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Reduced-dose prasugrel monotherapy without aspirin after PCI with the SYNERGY stent in East Asian patients presenting with chronic coronary syndromes or non-ST-elevation acute coronary syndromes: rationale and design of the ASET Japan pilot study

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KEYWORDS

- ACS/NSTE-ACS
- clinical trials
- stable angina

Abstract

The Acetyl Salicylic Elimination Trial (ASET) Japan pilot study is a multicentre, single-arm, open-label, proof-of-concept study with a stopping rule based on the occurrence of definite stent thrombosis. This study aims to demonstrate the feasibility and safety of low-dose prasugrel monotherapy following percutaneous coronary intervention (PCI) in Japanese patients presenting with chronic coronary syndromes (CCS) or non-ST-elevation acute coronary syndromes (NSTE-ACS). Four hundred patients with a SYNTAX score <23 requiring PCI due to CCS or NSTE-ACS will be screened and considered eligible for the study. The enrolment is planned in two phases: 1) 200 patients presenting with CCS, followed by 2) 200 patients presenting with NSTE-ACS. After optimal PCI with implantation of a SYNERGY (Boston Scientific) stent, patients will be enrolled and loaded with prasugrel 20 mg, followed by a maintenance dose of prasugrel 3.75 mg once daily without aspirin continued for 3 months in Phase 1 (CCS patients), and for 12 months in Phase 2 (NSTE-ACS patients). After these follow-up periods, prasugrel will be replaced by standard antiplatelet therapy according to local practice. The primary endpoint is a composite of cardiac death, target vessel myocardial infarction, or definite stent thrombosis after the index procedure. The primary bleeding endpoint is any Bleeding Academic Research Consortium type 3 or 5 bleeding occurring within 3 months of the index PCI for CCS patients, or 12 months for NSTE-ACS patients. The ASET Japan study is designed to demonstrate the feasibility and safety of reduced-dose prasugrel monotherapy after PCI in East Asian patients with acute and chronic coronary syndromes.

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Abbreviations

ACS	acute coronary syndrome
AHA	American Heart Association
ARC	Academic Research Consortium
BARC	Bleeding Academic Research Consortium
CCS	chronic coronary syndrome
CEC	clinical event committee
DAPT	dual antiplatelet therapy
DES	drug-eluting stent
DSMB	Data Safety and Monitoring Board
ESC	European Society of Cardiology
MI	myocardial infarction
NSTE-ACS	non-ST-elevation acute coronary syndrome

Introduction

Following coronary stent implantation, dual antiplatelet therapy (DAPT) is prescribed to prevent acute and late stent thrombosis and to minimise repeat ischaemic events due to progressive atherosclerosis; however, its use increases the risk of bleeding complications[1,2]. In patients not at high bleeding risk, the current European and US guidelines recommend DAPT after percutaneous coronary intervention (PCI) with drug-eluting stents (DES) for at least 6 months in chronic coronary syndromes (CCS) and at least 12 months in acute coronary syndromes (ACS)[3,4], whereas in patients at high bleeding risk, an abbreviated regimen of 1-3 months is suggested[5]. However, there are currently no recommendations regarding aspirin-free strategies. The history and recent trials of antiplatelet therapy are summarised in **Supplementary Appendix 1**, **Supplementary Table 1** and **Supplementary Figure 1**-**Supplementary Figure 3**.

