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ORIGINAL ARTICLE

Aspirin-Free Prasugrel Monotherapy After Percutaneous Coronary Intervention in Patients With Non-ST Elevation Acute Coronary Syndrome

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Background: In the presence of a potent $P2Y_{12}$ inhibitor such as prasugrel, the additional clinical antithrombotic benefit of aspirin is unclear. The feasibility of prasugrel monotherapy without aspirin after percutaneous coronary intervention (PCI) has been demonstrated in chronic coronary syndrome, but is yet to be assessed in patients with non-ST elevation acute coronary syndrome (NSTE-ACS) and low anatomical complexity.

Methods and Results: ASET-Japan is a single-arm study investigating the safety of prasugrel 12-month monotherapy with a locally approved dose (loading 20 mg; maintenance 3.75 mg), started immediately after successful PCI using platinum-chromium everolimus-eluting SYNERGY stents. The primary ischemic endpoint is a composite of cardiac death, spontaneous target vessel myocardial infarction, or definite stent thrombosis; the primary bleeding endpoint is Bleeding Academic Research Consortium (BARC) Type 3 and 5 bleeding. ASET-Japan recruited 101 NSTE-ACS patients from 11 Japanese sites. The mean (±SD) age was 69.1±12.3 years and 36.6% had a PRECISE-DAPT score >25. The mean anatomical SYNTAX score was 7.9±4.7. At 1 year, the primary ischemic endpoint occurred in 1 patient (1.0%; cardiac death). Two BARC Type 3a bleeding events occurred (2.0%): 1 due to a gastric ulcer and 1 to a descending colon malignancy.

Conclusions: Low-dose (3.75 mg/day) prasugrel monotherapy started immediately after SYNERGY stent deployment was feasible and safe in selected NSTE-ACS patients.

Key Words: Acute coronary syndrome (ACS); Antiplatelet monotherapy; Drug-eluting stent (DES); Percutaneous coronary intervention (PCI); Prasugrel

Dual antiplatelet therapy (DAPT) with aspirin and a $P2Y_{12}$ inhibitor is the standard of care following percutaneous coronary intervention (PCI) with a drug-eluting stent (DES), with a longer duration typically recommended for those patients presenting with acute coronary syndrome (ACS) compared with chronic coronary syndrome (CCS). The 2019 Japanese ACS guidelines[1] and the latest guidelines from the European Society of Cardiology (ESC)[2] both give 12-month DAPT a Class I, Level of Evidence A recommendation in patients with ACS

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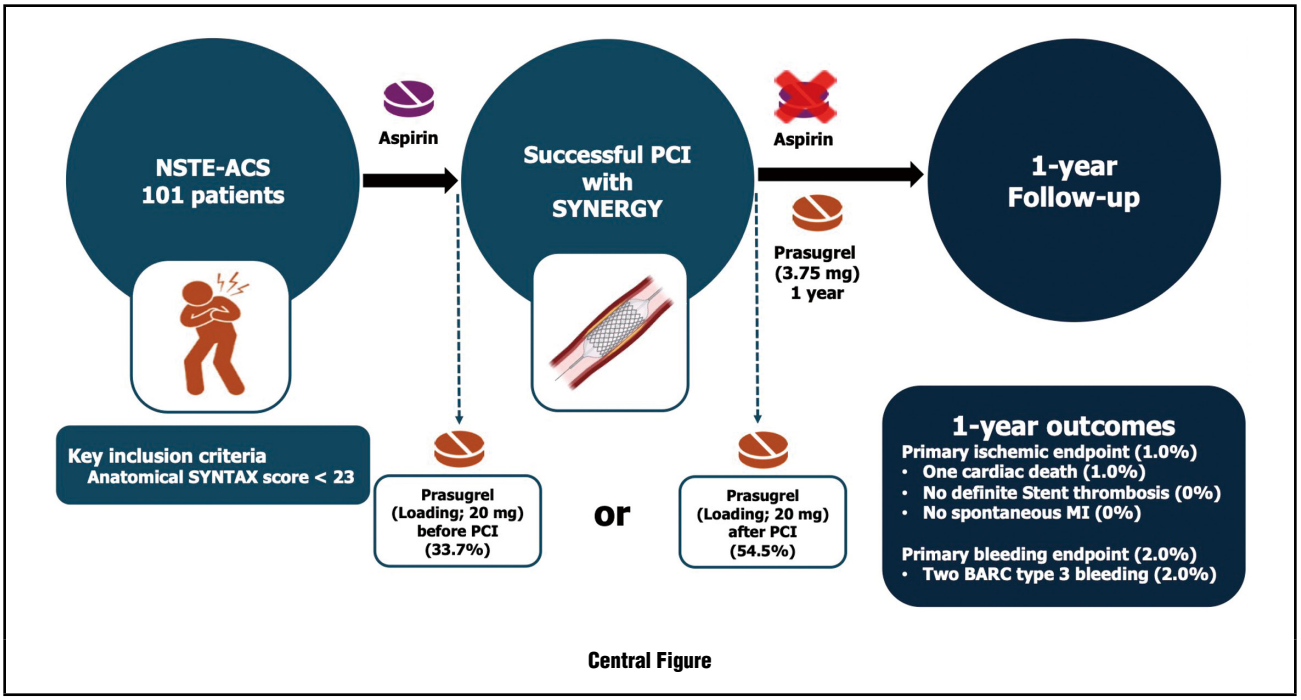

Central Figure

treated with PCI.

