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Aspirin-Free Prasugrel Monotherapy Following Coronary Artery Stenting in Patients With Stable CAD

The ASET Pilot Study

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ABSTRACT

OBJECTIVES The aim of this study was to evaluate the hypothesis that prasugrel monotherapy following successful everolimus-eluting stent implantation is feasible and safe in patients with stable coronary artery disease (CAD).

BACKGROUND Recent studies have suggested that short dual-antiplatelet therapy strategies may provide an adequate balance between ischemic and bleeding risks. However, the complete omission of aspirin immediately after percutaneous coronary intervention (PCI) has not been tested so far.

METHODS The study was a multicenter, single-arm, open-label trial with a stopping rule based on the occurrence of definite stent thrombosis (if >3, trial enrollment would be terminated). Patients undergoing successful everolimus-eluting stent implantation for stable CAD with SYNTAX (Synergy Between PCI With Taxus and Cardiac Surgery) scores <23 were included. All participants were on standard dual-antiplatelet therapy at the time of index PCI. Aspirin was discontinued on the day of the index procedure but given prior to the procedure; prasugrel was administered in the catheterization laboratory immediately after the successful procedure, and aspirin-free prasugrel became the therapy regimen from that moment. Patients were treated solely with prasugrel for 3 months. The primary ischemic endpoint was the composite of cardiac death, spontaneous target vessel myocardial infarction, or definite stent thrombosis, and the primary bleeding endpoint was Bleeding Academic Research Consortium types 3 and 5 bleeding up to 3 months.

RESULTS From February 22, 2018, to May 7, 2019, 201 patients were enrolled. All patients underwent PCI for stable CAD. Overall, 98.5% of patients were adherent to prasugrel at 3-month follow-up. The primary ischemic and bleeding endpoints occurred in 1 patient (0.5%). No stent thrombosis events occurred.

CONCLUSIONS Aspirin-free prasugrel monotherapy following successful everolimus-eluting stent implantation demonstrated feasibility and safety without any stent thrombosis in selected low-risk patients with stable CAD. These findings may help underpin larger randomized controlled studies to evaluate the aspirin-free strategy compared with traditional dual-antiplatelet therapy following PCI. (Acetyl Salicylic Elimination Trial: The ASET Pilot Study [ASET]; NCT03469856) (J Am Coll Cardiol Intv 2020;13:2251-62) © 2020 Published by Elsevier on behalf of the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome(s)

BARC = Bleeding Academic Research Consortium

CAD = coronary artery disease

CK-MB = creatine kinase myocardial band

DAPT = dual-antiplatelet therapy

DES = drug-eluting stent(s)

DS = diameter stenosis

DSMB = Data and Safety Monitoring Board

EES = everolimus-eluting stent(s)

HPR = high platelet reactivity

IVUS = intravascular ultrasound

MI = myocardial infarction

PCI = percutaneous coronary intervention

Pt-EES = platinum-chromium everolimus-eluting stent(s)

RCT = randomized controlled trial

ULN = upper limit of normal

Patients with coronary artery disease (CAD) undergoing percutaneous coronary intervention (PCI) are traditionally treated with aspirin and a $P2Y_{12}$ inhibitor during the first period post-procedure (so-called dual-antiplatelet therapy [DAPT]), followed by withdrawal of the $P2Y_{12}$ inhibitor and maintenance of aspirin as the single antiplatelet drug thereafter (1). However, the best antithrombotic approach after stenting is still an open matter, currently under intense clinical investigation. The adequate duration of DAPT, as well as the best agent for the subsequent monotherapy phase, have been scrutinized in recent studies (2). In this regard, a number of recent trials have shown promising results with a scheme comprising short DAPT duration (i.e., 1 to 3 months) followed by the administration of solely a $P2Y_{12}$ antagonist, instead of aspirin (3-6). However, the complete omission of aspirin immediately after PCI has not been tested so far.

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Prasugrel is an irreversible oral $P2Y_{12}$ receptor inhibitor that shows less variability in platelet inhibition and has a faster onset of action than clopidogrel. An in vitro study suggested that aspirin demonstrated little additional inhibition in the presence of strong blockade by prasugrel (7). Additionally, the administration of aspirin has been linked to ominous hemorrhagic complications (8). Therefore, we hypothesized that single-antiplatelet therapy with prasugrel started immediately after PCI would result in adequate stent thrombotic protection while avoiding excess bleeding risk. To test this concept, we designed a proof-of-concept single-arm trial in which selected low-risk patients with stable CAD received prasugrel monotherapy immediately following successful PCI with everolimus-eluting stents (EES).

METHODS

STUDY DESIGN WITH STOPPING RULE. The design of the ASET (Acetyl Salicylic Elimination Trial) pilot study (NCT03469856) was previously described elsewhere (9). The study was a multicenter, single-arm, open-label, first-in-human, proof-of-concept pilot trial. Because of the exploratory nature of this study, no formal sample size calculations were performed. On the basis of previous pilot studies with similar designs, such as the BENESTENT II pilot study, which evaluated a heparin-coated Palmaz-Schatz stent with or without intravenous heparin infusion immediately post-treatment, a sample of 200 patients was planned, with a safety stopping rule based on the occurrence of definite stent thrombosis (10). The BENESTENT II pilot, first-in-human study was successfully completed without any stent thrombosis in 200 patients and was followed by the large randomized BENESTENT II trial, with 827 patients (11). In the present trial, if during the enrollment period more than 3 cases of definite stent thrombosis occurred following the index procedure up to 3-month follow-up, patient recruitment would be terminated.

