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LATE BREAKING CLINICAL TRIAL (JCS 2023)

Prasugrel Monotherapy After Percutaneous Coronary Intervention With Biodegradable-Polymer Platinum-Chromium Everolimus Eluting Stent for Japanese Patients With Chronic Coronary Syndrome (ASET-JAPAN)

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Background: P2Y12 inhibitor monotherapy without aspirin immediately after percutaneous coronary intervention (PCI) has not been tested in East Asian patients, so in this study we aimed to assess the safety and feasibility of reduced dose (3.75 mg/day) prasugrel monotherapy in Japanese patients presenting with chronic coronary syndrome (CCS).

Methods and Results: ASET-JAPAN is a prospective, multicenter, single-arm pilot study that completed enrolment of 206 patients from 12 Japanese centers in September 2022. Patients with native de-novo coronary lesions and a SYNTAX score <23 were treated exclusively with biodegradable-polymer platinum-chromium everolimus-eluting stent(s). Patients were loaded with standard dual antiplatelet therapy (DAPT) and following successful PCI and optimal stent deployment, they received low-dose prasugrel (3.75 mg/day) monotherapy for 3 months. The primary ischemic endpoint was a composite of cardiac death, spontaneous target-vessel myocardial infarction, or definite stent thrombosis. The primary bleeding endpoint was Bleeding Academic Research Consortium (BARC) type 3 or 5. At 3-month follow-up, there were no primary bleeding or ischemic events, or any stent thrombosis.

Conclusions: This pilot study showed the safety and feasibility of prasugrel monotherapy in selected low-risk Japanese patients with CCS. This "aspirin-free" strategy may be a safe alternative to traditional DAPT following PCI.

Key Words: Antiplatelet monotherapy; Coronary artery disease; Drug-eluting stent; Prasugrel; Percutaneous coronary intervention

Dual antiplatelet therapy (DAPT) with aspirin and P2Y12 inhibitors has been the standard of care after percutaneous coronary intervention (PCI) to prevent thrombotic and ischemic events,[1,2] but long-term use is associated with an increased risk of bleeding events.[3] Recently, several randomized controlled trials (RCTs) have shown promising results with short durations of DAPT (i.e., 1–3 months) followed by P2Y12 inhibitor monotherapy;[4,5] however, an "aspirin-free strategy" has only been tested in 1 pilot study.[6] Prasugrel, a 3rd-generation thienopyridine, provides greater, more rapid, and more consistent platelet inhibition than its predecessor, clopido-

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grel.[7] Preclinical data demonstrated that the active metabolites contribute to strong inhibition of platelet activity without the need of a synergistic effect from aspirin.[8] Furthermore, daily use of aspirin results in an increased risk of gastrointestinal mucosal damage and subsequent bleeding, which may lead to adverse cardiovascular and non-cardiovascular events.[1] The Acetyl Salicylic Elimination Trial (ASET) pilot study conducted in Brazil demonstrated the safety and feasibility of prasugrel monotherapy without aspirin immediately after optimal PCI with biodegradable-polymer platinum-chromium everolimus-eluting stent(s) (EES) in patients presenting with chronic coronary syndrome (CCS).[6]

East Asians have a higher prevalence of the loss of function of CYP2C19*2 and *3 alleles, which is associated with high on-treatment platelet reactivity, and although their thrombotic event rate is similar or even lower after PCI compared with Caucasians, their risk of bleeding events is greater.[9] This phenomenon, referred to as the "East Asian paradox", suggests a need to modify DAPT regimens according to ethnicity.[10] Therefore, the ASET-Japan pilot study was designed to explore the feasibility and safety of an adjusted dose of prasugrel monotherapy (3.75 mg/day), without aspirin, after optimal PCI using biodegradable-polymer platinum-chromium EES in Japanese patients with CCS or stabilized non-ST-segment elevation acute coronary syndromes.

Methods

Study Design

The design of the ASET-Japan pilot study has been described elsewhere, but briefly it is a multicenter, single-arm, open-label, proof-of-concept trial conducted in 12 Japanese centers with a stopping rule based on the occurrence of definite stent thrombosis (ST).[11,12] The certified review board and local ethics committee at each participating center approved the study protocol (Reference no. CRB4180003). All enrolled patients provided written informed consent and the study complied with the Declaration of Helsinki. The study protocol was registered at the Japanese Registry of Clinical Trials (identifier: jRCTs042200053) and ClinicalTrials.gov (identifier: NCT05117866). Herein, we report the primary endpoints from Phase 1 of the study in CCS patients.

