, there was a significant reduction in the incidence of ischemic events in patients in whom colchicine was initiated within three days of the index MI (15). In addition, colchicine has shown to exert antiplatelet effects in vitro via inhibition of key proteins involved in cytoskeleton rearrangement (33). However, clinical data regarding the early administration of colchicine in patients with ACS who have been treated with PCI are limited (34).

In the present study, inflammatory levels were rapidly reduced. In the acute phase of MI, cardiomyocyte necrosis generates damage-associated molecular patterns, which in turn activate the complement cascade and stimulate toll-like receptor and interleukin-1 signaling (35,36). These factors trigger an intense inflammatory response that may lead to adverse myocardial remodeling (37). Furthermore, MI liberates hematopoietic stem and progenitor cells from the bone marrow niches via the sympathetic nervous system, which accelerates systemic atherosclerosis by recruiting monocytes within the plaques (38). Since colchicine is preferentially concentrated in leukocytes, its anti-inflammatory effects are marked at low doses (32). Moreover, colchicine may prevent MI-related Dressler's syndrome, which was not observed in the present study. Similar to other studies (12,13), low-dose colchicine was tolerable for immediate administration after PCI and subsequent maintenance dosing.

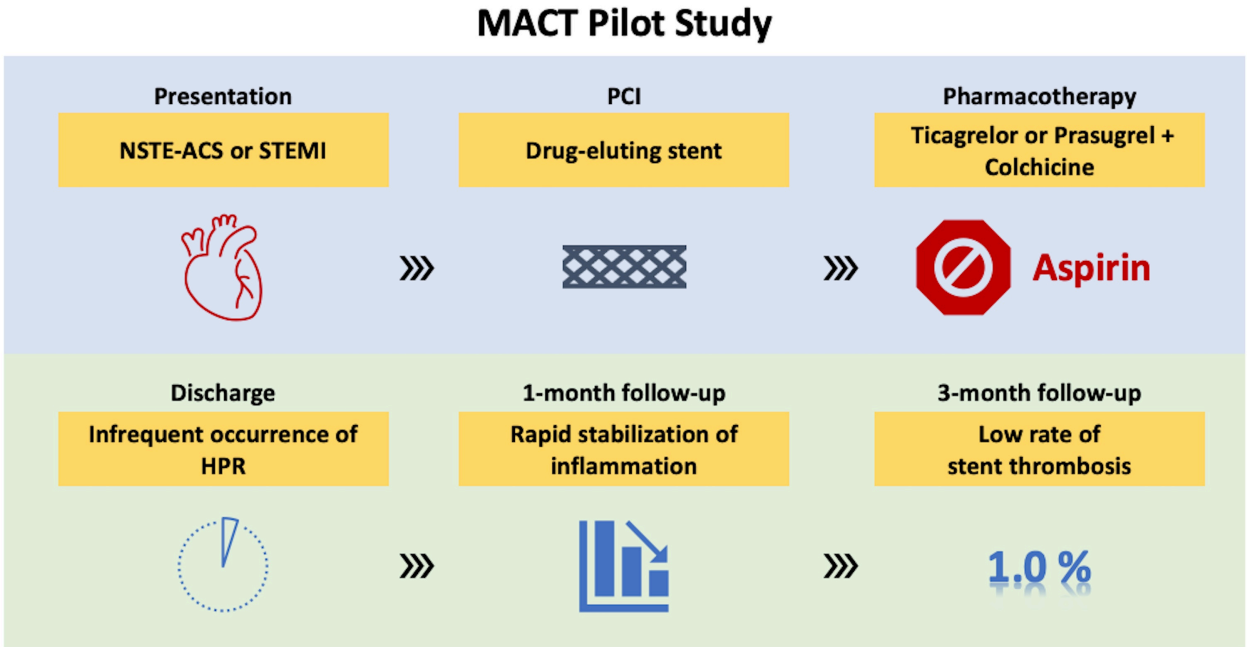
In addition to the pre-specified analyses, we evaluated the bleeding and ischemic risks of patients according to the PRECISE-DAPT score and PCI complexity. Most patients in the present study were at a low risk of bleeding and did not undergo complex PCI. A sub-study of the SMART-DATE trial indicated that the prevalence of ACS in patients at high bleeding risk was 27.5% (39). Giustino et al. defined complex PCI and determined that its frequency was 17.5% in a pooled dataset that included six randomized clinical trials (10). The present study mostly included ACS patients with hemodynamic stability; our cohort may under-

represent patients with bleeding or ischemic risk met in daily practice. Nevertheless, the advantage of the immediate aspirin withdrawal might be particularly attractive in patients at high bleeding risk with an impact on relevant endpoints (40). Therefore, further studies are warranted to evaluate the efficacy and safety of this experimental strategy especially in patients at high bleeding or ischemic risk.

