

Review Article



Protocol Update and Issues in EASTYLE Trial

Moo Hyun Kim , MD, FACC, FSCAI¹, and Young-Hoon Jeong , MD, PhD²

¹Department of Cardiology, Dong-A University Hospital, Busan, Korea

²Department of Cardiology, Chung-Ang University Gwangmyeong Hospital, Gwangmyeong, Korea

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Correspondence to

Moo Hyun Kim, MD, FACC, FSCAI

Department of Cardiology, Dong-A University
Hospital, 26 Daesingongwon-ro, Seo-gu,
Busan 49201, Korea.

Email: kimmh@dau.ac.kr

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ORCID iDs

Moo Hyun Kim

<https://orcid.org/0000-0003-3468-6453>

Young-Hoon Jeong

<https://orcid.org/0000-0003-0403-3726>

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Conflict of Interest

The authors have no conflict of interest.

Author Contributions

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Jeong YH; Formal analysis: Kim MH; Funding

ABSTRACT

The EASTYLE study is currently ongoing, based on the hypothesis that ticagrelor reduction and a 3-month aspirin removal strategy (Hybrid De-escalation) as part of the de-escalation strategy can reduce cardiovascular complications (net clinical outcome). There have been no previous studies on the reduction effect of ticagrelor, and this study involves 35 sites in Korea, showing a registration rate of around 20% currently. Registration is expected to close in early or mid 2025, and results are anticipated to be announced around the same time as the ELECTRA-SIRIO 2 study.

Keywords: Acute myocardial infarction; Bleeding; Ticagrelor; DAPT

INTRODUCTION

After percutaneous coronary intervention (PCI) for coronary artery disease, dual anti-platelet therapy (DAPT) comprising aspirin plus a P2Y₁₂ inhibitor is essential for treating patients.^{1,2} In ACS patients, the use of more potent DAPT (prasugrel or ticagrelor) was shown to reduce ischemic cardiovascular events compared to clopidogrel, and ticagrelor in particular reduced mortality.^{3,4} However, potent DAPT is associated with significant side effects including increased bleeding risk. Therefore, to address the clinical challenge of minimizing ischemic events while reducing bleeding risk, it is necessary to tailor antiplatelet therapy based on such risk. Particularly in patients at high bleeding risk (HBR), the adverse effects of long-term antiplatelet therapy-induced bleeding are closely associated with long-term survival, making it even more crucial.⁵ Recently, the Academic Research Consortium (ARC) released definitions for HBR and emphasized the need for optimal DAPT therapy in these patients.⁶ Achieving a balance between ischemic and bleeding complications after stent placement in myocardial infarction (MI) patients remains a critical dilemma for clinicians.

In 2012, Jeong et al.,⁷ first proposed the concept of the “East Asian Paradox,” suggesting that ischemic events are less common but bleeding risks are higher in East Asians compared to Caucasians, necessitating a tailored antiplatelet therapy approach. This is because East Asians exhibit higher responsiveness to antiplatelet therapy compared to Caucasians, necessitating a specialized approach in terms of dosage, inhibition profile, and maintenance duration of DAPT (**Fig. 1**).^{8,9}

acquisition: Jeong YH; Investigation: Kim MH; Methodology: Jeong YH; Project administration: Kim MH; Resources: Jeong YH; Software: Kim MH; Supervision: Jeong YH; Validation: Kim MH; Visualization: Jeong YH; Writing - original draft: Kim MH; Writing - review & editing: Jeong YH.



Fig. 1. East-Asian paradox.
Adopted from Kim et al.⁹
CV = cardiovascular; DOAC = direct oral anticoagulant; ICAS = intracranial atherosclerosis; GI = gastrointestinal; PCI = percutaneous coronary intervention; DAPT = dual anti-platelet therapy.

