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ORIGINAL RESEARCH

Prasugrel Monotherapy After Percutaneous Coronary Intervention for Chronic Coronary Syndrome

Insights From ASET Pilot Studies

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ABSTRACT

BACKGROUND The ASET (Acetyl-Salicylic Elimination Trial) pilot studies recently investigated $P2Y_{12}$ inhibitor monotherapy without aspirin immediately after percutaneous coronary intervention (PCI) in Brazil and Japan.

OBJECTIVES This comparative analysis of the 2 ASET pilot studies aimed to summarize clinical outcomes and assess geographic and ethnic differences in baseline demographics and procedures.

METHODS Patients undergoing successful platinum-chromium everolimus-eluting stent implantation for chronic coronary syndrome were included. Following the index PCI, patients received prasugrel monotherapy with a maintenance dose of 10 mg/day in Brazil and 3.75 mg/day in Japan. The primary ischemic endpoint was the composite of cardiac death, spontaneous target vessel myocardial infarction, or definite stent thrombosis. The primary bleeding endpoint was Bleeding Academic Research Consortium types 3 and 5 bleeding at up to 3 months.

RESULTS Of 409 enrollments, 3-month follow-up was completed in 406 patients. Mean age was 64.3 ± 8.4 years, and 73% were men. Overall, post-TIMI flow grade 3 was achieved in 99.8%. Intravascular imaging for poststent optimization was used in 16.8% and 99.6% of treated lesions in Brazil and Japan, respectively. The primary ischemic and bleeding endpoints occurred in the same patient (0.2%). No stent thrombosis events occurred.

CONCLUSIONS Prasugrel monotherapy following PCI was safe and feasible in selected low-risk chronic coronary syndrome patients after optimal platinum-chromium everolimus-eluting stent implantation regardless of the ethnic and geographic differences in baseline demographics, procedures, and prasugrel dosage. Randomized controlled trials will be needed to compare $P2Y_{12}$ inhibitor monotherapy without aspirin with the current standard of care.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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ABBREVIATIONS AND ACRONYMS

BARC = Bleeding Academic Research Consortium

CAD = coronary artery disease

CCS = chronic coronary syndrome

DAPT = dual antiplatelet therapy

NSTE-ACS = non-ST-segment elevation acute coronary syndrome

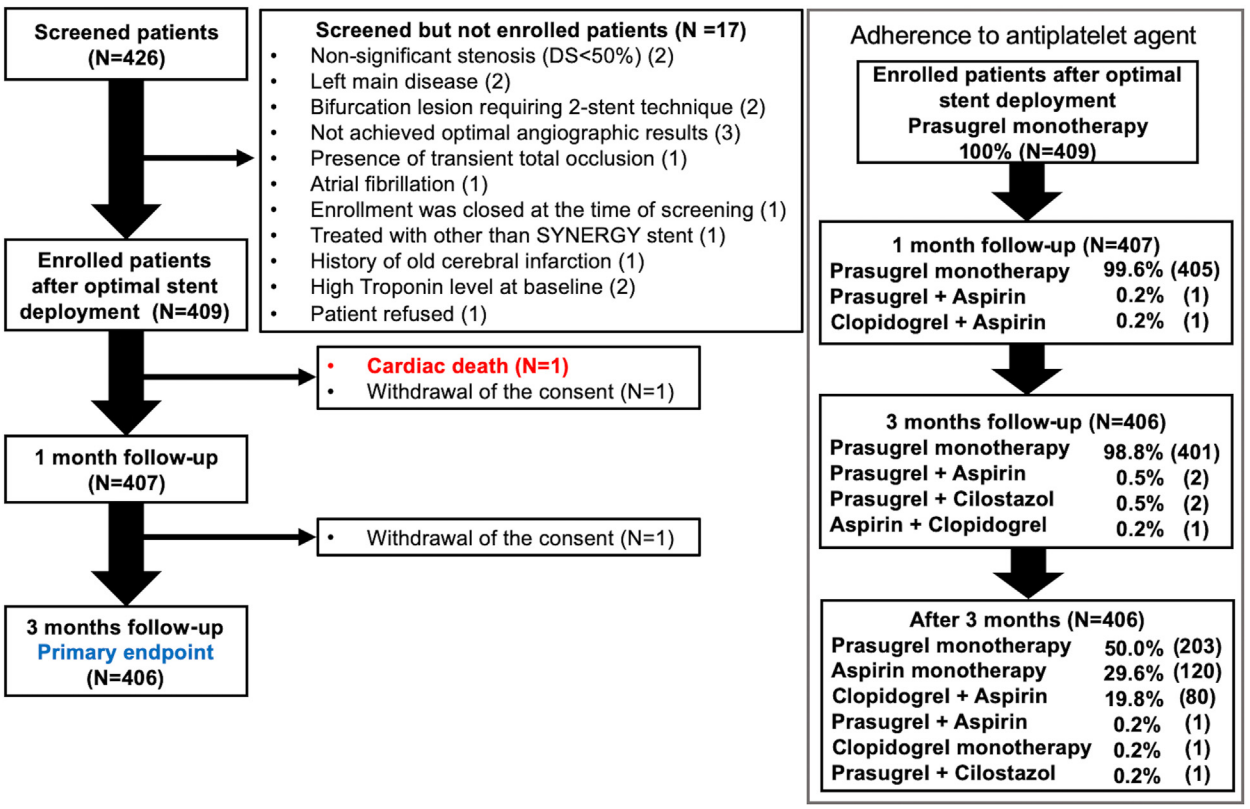
PCI = percutaneous coronary intervention

ST = stent thrombosis

For 3 decades, dual antiplatelet therapy (DAPT) with aspirin and $P2Y_{12}$ inhibitors has been the mainstay pharmacological regimen after percutaneous coronary intervention (PCI), contributing significantly to reductions in thrombotic and ischemic events.[1] Aspirin has historically been prescribed as an antiplatelet agent for secondary prevention following PCI; however, the associated risks of cardiovascular and noncardiovascular events following aspirin-related gastrointestinal bleeding complications are well documented and result in aspirin's use being a double-edged sword.[2] Consequently, several randomized controlled trials (RCTs) have investigated shortening DAPT to 1 to 3 months post-PCI by early discontinuation of aspirin, and have shown that this leads to a reduction in bleeding complications without any increased risk of ischemic and thrombotic events.[3-5] These favorable outcomes with short DAPT strategies have raised the possibility that the complete omission of aspirin immediately after PCI could be even more beneficial.