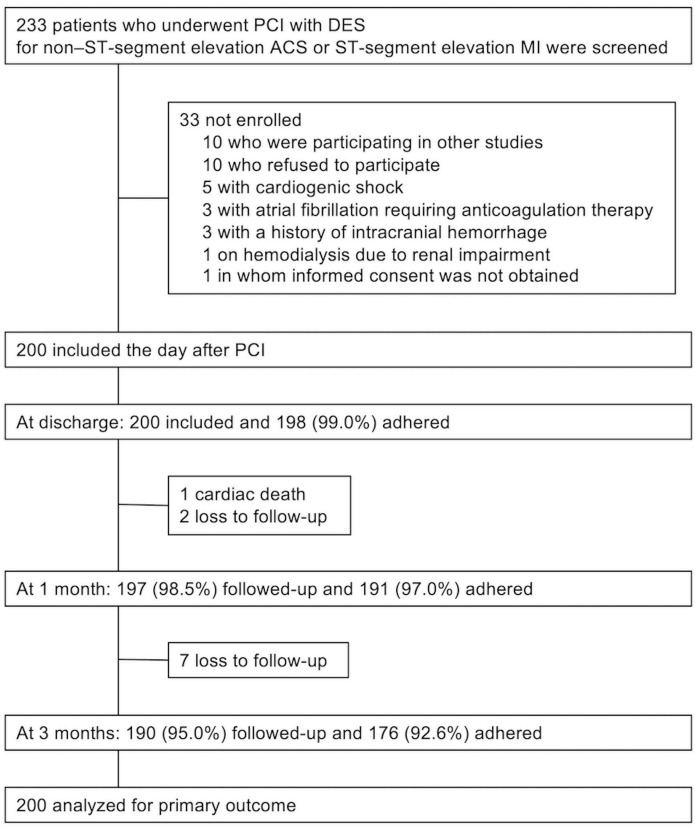
Limitations. First, all enrolled patients were Asian who were at relatively low bleeding and ischemic risk. Although ticagrelor or prasugrel is effective regardless of ethnicity (41), clinical data supporting this de-escalation strategy are limited. Second, there was no control group for comparison with the experimental group. Thus, it is not clear whether the reduction of hs-CRP resulted from colchicine or the physiologic response after ACS. Third, this study did not evaluate long-term clinical outcomes, and there was a relatively high rate of patients who were lost to follow-up despite the relatively brief duration of follow-up. Fourth, compliance with study medications was only assessed as reported by the patient and may therefore not have reflected true compliance. Lastly, the association between hs-CRP on admission and platelet reactivity was not evaluated (42).