Inclusion and Exclusion Criteria

The inclusion and exclusion criteria have been previously reported,[11] but in brief, patients requiring PCI for CCS who had an anatomical SYNTAX (SYNergy between PCI with TAXUS and Cardiac Surgery) score <23 were screened and considered for enrolment.[11] All planned procedures had to be performed using the SYNERGY EES (Boston Scientific, Marlborough, MA, USA). For patients having staged procedures, the last planned procedure was considered the index procedure (**Supplementary Table 1**, **Supplementary File**).

Protocol for Antiplatelet Therapy

Unless patients were on long-term DAPT (≥5 days prior to the index PCI) they were loaded 2 h prior to their index PCI with standard DAPT (aspirin 81–330 mg and clopidogrel 300 mg, or prasugrel 20 mg, or ticagrelor 180 mg). Post-PCI all enrolled patients received prasugrel monotherapy at a maintenance dose of 3.75 mg/day until 3-month follow-up. Aspirin was not prescribed after the index PCI.

PCI Procedures

The index PCI was performed with the intention of achieving an optimal result in ≥1 lesion with angiographic diameter stenosis ≥50%, as identified by the local interventional cardiologist. Periprocedural anticoagulation was used at the operator's discretion according to local guidelines. All target lesions were treated exclusively with SYNERGY EES(s).

Inclusion in the trial required the achievement of optimal stent implantation according to local standards of care using angiography, quantitative coronary angiography (QCA) and/or intracoronary imaging (intravascular ultrasound [IVUS] or optical coherence tomography [OCT]), and was defined as successful stent implantation in the target lesion with a visual residual diameter stenosis <20%, and no edge dissection, thrombus, major side branch occlusion, "no-reflow", major stent under-expansion or major incomplete stent apposition.[13] Use of intracoronary imaging pre- and/or post-stent implantation for optimization was left to the operator's discretion.

Clinical Follow-up Data Collection

Clinical follow-up to assess for adverse clinical events and

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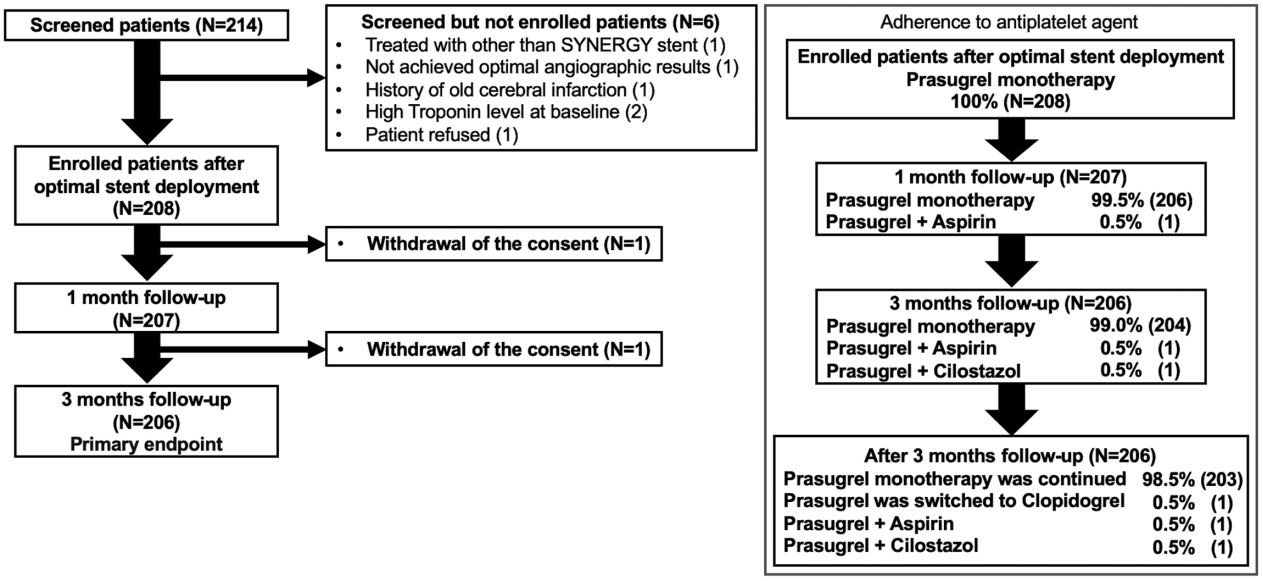

Figure 1. Flow chart of ASET-JAPAN pilot study.

monitor the adherence to medications was performed by telephone at 1 month, and by an in-person visit at 3 months. During follow-up visits the data on cardiovascular drug use and any serious adverse events were collected using an electronic data collection system.