In the present trial, the cutoff rate for definite stent thrombosis was determined on the basis of the incidence of stent thrombosis in the Bern-Rotterdam registry (1.2% at 30 days and 1.7% at 1 year) (12) and considering the current development of PCI (13,14). All potential patients provided written informed consent prior to undergoing any study-specific procedures, including screening and diagnostic angiography potentially leading to "ad hoc" PCI. The central ethics committee (Comissão de Ética Para Análise de Projetos de Pesquisa) and local ethics committee at

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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 *JACC: Cardiovascular Interventions* author instructions page.

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each participating center approved the study protocol.

STUDY PARTICIPANTS. Patients requiring PCI for stable CAD with baseline SYNTAX (Synergy Between PCI With Taxus and Cardiac Surgery) scores <23 were screened and considered eligible for the study. Complete inclusion and exclusion criteria are listed in **Table 1**. We excluded patients with absolute or relative contraindications to prasugrel use or high-risk features for PCI (left main disease, chronic total occlusion, bifurcation lesion requiring 2-stent treatment, saphenous or arterial graft lesion, and severe calcified lesion requiring the use of the Rotablator system) to minimize the potential ischemic risks of implementing prasugrel monotherapy immediately after PCI. Patients who required staged procedures were also excluded to avoid heterogeneity in the duration of pharmacological treatment between index and staged procedures. Patients with history of acute coronary syndromes (ACS) within 12 months before the index procedure were excluded because these patients are recommended to receive DAPT for 12 months.

PATIENT SCREENING BEFORE INDEX PCI. The baseline anatomic SYNTAX score was calculated at each site by the investigators and recorded. A standard 12-lead electrocardiogram was recorded within 72 h prior to PCI, and cardiac biomarkers (creatine kinase-myocardial band [CK-MB] or troponin) were collected prior to PCI to detect and rule out ACS. For inclusion, the value of CK-MB was required to be <2 times the upper limit of normal (ULN). If the value of troponin was elevated more than the ULN at baseline (within 72 h prior to the start of PCI) without any ST-T-segment changes and/or typical symptoms, an additional blood sample was collected prior to PCI. If the second blood test showed either a stable level of troponin (<20% increase over the value of baseline troponin) or a decrease in troponin level, with a normal range of CK-MB and normal results on electrocardiography, the patient could be enrolled in the study.

INDEX PCI. Participants were loaded with standard DAPT (300 mg aspirin and 600 mg clopidogrel unless patients were previously on long-term therapy) at least 2 h prior to index PCI. Index PCI was performed with intention to achieve complete revascularization of all vessels with at least 1.5-mm diameter showing stenoses of 50% or more, as identified by the local interventional cardiologist (15). Periprocedural anticoagulation was used at the operator's discretion according to local or international guidelines (1,16).

All target lesions were exclusively treated with the platinum-chromium EES (Pt-EES). The Pt-EES elutes everolimus for 3 months from a 4-μm biodegradable poly(lactic-co-glycolic acid) coating that is located only on the abluminal side of 74-, 79-, and 81-μm platinum-chromium struts (for stent sizes ≤2.5, 3.0 to 3.5, and 4.0 mm, respectively) and is resorbed within 4 months.

The investigators performed the procedure aiming to achieve optimal stent implantation according to local standard of care by angiography. The use of quantitative coronary angiography and/or intracoronary imaging (intravascular ultrasound [IVUS] or optical coherence tomography) was recommended but left to the discretion of the operator. The achievement of optimal stenting was judged by each investigator according to recommended criteria shown in Supplemental Table 1 and Supplemental Figure 1 (17–19). All angiographic recordings were analyzed off-line by an independent academic core laboratory (Academic Research Team, Rotterdam, the Netherlands) using quantitative coronary angiographic software (Coronary Angiography Analysis System version 5.9; Pie Medical Imaging, Maastricht, the Netherlands).

ANTIPLATELET TREATMENT. After achievement of optimal Pt-EES implantation on standard DAPT administrated prior to the index procedure, patients were enrolled in the study and loaded with 60 mg prasugrel while still in the catheterization laboratory to avoid further delay or omission of the loading dose (**Central Illustration**). In patients already on long-term ticagrelor, we recommended that the investigator administer 60 mg prasugrel in the catheterization laboratory and discontinue ticagrelor just after the procedure. In patients already on long-term prasugrel, there was no need for an additional loading dose, and patients were treated with 10 mg prasugrel once a daily for 3 months. Upon enrollment, aspirin was discontinued on the day of the index procedure, and the prescription was maintained aspirin-free throughout the 3-month follow-up period.

STUDY FOLLOW-UP. After the index procedure, an assessment of the patient's clinical status was performed. Cardiac biomarkers were measured at discharge or 3 to 8 h post-procedure. A standard 12-lead electrocardiogram was also recorded at discharge or within 24 h post-procedure. Before hospital discharge, all patients were diligently educated about the importance of compliance with medication and the risk for stopping prasugrel using a specific educational study card. This card contained important information on the study drug and