In 2020, the ASET (Acetyl Salicylic Elimination Trial) pilot study was conducted in Brazil in 201 patients with chronic coronary syndrome (CCS), and demonstrated the safety and feasibility of prasugrel monotherapy with a maintenance dose of 10 mg started immediately after implantation of a biodegradable-polymer platinum-chromium everolimus-eluting stent (EES).[6] The follow-on ASET Japan study was conducted in the same fashion using an adjusted dose of prasugrel (3.75 mg/d) in 206 Japanese patients with CCS.[7] These 2 pilot studies suggest that $P2Y_{12}$ inhibitor monotherapy post-PCI is a viable strategy in certain clinical circumstances and selected patients of different ethnicities.[6,7] Consequently, before testing this aspirin-free strategy in "higher-risk" populations with different ethnicities, ischemic syndromes, and bleeding propensities, it

FIGURE 1 Flowchart of the Trial



Study flowchart and the adherence to an antiplatelet agent. Of 426 patients, 3-month follow-up was achieved in 406 patients. Cardiac death occurred in 1 patient during the follow-up period. After optimal stent deployment, prasugrel monotherapy was given to all patients. At 3 months, prasugrel monotherapy was continued in 98.8% of the population. DS = diameter stenosis.

was felt scientifically important to pool data from both ASET pilot studies and compare the geographical differences in baseline demographics, procedures, and outcomes.

This comparative analysis of the ASET pilot studies therefore aims to summarize 3-month outcomes of a strategy of $P2Y_{12}$ inhibitor monotherapy post-PCI in patients with differences in baseline demographic and procedural approaches before engaging in a major RCT to formally test the efficacy and risk-benefit of an aspirin-free strategy.

METHODS

STUDY DESIGN AND POPULATIONS. The present report is a comparative study of the ASET Brazil (NCT03469856) and ASET Japan (NCT05117866) pilot studies. The designs of both trials have been previously described.[8,9] Briefly, the 2 trials were single-arm, multicenter, open-label, first-in-human, proof of concept studies conducted at 9 centers in Brazil and 12 centers in Japan. Patients requiring PCI for CCS with an anatomical SYNTAX (SYNergy between PCI with TAXUS and Cardiac Surgery) score <23 before revascularization were screened for enrollment. The continuation and completion of the 2 trials were regulated by a stopping rule involving the occurrence of more than 3 definite stent thrombosis (ST) events.[10] A full list of inclusion and exclusion criteria are shown in Supplemental Table 1 and 2. ASET Brazil was certified by the central ethics committee (Comissão de Ética Para Análise de Projetos de Pesquisa) and the local ethics committee at each participating center. ASET Japan was certified by the Certified Review Board at Fujita Health University. The present study complied with the declaration of Helsinki and all enrolled patients provided written informed consent.

INDEX PCI. All patients were loaded with standard DAPT unless they were previously on long-term therapy. In Brazil, this comprised of aspirin 300 mg and clopidogrel 600 mg, whilst in Japan, in accordance with guidelines from the Japanese Circulation Society this included aspirin 81 to 330 mg together with either clopidogrel 300 mg, prasugrel 20 mg, or ticagrelor 180 mg given at least 2 hours before the procedure.[11] The index PCI was performed with the intention to achieve complete revascularization in a patient with at least 1 lesion with an angiographic diameter stenosis ≥50%, as identified by the local interventional cardiologist. Periprocedural anticoagulation was used at the operator's discretion according to local or international guidelines.[12]

TABLE 1 Baseline Patient Characteristics

	Total (N = 407)	Brazil (n = 201)	Japan (n = 206)	*P* Value
Age, y	64.3 ± 10.0	59.5 ± 7.7	69.0 ± 9.8	<0.001
Male	298 (73.2)	130 (64.7)	168 (81.6)	<0.001
Female	109 (26.8)	71 (35.3)	38 (18.4)	<0.001
Body mass index, kg/m^2	26.7 ± 4.6	28.8 ± 4.4	24.6 ± 3.9	<0.001
Medical history				
Current smoking	69 (17.0)	33 (16.4)	36 (17.5)	0.776
Diabetes mellitus	148 (36.4)	74 (36.8)	74 (35.9)	0.851
Insulin dependent	31 (7.6)	16 (8.0)	15 (7.3)	0.840
Hypertension	351(86.2)	186 (92.5)	165 (80.1)	<0.001
Dyslipidemia	316 (77.6)	140 (69.7)	176 (85.4)	<0.001
Family history of CAD	130 (31.9)	118 (61.8)	12 (5.8)	<0.001
Previous myocardial infarction	45 (11.1)	18 (9.0)	27 (13.1)	0.246
Established PAD	24 (5.9)	11 (5.5)	13 (6.3)	0.349
COPD	14 (3.4)	4 (2.0)	10 (4.9)	0.094
Heart failure	21 (5.2)	5 (2.5)	16 (7.8)	0.013
Major bleeding[a]	5 (1.2)	1 (0.5)	4 (1.9)	0.194
Renal insufficiency[b]	71 (17.4)	0 (0)	71 (34.5)	<0.001
Previous PCI	76 (18.7)	25 (12.4)	51 (24.8)	0.001
Previous CABG	7 (1.7)	3 (1.5)	4 (1.9)	0.514
LVEF, %	62.2 ± 9.2	64.3 ± 7.7	60.5 ± 10.0	<0.001
Anatomical SYNTAX score	7.6 ± 4.6	7.2 ± 4.5	8.0 ± 4.6	0.066

Values are mean ± SD or n (%). [a]History of bleeding events requiring hospitalization within 1 year. [b]Impaired renal function is defined as estimated glomerular filtration rate of creatinine clearance <60 mL/min/1.73 m^2.

CABG = coronary artery disease; CAD = coronary artery disease; COPD = chronic obstructive pulmonary artery disease; LVEF = left ventricular ejection fraction; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; SYNTAX = Synergy Between PCI With Taxus and Cardiac Surgery.