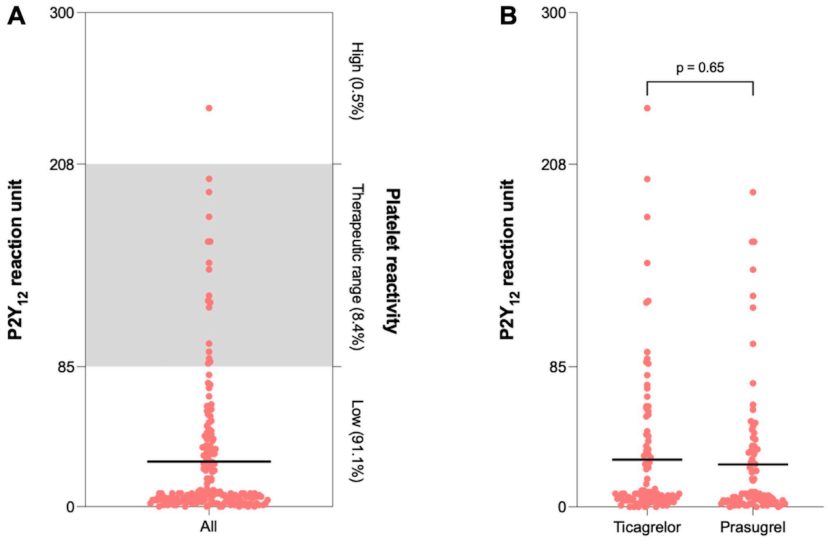
Conclusion

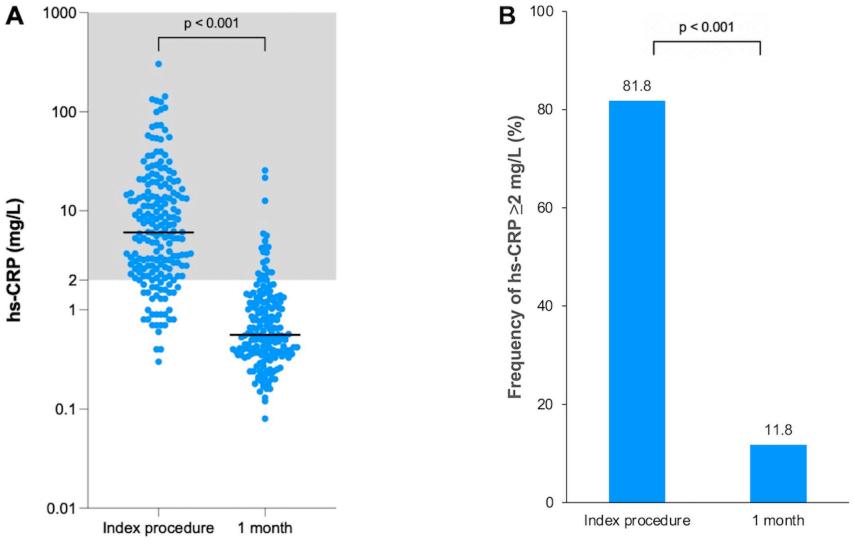
The feasibility of discontinuing aspirin therapy and administering low-dose colchicine on the day after PCI in addition to ticagrelor or prasugrel P2Y12 inhibitors, with associated benefits for platelet function and inflammatory profiles in ACS patients, warrants further investigation (**Central Illustration**).



Ticagrelor or Prasugrel Mono Antiplatelet and Colchicine Therapy is feasible immediately after PCI in ACS


233 patients who underwent PCI with DES
for non–ST-segment elevation ACS or ST-segment elevation MI were screened
33 not enrolled
10 who were participating in other studies
10 who refused to participate
5 with cardiogenic shock
3 with atrial fibrillation requiring anticoagulation therapy
3 with a history of intracranial hemorrhage
1 on hemodialysis due to renal impairment
1 in whom informed consent was not obtained
200 included the day after PCI
At discharge: 200 included and 198 (99.0%) adhered
1 cardiac death
2 loss to follow-up
At 1 month: 197 (98.5%) followed-up and 191 (97.0%) adhered
7 loss to follow-up
At 3 months: 190 (95.0%) followed-up and 176 (92.6%) adhered
200 analyzed for primary outcome


A
300
208
85
0
P2Y12 reaction unit
All
High (0.5%)
Therapeutic range (8.4%)
Low (91.1%)
Platelet reactivity
B
300
208
85
0
P2Y12 reaction unit
p = 0.65
Ticagrelor
Prasugrel


A
1000
100
10
2
1
0.1
0.01
hs-CRP (mg/L)
p < 0.001
Index procedure
1 month
B
100
80
60
40
20
0
Frequency of hs-CRP ≥2 mg/L (%)
p < 0.001
81.8
11.8
Index procedure
1 month