TABLE 1 Inclusion and Exclusion Criteria

Inclusion criteria
1. Successful PCI with optimal stent implantation of one or more SYNERGY stents
2. SYNERGY stent implantation was performed to treat: a. Presence of 1 or more de novo lesion with diameter stenosis ≥50% by visual estimation in at least 1 native coronary artery with reference vessel diameter ranging from 2.25 to 4.00 mm without left main stem involvement b. Stable coronary artery disease and evidence of myocardial ischemia by symptoms or noninvasive test (e.g., treadmill exercise test, radionuclide scintigraphy, stress echocardiography) c. Anatomic SYNTAX score <23 prior to PCI
3. Patient has provided written informed consent as approved by the ethics committee of the respective clinical site
Exclusion criteria
1. <18 or ≥75 yrs of age
2. Weight <60 kg
3. Glomerular filtration rate <60 ml/min
4. Previous PCI in the past 12 months
5. Current or previous acute coronary syndrome within 12 months
6. Patients with planned PCI or surgical intervention to treat any cardiac or noncardiac condition within the next 6 months
7. Concomitant cardiac valve disease requiring surgical therapy
8. Following lesion characteristics: left main disease, chronic total occlusion, bifurcation lesion requiring 2-stent treatment, saphenous or arterial graft lesion, and severe calcified lesion requiring use of the Rotablator system
9. Patient concomitantly treated with any other nonstudy stent in the same procedure
10. History of definite stent thrombosis
11. History of stroke or transient ischemic cerebrovascular accident
12. Atrial fibrillation or other indication for oral anticoagulant therapy
13. Hemoglobin <10 g/dl or other evidence of active bleeding
14. Peptic ulceration documented by endoscopy within the past 3 months unless healing proved by repeat endoscopy
15. Any other condition deemed by the investigator to place patient at excessive risk for bleeding with prasugrel
16. Known allergy to aspirin, prasugrel, or diagnosed lactose intolerance
17. Treatment in the past 10 days or requirement for ongoing treatment with a strong CYP3A4 inhibitor or inducer
18. Women of child-bearing potential unless negative pregnancy test result at screening and willing to use effective contraception for the duration of treatment with study medication
19. Woman who is breastfeeding at time of enrollment
20. Participation in another trial with an investigational drug or stent
21. Comorbidity associated with life expectancy <1 yr
22. Assessment that the subject is not likely to comply with the study procedures
23. Known drug or alcohol dependence within the past 12 months as judged by the investigator

PCI = percutaneous coronary intervention; SYNTAX = Synergy Between PCI With Taxus and Cardiac Surgery.

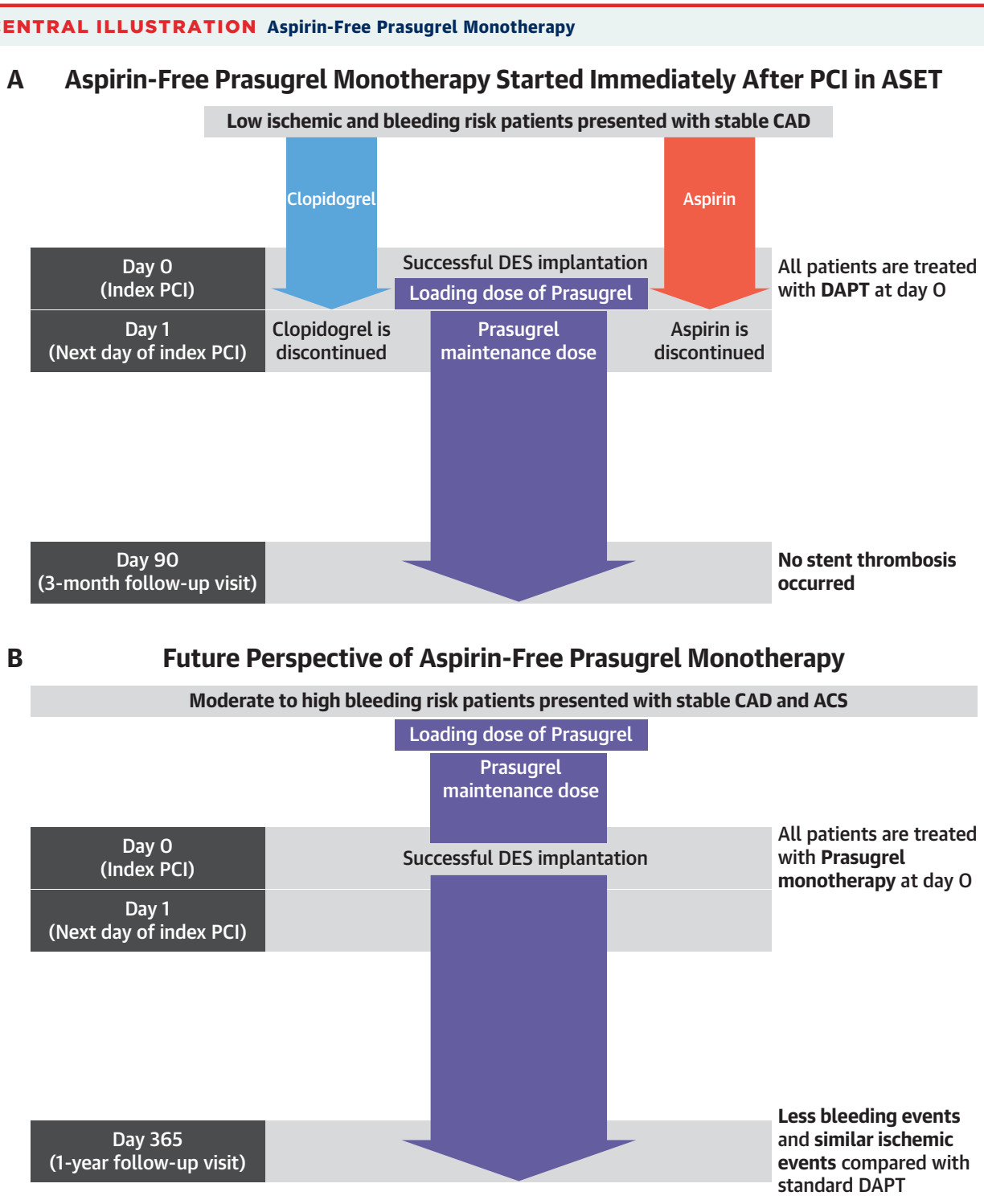
a warning on the risks of discontinuing the study drug without consultation of the research staff. If prasugrel needed to be discontinued for any reason, aspirin and clopidogrel should be considered as alternative treatment after consultation with the research staff.