At 3 months, following discontinuation of the per-protocol prasugrel, the choice and duration of antiplatelet therapy was left to the investigator's discretion. However, as a part of the protocol, but not included in the primary endpoint, investigators were asked to report any adverse ischemic and bleeding events occurring in the 30 days following prescription of their chosen antiplatelet(s).

Study Endpoints

The primary ischemic endpoint was a composite of cardiac death, target-vessel myocardial infarction (MI) >48 h after the index PCI, or definite ST occurring ≤3 months after the index procedure.[14] The primary bleeding endpoint was Bleeding Academic Research Consortium (BARC) type 3 or 5 bleeding occurring ≤3 months after the index PCI.[15] Spontaneous MI was defined according to the Fourth Universal definition, and periprocedural MI (<48 h post-PCI) was defined according to the 2013 Society for Cardiovascular Angiography and Interventions (SCAI) definition.[16,17] Death and ST were defined according to the Academic Research Consortium (ARC)-2 definition.[12] Secondary endpoints included all-cause death, stroke (subclassified as ischemic, hemorrhagic, or unknown), all MIs; repeat revascularization, definite, probable, or possible ST, BARC types 1–5 bleeding, and each individual component of the primary endpoint. All clinical endpoints were adjudicated by an independent clinical events committee (**Supplementary Appendix**). An independent Data and Safety Monitoring Board oversaw the safety of all patients during enrolment and follow-up, and was assigned the critical role of applying the stopping rule (**Supplementary Appendix**), which stated that study recruitment would have to be terminated if during active enrolment of the trial there were ≥3 cases of definite ST ≤3 months after the index PCI. Importantly, operators were obliged to report ST events ≤24 h, and this was monitored daily.

Retrospective Analysis by Imaging Corelab

QCA, Murray law-based quantitative flow ratio (μQFR), and quantitative IVUS/OCT analyses were performed retrospectively by a central academic core laboratory (CORRIB CORE lab, University of Galway, Ireland) using dedicated offline software (CAAS v8.2.4, Pie Medical Imaging, Maastricht, the Netherlands; AngioPlus Core, Pulse Medical Imaging Technology, Shanghai, China; and QIvus v3.1, MEDIS, Leiden, the Netherlands, respectively).

Statistical Analysis

Continuous variables are expressed as mean±standard deviation (SD) or as median with interquartile range as appropriate. Categorical variables are expressed as frequencies and percentages. All analyses were performed using SPSS Statistics version 27 (IBM Corp., Armonk, NY, USA).

Results

Study Population

The flow chart of the study is shown in **Figure 1**. During the recruitment period 214 patients with CCS were screened and 208 were enrolled. After enrollment, 2 patients withdrew their consent and explicitly requested that their data is not included in this report; therefore, the primary endpoint was assessed in 206 patients. All participating sites, recruitment numbers, and the total number of PCIs performed for CCS during the enrolment period at each site are shown in **Supplementary Table 2** (**Supplementary File**).

Table 1. Baseline Patient Characteristics (n=206)*	
Age, years	69.0±9.8
Male	168 (81.6)
Female	38 (18.4)
Body mass index, kg/m^2	24.6±3.9
Medical history	
Current smoking	36 (17.5)
Diabetes mellitus	74 (35.9)
Insulin-dependent	15 (7.3)
Hypertension	165 (80.1)
Dyslipidemia	176 (85.4)
Family history of coronary artery disease†	12 (5.8)
Previous MI	27 (13.1)
Established peripheral vascular disease	13 (6.3)
Chronic obstructive pulmonary disease	10 (4.9)
Heart failure	16 (7.8)
Major bleeding‡	4 (1.9)
Renal insufficiency§	71 (34.4)
Previous PCI	51 (24.8)
Previous coronary bypass artery graft	4 (1.9)
Left ventricular ejection fraction, %	60.5±10.0
Anatomical SYNTAX score	8.0±4.6
Clinical presentation	
Newly developed exertional angina (without cardiac biomarker rise)	2 (1.0)
Chronic coronary syndrome	167 (81.1)
Silent myocardial ischemia	37 (18.0)
CCS classification	
I	68 (40.7)
II	86 (51.5)
III	11 (6.6)
IV	2 (1.2)

Data are mean±SD, or n (%). *Two patients withdrew their consent after enrollment and explicitly requested that their data is not included in this report. Therefore, the number of the enrolled patient was 208 but the data presented in this table is based on 206 patients. †History of coronary artery disease in 1st-degree relative. ‡History of bleeding events requiring hospitalization within 1 year. §Renal insufficiency defined as estimated glomerular filtration rate of creatinine clearance <60 mL/min/1.73 m^2. CCS, Canadian Cardiovascular Society; MI, myocardial infarction; PCI, percutaneous coronary intervention.