References

1. Collet JP., Thiele H., Barbato E., et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J 2021;42(14):1289–367. Doi: 10.1093/eurheartj/ehaa575.
2. Writing Committee M., Lawton JS., Tamis-Holland JE., et al. 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. J Am Coll Cardiol 2022;79(2):e21–129. Doi: 10.1016/j.jacc.2021.09.006.
3. Palmerini T., Bacchi Reggiani L., della Riva D., et al. Bleeding-Related Deaths in Relation to the Duration of Dual-Antiplatelet Therapy After Coronary Stenting. J Am Coll Cardiol 2017;69(16):2011–22. Doi: 10.1016/j.jacc.2017.02.029.
4. Vranckx P., Valgimigli M., Juni P., et al. Ticagrelor plus aspirin for 1 month, followed by ticagrelor monotherapy for 23 months vs aspirin plus clopidogrel or ticagrelor for 12 months, followed by aspirin monotherapy for 12 months after implantation of a drug-eluting stent: a multicentre, open-label, randomised superiority trial. Lancet 2018;392(10151):940–9. Doi: 10.1016/S0140-6736(18)31858-0.
5. Hahn JY., Song YB., Oh JH., et al. Effect of P2Y12 Inhibitor Monotherapy vs Dual Antiplatelet Therapy on Cardiovascular Events in Patients Undergoing Percutaneous Coronary Intervention: The SMART-CHOICE Randomized Clinical Trial. JAMA 2019;321(24):2428–37. Doi: 10.1001/jama.2019.8146.
6. Mehran R., Baber U., Sharma SK., et al. Ticagrelor with or without Aspirin in High-Risk Patients after PCI. N Engl J Med 2019;381(21):2032–42. Doi: 10.1056/NEJMoa1908419.
7. Watanabe H., Domei T., Morimoto T., et al. Effect of 1-Month Dual Antiplatelet Therapy Followed by Clopidogrel vs 12-Month Dual Antiplatelet Therapy on

Cardiovascular and Bleeding Events in Patients Receiving PCI: The STOPDAPT-2 Randomized Clinical Trial. JAMA 2019;321(24):2414–27. Doi: 10.1001/jama.2019.8145.

8. Kim BK., Hong SJ., Cho YH., et al. Effect of Ticagrelor Monotherapy vs Ticagrelor With Aspirin on Major Bleeding and Cardiovascular Events in Patients With Acute Coronary Syndrome: The TICO Randomized Clinical Trial. JAMA 2020;323(23):2407–16. Doi: 10.1001/jama.2020.7580.
9. Watanabe H., Morimoto T., Natsuaki M., et al. Comparison of Clopidogrel Monotherapy After 1 to 2 Months of Dual Antiplatelet Therapy With 12 Months of Dual Antiplatelet Therapy in Patients With Acute Coronary Syndrome: The STOPDAPT-2 ACS Randomized Clinical Trial. JAMA Cardiol 2022;7(4):407–17. Doi: 10.1001/jamacardio.2021.5244.
10. Giustino G., Chieffo A., Palmerini T., et al. Efficacy and Safety of Dual Antiplatelet Therapy After Complex PCI. J Am Coll Cardiol 2016;68(17):1851–64. Doi: 10.1016/j.jacc.2016.07.760.
11. Ridker PM., Everett BM., Thuren T., et al. Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease. N Engl J Med 2017;377(12):1119–31. Doi: 10.1056/NEJMoa1707914.
12. Tardif JC., Kouz S., Waters DD., et al. Efficacy and Safety of Low-Dose Colchicine after Myocardial Infarction. N Engl J Med 2019;381(26):2497–505. Doi: 10.1056/NEJMoa1912388.
13. Nidorf SM., Fiolet ATL., Mosterd A., et al. Colchicine in Patients with Chronic Coronary Disease. N Engl J Med 2020;383(19):1838–47. Doi: 10.1056/NEJMoa2021372.

14. Fiolet ATL., Opstal TSJ., Mosterd A., et al. Efficacy and safety of low-dose colchicine in patients with coronary disease: a systematic review and meta-analysis of randomized trials. Eur Heart J 2021;42(28):2765–75. Doi: 10.1093/eurheartj/ehab115.

15. Bouabdallaoui N., Tardif JC., Waters DD., et al. Time-to-treatment initiation of colchicine and cardiovascular outcomes after myocardial infarction in the Colchicine Cardiovascular Outcomes Trial (COLCOT). Eur Heart J 2020;41(42):4092–9. Doi: 10.1093/eurheartj/ehaa659.

16. Kogame N., Guimaraes PO., Modolo R., et al. Aspirin-Free Prasugrel Monotherapy Following Coronary Artery Stenting in Patients With Stable CAD: The ASET Pilot Study. JACC Cardiovasc Interv 2020;13(19):2251–62. Doi: 10.1016/j.jcin.2020.06.023.

17. Cutlip DE., Windecker S., Mehran R., et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115(17):2344–51. Doi: 10.1161/CIRCULATIONAHA.106.685313.

18. Mehran R., Rao S V., Bhatt DL., et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation 2011;123(23):2736–47. Doi: 10.1161/CIRCULATIONAHA.110.009449.

19. Tantry US., Bonello L., Aradi D., et al. Consensus and update on the definition of on-treatment platelet reactivity to adenosine diphosphate associated with ischemia and bleeding. J Am Coll Cardiol 2013;62(24):2261–73. Doi: 10.1016/j.jacc.2013.07.101.