With the advancement of the concepts of ‘HBR’ and the ‘East Asian Paradox,’ coupled with improvements in the structure and performance of next-generation drug-eluting stent (DES) stents, there is growing interest in the gradual de-escalation strategy of antiplatelet therapy for patients who require lifelong antiplatelet treatment.^{10,11} Decisions regarding the use of potent P2Y₁₂ inhibitors like prasugrel or ticagrelor, as well as the duration of DAPT, should be made by evaluating the balance between reducing ischemic events and increased bleeding risk simultaneously.⁹ Various DAPT de-escalation strategies are currently being investigated in clinical research, including: 1) reducing the duration of DAPT maintenance; 2) early discontinuation of aspirin; and 3) dose reduction or switching P2Y₁₂ inhibitor therapy (Table 1).

Significant clinical benefits of early discontinuation therapy with aspirin have been observed in several studies (GLOBAL-LEADERS, TWILIGHT, SMART-CHOICE, TICO).¹²⁻¹⁵ For example, the TWILIGHT study compared two groups of high-risk patients who had received stent procedures, one group completing 3 months of DAPT therapy followed by 12 months of

Table 1. De-escalation strategy for DAPT in East Asian patients

Strategy	Study
Shortened DAPT period	SMART-DATE
Aspirin discontinuation	TICO, STOP-DAPT2, SMART-CHOICE, EASTYLE, GLOBAL-LEADERS, TWILIGHT
Reduced potency of P2Y ₁₂ inhibition	
Phenotype- or genotype-guided strategy	A-MATCH, TAILOR-PCI
Reduced-dose strategy	A-MATCH, HOST-RP-ACS, EASTYLE
Switching strategy	TALOS-AMI

DAPT = dual anti-platelet therapy.

ticagrelor monotherapy and the other receiving 12 months of DAPT therapy with ticagrelor and aspirin.¹³ While there was no difference in ischemic clinical events between the two groups, significant superiority was noted in the ticagrelor monotherapy group over the DAPT maintenance group regarding major bleeding (BARC type 2, 3, or 5) (hazard ratio [HR], 0.56; 95% confidence interval [CI], 0.45–0.68; $P < 0.001$ for superiority test).¹⁵

Moreover, potent P2Y₁₂ inhibitors such as prasugrel or ticagrelor are known to have approximately 40–50% higher active metabolite concentrations in East Asians compared to Caucasians, even when administered at the same dosage.⁹ Therefore, appropriate drug dosages for ischemic clinical events and bleeding risk considerations may differ for East Asian MI patients.^{16,17} A notable study confirming the clinical efficacy of prasugrel dose reduction therapy is the HOST-RP-ACS study, which compared the occurrence of clinical events between two groups: one receiving standard-dose prasugrel therapy for 1 month followed by maintenance therapy (10-mg prasugrel) and the other receiving reduced-dose therapy (5-mg prasugrel).¹⁶ While there was no difference in ischemic clinical events between the two groups, a significant reduction in major bleeding (BARC type 2, 3, or 5) was observed in the reduced-dose group compared to the maintenance group (HR, 0.48; 95% CI, 0.32–0.73; $P = 0.007$). Thus, the current treatment guidelines should consider the introduction of dose reduction therapy after the acute phase, and its implementation should be considered essential, especially in East Asian patients.

THE NEED FOR A NEW TRIAL OF REDUCED DOSE OF TICAGRELOR

Unlike prasugrel, there is currently a lack of research on ticagrelor dose reduction therapy for initial treatment of MI patients, highlighting the urgent need for studies on appropriate reduction and maintenance periods specifically for Koreans. The PLATO study, conducted on patients with acute coronary syndrome, demonstrated a significant reduction in ischemic clinical events with ticagrelor compared to clopidogrel.⁴ However, it also showed that the rate of major bleeding events increased with older age (HR, 1.27; 95% CI, 1.14–1.42 for a 5-year increase) and lower body weight (HR, 0.90; 95% CI, 0.82–0.99 for a 5 kg increase) post-intervention.¹⁸ Therefore, East Asians may not benefit from the standard dose ticagrelor therapy because potent P2Y₁₂ inhibitors (ticagrelor or prasugrel) had similar rate of major adverse cardiac event (MACE), but had increased bleeding in acute MI patients.¹⁹ Another KAMIR-NIH registry targeting Korean MI patients found a higher risk of major bleeding with ticagrelor use in patients aged 75 or older or with a body weight below 60 kg compared to clopidogrel.²⁰