All target lesions were exclusively treated with the biodegradable-polymer platinum-chromium EES. The index procedure was performed with the intention of achieving optimal stent implantation according to local standards of care; use of intracoronary imaging resent and/or poststent implantation was left to the operator's discretion. Patients were enrolled into the study after the index PCI, and only if in the operator's clinical judgement, the angiographic and/or intravascular results were satisfactory.

ANTIPLATELET THERAPY AND FOLLOW-UP. After achieving satisfactory stent implantation, patients were loaded with prasugrel (60 mg in Brazil and 20 mg in Japan) in the catheterization laboratory to ensure the loading dose was given and to avoid any inappropriate delays. Patients who were loaded with prasugrel preprocedure or had been on long-term prasugrel did not receive additional loading. Aspirin was discontinued on the day of the index PCI. All enrolled patients were treated with prasugrel monotherapy for up to 3 months with a maintenance dose of 10 mg/d in Brazil, and 3.75 mg/d in Japan. After 3 months, the antiplatelet treatment and strategy was left to the discretion of the treating physician. An

TABLE 2 Lesion and Procedural Characteristics

	Total (N = 407)	Brazil (n = 201)	Japan (n = 206)	*P* Value
Vascular access site per patient				<0.001
Femoral	38 (9.3)	31 (15.4)	7 (3.4)	
Radial	363 (89.2)	170 (84.6)	193 (93.7)	
Brachial	6 (1.5)	0 (0)	6 (2.9)	
Lesions treated per patient				0.002
1 lesion	347 (85.3)	159 (79.1)	188 (91.2)	
2 lesions	53 (13.0)	36 (17.9)	17 (8.3)	
≥3 lesions	7 (1.7)	6 (3.0)	1 (0.5)	
Number of stents used per patient				<0.001
Patients with				
1 stent	320 (78.6)	142 (70.6)	178 (86.4)	
2 stents	77 (18.9)	50 (24.9)	27 (13.1)	
≥3 stents	10 (2.5)	9 (4.5)	1 (0.5)	
Total stent length per patient, mm	30.6 ± 15.6	32.7 ± 18.0	28.6 ± 12.5	0.008
Procedure time, min	54.6 ± 28.5	45.8 ± 26.5	63.2 ± 27.8	<0.001
Prasugrel loading dose given after successful PCI procedure	206 (50.6)	201(100)	5 (2.4)	<0.001
Per-Lesion Characteristics	**Total (N = 475)**	**Brazil (n = 250)**	**Japan (n = 225)**	***P* Value**
Treated lesions				0.019
Left main coronary artery	3 (0.6)	0 (0)	3 (1.4)	
Left anterior descending coronary artery	273 (57.5)	131 (52.4)	142 (63.1)	
Left circumflex coronary artery	81 (17.1)	47 (18.8)	34 (15.0)	
Right coronary artery	118 (24.8)	72 (28.8)	46 (20.5)	
AHA lesion type				<0.001
A	95 (20.0)	39 (15.6)	56 (24.9)	
B1	164 (34.5)	80 (32.0)	84 (37.3)	
B2	103 (21.7)	51 (20.4)	52 (23.1)	
C	113 (23.8)	80 (32.0)	33 (14.7)	
Imaging device use for stent optimization				<0.001
No use of imaging modality	209 (44.0)	208 (83.2)	1 (0.4)	
IVUS	194 (40.8)	42 (16.8)	152 (67.5)	
OCT/OFDI	72 (15.2)	0 (0)	72 (32.1)	
Direct stenting	211 (44.2)	168 (67.2)	43 (19.1)	<0.001
Postdilatation	285 (60)	144 (57.6)	141 (62.7)	0.260
Preprocedural TIMI flow grade				0.005
0	2 (0.4)	0 (0)	2 (0.9)	
1	7 (1.5)	4 (1.6)	3 (1.3)	
2	27 (5.7)	6 (2.4)	21 (9.3)	
3	439 (92.4)	240 (96.0)	199 (88.5)	
Postprocedural TIMI flow grade				1.000
0	0 (0)	0 (0)	0	
1	0 (0)	0 (0)	0	
2	1 (0.2)	1 (0.4)	0	
3	474 (99.8)	249 (99.6)	225 (100)	
Per-Stent Characteristics	**Total (N = 507)**	**Brazil (n = 272)**	**Japan (n = 235)**	***P* Value**
Stent length, mm	24.6 ± 8.5	24.2 ± 8.4	25.0 ± 8.7	0.243
Stent nominal diameter, mm	3.0 ± 0.5	3.0 ± 0.4	3.0 ± 0.5	0.452

AHA = American Heart Association; IVUS = intravascular ultrasound; OCT = optical coherence tomography; OFDI = optical frequency domain imaging; PCI = percutaneous coronary intervention.

additional and observational period of 1 month was incorporated into the trial to assess the impact of either de-escalation or continuation of prasugrel. Of note, in Brazil, prasugrel was not reimbursed, but was provided free of charge during the trial, whereas in Japan it is reimbursed and was continued in the observational period. Optimal medical therapy with strict control of low-density lipoprotein cholesterol was strongly recommended along with optimization of all medication therapy according to current guidelines.[13] Clinical follow-up was performed at 1 month by telephone contact and in-person visit at 3 months to assess adherence and clinical events. An observational period of 1 month following the mandated duration of 3 months of monotherapy with prasugrel was completed to allow a switch to standard-of-care treatment.

STUDY ENDPOINTS. The primary ischemic endpoint was a composite of cardiac death, target-vessel myocardial infarction (MI) >48 hours after the index PCI, or definite ST occurring ≤3 months of the index procedure. The primary bleeding endpoint was Bleeding Academic Research Consortium (BARC) type 3 or 5 bleeding occurring ≤3 months of the index PCI.[14] Spontaneous MI was defined according to the Fourth Universal definitions, whereas periprocedural MI (<48 hours post-PCI) was defined according to the 2013 Society for Cardiovascular Angiography and Interventions definition.[15,16] Death and ST were defined according to the Academic Research Consortium-2 definition.[17] Secondary endpoints included all-cause death, stroke (subclassified as ischemic, hemorrhagic, or unknown), all Mis, repeat revascularization, definite or probable ST, BARC types 1 to 5 bleeding, and each itemized component of the primary endpoint. The patient-oriented composite endpoint was defined as a composite of all-cause death, any stroke, any MI, or revascularization. The device-oriented composite endpoint was defined as a composite of cardiovascular death, target vessel MI, or clinically driven target lesion revascularization. Net clinical adverse events were defined as a composite of patient-oriented composite endpoint and BARC type 3 or 5 bleeding. All clinical endpoints were adjudicated by an independent clinical events committee elected in the 2 respective countries (Supplemental Appendix). An independent data and safety monitoring board in each respective country oversaw the safety of all patients during enrollment and follow-up and was assigned the critical role of applying the