Table 2. Lesion and Procedural Characteristics*	
Patients (n=206)	
Vascular access site per patient	
Femoral	7 (3.4)
Radial	193 (93.7)
Brachial	6 (2.9)
Guiding catheter size	
6Fr	148 (71.8)
7Fr	57 (27.7)
8Fr	1 (0.5)
No. of lesions treated per patient	
1	188 (91.2)
2	17 (8.3)
≥3	1 (0.5)
Treated lesions (n=225)	
Left main coronary artery	3 (1.4)
Left anterior descending coronary artery	142 (63.1)
Left circumflex coronary artery	34 (15.0)
Right coronary artery	46 (20.5)
AHA lesion type	
A	56 (24.9)
B1	84 (37.3)
B2	52 (23.1)
C	33 (14.7)
Imaging for stent optimization	
None (angiography alone)	1 (0.4)
IVUS	152 (67.5)
OCT/OFDI	72 (32.1)
Prelesion preparation	
Direct stenting	43 (19.1)
Predilatation with non-compliant or compliant balloon	128 (56.9)
Predilatation with cutting balloon	30 (13.3)
Predilatation with scoring balloon	22 (9.8)
Rotational atherectomy	1 (0.4)
Directional coronary atherectomy	1 (0.4)
Post-dilatation	141 (62.7)
Preprocedural TIMI flow grade	
0	2 (0.9)
1	3 (1.3)
2	21 (9.3)
3	199 (88.5)
Postprocedural TIMI flow grade	
0	0
1	0
2	0
3	225 (100)
No. of stents used per patient	
1	178 (86.4)
2	27 (13.1)
≥3	1 (0.5)
Total stent length per patients, mm	28.6±12.4
Per stent characteristics (n=235 stents)	
SYNERGY stent used	235 (100)
Stent length, mm	25.0±8.7
Stent nominal diameter, mm	3.0±0.5
Procedure time, min	63.2±27.8
Days in hospitalization	3 (3–4)
Prasugrel loading dose (20 mg) given after successful PCI procedure	5 (2.4)

Data are mean±SD, n (%), or median (interquartile range). *Two patients withdrew their consent after enrollment and explicitly requested that their data is not included in this report. Therefore, the number of the enrolled patient was 208 but the data presented in this table is based on 206 patients. AHA, American Heart Association; IVUS, intravascular ultrasound; OCT, optical coherence tomography; OFDI, optical frequency domain imaging; PCI, percutaneous coronary intervention; TIMI, Thrombolysis in Myocardial Infarction.

(**Table 2** continued the next column.)

Table 3. Pre- and Postprocedure QCA, Intravascular Imaging, and Postprocedure Quantitative Flow Ratio Analyses

QCA* (n=224 lesions)	
Preprocedure	
Reference diameter (mm)	2.78±0.69
Minimum lumen diameter (mm)	1.12±0.50
DS (%)	59±14
Lesion length (mm)	14.4±8.0
Postprocedure	
Reference diameter (mm)	2.87±0.66
Minimum lumen diameter (mm)	2.46±0.64
DS (%)	14±9
Residual DS >20%, % (n)	19.6 (44)
IVUS (n=147 lesions)	
Stent length (mm)	27.6±12.1
Mean stent area (mm^2)	7.42±2.96
Minimum stent area (mm^2)	5.72±2.35
Minimum stent area >5.5 mm^2, % (n)	46.3 (68)
Minimum lumen area (mm^2)	5.69±2.38
Minimum lumen diameter (mm)	2.60±0.51
Proximal reference area (mm^2)	8.68±3.96
Distal reference area (mm)	6.37±3.04
Stent expansion index (%)	80.1±18.2
Stent expansion index <80%, % (n)	51.0 (75)
Thrombus, % (n)	5.4 (8)
Major dissection, % (n)	0
OCT (n=60 lesions)	
Stent length (mm)	26.0±8.9
Mean stent area (mm^2)	7.71±2.74
Minimum stent area (mm^2)	6.21±2.50
Minimum stent area >4.5 mm^2, % (n)	67.7 (40)
Minimum lumen area (mm^2)	5.97±2.34
Minimum lumen diameter (mm)	2.70±0.53
Proximal reference area (mm^2)	7.69±2.80
Distal reference area (mm^2)	6.50±3.27
Stent expansion index (%)	88.1±15.6
Stent expansion index <80%, % (n)	30.0 (18)
Thrombus, % (n)	11.7 (7)
Major dissection, % (n)	0
QFR (n=217 treated vessels)	
Postprocedure μQFR (mean±SD)	0.93±0.05
Postprocedure μQFR ≥0.91, % (n)	77.9 (169)