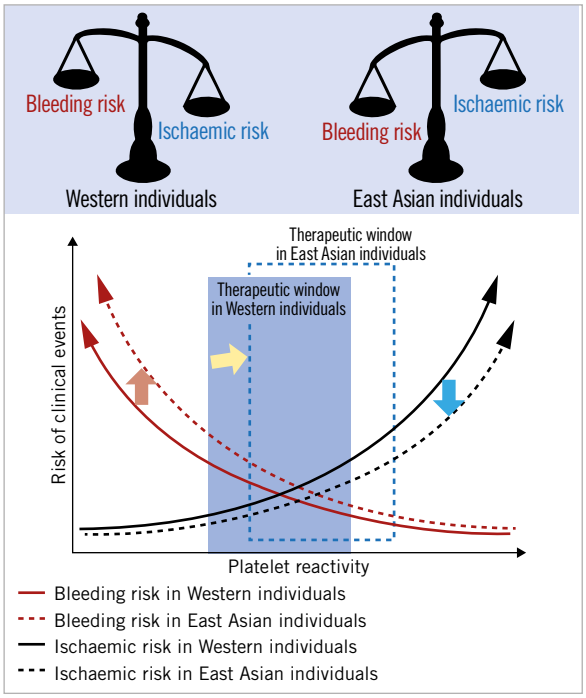

Figure 1. *The East Asian paradox. Postulated differences in the optimal "therapeutic window" of platelet reactivity between Western (blue square) and East Asian populations (blue dotted square). Compared to Western individuals, East Asian individuals have lower ischaemic risk at a same level of platelet reactivity (blue arrow); however, bleeding risk in East Asian individuals is higher than Western individuals (red arrow). The optimal "therapeutic window" of platelet reactivity might differ between Western and East Asian patients (yellow arrow).*

THE EAST ASIAN PARADOX AND OPTIMAL DOSE OF ANTIPLATELET THERAPY

East Asian patients have a higher prevalence of high on-treatment platelet reactivity compared with Caucasian patients, whilst their thrombotic event rate after PCI is similar, or even lower[6]. Conversely, the risk of bleeding events in East Asian patients appears to be greater than in Western patients[7]. This phenomenon, referred to as the "East Asian paradox", suggests that the optimal therapeutic dose of antiplatelets may be different between East Asian and Western patients **(Figure 1)**.

Based on this hypothesis, a recent clinical trial has shown the efficacy of adjusted-dose prasugrel in Japanese patients[8]. The multicentre PRASFIT-ACS study in ACS patients showed no significant difference in ischaemic and bleeding events between patients randomised to DAPT followed by low-dose prasugrel (3.75 mg daily) and aspirin (81-330 mg daily) compared to DAPT followed by standard-dose clopidogrel (75 mg daily) and aspirin (81-330 mg daily)[8].

Consequently, current guidelines in Japan and Taiwan recommend a reduction in the maintenance dose of prasugrel to 3.75 mg daily after coronary stent deployment[9,10]. The current recommended doses of oral antiplatelet therapy after PCI with stent implantation in patients with CCS and non-ST-elevation ACS (NSTE-ACS) are summarised in **Table 1**. The PENDULUM mono study was a multicentre, non-interventional, prospective registry that assessed the frequency of bleeding complications and cardiovascular events associated with adjusted-dose prasugrel monotherapy (3.75 mg daily) after PCI in high bleeding risk Japanese patients[11]. In this trial, 65.7% of patients switched to low-dose prasugrel monotherapy at 3 months and up to 83.5% switched at 12 months following their PCI. At 12 months, the cumulative incidence of bleeding complications, defined as Bleeding Academic Research Consortium (BARC) type 2, 3 or 5 after the periprocedural period (from 1 to 12 months after PCI), was 3.2%, and the rate of major adverse cardiac and cerebrovascular events (MACCE), defined as the composite of all-cause death, myocardial infarction (MI), stroke, cerebral infarction, and stent thrombosis, was 3.8%. Furthermore, a prespecified analysis in the PENDULUM mono and the PENDULUM registry comparing single antiplatelet therapy (SAPT) with prasugrel versus DAPT showed that SAPT significantly reduced BARC 2, 3, and 5 bleeding between 0 and 12 months after the index PCI without increasing ischaemic events[11,12]. These observational studies suggest that adjusted-dose prasugrel monotherapy may be safely

Table 1. Current guidelines for the dosing of oral antiplatelet therapy after percutaneous coronary intervention with stent implantation due to chronic coronary syndrome and non-ST-elevation acute coronary syndrome.

	Loading dose			Maintenance dose		
	JCS	ESC	ACC/AHA	JCS	ESC	ACC/AHA
Aspirin	162-324 mg	150–300 mg	162–325 mg	81–162 mg, once daily	75–100 mg, once daily	81 mg, once daily
Clopidogrel	300 mg	600 mg	600 mg	75 mg, once daily	75 mg, once daily	75 mg, once daily
Prasugrel	20 mg	**60 mg	†60 mg	3.75 mg, once daily	‡10 mg, once daily	¶10 mg, once daily
Ticagrelor	*180 mg	**180 mg	†180 mg	††90 mg, twice daily	§90 (60) mg, twice daily	‖90 mg, twice daily