TABLE 3 Quantitative Coronary Angiogram and Murray Law-Based Quantitative Flow Ratio Results

	Total	Brazil	Japan	*P* value
QCA				
Preprocedure DS, %	59.2 ± 13.1	58.9 ± 11.9	59.6± 14.4	0.614
Postprocedure DS, %	12.6 ± 8.3	11.4 ± 7.1	13.9 ± 9.2	0.001
Residual diameter stenosis <20%, %	82.70	87.20	77.80	0.031
μQFR				
Preprocedure QFR	0.69 ± 0.16	0.72 ± 0.16	0.67 ± 0.16	<0.001
Postprocedure QFR ≤0.80, %	78.2	89.9	67.5	<0.001
Postprocedure QFR	0.93 ± 0.05	0.94 ± 0.04	0.93 ± 0.05	0.004
Postprocedure QFR ≥0.91, %	82.6	87.0	77.9	0.011
ΔQFR	0.24 ± 0.15	0.22 ± 0.15	0.26 ± 0.16	0.006
Post in-stent gradient	0.01 ± 0.010	0.01 ± 0.010	0.01 ± 0.010	0.089

Values are mean ± SD or %.
DS = diameter stenosis; QCA = quantitative coronary angiography; μQFR = Murray low-based quantitative flow-ratio.

stopping rule, which stated that study recruitment would have to be terminated if, during active enrollment of the trial, there were ≥3 cases of definite ST within the first 3 months of the index PCI. Importantly, operators were mandated to report ST events ≤24 hours.

STATISTICAL ANALYSIS. Continuous variables are expressed as mean ± SD or as median (IQR) as appropriate. Categorical variables are expressed as frequencies and percentages. Continuous variables were compared using the Student's *t*-test when normally distributed and the Mann-Whitney *U* test when not normally distributed. Analysis of covariance was used for adjusting the following baseline variables: age, sex, body mass index, hypertension, dyslipidemia, prior PCI, heart failure, family history of coronary artery disease (CAD), and left ventricular ejection fraction. If one of the cells had an expected count of <5, Fisher exact test was used. Statistical significance was defined as a 2-sided *P* value ≤0.05. All analyses were performed using SPSS Statistics version 27 (IBM Corp).

RESULTS

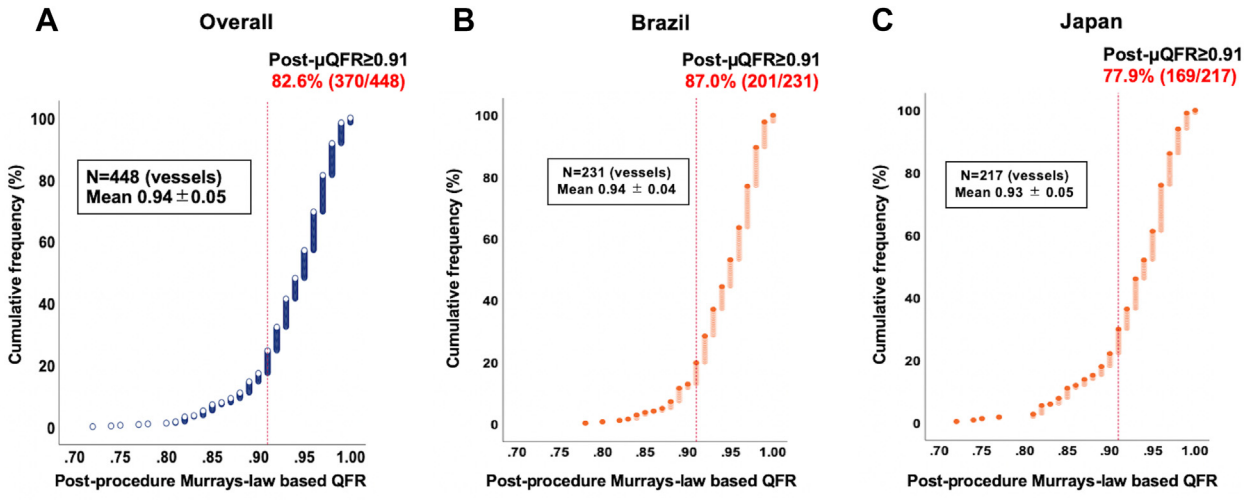
SCREENING AND ENROLLMENT. During the recruitment period, 426 patients were screened, with 409 formally enrolled after satisfactory stent deployment. In the ASET-Japan 2, patients withdrew their consent after enrollment and explicitly requested that their data were not included in this report. One Brazilian patient died at day 3 following the index procedure. Therefore, 3 months follow-up was achieved in 406 patients (Figure 1).

BASELINE PATIENT CHARACTERISTICS. Baseline characteristics are shown in Table 1. The Japanese population was older, and the proportion of men was significantly higher than in the Brazilian population. The presence of hypertension was significantly higher in Brazil than Japan, whereas the opposite was seen for dyslipidemia. Family history of CAD was significantly different between the 2 populations as was the number of patients with prior PCI. Impaired renal function was defined as the estimated glomerular filtration rate of creatinine clearance <60 mL/min/1.73 m^2. Compared with the Brazilian population, the Japanese population was older and had a smaller body mass index; the proportion of patients below this level of creatinine clearance differed significantly from the Brazilian cohort.

LESION AND PROCEDURAL CHARACTERISTICS. Lesion and procedural characteristics are summarized in Table 2. Overall, the index PCI was performed via radial access in 89.2% of the population with a significant difference between Brazil and Japan. At the time of study enrollment, prasugrel was not officially approved in Brazil; therefore, a 60-mg loading dose was only given to enrolled patients after the index procedure and optimal stent deployment.