Data are mean±SD, n (%). *Due to incompatibility of software, of 225 treated lesions, QCA could not assess 1 lesion (0.4%). DS, diameter stenosis; IVUS, intravascular ultrasound; OCT, optical coherence tomography; QCA, quantitative coronary angioplasty analysis; μQFR, Murray law-based quantitative flow ratio; SD, standard deviation.

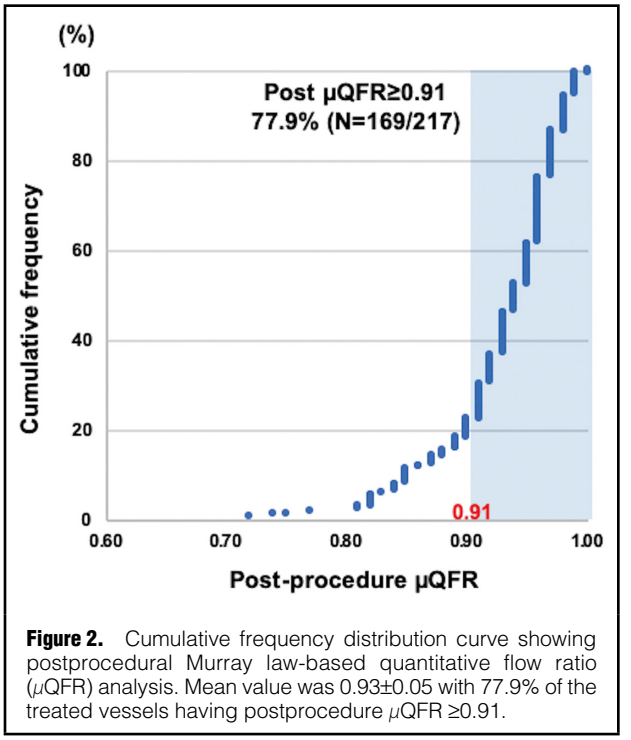

Figure 2. Cumulative frequency distribution curve showing postprocedural Murray law-based quantitative flow ratio (μQFR) analysis. Mean value was 0.93±0.05 with 77.9% of the treated vessels having postprocedure μQFR ≥0.91.

Baseline Patient Characteristics

Baseline characteristics of the patients are shown in **Table 1**. The mean age was 69.0±9.8 years and 81.6% were male. The prevalence of diabetes mellitus was 35.9%, with 7.3% insulin-dependent, and 24.8% of patients had undergone prior PCI. The mean site-reported anatomical SYNTAX score was 8.0±4.6. Two patients had a newly developed exertional angina without a rise of cardiac biomarkers.

Overall, 39.8% of the cohort met the Japanese high bleeding risk (J-HBR) criteria.[2] The Patterns of Non-adherence to Antiplatelet Regimen In Stented patients (PARIS) and the Coronary REvascularization Demonstrating Outcome Study in CREDO-Kyoto thrombotic and bleeding risk scores of patients are shown in **Supplementary Figure** (**Supplementary File**).[18,19]

Lesion and Procedural Characteristics

Lesion and procedural characteristics are shown in **Table 2**. Radial access was selected in the majority (93.7%); 92% of patients received 1 SYNERGY stent, and ≥50% of lesions were American Heart Association (AHA) type A or B1. Periprocedural MI occurred in 0.5%.

Although optimal stent deployment was a prerequisite of enrolment, 19.6% of stented lesions were retrospectively found to have a residual diameter stenosis ≥20% by QCA (**Table 3**). Postprocedure Thrombolysis In Myocardial Infarction flow grade 3 was achieved in all cases.[20] Intravascular imaging was performed in 224 lesions (99.6%), of which 3 could not be analyzed due to suboptimal image quality and 12 due to lack of visualization of the entire stent. A minimum stent area (MSA) ≥5.5 mm^2 by IVUS or ≥4.5 mm^2 by OCT was achieved in 46.6% and 67.7% of the lesions, respectively. Stent expansion index <80% was seen in 51.0% and 30.0% of lesions using IVUS and OCT, respectively. No major dissection was identified. The mean postprocedure μQFR was 0.93±0.05, and μQFR ≥0.91 was achieved in 77.9% of the 217 treated vessels[21] (**Figure 2**). Medications that would have influenced the primary outcomes are summarized in **Table 4**.