However, this 12-month DAPT regimen has been challenged because it was established without robust prospective evidence and potentially leads to overtreatment and associated bleeding. Notably, this standard 12-month duration for DAPT was introduced on the back of findings from the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial in which the average duration of DAPT was 9, not 12, months.[3] Furthermore, contemporary studies investigating the clinical benefit of shorter durations of DAPT in ACS suggest the lack of additional benefit with 12-month DAPT regimens in ACS patients at high bleeding risk (HBR).[4–6] Recent meta-analyses demonstrated that treating patients with ACS with monotherapy using a potent $P2Y_{12}$ inhibitor halves the incidence of bleeding without increasing ischemic events compared with standard DAPT.[7–13] Studies investigating de-escalating DAPT or shortening its duration have consistently demonstrated a reduction in bleeding complications without increasing the risk of cardiovascular or ischemic events compared with a 12-month regimen.

The locally approved standard dose of $P2Y_{12}$ inhibitor is lower in Japanese and Taiwanese patients compared with the rest of the world.[14] Pharmacokinetic studies in healthy populations have shown that East Asian patients, including Japanese, Korean, and Chinese patients, have blood concentrations of active prasugrel metabolites ≥40% higher than patients in Europe and the US, resulting in a significant suppression of platelet aggregation.[15] The "East Asian paradox" is the term given to the phenomenon whereby East Asian populations have a higher risk of bleeding and a lower risk of ischemia compared with European populations. The Prasugrel Compared With Clopidogrel for Japanese Patients With ACS Undergoing PCI (PRASFIT-ACS) trial[16] compared low-dose prasugrel and clopidogrel in patients with ACS. The prasugrel group, which received an initial loading dose of 20 mg prasugrel in combination with aspirin, followed by a low maintenance dose of 3.75 mg/day prasugrel from the next day, had a lower rate of cardiovascular events than the clopidogrel group without an increase in major bleeding events.[16] The results of that study and the pharmacokinetic study[15] were the basis for the decision to use a 20-mg loading dose of prasugrel and a 3.75-mg maintenance dose in Japanese patients with CCS and ACS. Previously, the safety of prasugrel monotherapy after PCI was demonstrated in 206 Japanese patients with CCS (The Acetyl Salicylic Elimination Trial Japan [ASET-Japan] Phase 1).[17] Since the safety of an aspirin-free strategy in ACS had never been demonstrated, the present study (ASET-Japan Phase 2) was designed to include low-risk ACS patients to carefully investigate the safety of this approach in a stepwise extension of the population from CCS.

The feasibility of low-dose prasugrel monotherapy

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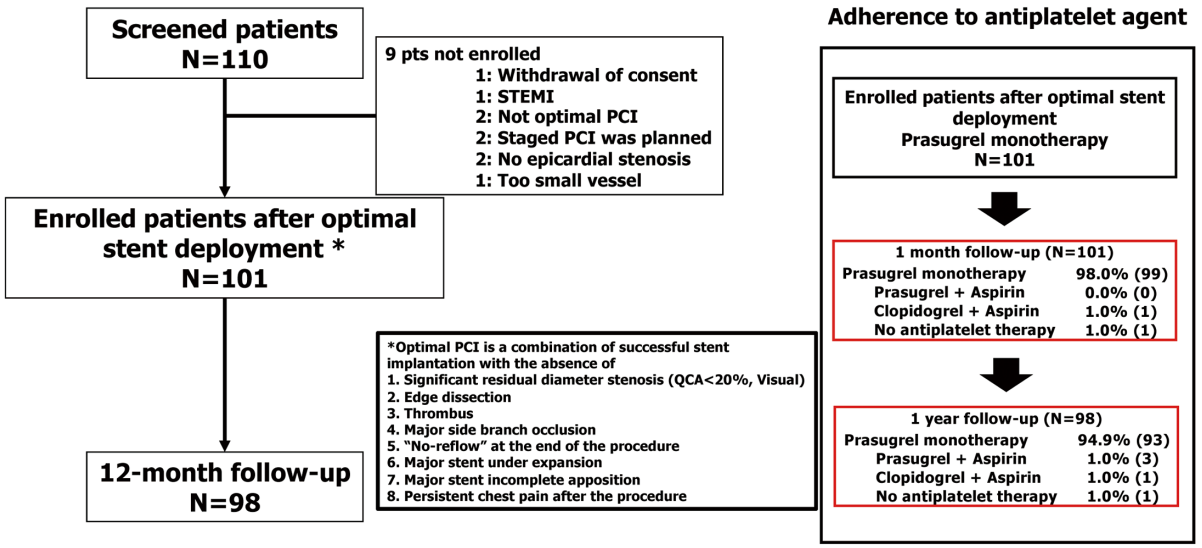

Figure 1. Study flowchart for the The Acetyl Salicylic Elimination Trial Japan (ASET-Japan) Non-ST Elevation Acute Coronary Syndrome (NSTE-ACS) study. PCI, percutaneous coronary intervention; QCA, quantitative coronary angiography; STEMI, ST-elevation myocardial infarction.

after PCI has been demonstrated in Japanese patients with CCS and low anatomical complexity.[17] As an extension of the ASET-Japan CCS study, this ASET-Japan non-ST elevation ACS (NSTE-ACS) study evaluated the feasibility and safety of low-dose prasugrel monotherapy (3.75 mg/day) without aspirin after optimal PCI using biodegradable polymer platinum-chromium everolimus-eluting stents (EES) in selected Japanese patients with NSTE-ACS.