In terms of lesion complexity, the number of patients receiving treatment for more than 1 lesion was significantly higher in Brazil, as was the prevalence of using 2 or more stents and the total overall length of stents. Calcified lesions necessitating rotational atherectomy was one of the exclusion criteria in Brazil, not in Japan. In the ASET-Japan, rotational atherectomy was performed in only 1 lesion (0.4%). Of note, poststent optimization using intravascular imaging was performed in 99.6% of patients in ASET Japan, compared with only 16.8% in ASET Brazil. Postprocedure TIMI flow grade 3 was achieved in 99.8% of the pooled population.

FIGURE 2 Cumulative Frequency Curve Showing Postprocedure Murray Law-Based Quantitative Flow Ratio



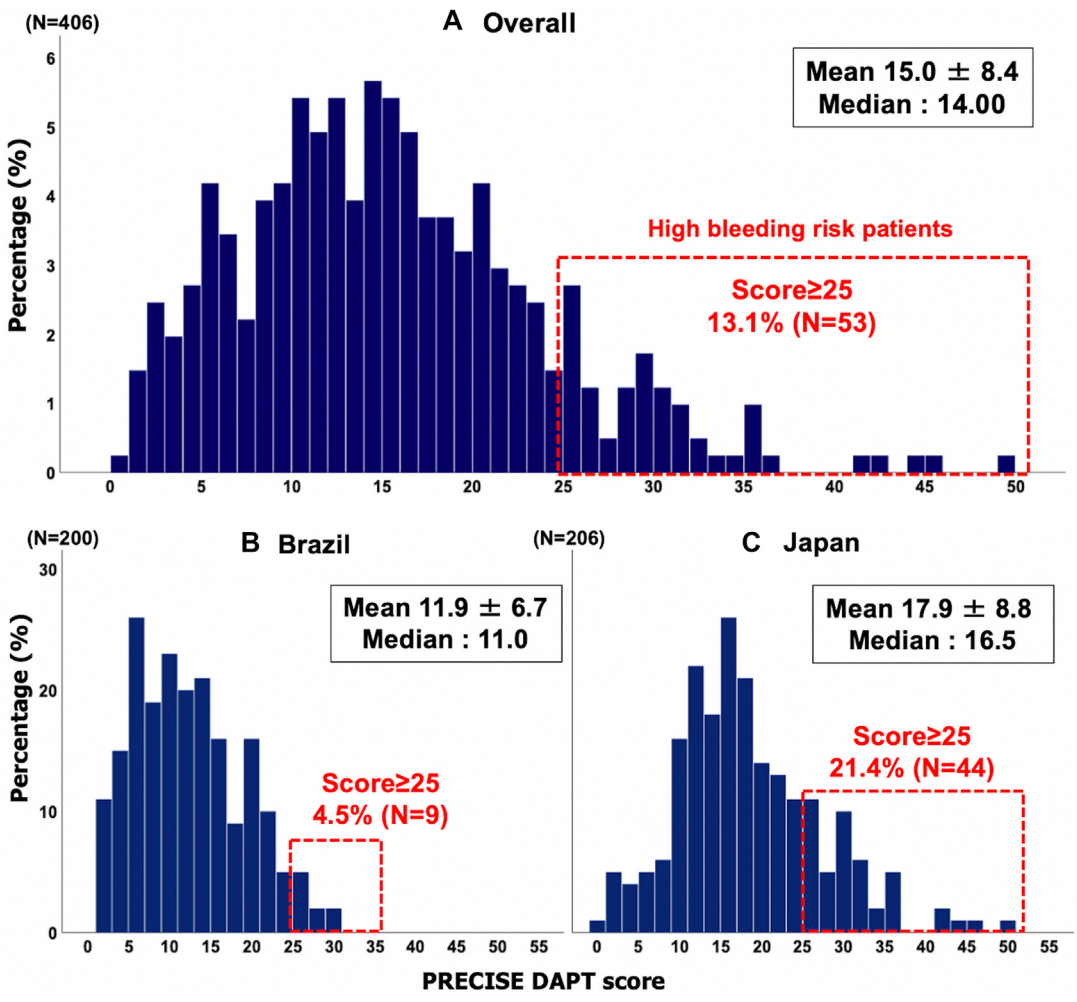
Cumulative curves of postprocedure Murray law-based quantitative flow ratio (μQFR) in overall (A), Brazilian (B), and Japanese populations (C). The red dotted line indicates postprocedure μQFR of 0.91. The proportions of treated vessels in which postprocedure μQFR was ≥0.91 were 82.6%, 87.0%, and 77.9%, respectively. There is a significant difference between Brazil and Japan ($P = 0.011$).

ANGIOGRAPHICAL AND PHYSIOLOGICAL ASSESSMENT AFTER INDEX PCI. Preprocedure and postprocedure quantitative coronary artery and Murray law-based quantitative flow ratio (μQFR) were retrospectively assessed by the central academic core laboratory using dedicated off-line software (CAAS version 8.2.4, Pie Medical Imaging; AngioPlus Core, Pulse Medical Imaging Technology). Overall, 82.7% of patients had a residual poststenting diameter stenosis (DS) <20%, with a greater proportion among patients treated in Brazil, who also had a significantly lower mean postprocedure DS (**Table 3**). The overall and country-specific cumulative frequency distribution curves of postprocedure μQFR are shown in **Figure 2**. The overall mean postprocedure μQFR was 0.94, with a significantly higher value in Brazilian patients (Brazil 0.94 vs Japan 0.93; $P = 0.004$). The proportion of treated vessels having a postprocedure μQFR ≥0.91 was 82.6% with rates of 87.0% and 77.9%, respectively, in Brazil and Japan ($P = 0.011$).[18] The results of preprocedure and postprocedure μQFR and diameter stenosis between the 2 countries adjusted by baseline variables are shown in Supplemental Table 3.