Antiplatelet Therapy Before and After the Index PCI

Of the 206 patients, 156 were on a chronic prasugrel regimen at the time of the index procedure (≥5 days); 16 patients received a loading dose of prasugrel 20 mg ≥2 h prior to the index procedure and 15 patients received the loading dose within 2 h of the index procedure. Of those 31 patients who

Table 4. Medications at Discharge and Follow-up

Medication (n=206)	Discharge	1 month	3 months
Statin	190 (92.2)	191 (92.7)	191 (92.7)
Ezetimibe	63 (30.6)	73 (35.4)	75 (36.4)
Proprotein convertase subtilisin kexin-9 inhibitors	0 (0)	0 (0)	2 (1.0)
Proton pump inhibitor	159 (77.2)	157 (76.2)	155 (75.2)

Data are n (%).

Table 5. Clinical Outcomes During 3-Month Follow-up

Clinical outcomes	
Primary ischemic endpoint: Composite of cardiac death, target-vessel spontaneous MI, or definite ST	0 (0)
Cardiac death	0 (0)
Target-vessel spontaneous MI (48 h after index PCI)	0 (0)
Definite ST	0 (0)
Primary bleeding endpoint: BARC type 3 or 5 bleeding	0 (0)
Secondary endpoints	
All-cause death	0 (0)
Cardiac death	0 (0)
Stroke	
Ischemic	1 (0.5)
Hemorrhagic	0 (0)
Unknown	0 (0)
MI	
Target-vessel related	0 (0)
Non-target-vessel related	1 (0.5)
Bleeding: BARC types 1–5	
Type 1	4 (2.0)
Type 2	1 (0.5)
Type 3a	0 (0)
Type 3b	0 (0)
Type 3c	0 (0)
Type 4	0 (0)
Type 5a	0 (0)
Type 5b	0 (0)
All revascularizations	
Non-target-vessel revascularization	1 (0.5)
ST	
Definite	0 (0)
Probable	0 (0)

Data are n (%). BARC, bleeding academic research consortium; MI, myocardial infarction; PCI, percutaneous coronary intervention; ST, stent thrombosis.

received a loading dose of prasugrel before the index PCI, 13 were on aspirin monotherapy, 1 was on clopidogrel monotherapy, and 2 were on DAPT with aspirin and clopidogrel at the time of the index procedure. A total of 13 patients received the loading dose of prasugrel during the index procedure, and of them, 6 were on aspirin monotherapy, 1 was on clopidogrel monotherapy, and 2 were on DAPT with clopidogrel and aspirin. Only 5 patients received the loading dose of prasugrel after the index procedure, and of them, 3 were on chronic DAPT with aspirin and clopidogrel, and 2 were on aspirin monotherapy at the time of the index procedure. The 1 patient who was on DAPT (aspirin and clopidogrel) was switched to prasugrel monotherapy without receiving a loading dose of prasugrel after the index procedure.

Clinical Outcomes

No primary ischemic or bleeding endpoints occurred during the 3-month follow-up period. All adverse events adjudicated by the clinical event committee are summarized in **Table 5**. Narratives of adjudicated cases with secondary endpoints are also summarized elsewhere (**Supplementary File**).

Adherence to Antiplatelet Agents in Patients Without Major Adverse Cardiovascular Events

Adherence to antiplatelet agents is shown in **Figure 1** and overall 98.5% of patients were adherent to the study medication at 3-month follow-up in the cross-sectional analysis. Of note, after the 3-month follow-up the investigators continued to prescribe prasugrel monotherapy in 98.5% of the population. Narratives of non-adherent patients are summarized elsewhere (**Supplementary File**).

Discussion

The main findings of this first prospective study assessing the safety and feasibility of low-dose of prasugrel monotherapy following PCI in East Asians with CCS are: (1) with an adjusted dose (3.75 mg/day) of prasugrel monotherapy, there were no primary thrombotic or bleeding events, or any cases of ST, within 3 months of PCI using SYNERGY EES in patients with CCS; (2) intracoronary imaging guidance with IVUS or OCT was used for stent optimization in 99.6% of lesions despite not being protocol mandated.