Clinical follow-up was performed at 1 month by telephone contact to assess treatment adherence and clinical events. After 3 months, an in-person visit was performed, and prasugrel monotherapy was replaced by aspirin monotherapy or DAPT according to physician's discretion. When switching from prasugrel back to aspirin monotherapy, a loading dose of aspirin was recommended and was to be given in the hospital at the time of the 3-month follow-up visit.

Telephone contact was made at 4 months (final follow-up) for an observational assessment of the switch to standard-of-care treatment (aspirin alone or DAPT). An assessment of angina status, cardiovascular drug use, and any serious adverse events was made during clinical follow-up visits.

ADHERENCE TO PRASUGREL. The number of remaining prasugrel tablets at 3-month follow-up was recorded to assess adherence to prasugrel. Discontinuation and restart of any antiplatelet agents up to 4 months were recorded with the date and reason (20). Adherence to prasugrel was assessed using 2 methods: cross-sectional binary assessment at each follow-up visit and tablet-count assessment using a drug accountability report at 3-month follow-up (i.e., [number of prasugrel tablets prescribed at discharge − number of remaining prasugrel tablets at 3-month follow-up]/number of prasugrel tablets required from discharge to 3-month follow-up).

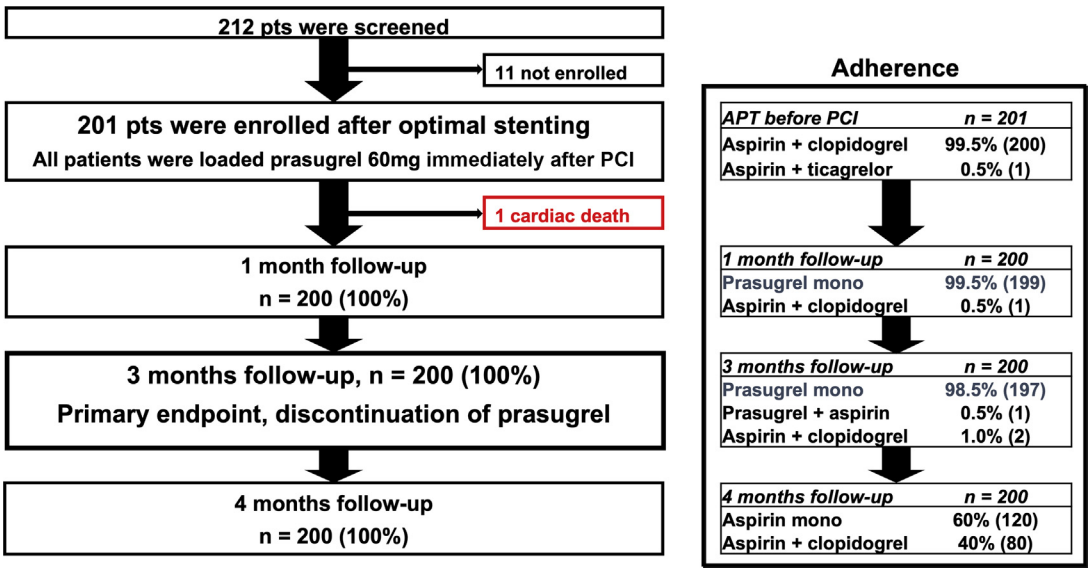
CENTRAL ILLUSTRATION Aspirin-Free Prasugrel Monotherapy



Kogame, N. et al. J Am Coll Cardiol Intv. 2020;13(19):2251–62.

(A) Aspirin-free prasugrel monotherapy in ASET (Acetyl Salicylic Elimination Trial). **(B)** Future perspective of aspirin-free prasugrel monotherapy. ACS = acute coronary syndrome; CAD = coronary artery disease; DAPT = dual-antiplatelet therapy; DES = drug-eluting stent; PCI = percutaneous coronary intervention.

FIGURE 1 Study Flowchart With Adherence to Antiplatelet Agent



APT = antiplatelet therapy; mono = monotherapy; PCI = percutaneous coronary intervention; pts = patients.

STUDY ENDPOINTS. The primary ischemic endpoint was a composite of cardiac death, spontaneous target vessel myocardial infarction (MI) (48 h after the index procedure), or definite stent thrombosis up to 3 months after the index procedure.

The primary bleeding endpoint was any Bleeding Academic Research Consortium (BARC) type 3 or 5 bleeding up to 3 months after the index procedure. Secondary endpoints included all-cause death; stroke (subclassified as ischemic, hemorrhagic, or unknown); all MIs; repeat revascularization; definite, probable, or possible stent thrombosis; BARC types 1 to 5 bleeding; and each individual component of the primary endpoint.

All deaths were considered cardiac unless an undisputed noncardiac cause was present. Spontaneous MI was defined according to the third universal definition (21). Periprocedural MI (<48 h post-PCI) was defined according to the 2013 definition of the Society for Cardiovascular Angiography and Interventions (22). Stent thrombosis was defined and classified according to the Academic Research Consortium-2 definition (23). BARC bleeding was defined as previously reported (24). All endpoints were independently adjudicated by the clinical event committee. An independent Data and Safety and Monitoring Board (DSMB) oversaw the individual and collective safety of the patients in the study during enrollment and follow-up. To provide the steering committee with timely feedback on potential safety issues, the DSMB reviewed the data 3 times during the trial: when the 50th patient enrolled, when the 125th patient enrolled, and when the 200th patient completed 1-month follow-up. The members of the clinical event committee and DSMB are listed in the Supplemental Appendix.