Methods

Study Design

The design of the ASET-Japan pilot study has been described elsewhere;[18] briefly, it is a multicenter, single-arm, open label, proof-of-concept trial conducted at 11 Japanese centers with a stopping rule based on the occurrence of definite stent thrombosis (ST). This study was approved by the Certified Review Board at Fujita Health University (Reference no. CRB4180003), with additional approval obtained from local ethics committees at participating centers if necessary. All enrolled patients provided written informed consent, and the study complied with the Declaration of Helsinki. The study protocol was registered with the Japanese Registry of Clinical Trials (jRCTs042200053) and ClinicalTrials.gov (NCT05117866). The trial initially planned to recruit 200 NSTE-ACS patients;, however, due to a prolonged enrolment period caused by the COVID-19 pandemic and subsequent financial constraints, a protocol amendment was made and study enrolment was terminated after 101 patients had been recruited.

Inclusion and Exclusion Criteria

The inclusion and exclusion criteria have been reported elsewhere (**Supplementary Table 1**).[18] Briefly, patients requiring PCI for ACS who had an anatomical SYNTAX score <23 were screened and considered for enrolment. The SYNTAX score was calculated on angiography performed at the time of presentation of NSTE-ACS. 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. Any patient without optimal acute implantation results, as defined by protocol criteria, was considered a screening failure and excluded from enrollment; detailed reasons for these screening failures are presented in **Figure 1**.

PCI Procedures

The index PCI was performed with the intention of achieving an optimal result in ≥1 lesions 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 a SYNERGY EES. The definition of an optimal acute coronary stenting result is a combination of successful stent implantation at the target lesion with the absence of significant residual diameter stenosis (<20%), edge dissection, thrombus, major side branch occlusion, no reflow at the end of the procedure, major stent underexpansion or major stent incomplete apposition, and the absence of persistent chest pain after the procedure.

All patients were loaded according to local practice with standard DAPT (aspirin 81–330 mg and clopidogrel 300 mg, prasugrel 20 mg, or ticagrelor 180 mg unless the patient is on long-term [≥5 days prior to the index PCI] therapy with prasugrel) before their PCI procedure.

Inclusion in the trial required the achievement of optimal

Table 1. Baseline Patient Characteristics (n=101)	
Age (years)	69.1±12.3
Sex	
Male	75 (75.2)
Female	24 (24.8)
Body mass index (kg/m^2)	24.9±3.4
Current smoking	25 (24.8)
Diabetes	28 (27.7)
Insulin-dependent	3 (3.0)
Hypertension	72 (71.3)
Dyslipidemia	64 (63.4)
Family history of CAD[A]	10 (9.9)
Established PVD	6 (5.9)
COPD	7 (6.9)
History of HF	2 (2.0)
History of major bleeding[B]	1 (1.0)
Renal insufficiency[C]	14 (13.9)
Previous PCI	15 (14.9)
Previous MI	10 (9.9)
Previous CABG	3 (3.0)
LVEF (%)	58±9
Anatomical SYNTAX score	8±5
Clinical presentation	
Unstable angina	20 (19.4)
NSTEMI	81 (80.6)
Cardiac arrest	0 (0)
Cardiogenic shock	0 (0)
Current HF	0 (0)
GRACE risk score	108±25
Low risk (≤108)	50 (49.5)
Intermediate risk (109–140)	40 (39.6)
High risk (>140)	11 (10.9)
Cardiac troponin normalized by ULN[D]	
Before PCI	
Troponin I (n=58)	3.64 [0.91–38.73]
Troponin T (n=40)	2.50 [1.21–9.09]
After PCI	
Troponin I (n=43)	13.85 [4.36–48.77]
Troponin T (n=28)	5.91 [1.93–27.30]

Data are mean±SD, median [interquartile range], or n (%). [A]History of coronary artery disease (CAD) in a first-degree relative. [B]History of bleeding events requiring hospitalization within the previous 1 year. [C]Renal insufficiency was defined as an estimated glomerular filtration rate <60 mL/min/1.73 m^2. [D]Cardiac troponin levels were standardized by dividing the absolute value by the upper limit of normal (ULN) specific to each participating site. A ratio of 1.0 corresponds to the institutional ULN; values >1.0 indicate elevation above the normal range. CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; GRACE, Global Registry of Acute Coronary Events; HF, heart failure; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSTEMI, non-ST segment elevation myocardial infarction; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease.

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 underexpansion, or major incomplete stent apposition.[19] The use of intracoronary imaging before and/or after stent implantation for optimization was left to the discretion of the operator.