Short History of DAPT

When the first-in-man "percutaneous transluminal coronary angioplasty (PTCA)" was performed in 1977, low-dose aspirin was administered as an adjunctive pharmacological treatment to vitamin K antagonists to prevent acute thrombotic events after the procedure.[22] With the inception of coronary stents, P2Y12 inhibitors in combination with aspirin became the standard regimen following PCI; however, confronted with an excess of bleeding the era of extensive research on the optimal duration and dosage of DAPT was initiated to establish the benefit-risk ratio between ischemia and bleeding.[23] Recent RCTs demonstrated that strategies using short (1–3 month) DAPT were associated with less bleeding events without a global increased risk of ischemic events when compared with standard 12 months' DAPT.[5,24] In 2013, the GLOBAL LEADERS was the first trial investigating the potential

benefit of 1-month DAPT followed by monotherapy of a P2Y12 inhibitor (i.e., ticagrelor),[24] with the trial's foundation based on reports showing on the one hand an absence of any synergistic effect of aspirin when added to prasugrel's inhibition of the 6 agonists that trigger the adhesion and the aggregation of platelets, and on the other hand, double-blind gastroscopy data showing respective incidences of ulceration and erosion of 20% and 40% after only 7 days of aspirin. Both studies from 2011 motivated trialists to explore de-escalation and/or elimination of aspirin in the post-PCI pharmacological regimen.[8,25] Furthermore, an independent analysis of the Platelet Inhibition and Patient Outcome (PLATO) trial by the US Food and Drug Administration revealed that high-dose aspirin (200–300 mg) increased the hazard ratio estimated for major adverse cardiovascular/cerebrovascular events (MACCE), while low-dose aspirin decreased it.[26] It was extrapolated that the absence of aspirin could further reduce the hazard ratio. Daily aspirin, even in low doses, is associated with an increased risk of gastrointestinal and intracranial bleeding, with the former considerably increasing the risk of death and MI after PCI.[25,27] Notably, spontaneous bleeding after PCI has a similar effect on long-term mortality rates to spontaneous MI, regardless of the indication for PCI.[28]

High Bleeding Risk (HBR) Concept and the Asian Paradox

HBR has recently gained academic and clinical interest because of the remarkable reduction in thrombotic events with newer generation drug-eluting stents (DES) with thin or ultra-thin struts. Current Japanese guidelines focusing on DAPT have introduced specific HBR (J-HBR) criteria, while also recommending the evaluation of bleeding risk as the first step in selecting antithrombotic therapies post-PCI.[2] East Asians are more prone to gastrointestinal bleeding and intracranial hemorrhage than Caucasians, which can partly be explained by their higher prevalence of *Helicobacter pylori* infection, intracranial atherosclerosis, and post-stroke hemorrhagic transformation when exposed to antithrombotic therapy.[23,29] In the CREDO-Kyoto Registry cohort 3 study, 64% of patients undergoing PCI were considered at HBR according to the J-HBR criteria, with 58.8% of them also at high thrombotic risk based on the CREDO-Kyoto risk score.[30] The STOPDAPT-2 trial demonstrated that 1-month DAPT significantly reduced the risk of major bleeding without affecting thrombotic risk compared to 12-month DAPT in the Japanese population.[5] Currently, there are numerous bleeding and ischemic risk scores and we arbitrarily selected one of the first to be published, and one specific to Japan, based on the ARC-HBR criteria modified for Japanese patients by including several Japanese-specific factors associated with HBR.[2,18,19] It is noteworthy that despite being highly selected, 39.8% of the patients in the ASET-Japan trial met the J-HBR criteria; however, the proportion was much lower than in previous trials.

Another important factor is the genetic polymorphism of CYP2C19 among East Asians. The recent Korean PTRG-DES study demonstrated that high P2Y12 reaction units (PRU ≥252) were associated with a higher incidence of all-cause death and MACCE, but not major bleeding up to 5 years after PCI compared with intermediate (188–252) or low (PRU <188) groups.[31] Similarly, the Japanese PENDULUM registry showed that a composite of thrombotic/ischemic events was more common in HBR patients with higher (>208) vs. lower (≤208) PRU, with no difference in major bleeding observed regardless of bleeding risk.[32] The latter double-blind RCT also addressed the effect of CYP2C19 polymorphisms on platelet aggregation in a comparison of standard dose clopidogrel (loading 300 mg and maintenance 75 mg) and reduced-dose prasugrel (20 mg and 3.75 mg, respectively) in Japanese patients scheduled for PCI.[33] Intermediate and poor metabolizers were identified in 48.5% and 19.4% of the overall population, respectively. Notably, by 4 weeks there were significant differences in platelet aggregation according to phenotype in the clopidogrel group, and consistent suppression of PRU was seen across the various phenotypes in the prasugrel group. Hence prasugrel would be more beneficial for Japanese patients in whom a considerable amount of CYP2C19 loss-of-function exists. In addition, several pharmacokinetic and pharmacodynamics studies have found that after the administration of prasugrel, the presence of the active metabolite was greater in East Asians than in Caucasians.[34] Consequently, these findings have prompted testing of reduced-dose prasugrel, which may provide a more optimal therapeutic window and a lower tendency toward bleeding in East Asians.[35]