STATISTICAL ANALYSIS. Continuous variables are expressed as mean ± SD or as median with interquartile range as appropriate. Categorical variables are expressed as frequencies and percentages. All analyses were done using SAS version 9.2 or higher (SAS Institute, Cary, North Carolina).

RESULTS

PATIENT SCREENING AND ENROLLMENT. From February 22, 2018, to May 7, 2019, 212 patients with SYNTAX scores <23 were screened, and 201 patients were enrolled after successful PCI in the trial at 9 centers in Brazil (**Figure 1**, Supplemental Table 2). Most of the reasons for nonenrollment were related to suboptimal results of PCI, such as left main coronary artery stenting, 2-stent technique for bifurcation

TABLE 2 Reasons Patients Were Screened but Not Enrolled

Reason Not Enrolled	N
Nonsignificant stenosis (diameter stenosis <50%)	2
Left main disease	2
Bifurcation lesion requiring 2-stent technique	2
Stent edge dissection	1
Side branch occlusion after stent implantation	1
Presence of transient total occlusion	1
Atrial fibrillation	1
Enrollment was closed at the time of screening	1
Total	11

lesion, and side branch occlusion after stenting in 7 patients. In addition, a few more noneligible cases related to nonsignificant stenosis and atrial fibrillation were seen (Table 2).

BASELINE CHARACTERISTICS. Baseline characteristics are shown in Table 3. The mean age was 59.5 ± 7.7 years, and 35.3% of patients were women. Diabetes mellitus was observed in 36.8% of patients. Before the procedure, 96.5% of patients (194 of 201) were diagnosed with stable CAD with normal troponin I or T values (less than the ULN), and 6 patients had CK-MB values <2 times the ULN. One patient was diagnosed with stable CAD without any pre-procedural measurement of cardiac enzymes, whereas the post-procedural troponin T and CK-MB levels was less than the ULN in this patient. The mean site-reported SYNTAX score was 7.2 ± 4.5.

LESION AND PROCEDURAL CHARACTERISTICS. Lesion and procedural characteristics are shown in Table 4. Diagnostic coronary angiograms from all 201 enrolled patients are shown in Supplemental Figure 2. The majority of patients underwent PCI using radial access (84.6%). One-half of lesions were classified as American Heart Association type B2 or C (52.4%). All patients were treated exclusively with Pt-EES. The median number of implanted stents per patients was 1 (interquartile range: 1 to 2), and the mean total stent length per patients was 32.7 ± 18.0 mm. Overlapping stents were observed in 19 patients. Direct stenting was performed in 67.2% of lesions, whereas post-dilatation was performed in 57.6% of lesions with mean maximum pressure of 18.6 atm. IVUS-guided stent optimization was performed in 16.8% of lesions. After the procedure, TIMI (Thrombolysis In Myocardial Infarction) flow grade 3 was achieved in 99.6% of lesions (249 of 250). All lesions achieved post-PCI diameter stenosis (DS) <20% by visual estimation, whereas 99.5% of lesions (249 of 250) achieved DS <30% by quantitative coronary angiography, with mean DS of 11.4 ± 7.1%. Peri-procedural MI occurred in 2 patients (1.0%).

TABLE 3 Baseline Characteristics (N = 201)

Age, yrs	59.5 ± 7.7
Male	130 (64.7)
Female	71 (35.3)
Body mass index, kg/m^2	28.8 ± 4.4
Medical history	
Current smoker	33 (16.4)
Diabetes mellitus	74 (36.8)
Insulin dependent	16 (8.0)
Hypertension	186 (92.5)
Dyslipidemia	140 (69.7)
Family history of coronary artery disease	118 (61.8)
Previous myocardial infarction	18 (9.0)
Established peripheral vascular disease	11 (5.5)
Chronic obstructive pulmonary disease	4 (2.0)
Heart failure	5 (2.5)
Major bleeding	1 (0.5)
Renal insufficiency*	0 (0)
Previous percutaneous coronary intervention	25 (12.4)
Previous coronary artery bypass grafting	3 (1.5)
Left ventricular ejection fraction, %	64.3 ± 7.7
SYNTAX score	7.2 ± 4.5
Clinical presentation	
Non–ST-segment elevation myocardial infarction	0 (0)
Unstable angina	0 (0)
Stable coronary artery disease	201 (100)
Stable angina	189 (94)
Silent ischemia	4 (2)
Angina equivalent	8 (4)

Values are mean ± SD or n (%). *Impaired renal function is defined as estimated glomerular filtration rate of creatinine clearance <60 ml/min/1.73 m^2 by the Modification of Diet in Renal Disease formula.

SYNTAX = Synergy Between PCI With Taxus and Cardiac Surgery.

OUTCOMES. All enrolled patients completed study follow-up over 4 months except 1 patient who died 3 days after the index procedure (Figure 1). The primary ischemic endpoint occurred in 1 patient up to 3-month follow-up (0.5%). The primary bleeding endpoint occurred in 1 patient (0.5%). These primary endpoints occurred in the same patient. The patient was a 68-year-old woman with a SYNTAX score of 3. She underwent successful PCI for a noncomplex target lesion in the mid right coronary artery. She was on long-term therapy with clopidogrel before the index procedure, so a clopidogrel loading dose was not administrated before the index procedure. Prasugrel 60 mg was loaded immediately after PCI. The patient maintained constant high blood pressure, and a few hours after the index procedure, she presented with severe headache and altered level of consciousness, becoming then comatose and requiring orotracheal

TABLE 4 Lesion and Procedural Characteristics (N = 201)