In a study of Korean acute coronary syndrome patients (40 subjects), reducing the ticagrelor dosage to 45 mg after 1 month showed no instances of ‘high platelet reactivity.’²¹ Similarly, in East Asians hospitalized for acute coronary syndrome (754 subjects), reducing the ticagrelor dosage to 45 mg after maintaining the standard dosage for 3 months resulted in no difference in ischemic clinical events compared to maintaining the dosage, but there was a significant reduction in the risk of major bleeding (adjusted HR, 0.24; 95% CI, 0.07–0.77; $P = 0.016$).²² Furthermore, the BLEEDING-ACS study conducted on Korean acute coronary syndrome patients demonstrated that reducing the ticagrelor dosage to 45 mg upon discharge resulted in a significant reduction in major bleeding without an increase in ischemic clinical events compared to maintaining the standard dosage of 90 mg (odds ratio, 0.28; 95% CI, 0.09–0.92; $P = 0.036$).²³ These effects were particularly pronounced in patients aged 65 or older or with a body mass index of 25 kg/m² or less.

EASTYLE TRIAL AT A GLANCE

Title	EASTYLE (DE-escAlation Strategy for Optimal Ticagrelor Therapy in Acute MYocardial Infarction PatiEnts) Trial
Trial registration and information	NCT04755387
Principal Investigators	Moo Hyun Kim, MD, Young Hoon Jeong, MD
Inclusion and exclusion criteria	
(1) Inclusion criteria	• Diagnosis of acute myocardial infarction. • Adult patients aged 19 and above. • Received Orsiro Mission stent intervention for coronary artery stenosis. • Patients who have consented to participate in the study.
(2) Exclusion criteria	• Refusal to participate in the study or deemed inappropriate by the investigator. • History of past cerebral hemorrhage or intracranial bleeding. • Presence of active bleeding at the time of medication administration (e.g., peptic ulcer, intracranial bleeding) or high risk of severe bleeding (e.g., high-risk gastrointestinal lesions, high-risk malignant tumors prone to bleeding). • Presence of bleeding diathesis or coagulopathy (including platelet count < 100,000/mm³ or hemoglobin < 10 g/dL before correction, bleeding requiring transfusion within 30 days, chest/abdominal/brain surgery within 90 days, or situations deemed at a high risk of trauma by the investigator). • Hypersensitivity to stent metals, contrast agents, or antiplatelet agents (ticagrelor, aspirin). • Severe hepatic impairment (Child-Pugh class B or above). • Need for anticoagulant therapy (warfarin or non-vitamin K antagonist oral anticoagulant). • Pregnant or lactating women. • Genetic disorders such as galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption. • Expected survival period of less than 1 year due to concomitant medical conditions.

RESEARCH OBJECTIVES AND ASSESSMENT CRITERIA: PROTOCOL UPDATE

Research objectives

Evaluation of the optimal stepwise de-escalation strategy of DAPT, including ticagrelor, in East Asian patients diagnosed with MI (assessment of clinical efficacy and safety of initial ticagrelor dose reduction therapy after stent placement for MI and mid-term aspirin discontinuation therapy).

Primary end point

Major bleeding clinical events (BARC type 2, 3, or 5) during the 12 months after stent placement. The primary endpoint was modified from BARC 2,3,5 bleeding to the NET clinical endpoint (MACE: all-cause death, non-fatal MI, stent thrombosis, non-fatal stroke + BARC 2,3,5 bleeding), and the secondary endpoint was modified from the NET clinical endpoint to examining the ratio of MACE and bleeding.