COMPARISON OF BLEEDING RISK BETWEEN THE 2 POPULATIONS. Bleeding risk was assessed by the PRECISE DAPT (Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy) score (**Figure 3**).[19] The proportion of patients classified as high bleeding risk (HBR) caused by a PRECISE DAPT score ≥25 was 13.1% in the pooled population with rates in Japanese and Brazilian patients of 21.4% and 4.5%, respectively. Similar trends were observed in bleeding and thrombotic risk when using the PARIS (Patterns of Non-Adherence to Anti-Platelet Regimen in Stented Patients) score (Supplemental Figure 1).[20]

ADHERENCE TO ANTIPLATELET AGENTS AND CLINICAL OUTCOMES. Clinical outcomes are reported in **Table 4**. Three-month follow-up was completed in 406 patients, with 98.8% of patients adhering to the study medication in the cross-sectional analysis (**Figure 1**). The 1 primary ischemic and bleeding endpoint occurred in a single patient 3 days after the index procedure. This patient was a 68-year-old Brazilian woman who was on long-term therapy with clopidogrel; therefore, clopidogrel loading dose was not administrated before the index procedure. Prasugrel 60 mg was given after the index procedure. This patient presented massive intracranial hemorrhage caused by uncontrolled hypertension, and died 3 days after the index PCI. This event was adjudicated as a cardiac death, BARC type 5b bleeding, and hemorrhagic stroke, and a full narrative has been previously reported.[6] No ST occurred during the follow-up period. Secondary endpoints are listed in Supplemental Table 4, and detailed information about spontaneous or periprocedural MI that occurred during 3-month follow-up is shown in

FIGURE 3 Distribution of PRECISE DAPT Score



Distribution of PRECISE DAPT score in the pooled (A), Brazilian (B), and Japanese populations (C). A high bleeding risk score is defined as a score ≥25. The proportions with a high bleeding risk were 82.6%, 87.0%, and 77.9%, respectively. The red dotted line indicates post-procedure Murray law-based quantitative flow ratio of 0.91. *In ASET (Acetyl-Salicylic Elimination Trial) Brazil, the PRECISE DAPT score was not assessed in 1 patient because of a missing hemoglobin value. PRECISE DAPT = Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy Patterns of Non-Adherence to Anti-Platelet Regimen in Stented Patients.

Supplemental Appendix. Notably, there were also no primary ischemic and bleeding endpoints during the 1-month observational period following the completion of 3 months of prasugrel monotherapy. During this period, Brazilian patients reverted to aspirin or DAPT because prasugrel was not reimbursed in Brazil for PCI in CCS, whereas 98.5% of Japanese patients continued with prasugrel monotherapy. Narratives of nonadherent patients are summarized in the Supplemental Appendix.

DISCUSSION

This comparative analysis demonstrated over a period of 3 months the safety and feasibility of prasugrel monotherapy in patients with CCS following clinical and angiographically optimal stenting with biodegradable polymer EES. Aspirin was discontinued immediately after the index procedure, and adjusted maintenance doses of prasugrel (10 mg in Brazil and 3.75 mg in Japan) were continued up to

TABLE 4 Primary Ischemic and Bleeding Endpoint During 3-Month Follow-Up

	Total (N = 407)	Brazil (n = 201)	Japan (n = 206)
Primary ischemic endpoint			
Composite of cardiac death, TV spontaneous myocardial infarction, or definite stent thrombosis	1 (0.2)[a]	1 (0.5)[a]	0 (0)
Cardiac death	1 (0.2)[a]	1 (0.5)[a]	0 (0)
TV spontaneous myocardial infarction	0 (0)	0 (0)	0 (0)
(48 h after the index PCI)			
Definite stent thrombosis	0 (0)	0 (0)	0 (0)
Primary bleeding endpoint			
BARC type 3 or 5 bleeding	1 (0.2)[a]	1 (0.5)[a]	0 (0)
Type 3a	0 (0)	0 (0)	0 (0)
Type 3b	0 (0)	0 (0)	0 (0)
Type 3c	0 (0)	0 (0)	0 (0)
Type 5a	0 (0)	0 (0)	0 (0)
Type 5b	1 (0.2)[a]	1 (0.5)[a]	0 (0)
Stent thrombosis			
Definite	0 (0)	0 (0)	0 (0)
Probable	0 (0)	0 (0)	0 (0)

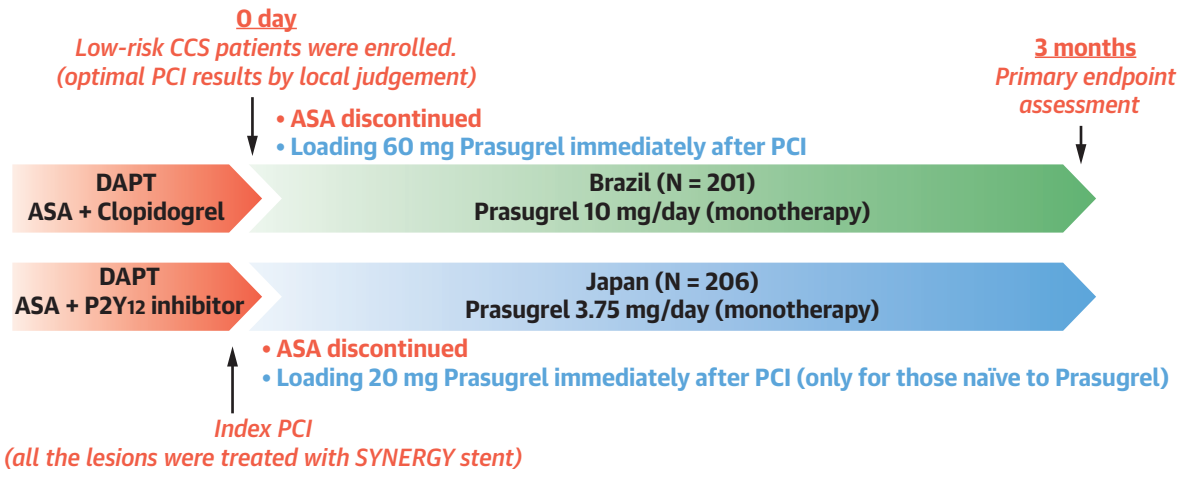
[a]This event occurred in the same patient.
BARC = bleeding academic research consortium; PCI = percutaneous coronary intervention; TV = target vessel.

3-month follow-up. Overall, the primary ischemic and bleeding endpoint occurred in a single patient (0.2%), with no ST occurring during follow-up (**Central Illustration**). These data tentatively suggest that in selected patients an "aspirin-free" strategy could be a viable option for antiplatelet therapy after PCI, without increasing the risk of ischemic events, regardless of ethnic differences, the prevalence of CAD, dose of $P2Y_{12}$ inhibitor, and periprocedural management.