Protocol for Antiplatelet Therapy

After achievement of optimal SYNERGY stent implantation, patients were enrolled in the study and were loaded with 20 mg prasugrel immediately after enrollment while still in the catheter laboratory to avoid any further delay in loading with the study drug (if the patient had already been loaded prior to the procedure or was on long-term prasugrel, there was no need for additional loading) and maintained on 3.75 mg prasugrel once daily for 12 months. For patients who had been loaded with 20 mg prasugrel just before the PCI, the next maintenance dose of prasugrel (3.75 mg) was administrated the day after the index procedure.

Collection of Clinical Follow-up Data

Clinical follow-up was performed with outpatient visits at 1 and 12 months and telephone contact at 3, 6, and 13 months. An assessment of angina status, cardiovascular drug use, and any serious adverse events was recorded during clinical follow-up visits. Optimal medical therapy, with strict control of low-density lipoprotein cholesterol, was strongly recommended, along with optimization of all medications according to current guidelines. Information regarding the use of other medications (e.g., β-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers) was also collected.[18]

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 ≤12 months after the index procedure.[20] The primary bleeding endpoint was Bleeding Academic Research Consortium (BARC) Type 3 or 5 bleeding occurring ≤12 months after the index PCI.[21] Spontaneous MI was defined according to the fourth universal definition,[22] and periprocedural MI (<48 h after PCI) was defined according to the 2013 Society for Cardiovascular Angiography and Interventions definition.[23] Death and ST were defined according to the Academic Research Consortium-2 definition.[24] 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, which stated that study recruitment would have to be terminated if during active trial enrolment there were ≥3 cases of definite ST ≤3 months of the index PCI. Importantly, operators were obliged to report ST events ≤24 h, and this was monitored daily.

Retrospective Analysis by an Imaging Core Laboratory

QCA, Murray law-based quantitative flow ratio (μQFR), and quantitative IVUS/OCT analyses were performed retrospectively by a central academic core laboratory

Table 2. Lesion and Procedural Characteristics (n=101 Patients, n=117 Lesions)	
Access	
Femoral	10 (9.9)
Radial	91 (90.1)
Brachial	0 (0.0)
Guideline catheter size	
5 Fr	1 (1.0)
6 Fr	56 (55.4)
7 Fr	44 (43.6)
8 Fr	0 (0.0)
No. lesions treated per patient	
1	88 (87.1)
2	20 (19.8)
≥3	3 (3.0)
No. stents used per patient	
1	90 (89.1)
2	11 (10.9)
≥3	0 (0.0)
Total stent length per patient (mm)	32.9±9.5
Treated lesions (n=117)	
Left main coronary artery	3 (2.6)
Left anterior descending coronary artery	62 (53.0)
Left circumflex coronary artery	20 (17.1)
Right coronary artery	32 (27.4)
AHA lesion type	
A	33 (28.2)
B1	37 (31.6)
B2	28 (23.9)
C	19 (16.2)
Imaging for stent optimization	
Angiography alone	0 (0.0)
IVUS	76 (75.2)
OCT/OFDI	25 (24.8)
Preprocedural lesion preparation	
Direct stenting	29 (24.8)
Predilatation with non-compliant or compliant balloon	67 (57.3)
Predilatation with cutting balloon	6 (5.1)
Predilatation with scoring balloon	9 (7.7)
Rotational atherectomy	0 (0.0)
Directional coronary atherectomy	0 (0.0)
Other	6 (5.1)
Post-dilatation	70 (59.8)
TIMI flow grade	
Preprocedural	
0	10 (8.5)
1	15 (12.8)
2	34 (29.1)
3	58 (49.6)
Postprocedural	
0	0 (0.0)
1	0 (0.0)
2	0 (0.0)
3	117 (100.0)
Per-stent characteristics (n=112 stents)	
SYNERGY stent used	112 (100.0)
Stent length (mm)	27.0±9.5
Stent nominal diameter (mm)	3.4±2.5
Procedure time (min)	69±27
Duration of hospitalization (days)	5.0 [2.0–9.0]
Timing of prasugrel loading dose (20 mg)	
After successful PCI procedure	55 (54.5)
Before PCI	34 (33.7)
Loading dose not given[A]	12 (11.9)
Loading dose of aspirin on date of PCI	49 (48.5)
On maintenance dose of aspirin on date of PCI	52 (51.5)

Data are given as the mean±SD, median [interquartile range], or n (%). [A]Patients on a maintenance dose of prasugrel (3.75 mg) on the date of the PCI, so a loading dose was not given. 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.)

(CORRIB CORELAB, University of Galway, Galway, Ireland) using dedicated offline software (CAAS v8.2.4 [Pie Medical Imaging, Maastricht, Netherlands], AngioPlus Core [Pulse Medical Imaging Technology, Shanghai, China], and QIvus v3.1 [MEDIS, Leiden, Netherlands], respectively).

Statistical Analysis

Continuous variables are expressed as the mean±SD or as the median with interquartile range, as appropriate. Categorical variables are expressed as frequencies and percentages. Binomial exact calculation was used to calculate 95% confidence intervals (CIs). All analyses were performed using SPSS Statistics version 27 (IBM Corp., Armonk, NY, USA).

Because this study was designed as a feasibility study, no formal sample size calculation was performed; however, as mentioned above, the stopping rule was implemented to ensure the safety of enrolled patients. Based on previous studies with similar designs, a sample of 200 CCS patients and 200 NSTE-ACS patients were to be enrolled. However, in NSTE-ACS patients, if more than three (>3) patients experience definite ST following index procedure (day 0) till 12 months follow-up, or if more than two (>2) sudden death cases occur till 30 days follow-up, the trial would be stopped.