Determination of target sample size

In the TWILIGHT study, which confirmed DAPT de-escalation therapy based on ticagrelor (involving 7,119 subjects), the rates of BARC 2, 3, or 5 bleeding events were 4.0% and 7.1% in the 3-month DAPT group and the 12-month DAPT group, respectively.¹⁶ Similarly, the EASTYLE study, with BARC 2, 3, or 5 bleeding as the primary endpoint and aspirin discontinuation timing similar to the TWILIGHT study, was predicted to have events occurring to a similar extent. For the comparison analysis of the superiority of the EAST strategy over the WEST strategy regarding BARC 2, 3, or 5 bleeding events, assuming a 4%

occurrence in the EAST strategy and a 7% occurrence in the WEST strategy, a superiority margin of 0.4% was calculated.

In the modified protocol, net adverse clinical events (NACE) was redefined, and the de-escalation strategy, compared to standard therapy, reduced bleeding complications by 44% in Westerners and an average of 50% in Koreans. Assuming that halving BARC 2, 3, or 5 bleeding and not increasing ischemic cardiac events constitutes a 50% reduction, it is expected that standard therapy will have 11% (7.1% + 3.9%) NACE, while the de-escalation strategy will have 7.45% (3.55% + 3.9%) NACE in this study. With a type 1 error of 0.05, 80% power, and a dropout rate of 10%, the required sample size for each group is at least 1,040 individuals, which becomes at least 1,156 individuals when applying a dropout rate of 10%. Therefore, the required total sample size is 2,312 individuals.

Protocol amendments

Originally, due to the potent antiplatelet effect of ticagrelor, it was deemed desirable to initiate weight adjustments earlier. Therefore, the protocol included: 1) allowance for weight adjustment before discharge or within 1 month and 2) specified the use of low-dose ticagrelor in underweight and elderly patients. However, due to the lack of approval from the regulatory agency for the 45 mg twice a day (bid) regimen as there was no existing half-dose preparation for at least 1 month during the regulatory approval process, the final protocol was modified to the present form. It was converted into a protocol similar to the ELECTRA-SIRIO 2 Trial, becoming a protocol with only two arms out of the three arms in the ELECTRA-SIRIO 2 study.²⁴ On the other hand, there are also expected advantages for the protocol modification. Since both the European ELECTRA-SIRIO 2 trial and the EASTYLE study in East Asia are being conducted simultaneously, it is expected that at the time of presenting the results, they will be almost identical protocols, allowing for the advantage of comparing differences between Asians and Caucasians (**Figs. 2 and 3**).