Vascular access site per patient	
Femoral	31 (15.4)
Radial	170 (84.6)
Brachial	0 (0.0)
Lesions treated per patient	
1 lesion	159 (79.1)
2 lesions	36 (17.9)
≥3 lesions	6 (3.0)
Treated lesions (250 lesions)	
Left main coronary artery	0 (0.0)
Left anterior descending coronary artery	131 (52.4)
Left circumflex coronary artery	47 (18.8)
Right coronary artery	72 (28.8)
AHA lesion type	
A	39 (15.6)
B1	80 (32.0)
B2	51 (20.4)
C	80 (32.0)
Direct stenting	168 (67.2)
IVUS used for stent optimization	42 (16.8)
Minimal luminal area, mm^2	7.1 ± 3.5
Stent area, mm^2	7.5 ± 3.0
Post-dilatation performed	144 (57.6)
Diameter stenosis by quantitative coronary angiography	
Pre-procedure, %	58.9 ± 11.9
Post-procedure, %	11.4 ± 7.1
<30%	1 (0.4)
Pre-procedural TIMI flow grade	
0	0 (0.0)
1	4 (1.6)
2	6 (2.4)
3	240 (96.0)
Post-procedural TIMI flow grade	
0	0 (0.0)
1	0 (0.0)
2	1 (0.4)
3	249 (99.6)
Number of stents used per patient	1 (1-2)
Patients with	
No stents	0 (0.0)
1 stent	142 (70.6)
2 stents	50 (24.9)
≥3 stents	9 (4.5)
Total stent length per patient, mm	32.7 ± 18.0
Per stent characteristics (272 stents)	
Pt-EES used	272 (100)
Stent length, mm	24.2 ± 8.4
Stent nominal diameter, mm	3.00 ± 0.43
Procedure time, min	45.8 ± 26.5
Days in hospital	2 (2-3)
Prasugrel loading dose given after successful PCI procedure	201 (100)

Values are n (%), mean ± SD, or median (interquartile range).

AHA = American Heart Association; IVUS = intravascular ultrasound; PCI = percutaneous coronary intervention; Pt-EES = platinum-chromium everolimus-eluting stent; TIMI = Thrombolysis In Myocardial Infarction.

intubation. Computed tomography revealed massive intracranial bleeding, and the patient was referred for emergency neurosurgical decompression. After surgery, there was severe deterioration of neurological status, and the patient eventually died 3 days after index procedure. This event was adjudicated as cardiac death, BARC type 5b bleeding, and hemorrhagic stroke. The complete list of clinical outcomes is presented in Table 5. In terms of secondary endpoints, no spontaneous MI or stent thrombosis was observed up to 3-month follow-up, while 1 non-target vessel revascularization was observed.

ADHERENCE TO ANTIPLATELET AGENTS. Adherence to antiplatelet agents is shown in Figure 1. First of all, before the index procedure, all participants were on standard DAPT by design. Of these, 99.5% were on DAPT with aspirin plus clopidogrel. One hundred four patients were prescribed a clopidogrel loading dose, whereas 96 were on long-term therapy with a clopidogrel maintenance dose. Only 1 patient was on long-term DAPT with aspirin plus ticagrelor before PCI. Immediately after PCI, all 201 patients received loading doses of prasugrel 60 mg, and aspirin was discontinued on the day of the index procedure. At 3-month follow-up, 3 patients were not adherent to study medication. Two patients presented with recurrent angina during follow-up. One underwent revascularization for a nontarget vessel and subsequently restarted DAPT (aspirin and clopidogrel). The other restarted DAPT (aspirin and clopidogrel) without having undergone invasive coronary angiography, and angina subsequently subsided. The remaining patient did not discontinue prasugrel up to 3-month follow-up but restarted aspirin 10 days before the 3-month visit by his own decision. Overall, 98.5% of patients were adherent to study medication at 3-month follow-up in the cross-sectional analysis. In drug accountability analysis for prasugrel among 198 patients with available data, adherence to prasugrel was 98.3% (18,055 of 18,353 tablets). Both analyses demonstrated high adherence to prasugrel monotherapy without any side effects. At 4-month follow-up, 60% of patients were receiving aspirin monotherapy, and the remaining patients received DAPT with aspirin and clopidogrel.

DISCUSSION

We present here a proof-of-concept trial in which selected patients with stable CAD were treated with aspirin-free prasugrel monotherapy following successful Pt-EES implantation. One patient experienced a primary bleeding endpoint. Importantly, no stent thrombosis event occurred. This finding is not surprising, but to the best of our knowledge, this is the first prospective experience of withholding aspirin the day after index PCI while administrating monotherapy with a $P2Y_{12}$ inhibitor (25).

Recently, several randomized controlled trials (RCTs) have been conducted to investigate different antithrombotic strategies, including monotherapy with a $P2Y_{12}$ inhibitor, aiming to assess the best balance between ischemic and bleeding risks after PCI. The STOPDAPT-2 (Short and Optimal Duration of Dual Antiplatelet Therapy-2 Study) trial showed that 1-month DAPT followed by clopidogrel monotherapy provided a beneficial net clinical effect for ischemic and bleeding events, compared with 12-month DAPT with aspirin and clopidogrel (3). Likewise, in the SMART-CHOICE (Comparison Between $P2Y_{12}$ Antagonist Monotherapy and Dual Antiplatelet Therapy After DES) study, 3 months of DAPT followed by $P2Y_{12}$ inhibitor monotherapy for 9 months was noninferior to 12 months of DAPT (4). Similar results were reported in a high-risk population from the large-scale randomized TWILIGHT (Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention) study (5) and in patients with ACS from the TICO (Ticagrelor With or Without Aspirin in Acute Coronary Syndrome After PCI) trial (6). Additionally, although not showing superiority, the GLOBAL LEADERS (A Clinical Study Comparing Two Forms of Anti-platelet Therapy After Stent Implantation) trial suggested no harm of a scheme comprising 1-month DAPT (aspirin and ticagrelor) followed by 23-month ticagrelor monotherapy (26). It is interesting to note that all those trials included patients undergoing PCI in both acute and stable settings.