20. Carrero JJ., Andersson Franko M., Obergfell A., Gabrielsen A., Jernberg T. hsCRP Level and the Risk of Death or Recurrent Cardiovascular Events in Patients With Myocardial Infarction: a Healthcare-Based Study. J Am Heart Assoc 2019;8(11):e012638. Doi: 10.1161/JAHA.119.012638.

21. Costa F., van Klaveren D., James S., et al. Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score: a pooled analysis of individual-patient datasets from clinical trials. Lancet 2017;389(10073):1025–34. Doi: 10.1016/S0140-6736(17)30397-5.

22. Moreno R., Fernandez C., Hernandez R., et al. Drug-eluting stent thrombosis: results from a pooled analysis including 10 randomized studies. J Am Coll Cardiol 2005;45(6):954–9. Doi: 10.1016/j.jacc.2004.11.065.

23. Armstrong PC., Leadbeater PD., Chan M V., et al. In the presence of strong P2Y12 receptor blockade, aspirin provides little additional inhibition of platelet aggregation. J Thromb Haemost 2011;9(3):552–61. Doi: 10.1111/j.1538-7836.2010.04160.x.

24. Baber U., Zafar MU., Dangas G., et al. Ticagrelor With or Without Aspirin After PCI: The TWILIGHT Platelet Substudy. J Am Coll Cardiol 2020;75(6):578–86. Doi: 10.1016/j.jacc.2019.11.056.

25. Teng R., Maya J., Butler K. Evaluation of the pharmacokinetics and pharmacodynamics of ticagrelor co-administered with aspirin in healthy volunteers. Platelets 2013;24(8):615–24. Doi: 10.3109/09537104.2012.748185.

26. Tello-Montoliu A., Thano E., Rollini F., et al. Impact of aspirin dose on adenosine diphosphate-mediated platelet activities. Results of an in vitro pilot investigation. Thromb Haemost 2013;110(4):777–84. Doi: 10.1160/TH13-05-0400.

27. Valgimigli M., Bueno H., Byrne RA., et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2018;39(3):213–60. Doi: 10.1093/eurheartj/ehx419.

28. Montalto C., Costa F., Leonardi S., et al. Dual antiplatelet therapy duration after percutaneous coronary intervention in patients with indication to oral anticoagulant therapy. A systematic review and meta-analysis of randomized controlled trials. Eur Heart J Cardiovasc Pharmacother 2022;0:1–11. Doi: 10.1093/EHJCVP/PVAC065.

29. van der Sangen NMR, Claessen B, Kucuk IT, et al. Single antiplatelet therapy directly after percutaneous coronary intervention in non-ST-segment elevation acute coronary syndrome patients: the OPTICA study. EuroIntervention. 2023. Doi: 10.4244/EIJ-D-22-00886.

30. Cho JY., Lee SY., Yun KH., et al. Factors Related to Major Bleeding After Ticagrelor Therapy: Results from the TICO Trial. J Am Heart Assoc 2021;10(7):e019630. Doi: 10.1161/JAHA.120.019630.

31. Libby P. Mechanisms of acute coronary syndromes and their implications for therapy. N Engl J Med 2013;368(21):2004–13. Doi: 10.1056/NEJMra1216063.

32. Imazio M., Nidorf M. Colchicine and the heart. Eur Heart J 2021;42(28):2745–60. Doi: 10.1093/eurheartj/ehab221.

33. Cimmino G., Tarallo R., Conte S., et al. Colchicine reduces platelet aggregation by modulating cytoskeleton rearrangement via inhibition of cofilin and LIM domain kinase 1. Vascul Pharmacol 2018;111:62–70. Doi: 10.1016/j.vph.2018.09.004.

34. Deftereos S., Giannopoulos G., Angelidis C., et al. Anti-Inflammatory Treatment With Colchicine in Acute Myocardial Infarction: A Pilot Study. Circulation 2015;132(15):1395–403. Doi: 10.1161/CIRCULATIONAHA.115.017611.

35. Frangogiannis NG. The inflammatory response in myocardial injury, repair, and remodelling. Nat Rev Cardiol 2014;11(5):255–65. Doi: 10.1038/nrcardio.2014.28.