Results

Study Population

The study flowchart is shown in **Figure 1**. During the recruitment period, 795 patients with NSTE-ACS were treated by PCI, 101 (12.7%) of whom were enrolled in the study. As described above, enrolment was stopped at 101 patients due to the prolonged study duration and associated budgetary restrictions. After enrolment, 2 patients withdrew consent. The number of patients recruited and the total number of PCIs performed for NSTE-ACS during the enrolment period at each site are presented in **Supplementary Table 2**.

Table 3. Pre- and Post-Procedural QCA, Intravascular Imaging, and Quantitative Flow Ratio Analyses	
QCA	
Before procedure (n=96 lesions)	
Reference diameter (mm)	2.79±0.61
Minimum lumen diameter (mm)	0.96±0.46
DS (%)	66.03±13.15
Lesion length (mm)	23.62±11.68
After procedure (n=100 lesions)	
In-stent analysis	
Minimum lumen diameter (mm)	2.61±0.49
Reference diameter (mm)	3.04±0.05
DS (%)	10.71±7.78
Residual DS >20%, % (n)	9 (9.0)
Segment length (mm)	30.59±15.90
In-segment analysis (including 5 mm proximal and distal to stent)	
Minimum lumen diameter (mm)	2.30±0.51
Reference diameter (mm)	2.82±0.61
DS (%)	18.36±9.92
Segment length (mm)	39.07±15.44
μQFR (n=107 treated vessels)	
Before procedure	0.79±0.21
After procedure	0.94±0.06
Post-procedural μQFR ≥0.91	85 (79.4)
Post-procedural IVUS (n=74 lesions)	
Stent length (mm)	27.93±9.43
Mean stent area (mm^2)	7.74±2.57
Minimum stent area (mm^2)	5.93±2.20
Minimum stent area >5.5 mm^2	36 (48.6)
Minimum lumen area (mm^2)	5.89±2.22
Minimum lumen diameter (mm)	2.70±0.49
Proximal reference area (mm^2)	9.25±3.28
Distal reference area (mm^2)	6.79±3.08
Stent expansion index (%)	77.5±18.9
Stent expansion index <80%	45 (61)
UFR (n=74 lesions)	
Postprocedural UFR	0.92±0.06
Postprocedural UFR ≥0.91	51 (66.2)
Post-procedural OCT (n=26 lesions)	
Stent length (mm)	24.14±6.20
Mean stent area (mm^2)	8.62±1.91
Minimum stent area (mm^2)	6.64±1.77
Minimum stent area >4.5 mm^2	19 (76.0)
Minimum lumen area (mm^2)	6.46±1.73
Minimum lumen diameter (mm)	2.84±0.40
Proximal reference area (mm^2)	9.25±3.46
Distal reference area (mm^2)	8.81±4.49
Stent expansion index (%)	77.1±18.5
Stent expansion index <80%	12 (46.0)
OFR (n=16 lesions)	
Postprocedural OFR	0.95±0.03
Postprocedural OFR ≥0.91	13 (81.3)

Data are mean±SD or n (%). DS, diameter stenosis; IVUS, intravascular ultrasound; OCT, optical coherence tomography; QCA, quantitative coronary angiography; μQFR, Murray law-based quantitative flow ratio; OFR, optical coherence tomography-derived quantitative flow ratio; UFR, ultrasound-derived quantitative flow ratio.

Baseline Characteristics

Baseline patient characteristics are presented in **Table 1**. The mean age was 69.1±12.3 years and 75.1% of patients were male. The prevalence of diabetes was 27.7%, with 3.0% being insulin-dependent; 14.9% of patients had undergone prior PCI. The mean site-reported anatomical SYNTAX score was 7.9±4.7. The clinical indication for PCI was NSTE-ACS and unstable angina in 80.6% and 19.4% of patients, respectively. Overall, 36.6% of the cohort met the PRECISE DAPT criteria of HBR (≥25).[25]

Lesion and Procedural Characteristics

Lesion and procedural characteristics are presented in **Table 2**. Radial access was used predominantly (90.1%); 89.1% of patients received 1 SYNERGY stent, and ≥59.8% of lesions were American Heart Association Type A or B1. There were 2 periprocedural MIs according to biomarker elevations meeting the Society for Cardiovascular Angiography and Interventions definition, although neither patient had any symptoms or required any additional treatment after the PCI.

Although optimal stent deployment was a prerequisite of enrolment, 10.1% of stented lesions were retrospectively found to have a residual diameter stenosis ≥20% by QCA (**Table 3**). Post-procedure Thrombolysis In Myocardial Infarction Grade 3 flow was achieved in all patients. Intravascular imaging was performed in 112 (99.1%) lesions; of these, 12 lesions could not be analyzed due to suboptimal image quality and a lack of visualization of the entire stent. A minimum stent area >5.5 mm^2 by IVUS or >4.5 mm^2 by OCT was achieved in 48.6% and 76.0% of lesions, respectively. IVUS and OCT revealed a stent expansion index <80% in 61.0% and 46.0% of lesions, respectively (**Table 3**). The mean post-procedure μQFR was 0.92±0.06, with a μQFR ≥0.91 achieved in 81.7% of treated vessels (**Figure 2**).