Compared with patients treated with standard DAPT, those with moderate to high bleeding risk should derive benefit from a strategy of aspirin-free prasugrel monotherapy by reducing bleeding events without increasing ischemic events. In numerous RCTs with short DAPT followed by $P2Y_{12}$ inhibitor monotherapy, $P2Y_{12}$ inhibitor monotherapy was started at least 1 month after the index procedure (3–6). But until now, no trial has evaluated a $P2Y_{12}$ monotherapy strategy initiated immediately after drug-eluting stent (DES) implantation, and this type of strategy should be evaluated with special consideration for safety because of the high frequency of stent thrombosis observed during the first month (13). Therefore, before starting a RCT to prove the superiority of aspirin-free strategy in reducing bleeding, the safety concern with regard to an excess of early stent thrombosis should be excluded. If we aim to demonstrate the noninferiority of aspirin-free therapy against standard DAPT with respect to definite stent thrombosis at 3 months, we need more than 11,000 patients in each arm (expected 3-month definite stent thrombosis rate of standard DAPT group 0.44% from SYNTAX II [using Pt-EES and IVUS-guided stent optimization], noninferiority margin 0.22%, 1-sided alpha = 0.05, 80% power) (27). It is unrealistic or even unethical to implement such a trial without any evidence of feasibility and safety. Therefore, we needed a small first-in-human study with maximum consideration for safety (i.e., early stent thrombosis prevention), including careful patient selection using SYNTAX score, strict screening on the basis of cardiac enzyme levels, strong recommendation for imaging-guided stent optimization, strict protocol for switching antiplatelet drugs, and extended follow-up to 4 months, as well as patient education using a specific study card and stringent, careful data monitoring by a DSMB. In terms of changes in antiplatelet therapy regimen, we decided to initiate prasugrel monotherapy in the catheterization laboratory immediately after confirmation of successful EES implantation to minimize the risk for stent thrombosis, because suboptimal stent implantation or unexpected complex stenting is performed

TABLE 5 Clinical Outcomes at 3-Month Follow-Up (N = 201)

Primary ischemic endpoint: composite of cardiac death, TV spontaneous myocardial infarction, or definite stent thrombosis	1 (0.5)
Cardiac death	1 (0.5)
TV spontaneous myocardial infarction (48 h after PCI)	0 (0.0)
Definite stent thrombosis	0 (0.0)
Primary bleeding endpoint: BARC type 3 or 5 bleeding	1 (0.5)
BARC type 3a	0 (0.0)
BARC type 3b	0 (0.0)
BARC type 5a	0 (0.0)
BARC type 5b	1 (0.5)
Secondary endpoints	
All-cause death	1 (0.5)
Cardiac	1 (0.5)
Stroke	1 (0.5)
Ischemic	0 (0.0)
Hemorrhagic	1 (0.5)
Unknown	0 (0.0)
Transient ischemic attack	0 (0.0)
Myocardial infarction	2 (1.0)
Spontaneous	0 (0.0)
TV-related	0 (0.0)
Non-TV-related	0 (0.0)
Periprocedural	2 (1.0)
TV-related	2 (1.0)
Non-TV-related	0 (0.0)
Bleeding: BARC types 1–5	1 (0.5)
BARC type 5b	1 (0.5)
All revascularizations	1 (0.5)
Non-TV revascularization	1 (0.5)
Stent thrombosis	0 (0.0)
Definite	0 (0.0)
Probable	0 (0.0)
Possible	0 (0.0)

Values are n (%).

BARC = Bleeding Academic Research Consortium; PCI = percutaneous coronary intervention; TV = target vessel.

with a certain probability (3.3% [7 of 212] among all patients screened in the present trial). This strategy of switching $P2Y_{12}$ inhibitors is in line with international consensus on switching therapies and is supported by the pharmacodynamic studies (28–31). In a previous trial, it was demonstrated that a prasugrel loading dose following a clopidogrel loading dose results in a rapid and substantial decrease in high platelet reactivity (HPR) in patients undergoing PCI (31).

The safety profile of prasugrel monotherapy following DES implantation in this study may be attributed, at least in part, to the exclusive use of newer generation thin-strut biodegradable polymer EES, as these new stents demonstrated a lower rate of thrombotic complications compared with first-generation DES (14). Additionally, we included only patients with noncomplex, nonacute CAD in whom optimal PCI results were achieved. Although intracoronary imaging-guided stent optimization was strongly recommended by the protocol, only 16% of patients underwent IVUS-guided stent optimization. A low adoption of IVUS for stent optimization was somewhat disappointing, but in-stent DS <30% by quantitative coronary angiography was achieved in almost all lesions (99.5%), with a mean DS of 11.4 ± 7.1%.