THE RATIONALE OF PRASUGREL MONOTHERAPY. Previous RCTs have shown that $P2Y_{12}$ inhibitor monotherapy following short DAPT has contributed to reduce bleeding complications without any detrimental impact on ischemic events when compared with standard DAPT.[3,4] In the TWILIGHT (Ticagrelor with Aspirin or Alone in High-Risk Patients after Coronary Intervention) trial, which compared ticagrelor with or without aspirin after a probatory period of 3 months DAPT, the aspirin-free group had less bleeding events without any increase in thrombotic events, compared with groups receiving continuous DAPT.[4] The STOPDAPT-2 (Short and Optimal Duration of Dual Antiplatelet Therapy After Everolimus-Eluting Cobalt-Chromium Stent-2) trial demonstrated that 1-month DAPT followed by clopidogrel monotherapy secures additional clinical benefits compared with 12 months of DAPT, with significantly lower rates of a composite of cardiovascular and bleeding events resulting in the criteria for both noninferiority and superiority being met.[3] The PENDULUM mono study, which is a contemporary Japanese registry including only those patients not suitable for long-term DAPT after drug-eluting stent implantation because of their HBR status, showed no cases of ST in a population wherein 80% received only prasugrel monotherapy for a period of 12 months after PCI.[21] In addition, the efficacy of $P2Y_{12}$ inhibitor monotherapy has been assessed for the patients with complex PCI. Although STOPDAPT-2 ACS showed that clopidogrel monotherapy after 1 to 2 months of DAPT failed to attest noninferiority to standard 12 months of DAPT for the net clinical benefit with a numerical increase in cardiovascular events despite reduction in bleeding events, a recent meta-analysis also provided the evidence of the safety and efficacy of $P2Y_{12}$ inhibitor monotherapy in the context of complex PCI.[22] These evidences have implied that complete omission of aspirin immediately after PCI is possible; however, before conducting large-scale RCTs, it was felt mandatory to assess feasibility and safety in small pilot studies. In addition, it would be essential to retrospectively evaluate the results of the 2 pilot studies before expanding this "aspirin-free" strategy to large other ethnically diverse groups, considering the differences in bleeding risk and geographic differences in baseline demographics and procedural approaches (eg, usage of intravascular imaging).

THE POTENTIAL ADVANTAGE OF PRASUGREL MONOTHERAPY. The aspirin-free approach with prasugrel monotherapy is appealing considering the unique pharmacological effect of prasugrel, which as a thienopyridine antiplatelet agent, requires metabolic activation; however, despite this, it has less variability in platelet inhibition and a faster onset of action than clopidogrel.[23] A previous study has demonstrated the absence of any synergistic effect of aspirin when added to prasugrel's inhibition of 6 of the agonists that trigger the adhesion and the aggregation of platelets.[24] The other advantage of prasugrel is that it exerts its antiplatelet effect without being affected by CYP2C19 gene polymorphisms, which are seen with varying frequency across different biogeographical groups,[25] with, eg, 20% of Latino and 60% of East Asian populations carrying a nonfunctioning CYP2C19 allele.[26] Thus, potent $P2Y_{12}$ inhibitors that are less susceptible to biogeographical differences and provide sufficient inhibition of platelet aggregation are essential to achieve this "aspirin-free" strategy. Despite the variability of CYP2C19 polymorphisms between the 2 investigated

CENTRAL ILLUSTRATION **Overview of the ASET Pilot Studies and Primary Endpoint Results**



Event, % (n)	Overall (N = 407)	Brazil (n = 201)	Japan (n = 206)
Primary endpoint: (composite of cardiac death, target vessel spontaneous MI, or definite stent thrombosis)	0.2% (1)	0.5% (1)*	0
• Cardiac death	0.2% (1)*	0.5% (1)*	0
• Target vessel spontaneous MI	0	0	0
• Definite stent thrombosis	0	0	0
Primary bleeding endpoint (BARC type 3 or 5):			
• BARC type 5b	0.2% (1)*	0.5% (1)*	0

Masuda S, et al. JACC: Asia. 2024;4(3):171–182.

Low-risk chronic coronary syndrome (CCS) patients in which optimal platinum-chromium everolimus-eluting stent deployment was achieved were enrolled. Aspirin was discontinued after the index procedure, and the 2 dosages of prasugrel monotherapy (10 mg/d in Brazil or 3.75 mg/d in Japan) were continued for 3 months. The primary ischemic and bleeding endpoint occurred in the same patient. *Event occurred in the same patient.
ASA = acetylsalicylic acid; BARC = bleeding academic research consortium; CCS = chronic coronary syndrome; DAPT = dual antiplatelet therapy; MI = myocardial infarction; PCI = percutaneous coronary intervention.

populations, our results suggest that an adjusted dose of prasugrel monotherapy is still feasible and safe without needing adjunctive therapy with aspirin.

DIFFERENCES IN THE PROCEDURAL CHARACTERISTICS BETWEEN THE 2 COUNTRIES. Nearly the entire enrolled population (99.8%) achieved a post-procedure TIMI flow grade 3, whereas a post-PCI residual DS <20% by quantitative coronary artery was achieved in 82.7% of the population. Retrospective analysis shows excellent postprocedure μQFR results in the overall population (mean 0.94) with higher values than those seen in clinical trials investigating the impact on clinical outcomes of high usage of wire-based physiological assessment (mean 0.91) and intravascular imaging.[18] Although we acknowledge that there was a statistically significant difference in post-PCI μQFR values (0.94 ± 0.04 vs 0.93 ± 0.05; $P = 0.004$) between the 2 investigated populations, this small absolute difference is likely to be clinically irrelevant. The in-stent residual μQFR demonstrates that from a physiological viewpoint, successful stent

deployment was obtained in the large majority (82.6%) of treated lesions without a significant difference between Brazil and Japan, and indicates that the small difference in post-PCI μQFR values between the 2 populations could be explained by the proportion of pre-PCI μQFR ≤0.80 between the 2 populations. When comparing pre-PCI μQFR, the Brazilian population had significantly higher than those in Japan (mean pre-procedure μQFR 0.72 vs 0.67; $P < 0.001$), and the proportion of lesions in which pre-PCI μQFR ≤0.80 was also significantly different (67.5% vs 89.9%; $P < 0.001$). As in-stent residual μQFR did not differ between the 2 populations, it can be assumed that post-PCI μQFR depends on the value of pre-PCI μQFR.