Clinical Outcomes at 1 Year

At 1 year, clinical follow-up was completed in 98% of patients (n=98). The primary ischemic composite endpoint occurred in 1 (1.0%) patient who died due to a cardiac cause (**Table 4**). This patient died suddenly at home 11 months after trial enrolment and although they were transported to hospital, resuscitation was unsuccessful. A detailed investigation into the cause of death, such as an autopsy, was not conducted, and therefore the exact cause of death remains unknown. However, the event adjudication committee classified it as a cardiac death.

The primary bleeding composite endpoint occurred in 2 (2.0%) patients. Both patients had BARC Type 3a bleeding. One patient had bleeding due to descending colon cancer, and the other had bleeding due to multiple gastric ulcers, which were later diagnosed as cancer.

Adherence to Antiplatelet Therapy up to 12 Months

Medication use at discharge and at the 12-month follow-up according to the presence or absence of clinical events is summarized in **Supplementary Table 3**. Adherence to antiplatelet agents is shown in **Figure 1** (detailed adherence at each follow-up period is provided in **Supplementary Table 4**). At the 12-month follow-up, 93 (94.9%) patients were on prasugrel monotherapy, whereas 3 (3.2%) were on DAPT (aspirin and prasugrel; n=3), 1 (1.0%) was on aspirin monotherapy, and 1 (1.0%) was on clopidogrel monotherapy. These changes to antiplatelet medication were made at the discretion of the investigators and were Type

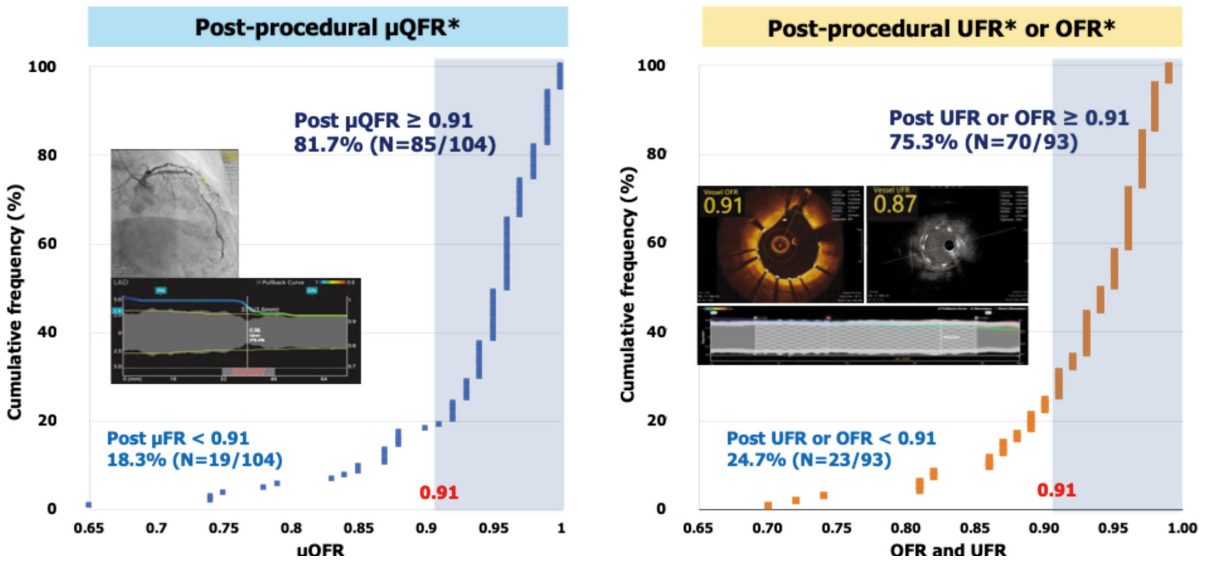

Figure 2. Cumulative frequency distribution curves of post-procedural Murray law-based quantitative flow ratio (μQFR; **Left**) and post-procedural fractional flow ratio based on intravascular imaging (**Right**) derived using optical coherence tomography (OFR; n=16) or intravascular ultrasound (UFR; n=77). *μQFR, UFR and OFR were analyzed using Angio plus, IVUS plus, and OCT plus by pulse software (Pulse Medical Imaging Technology, Shanghai, China).

3, Subtype I, and Subtype U non-adherence, as per the Non-adherence Academic Research Consortium (NARC) criteria.[26] One patient permanently discontinued all antiplatelet therapy because they were diagnosed with gastric cancer and multiple metastases after a BARC Type 3a bleeding event. This patient was treated conservatively and died 6 months after the index PCI. Due to the gastric cancer, the patient had difficulties with oral intake, leading to the oncologist permanently discontinuing prasugrel (NARC Type 3, Subtype M, Subtype R). In addition, 3 patients temporary discontinued prasugrel: 1 patient switched from prasugrel to aspirin for 20 days due to surgery for descending colon cancer and resumed prasugrel postoperatively (NARC Type 2, Subtype M, Subtype R); another patient had a 1-day interruption for treatment on a vocal cord polyp (NARC Type 2, Subtype M); and the last patient had a 5-day interruption for a polypectomy (NARC Type 2, Subtype M) (**Supplementary Table 5**).