36. Prabhu SD., Frangogiannis NG. The Biological Basis for Cardiac Repair After Myocardial Infarction: From Inflammation to Fibrosis. Circ Res 2016;119(1):91–112. Doi: 10.1161/CIRCRESAHA.116.303577.

37. Chen B., Frangogiannis NG. Immune cells in repair of the infarcted myocardium. Microcirculation 2017;24(1). Doi: 10.1111/micc.12305.

38. Dutta P., Courties G., Wei Y., et al. Myocardial infarction accelerates atherosclerosis. Nature 2012;487(7407):325–9. Doi: 10.1038/nature11260.

39. Choi KH., Song YB., Lee JM., et al. Clinical Usefulness of PRECISE-DAPT Score for Predicting Bleeding Events in Patients With Acute Coronary Syndrome Undergoing Percutaneous Coronary Intervention: An Analysis From the SMART-DATE Randomized Trial. Circ Cardiovasc Interv 2020;13(5):e008530. Doi: 10.1161/CIRCINTERVENTIONS.119.008530.

40. Costa F., Montalto C., Bhatt D., et al. Abbreviated dual antiplatelet therapy after PCI in patients at high bleeding risk: a collaborative meta-analysis of randomized trials. Eur Heart J 2022;43(Supplement_2). Doi: 10.1093/EURHEARTJ/EHAC544.1402.

41. Angiolillo DJ., Been L., Rubinstein M., Martin M., Rollini F., Franchi F. Use of the VerifyNow point of care assay to assess the pharmacodynamic effects of loading and maintenance dose regimens of prasugrel and ticagrelor. J Thromb Thrombolysis 2021;51(3):741–7. Doi: 10.1007/s11239-021-02386-7.

42. Patti G., Mangiacapra F., Ricottini E., et al. Correlation of platelet reactivity and C-reactive protein levels to occurrence of peri-procedural myocardial infarction in patients undergoing percutaneous coronary intervention (from the ARMYDA-CRP study) Am J Cardiol 2013;111(12):1739–44. Doi: 10.1016/j.amjcard.2013.02.028.

Figure Titles and Legends

Figure 1. Participant flow.

Figure 2. Distribution of platelet reactivity measured by VerifyNow test before discharge (A) and platelet reactivity on ticagrelor versus prasugrel therapy (B). Bars indicate mean values.

Figure 3. Change of hs-CRP level between index procedure and 1-month follow-up (A) and prevalence of high-inflammation criteria (hs-CRP ≥2 mg/L) (B). Bars indicate median values. hs-CRP, high-sensitivity C-reactive protein.

Central Illustration. The overview of Mono Antiplatelet and Colchicine Therapy (MACT). HPR, high platelet reactivity; NSTE-ACS, non-ST-segment elevation acute coronary syndrome; PCI, percutaneous coronary intervention, STEMI, ST-segment elevation myocardial infarction.

Perspectives

What Is Known?

Aspirin-free $P2Y_{12}$ inhibitor monotherapy reduces bleeding without increasing recurrent ischemia in patients undergoing PCI. Given the effect of anti-inflammatory therapy on reducing ischemia, $P2Y_{12}$ inhibitor monotherapy combined with anti-inflammatory therapy may maximize the treatment effect of reducing both bleeding and ischemia, especially in ACS patients undergoing PCI.

What Is New?

In ACS patients undergoing PCI, it is feasible to discontinue aspirin therapy and administer low-dose colchicine (0.6 mg daily) on the day after PCI in addition to ticagrelor or prasugrel P2Y12 inhibitors. This finding is associated with the marked inhibition of platelet reactivity and the rapid stabilization of inflammation following ACS.

What Is Next?

Randomized clinical trials are required to compare this explorative strategy with standard treatment in terms of platelet reactivity, post-ACS inflammatory response, and clinical outcome.

Table 1. Clinical and angiographic characteristics.