ISSUES IN THE EASTYLE TRIAL

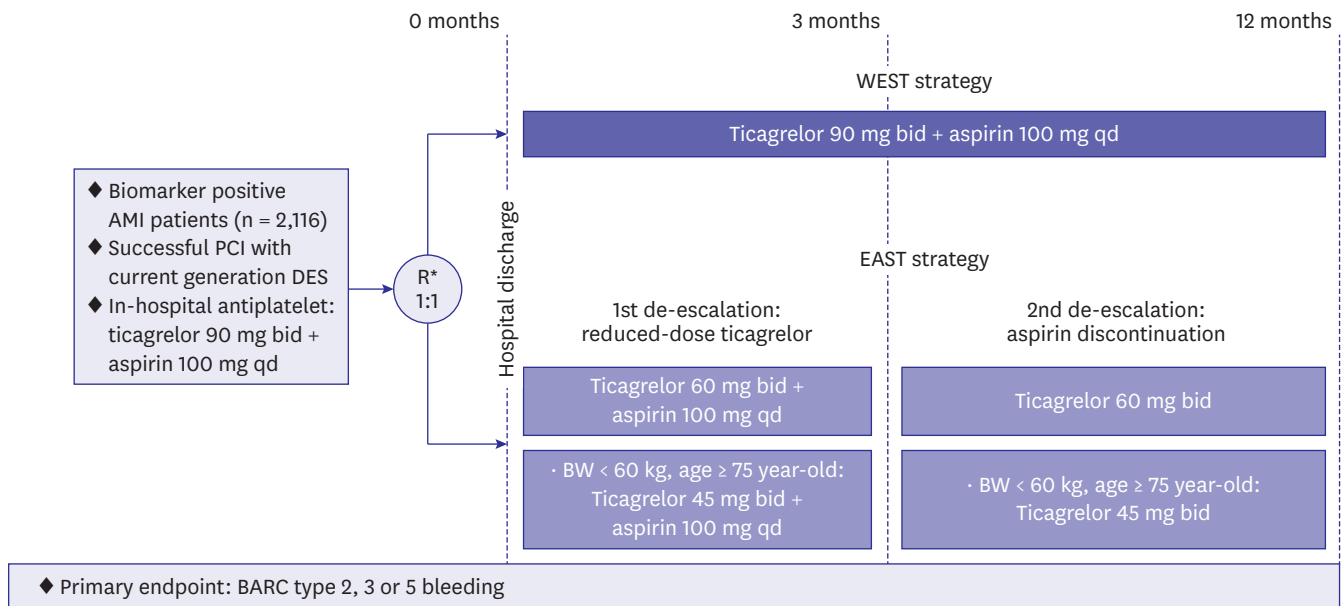
Ticagrelor dosage

The initial plan was to allow a 45 mg bid dose in underweight and elderly patients. However, due to the absence of a 45 mg dose being commercially available, the regulatory authority disallowed its use. Considering that prasugrel doses of 2.5 and 3.75 mg are used in Japan and Taiwan, respectively, it is regrettable that research on the low dose did not proceed concurrently. Previous studies have shown that the ticagrelor 90 mg bid maintenance dose has a stronger platelet inhibition effect than prasugrel 10 mg once a day,^{25,26} and low-dose therapy in East Asians, with 45 mg bid administration needing to be verified in the future due to the very low frequency of HBR.²¹

Loading or initial use of ticagrelor

Originally, only cases where ticagrelor was loaded initially were planned for registration. However, since the effect within the first month cannot be observed, a protocol amendment was made to allow registration for patients discharged after ticagrelor use, regardless of the initially loaded P2Y₁₂ inhibitor.

A Initial protocol



B Updated protocol

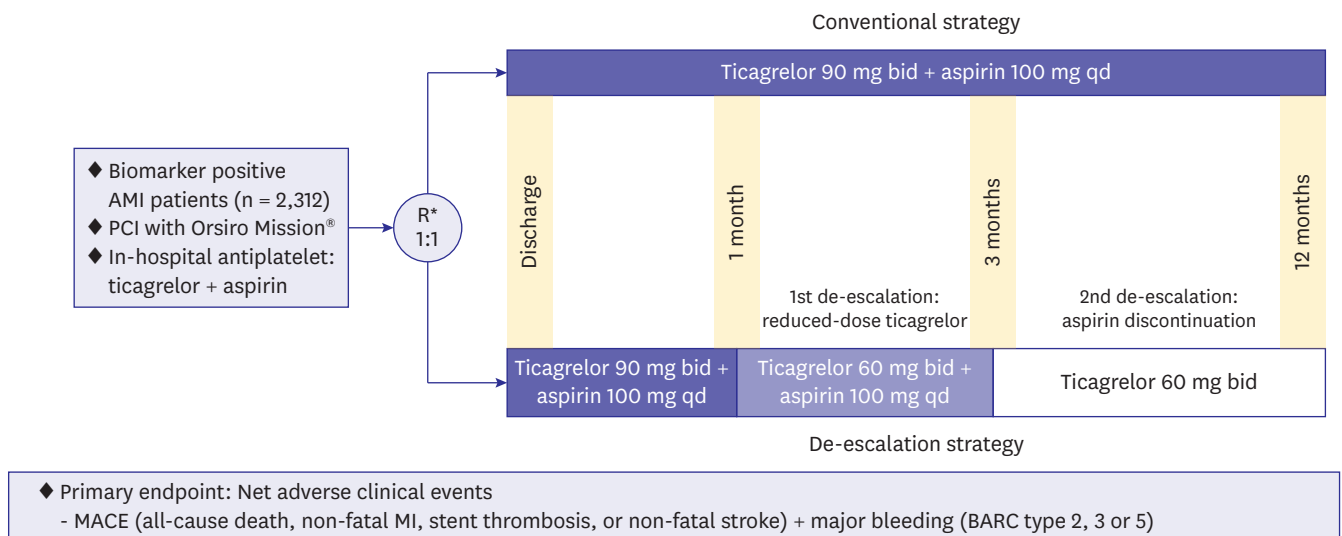


Fig. 2. Diagram of the protocol update. (A) Initial protocol and (B) updated protocol.