Discussion

In this select cohort of Japanese patients with NSTE-ACS and low anatomical disease complexity, low-dose prasugrel monotherapy was feasible and safe. At 1 year, the primary ischemic event rate was 1.0% and the primary bleeding event rate was 2.0% (two BARC Type 3a bleeding events).

The clinical feasibility and benefit of $P2Y_{12}$ inhibitor monotherapy after PCI has been investigated in many previous, and on-going, single-arm and randomized trials (**Table 5**). Salient observations from these studies are as follows.

- the dose of prasugrel was lower in the 3 Japanese studies (3.75 mg in ASET-Japan,[17] STOPDAPT-3,[27,28] and PREMIUM) than in the 4 non-Japanese studies (10 mg in ASETBrazil,[29] OPTICA,[30] LEGACY,[31] and NEOMINDSET[32])
- a specific type of stent was used in 4 studies,[17,27–29] whereas in 3 studies stent selection was left to the operator's discretion
- aspirin use during PCI ranged from 21% (STOPDAPT-3) to 100% depending on the timing of enrolment and/or randomization (before or after PCI).

As expected, studies with post-PCI enrolment had high rates of aspirin use at the time of the procedure because it had already been prescribed as per local practice (e.g., in the ambulance). The absence of aspirin during the index PCI may increase procedure-related thrombotic events, especially when the dose of prasugrel monotherapy is as low as 3.75 mg (STOPDAPT-3[27,28] and PREMIUM). The results of ongoing trials comparing $P2Y_{12}$ inhibitor monotherapy to DAPT, such as the NEOMINDSET (NCT04360720),[32] PREMIUM (NCT05709626), and LEGACY (NCT05125276)[31] trials, are awaited and will provide further clarity on the need for aspirin at the time of PCI, and its impact on ischemic and bleeding events.

One of the objectives at the time of the design of ASET-Japan was to provide preliminary event rates for a future large-scale study. Notwithstanding this, and despite the lack of preceding data, a randomized comparison between prasugrel monotherapy and STOPDAPT-3 has already been reported.[27] The STOPDAPT-3 trial enrolled 6,002 patients with ACS or HBR, randomizing them to prasugrel (3.75 mg/day) monotherapy or DAPT with aspirin (81–100 mg/day) and prasugrel (3.75 mg/day) following a 20-mg prasugrel loading dose in both groups. At 1 month after PCI, the aspirin-free strategy with low-dose prasugrel was comparable to the DAPT strategy for major bleeding (4.47% and 4.71%, respectively; hazard ratio 0.95; 95% CI 0.75–1.20; $P_{superiority}=0.66$) and non-inferior for cardiovascular events (4.12% and 3.69%, respectively; hazard

Table 4. Clinical Outcomes

	No. patients (%)	95% CI of event rate (%)
Primary ischemic endpoint: Composite of cardiac death, target-vessel spontaneous MI, or definite ST	1 (1.0)	0.02–5.3
Cardiac death	1 (1.0)	0.02–5.3
Target vessel spontaneous MI (48 h after index PCI)	0 (0)	0.00–3.59
Definite ST	0 (0)	0.00–3.59
Primary bleeding endpoint: BARC type 3 or 5 bleeding	2 (2.0)	0.24–6.97
Secondary endpoints		
All-cause death	2 (2.0)	0.24–6.97
Cardiac death	1 (1.0)	0.02–5.3
Stroke		
Ischemic	1 (1.0)	0.02–5.3
Hemorrhagic	0 (0)	0.00–3.59
Unknown	0 (0)	0.00–3.59
MI		
Target vessel-related	0 (0)	0.00–3.59
Non-target vessel-related	0 (0)	0.00–3.59
Bleeding: BARC Types 1–5		
Type 1	0 (0)	0.00–3.59
Type 2	1 (1.0)	0.02–5.3
Type 3a	2 (2.0)	0.24–6.97
Type 3b	0 (0)	0.00–3.59
Type 3c	0 (0)	0.00–3.59
Type 4	0 (0)	0.00–3.59
Type 5a	0 (0)	0.00–3.59
Type 5b	0 (0)	0.00–3.59
All revascularizations		
Target vessel revascularization	0 (0)	0.00–3.59
Non-target vessel revascularization	1 (1.0)	0.02–5.3
ST		
Definite	0 (0)	0.00–3.59
Probable	0 (0)	0.00–3.59

BARC, Bleeding Academic Research Consortium; CI, confidence interval; MI, myocardial infarction; PCI, percutaneous coronary intervention; ST, stent thrombosis.

ratio 1.12; 95% CI 0.87–1.45; $P_{\text{non-inferiority}}=0.01$).[27]