Given the overlap of risk factors for thrombotic and bleeding events, patients with low SYNTAX scores (<23) are less likely to have HBR profiles. Nevertheless, our results in CCS patients are encouraging enough to move on to Phase 2 of the study, enrolling NSTE-ACS patients. The ongoing randomized STOPDAPT-3 trial is also addressing the safety and efficacy of prasugrel monotherapy for patients with HBR or ACS compared with DAPT with aspirin and prasugrel for 1 month after index PCI using cobalt-chromium XIENCE EES (NCT04609111). These studies will provide clinically relevant insights into "aspirin-free" strategies after PCI.

ASET-BRAZIL and ASET-JAPAN

The primary results of the ASET-JAPAN study were similar to those of the Brazilian ASET pilot study, which was the first to demonstrate the safety and feasibility of prasugrel monotherapy, (10 mg as a maintenance dose) post-PCI in non-complex lesions in CCS patients using SYNERGY EES, opening a new avenue of investigation into antiplatelet therapy after PCI.[6] The anatomical SYNTAX score was comparable in the 2 ASET studies (average, Brazil 7.2 vs. Japan 8.0). However, the use of intracoronary imaging was higher in ASET-JAPAN (99.6% vs. 16.8%) than ASET-Brazil. The high rate of intravascular imaging has been observed in previous PCI studies conducted in Japan, presumably reflecting routine local practice of intravascular imaging (either IVUS or OCT) because it is fully reimbursed by the national healthcare system. For example, in the STOP-DAPT 2 and PENDULUM mono study in which intravascular imaging was not mandated by protocol, IVUS/OCT was performed in 99.1% and 96.1% of the population at the discretion of the operator.[5,36] In this pilot study, per protocol, patients were enrolled after successful stent implantation was clinically confirmed by the investigators after the index procedure. When post-hoc QCA was performed in the core laboratory, it revealed that in one-fifth of cases there was significant residual diameter stenosis (≥20%). Despite the high usage of intravascular imaging, optimal expansion (expansion index ≥80%) was achieved in only 55%. These results suggest that prasugrel monotherapy could be safely applied in CCS patients after successful stent implantation by clinical evaluation, without

applying the strict criteria confirmed by an independent core laboratory.

Study Limitations

The findings of this classical first-in-human study need to be considered ashypothesis-generating or as early proof of concept, considering the open-label design, in which the continuation or discontinuation was dependent on a predefined "stopping rule". The trial was conducted without a formal statistical power calculation.

Several limitations warrant consideration. Firstly, only 7.3% (n=206) of the 2,827 patients who underwent PCI during the recruitment period in the 12 Japanese centers were enrolled, which may imply a selection bias, and is a potential issue in terms of the generalizability of the ASET-Japan results to clinical practice inside and outside Japan. Second, only patients with optimal angiographic and/or intravascular results were meant to be enrolled. However, 1 patient, who consented to the study prior to the attempted PCI was not enrolled because the investigator was not fully satisfied with the procedural result. Furthermore, although intravascular imaging was not mandated per protocol, its extensive use, as commonly practiced in Japan, might be perceived by operators outside Japan, as a limitation, because this practice is not universally embraced worldwide. Thirdly, all the lesions in the study were exclusively treated with SYNERGY EES, and theoretically evidence from this study may not be automatically extrapolated to other DES technologies. Fourth, as the standard dose of prasugrel varies in East Asia, further research is needed to generalize our findings to other East Asian countries. The concept of "Asian" has never been defined unambiguously in the context of HBR and use of antithrombotic therapy. Finally, the short follow-up of 4 months did not allow evaluation of the hypothetical effect of an aspirin-free regimen on restenosis or other long-term ischemic events.

Conclusions

The ASET-Japan pilot study demonstrated for the first time that a novel antiplatelet strategy of prasugrel monotherapy (3.75mg) was safe and feasible after PCI with SYNERGY EES in selected Japanese patients with CCS.

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IRB Information

This study was certified by the Certified Review Board at Fujita Health University (Reference no. RB4180003).

Data Availability

The deidentified participant data will not be shared.

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Supplementary Files

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