Number of patients	200
Age (year old)	61.4 ± 10.7
Male	180 (90.0%)
Height (cm)	167.8 ± 6.2
Weight (kg)	70.5 ± 10.2
Body mass index (kg/m^2)	25.0 ± 3.1
Hypertension	103 (51.5%)
Diabetes mellitus	61 (30.5%)
Current smoking	96 (48.0%)
Dyslipidemia	61 (30.5%)
Previous myocardial infarction	12 (6.0%)
Previous percutaneous coronary intervention	14 (7.0%)
Previous coronary artery bypass grafting	1 (0.5%)
Previous stroke	12 (6.0%)
Clinical presentation	
Unstable angina	55 (27.5%)
Non–ST-segment elevation myocardial infarction	52 (26.0%)
ST-segment elevation myocardial infarction	93 (46.5%)
Left ventricular ejection fraction on echocardiography (%)	51.8 ± 8.5
<40 %	14 (7.0%)
PRECISE-DAPT score	14.4 ± 8.1
≥25	23 (11.5%)
Medication use	

Statin	200 (100%)
Beta-blocker	138 (69.0%)
Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker	136 (68.0%)
Coronary artery disease	
One vessel	143 (71.5%)
Two vessel	39 (19.5%)
Three vessel	18 (9.0%)
Culprit lesion location	
Left main artery	2 (1.0%)
Left anterior descending artery	109 (54.5%)
Left circumflex artery	31 (15.5%)
Right coronary artery	58 (29.0%)

Values are n, n (%), or mean ± standard deviation.

PRECISE-DAPT, Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy.

Table 2. Procedural characteristics.

Number of lesions	258
Pre-procedural TIMI flow grade	
0	95 (36.8%)
1	13 (5.0%)
2	23 (8.9%)
3	127 (49.2%)
Radial access	157 (60.9%)
Stent diameter (mm)	3.1 ± 0.4
Stent length (mm)	28.7 ± 12.0
Stent type	
Sirolimus-eluting stent	133 (51.6%)
Everolimus-eluting stent	54 (20.9%)
Amphilimus-eluting stent	52 (20.2%)
Zotarolimus-eluting stent	14 (5.4%)
Novolimus-eluting stent	5 (1.9%)
Post-dilatation with non-compliant balloon	100 (38.8%)
Thrombus aspiration	7 (2.7%)
Intravascular ultrasound use	16 (6.2%)
Optical coherence tomography use	3 (1.2%)
Post-procedural TIMI flow grade	
0	0
1	0
2	12 (4.7%)

3	246 (95.3%)
Number of patients	200
Number of vessels treated	1.2 ± 0.5
Number of lesions treated	1.3 ± 0.6
Number of stents implanted	1.4 ± 0.7
Total stent length (mm)	36.9 ± 21.3
Complex percutaneous coronary intervention	31 (15.5%)
3 vessels treated	5 (2.5%)
≥3 lesions treated	7 (3.5%)
≥3 stents implanted	15 (7.5%)
Total stent length >60 mm	28 (14.0%)
Bifurcation with 2 stents implanted	1 (0.5%)
Chronic total occlusion	4 (2.0%)

Values are n, n (%), or mean ± standard deviation.

TIMI, Thrombolysis In Myocardial Infarction.

Table 3. Adherence to study medications

Discharge	n=200
$P2Y_{12}$ inhibitors	200 (100%)
Ticagrelor	104 (52.0%)
Prasugrel	96 (48.0%)
Clopidogrel	0
Colchicine	198 (99.0%)
Aspirin	2 (1.0%)
1-month follow-up	n=197
$P2Y_{12}$ inhibitors	194 (98.5%)
Ticagrelor	99 (50.3%)
Prasugrel	95 (48.2%)
Clopidogrel	0
Colchicine	193 (98.0%)
Aspirin	2 (1.0%)
3-month follow-up	n=190
$P2Y_{12}$ inhibitors	182 (95.8%)
Ticagrelor	91 (47.9%)
Prasugrel	89 (46.8%)
Clopidogrel	2 (1.1%)
Colchicine	183 (96.3%)
Aspirin	5 (2.6%)

Table 4. Clinical outcomes at 3 months

Definite, probable, or possible stent thrombosis	2 (1.0%)
Definite stent thrombosis	1
Probable stent thrombosis	1
Possible stent thrombosis	0
All-cause death	1 (0.5%)
Cardiac death	1
All MI	1 (0.5%)
Target vessel-MI	1
All revascularization	2 (1.0%)
Target lesion revascularization	1
All-cause death, all MI, or all revascularization	3 (1.5%)
Cardiac death, target vessel-MI, or target lesion revascularization	2 (1.0%)
All bleeding	36 (18.0%)
BARC type 1	15
BARC type 2	20
BARC type 3	1
BARC type 5	0
BARC type 2, 3, or 5	21 (10.5%)
BARC type 3 or 5	1 (0.5%)

Values are n or n (Kaplan-Meier estimates)

BARC, Bleeding Academic Research Consortium; MI, myocardial infarction.