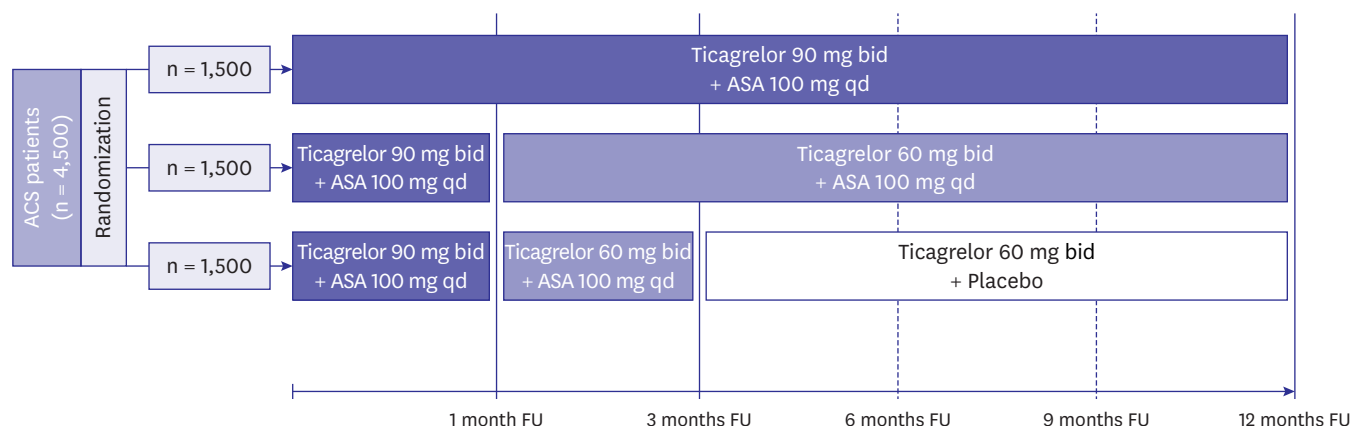
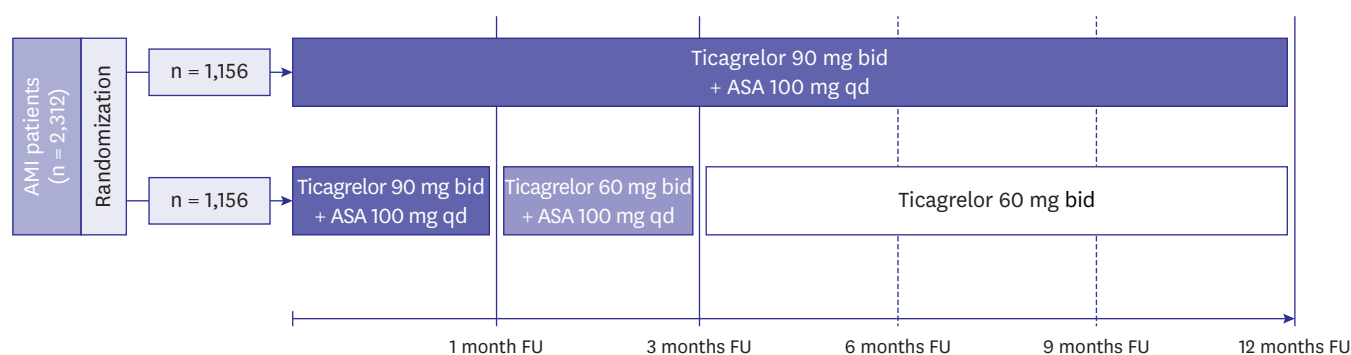
BARC = Bleeding Academic Research Consortium; BW = body weight; bid = twice a day; DES = drug-eluting stent; PCI = percutaneous coronary intervention; MACE = major adverse cardiac event; MI = myocardial infarction; qd = once a day.