Potent $P2Y_{12}$ blockade by prasugrel monotherapy with excellent adherence (98.5%) may have led to down-regulation of other markers of platelet reactivity, including arachidonic acid- and collagen-induced aggregation (32,33), resulting in no cases of stent thrombosis. Adherence to prasugrel in the present trial was relatively high compared with trials that implemented $P2Y_{12}$ monotherapy with ticagrelor (at 3 months, 86.0% and 87.3% in the GLOBAL LEADERS and TWILIGHT trials, respectively), although we enrolled far fewer patients the present trial than the others. In the ISAR-REACT 5 (Prospective, Randomized Trial of Ticagrelor Versus Prasugrel in Patients With Acute Coronary Syndrome) trial, among 4,018 patients with ACS randomized to either prasugrel or ticagrelor, the incidence of death, MI, or stroke was significantly lower among those who received prasugrel than among those who received ticagrelor, and the incidence of major bleeding was not significantly different between the 2 groups. In addition to the main findings, prasugrel was associated with a lower incidence of drug discontinuation at 1-year follow-up compared with ticagrelor (12.5% in the prasugrel arm vs. 15.2% in the ticagrelor arm; $p = 0.03$) (34), which can be at least partially explained by the specific side effects of ticagrelor (e.g., dyspnea) and its twice-daily prescription. Furthermore, in the present study we diligently educated participants about the importance of compliance with medication and the risk of stopping prasugrel using a specific study card, which may have contributed to the high adherence to prasugrel. These findings may suggest that prasugrel is a preferable drug as $P2Y_{12}$ inhibitor monotherapy compared with ticagrelor.

In the present trial, maximal consideration for early stent thrombosis resulted in the enrollment of patients with very low bleeding risk, but the efficacy of the aspirin-free strategy in reducing bleeding among patients at high bleeding risk is of interest and should be investigated in a large-scale RCT. The completion of the present trial without any stent thrombosis allows us ethically to plan further trials. Theoretically, patients with moderate to high bleeding risk are ideal candidates for a large RCT to prove efficacy in bleeding reduction, as shown in recent trials with short DAPT strategies followed by $P2Y_{12}$ monotherapy (5,35,36). Of note, these patients frequently have complex PCI features and ACS presentation, which are well-known ischemic risk factors and were systematically excluded from the present trial according to the exclusion criteria applied in this first-in-human study investigating for the first time a regimen of aspirin-free prasugrel monotherapy. Therefore, before starting a large RCT, an additional pilot study may be needed to demonstrate safety (absence of early stent thrombosis) in patients with more complex coronary syndromes (e.g., a non-ST-segment elevation ACS population as in the ASET Japan trial).

STUDY LIMITATIONS. First, this was a nonrandomized study without any comparator. Therefore, no conclusion could be drawn in terms of the superiority or inferiority of prasugrel monotherapy compared with conventional DAPT, as this was not the objective of this study.

Second, the external validity of the results of the present pilot study may be limited to a population selected with the stringent criteria of selection applied in the present study, which is only one exploratory step toward "an aspirin-free era post-PCI" (37). However, the completion of the present trial without any stent thrombosis allows us to plan further trials and expansion of the inclusion criteria (e.g., a non-ST-segment elevation ACS population as in the ASET Japan trial).

Third, the cutoff rate for definite stent thrombosis adopted in the present study was relatively high compared with the stent thrombosis outcomes of current stent trials with contemporary DES in which a definite stent thrombosis rate of 0.72% at a median

follow-up of 3.8 years with cobalt chromium EES or Pt-ES was reported (14).

Fourth, the administration of a prasugrel loading dose immediately after PCI may have contributed to the fatal intracranial bleeding in 1 patient, who was on long-term therapy with aspirin plus clopidogrel before PCI. A single event of intracranial hemorrhage in a very small sample size as in the ASET trial represents theoretically a rate of 0.5% over 3 months in very low risk patients and is concerning, as in previous RCTs with short DAPT strategies among higher risk patients than in the present trial, intracranial hemorrhage rates ranged from 0% to 0.13% over an observation period of 1 year (3,26). This single case of intracranial hemorrhage may have been caused more specifically by switching between $P2Y_{12}$ inhibitors with a loading dose of prasugrel rather than by aspirin-free prasugrel monotherapy itself. Initiation of prasugrel with or without aspirin prior to the procedure might be a desirable alternative in future trials, as switching from clopidogrel to prasugrel could then be avoided. Although prasugrel monotherapy starting before PCI is the desirable final strategy (**Central Illustration**), it was premature to implement that strategy during this first-in-human study without applying the switching of $P2Y_{12}$ inhibitors recommended in published research (28).

Finally, the lack of platelet function testing is a major limitation, as we have missed the opportunity to evaluate the incidence and impact of HPR under prasugrel treatment without aspirin in clinical practice. HPR has been observed in about 10% of patients treated with prasugrel (38) and might be associated with worse ischemic outcomes in patients on prasugrel monotherapy than on standard DAPT. However, an individual patient-level meta-analysis including more than 6,000 patients showed that HPR was not predictive of recurrent ischemic events in low-risk patients treated with clopidogrel (39). In the present trial, careful patient selection and strong recommendation for imaging-guided stent optimization may have minimized the risk for ischemic events in patients with HPR on prasugrel monotherapy.

CONCLUSIONS

Aspirin-free prasugrel monotherapy was feasible and safe following successful DES implantation in a population of selected patients with stable CAD with low anatomic complexity. Our findings may help underpin larger randomized controlled studies to evaluate the aspirin-free strategy compared with traditional DAPT following PCI.

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PERSPECTIVES

WHAT IS KNOWN? Recent studies have suggested that short DAPT strategies may provide an adequate balance between ischemic and bleeding risks. However, an aspirin-free strategy with a $P2Y_{12}$ inhibitor immediately after stent implantation has not yet been investigated in the context of a prospective trial.

WHAT IS NEW? Aspirin-free prasugrel monotherapy initiated immediately after Pt-EES implantation demonstrated feasibility and safety without any stent thrombosis in selected low-risk patients with stable CAD.

WHAT IS NEXT? These finding might pave the way for further exploration of the benefit of aspirin-free $P2Y_{12}$ inhibitor monotherapy in patients with coronary disease treated with PCI.

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KEY WORDS adjunctive pharmacotherapy, antiplatelet therapy, drug-eluting stent(s), stable coronary artery disease

APPENDIX For supplemental Methods, tables, and figures, please see the online version of this paper.