Compared with the STOPDAPT-3 trial, event rates in the ASET-Japan NSTE-ACS study were lower, with rates of the composite endpoint (cardiovascular death, MI, and definite ST) of 0% vs 4.12%, respectively, and BARC Type 3 or 5 bleeding of 2.0% vs. 4.55%, respectively. A plausible reason for these differences is the different populations enrolled in each study. In the ASET-Japan NSTE-ACS study, 36.0% of patients were classified as at HBR based on the PRECISE-DAPT score (**Supplementary Figure**).[33] Furthermore, in the ASET-Japan NSTE-ACS study, the proportion of patients with left main stem/left anterior descending artery lesions and multivessel disease was 55.6% and 10.9%, respectively; the mean SYNTAX score was as low as 7.9. In contrast, in STOPDAPT-3, 54.5% of patients were at HBR and 40% had multivessel disease;[34] therefore, compared with the ASET-Japan NSTE-ACS study population, patients in STOPDAPT-3 had relatively simple lesions and less bleeding risk, emphasizing that the feasibility observed in this study only applies to selected NSTE-ACS populations. There was 1 BARC Type 3 bleeding event in a patient with colon cancer. In the setting of emergency procedures for patients such as those with ACS, preoperative patient assessment could be insufficient and may miss the presence of malignancy.

Of note, the enrollment for the present study stopped prematurely, primarily due to the impact of the global pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus during the recruitment period. This delay subsequently resulted in financial constraints to completing the trial and eventually resulted in the premature termination of enrollment at a reduced sample size of 101 patients, instead of the initially planned 200 patients. The relatively small sample size may limit the sensitivity to detect a safety signal in low-frequency events such as early, late, or very late ST. Moreover, this reduction in sample size may affect the robustness and generalizability of our findings, specifically there may not be sufficient statistical power to detect rare complications (e.g., definite ST) that typically have incidence rates below 1%.[35] Although the results of the present study support the feasibility and preliminary safety of prasugrel monotherapy, caution is warranted in interpreting these outcomes, and larger, adequately powered trials are needed to confirm our exploratory observations.

Study Limitations

The present study has several limitations. First, in addition to the small sample size, as discussed above, this trial was a pilot study limited to Japanese patients with NSTE-ACS. As a result, the findings cannot be directly applied to other ethnic groups, such as Western populations usually treated with a 10-mg prasugrel maintenance dose. Second, the study was limited to patients with an anatomical SYNTAX score ≤23. Although it was not mandated in the protocol, intravascular imaging was performed in all patients, reflecting the local practice in Japan, as is demonstrated in other Japanese studies, including STOPDAPT-3 (intravascular imaging use: 93%).[31] The high usage of intravascular imaging is likely related to the optimal stent implantation, as well as the low ischemic event rate in this study. The inclusion was not specific for bleeding risk, resulting in the majority of patients (64% per PRECISE DAPT) being non-HBR.

Conclusions

In selected Japanese NSTE-ACS patients at low ischemic and bleeding risk, the use of low-dose prasugrel monotherapy and no aspirin after successful/optimal SYNERGY stent deployment was feasible and safe at the 1-year follow-up.

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Table 5. Overview of Antiplatelet Therapy Strategies in PCI Studies

Study	Population	Timing of enrolment	Timing of randomization	Stent type	$P2Y_{12}$ inhibitor monotherapy and loading/maintenance dose[A]	Aspirin at the time of procedure?
Randomized trials						
STOPDAPT-3[27,28] (NCT04609111)	STEMI and NSTE-ACS/HBR patients	Before PCI	Before PCI	XIENCE	Prasugrel 20 mg/3.75 mg	The protocol does not allow aspirin after randomization, but 21% of patients were on chronic aspirin on the date of the procedure
PREMIUM (NCT05709626)	STEMI	Before PCI	Before PCI	SYNERGY	Prasugrel 20 mg/3.75 mg	Not specified in ClinicalTrials.gov
NEOMINDSET[32] (NCT04360720)	STEMI and NSTE-ACS	After PCI	After PCI	Latest-generation DES	Prasugrel 60 mg/10 mg or icagrelor 180 mg/90 mg	Use any combination of antiplatelet agents permitted as per local practice
LEGACY[31] (NCT05125276)	NSTE-ACS	After PCI	After PCI	Not specified	The choice of a specific $P2Y_{12}$ inhibitor was at the discretion of the treating physician	Complete omission of aspirin immediately after PCI
Single-arm studies						
OPTICA[30] (NCT04766437)	NSTE-ACS	Before PCI	Not applicable	New-generation DES	Prasugrel 60 mg/10 mg or ticagrelor 180 mg/90 mg	93.3% of patients received loading or chronic aspirin
ASET-Japan NSTE-ACS (NCT05117866)	NSTE-ACS and CCS	After PCI	Not applicable	SYNERGY	Prasugrel 20 mg/3.75 mg	In NSTE-ACS population, 100% (101/101) of patients received aspirin on the day of or 1 day prior to PCI
ASET-Brazil[29] (NCT03469856)	CCS	After PCI	Not applicable	SYNERGY	Prasugrel 60 mg/10 mg	96.5% of patients received aspirin on the day of or 1 day prior to PCI

[A]In the $P2Y_{12}$ inhibitor monotherapy arm for randomized studies. CCS, chronic coronary syndrome; HBR, high bleeding risk; NSTE-ACS, non-ST elevation acute coronary syndrome; PCI, percutaneous coronary intervention; STEMI, ST elevation myocardial infarction.

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IRB Information

This study was approved by the Certified Review Board at Fujita Health University (Reference no. CRB4180003).

Data Availability

The deidentified participant data will not be shared.

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Supplementary Files

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