Survey and platelet test timing

The original plan was to conduct a survey at the 1-month mark, reflecting the point at which platelet doses vary, and to perform platelet function tests (if necessary), but due to protocol changes, this timing has been postponed from 1 to 3 months.

Effects of ticagrelor use in Asian vs. Caucasians

As previously mentioned, as the ELECTRA-SIRIO 2 study is currently underway in Europe, if both studies can end simultaneously, a comparative analysis of clinical effects between East Asian and Caucasians could be significant.

A ELECTRA-SIRIO2 trial**B EASTYLE trial****Fig. 3.** Protocol comparison. (A) ELECTRA-SIRIO2 trial and (B) EASTYLE trial.

ACS = acute coronary syndrome; ASA = aspirin; bid = twice a day; FU = follow-up; AMI = acute myocardial infarction; qd = once a day.

Progress and schedule of EASTYLE study

The progress of the EASTYLE study can be tracked on clinicaltrials.gov. Originally, it was scheduled to be completed by 2024, but was delayed for about 6 months due to ongoing discussions with the regulatory authority, with registration expected to be completed by 2025.

Stent use and funding sources

This study only allows enrollment of patients who have been treated with the Orsiro Mission stent (by BIOTRONIK Ltd., Oswego, OR, USA). The Orsiro Mission stent is a sirolimus-eluting DES designed to maintain consistent drug release through its biodegradable coating, reducing thrombosis formation. With stent struts measuring 60 μ m thin, it promotes rapid endothelialization and vascular healing, facilitating short-term dual antiplatelet therapy. However, the use of one specific stent can be a hurdle of the patient enrollment. The study is sponsored by one multinational stent company (BIOTRONIK Ltd.) and one Korean pharmaceutical company (Samjin Pharmaceuticals, Seoul, Korea). Also, this study was supported by a grant from the National Research Foundation of Korea funded by the Korea government (Ministry of Science and ICT) to Moo Hyun Kim.

Study limitation

The study has several limitations that should be considered when interpreting the results:

1. Generalizability: The study is focused on East Asian patients and it were stated as Caucasians and Asians, there are various races in both Caucasians and Asians.

Therefore, the findings may not be directly applicable to other populations with different genetic backgrounds, lifestyles, and healthcare systems.

2. Sample size: The study's sample size may impact the generalizability and statistical power of the results. It is essential to ensure that the sample size is adequate to detect meaningful differences in outcomes.
3. Study design: The study design, including the choice of endpoints, follow-up duration, and comparator groups, may influence the interpretation of the results. It is crucial to consider the study design's strengths and limitations when drawing conclusions.
4. Regulatory constraints: Regulatory constraints, such as the disallowance of a specific dosage regimen (e.g., 45 mg bid dose) due to commercial availability, may have influenced the study protocol and could impact the interpretation of the results.
5. Concurrent studies: The simultaneous conduct of multiple studies, such as the ELECTRA-SIRIO 2 study, may introduce confounding factors or influence the interpretation of results when comparing findings across different trials. Considering these limitations, it is important to interpret the study results cautiously and in the context of the study design and potential biases.

By acknowledging these limitations and critically evaluating the study findings in the context of these factors, researchers and clinicians can better understand the implications of the EASTYLE trial results and their relevance to clinical practice.

Summary

The EASTYLE study is currently ongoing, based on the hypothesis that ticagrelor reduction and a 3-month aspirin removal strategy (hybrid de-escalation) as part of the de-escalation strategy can reduce cardiovascular complications (net clinical outcome). There have been no previous studies on the reduction effect of ticagrelor, and this study involves 35 sites in Korea, showing a registration rate of around 20% currently. Registration is expected to close in 2025, and the results are anticipated to be announced around the same time as the ELECTRA-SIRIO 2 study.

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