The use of intravascular imaging for poststent optimization has apparently no impact on the primary endpoint in the investigated populations. Intravascular imaging was performed in 99.6% of patients in ASET Japan, as is common practice in Japan where imaging devices are fully reimbursed, whereas it was performed in only 16.8% of Brazilian patients despite recommendations for its use in stent optimization. Of note, patients presenting with complex lesions (eg, left main bifurcation lesions or chronic total occlusions)—for which intracoronary imaging is recommended by guidelines—were excluded in the ASET-Brazil, which may partially explain the low usage.[27] Nevertheless, our results suggest that prasugrel monotherapy can be safely used in selected CCS patients after successful stent implantation as judged clinically and angiographically, without necessarily relying on strict quantitative criteria derived from intravascular imaging.

HIGH BLEEDING RISK POPULATIONS. Compared with patients treated with standard DAPT, those with moderate to high bleeding risk should theoretically derive even more benefit from an aspirin-free strategy through the reduction in bleeding events without increasing ischemic events. Although the patients who presented with some HBR features were per protocol excluded from these pilot studies, some patients with clinical characteristics associated with HBR were enrolled, and rates differed significantly between the 2 countries. Compared with Brazilian patients, Japanese patients were older, had lower body mass indexes, and had high rates of renal insufficiency and prior heart failure. Consequently, according to the PRECISE DAPT and PARIS scores, more than 20% of Japanese patients were categorized as HBR compared with only 0.5% to 4.5% of Brazilians.[19,20] Despite the differences in bleeding risk between the 2 countries, the overall primary bleeding endpoint in this pooled population occurred in only 1 Brazilian patient, suggesting that this aspirin-free strategy is applicable even in patients with HBR.

FUTURE IN PERSPECTIVE. Our seminal observations and exploratory findings need to be confirmed in future randomized trials in patients with acute coronary syndrome and HBR. In 2023, the OPTICA (Optical Coherence Tomography-Guided PCI with Single Antiplatelet Therapy) trial assessed using ticagrelor or prasugrel monotherapy in 70 patients with non-ST-segment elevation acute coronary syndrome,[28] with the results demonstrating the feasibility and safety of this regimen with a primary ischemic endpoint, defined as the composite of all-cause mortality, MI, definite or probable ST, or stroke, occurring in 3 (4.0%) patients at 6-month follow-up. Currently, 4 ongoing RCTs (LEGACY [Less Bleeding by Omitting Aspirin in non-ST-segment Elevation Acute Coronary Syndrome Patients], STOPDAPT-3 [Short and Optimal Duration of Dual Antiplatelet Therapy After Everolimus-Eluting Cobalt-Chromium Stent-3], NEOMINDSET [PercutaNEOus coronary intervention followed by Monotherapy INstead of Dual antiplatelet therapy in the SETting of acute coronary syndromes], and PREMIUM [PRasugrel Monotherapy Following prImary percUtaneous Coronary Intervention for ST-elevation Myocardial Infarction]), which will enroll a total of 15,000 patients, are exploring novel strategies of monotherapy using $P2Y_{12}$ receptor inhibitors in patients with ACS and HBR.

STUDY LIMITATIONS. First, because of the nature of the pilot studies, the selection of the enrolled patients is inherently biased, because only low-risk patients with CCS who had successful platinum-chromium EES implantation were enrolled. Although patients presenting with complex lesions could have been enrolled in the ASET-Japan, only a few patients were included; therefore, the concept of an "aspirin-free" strategy cannot in any way be "generalized" and is strictly hypothesis generating. However, the benefit of short monotherapy of $P2Y_{12}$ inhibitor (only 1 month aspirin) in complex CAD according to the criteria of the European Society of Cardiology guidelines has been reported in the GLOBAL LEADERS trial.[5] Second, these pilot studies were tested in only 2 ethnicities and 2 geographic locations. Further research is needed to ensure that prasugrel monotherapy can be expanded to other ethnicities and geographies across the globe. Third,

ASET was a single-arm trial without any comparator; therefore, RCTs will be needed to assess clinical outcomes of this new pharmacological regimen when compared with the current standard of care. Fourth, the approval dose of prasugrel in Japan and Brazil was different, and despite this, the lower dose was still sufficient to prevent an excess in stent thrombosis in Japanese patients, which may be consequent to the high use of intravascular imaging but also the much-documented East-Asian paradox.[29,30] Fourth, because some parameters for calculating bleeding risk were missing specifically in the Brazilian cohort, only the PRECISE DAPT and PARIS scores could be assessed with regard to the bleeding risks. Fifth, although it has been reported that the risk of bleeding and thrombosis varies according to race, this comparative analysis lacked information on the proportion of each racial/ethnic group (eg, White and Black, South American and Asian populations); therefore, this study could not accurately report the potential risk of bleeding and thrombosis among racial/ethnic groups. Finally, all the lesions of modest complexity were treated with platinum-chromium EES. Although current meta-analyses demonstrate comparable clinical outcomes among newer generations of drug-eluting stents, we must acknowledge that this strategy was established with this specific stent technology.

CONCLUSIONS

Prasugrel without aspirin immediately after platinum-chromium EES implantation was safe and feasible in selected low-risk CCS patients regardless of geographical and ethnic differences. Adjusting the dose of prasugrel in Japan is an important difference from the treatment used in Brazil and possibly other non-Asian populations.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Prasugrel monotherapy following percutaneous coronary intervention with platinum-chromium EES was safe and feasible in patients with low-risk CCS regardless of geographical and ethnical differences.

TRANSLATIONAL OUTLOOK: By adjusting the maintenance dose of prasugrel, this strategy could be expanded to other Asian populations. Complete omission of aspirin could be beneficial for patients with high-bleeding risk and/or those who are not unable to take standard dual antiplatelet therapy. Large-scale randomized controlled trials will be needed to confirm the efficacy of this "Aspirin-free" strategy and to expand it to other geographies.

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KEY WORDS monotherapy, percutaneous coronary intervention, prasugrel

APPENDIX For an expanded Methods section as well as supplemental tables and a figure, please see the online version of this paper.