Reduced doses of $P2Y_{12}$ inhibitor are highlighted in bold. *Ticagrelor is not available for CCS patients. In patients with NSTE-ACS, a ticagrelor 180 mg loading dose may be considered in $P2Y_{12}$ receptor inhibitor-naive patients before PCI, when prasugrel or clopidogrel are not available or are contraindicated. **Prasugrel or ticagrelor on top of aspirin may be considered instead of clopidogrel for CCS patients undergoing PCI, considering the ischaemic (e.g., high SYNTAX score, prior stent thrombosis, location and number of implanted stents) and bleeding risks. †Prasugrel and ticagrelor are not available for CCS patients. ††Ticagrelor is considered when prasugrel is not available or contraindicated. ‡5 mg/day for patients aged ≥75 years or with a body weight <60 kg. §Ticagrelor 60 mg is the treatment option for DAPT in combination with aspirin 75–100 mg daily in post-myocardial infarction patients who have tolerated DAPT for 1 year with a high or moderate risk of an ischaemic event, and without a high bleeding risk. ¶In patients with ACS (NSTE-ACS or STEMI) treated with DAPT after coronary stent implantation who are not at high risk for bleeding complications and who do not have a history of stroke or TIA, it is reasonable to choose prasugrel over clopidogrel for maintenance $P2Y_{12}$ inhibitor therapy. ‖In patients with ACS (NSTE-ACS or STEMI) treated with DAPT after coronary stent implantation, it is reasonable to use ticagrelor in preference to clopidogrel for maintenance $P2Y_{12}$ inhibitor therapy. ACC/AHA: American College of Cardiology/American Heart Association; CCS: chronic coronary syndrome; DAPT: dual antiplatelet therapy; ESC: European Society of Cardiology; JCS: Japanese Circulation Society; NSTE-ACS: non-ST-elevation acute coronary syndrome; PCI: percutaneous coronary intervention; STEMI: ST-elevation myocardial infarction; TIA: transient ischaemic attack

used in Japanese patients, but this needs to be further demonstrated in prospective studies. In addition, if low-dose prasugrel monotherapy is appropriate for CCS patients, further prospective studies will be needed to explore its feasibility and safety in high-risk patients.

The objective of the present trial is to demonstrate the efficacy and safety of low-dose (3.75 mg daily) prasugrel monotherapy following PCI in Japanese patients presenting with CCS or NSTE-ACS.

Methods

STUDY DESIGN

The Acetyl Salicylic Elimination Trial (ASET) Japan Pilot Study (ClinicalTrials.gov: NCT05117866) is designed as a multicentre, single-arm, open-label, proof-of-concept trial with a stopping rule based on the occurrence of definite stent thrombosis[13]. The study flowchart is shown in **Figure 2**. The enrolment of patients across 12 sites in Japan is planned in two phases: 1) 200 patients presenting with CCS, followed by 2) 200 patients presenting with NSTE-ACS. The recruitment will start with patients presenting with CCS, and the Data Safety and Monitoring Board (DSMB) will closely monitor safety events and will meet when recruitment in the CCS cohort reaches 100. The DSMB will then advise the steering committee whether enrolment of the NSTE-ACS population should be started based on clinical events reported at that time. During Phase 1, patient recruitment will be stopped if three or more cases of definite stent thrombosis occur within three months of the index PCI. In Phase 2, enrolment will be stopped if three or more patients experience definite stent thrombosis within 12 months of the index PCI, or if there are two or more sudden deaths in the first 30 days. The cut-off rate for definite stent thrombosis was determined based on the previously reported incidence of stent thrombosis[14]. In the EVOLVE II Trial, the incidence of stent thrombosis was 0.4% at 30 days and 0.4% at 1 year[15], whilst it was 1.2% at 30 days and 1.5% at 1 year in the CARDIOBASE Bern PCI Registry[16].

SAMPLE SIZE CONSIDERATIONS

Due to the exploratory nature of this study, no formal sample size calculations were performed. Based on a previous pilot study[17], we decided to enrol 200 consecutive patients in each phase (for a of total 400 patients). The Benestent-II Pilot Study, which attempted to eliminate the convention of anti-vitamin K anticoagulation post-stenting that was in use at the time, was the first-in-human study to apply a stopping rule involving a fixed rate of stent thrombosis beyond which the study would have to be terminated. This first-in-human study was successfully completed without any stent thrombosis in 200 patients and was followed by the large randomised Benestent-II Pilot Study, with 827 patients treated without anticoagulation[18].

INFORMED CONSENT

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 certified review board (CRB), central ethics committee and local ethics committee at each participating centre approved the study protocol (CR20-023 and CR21-017 at the Fujita Health

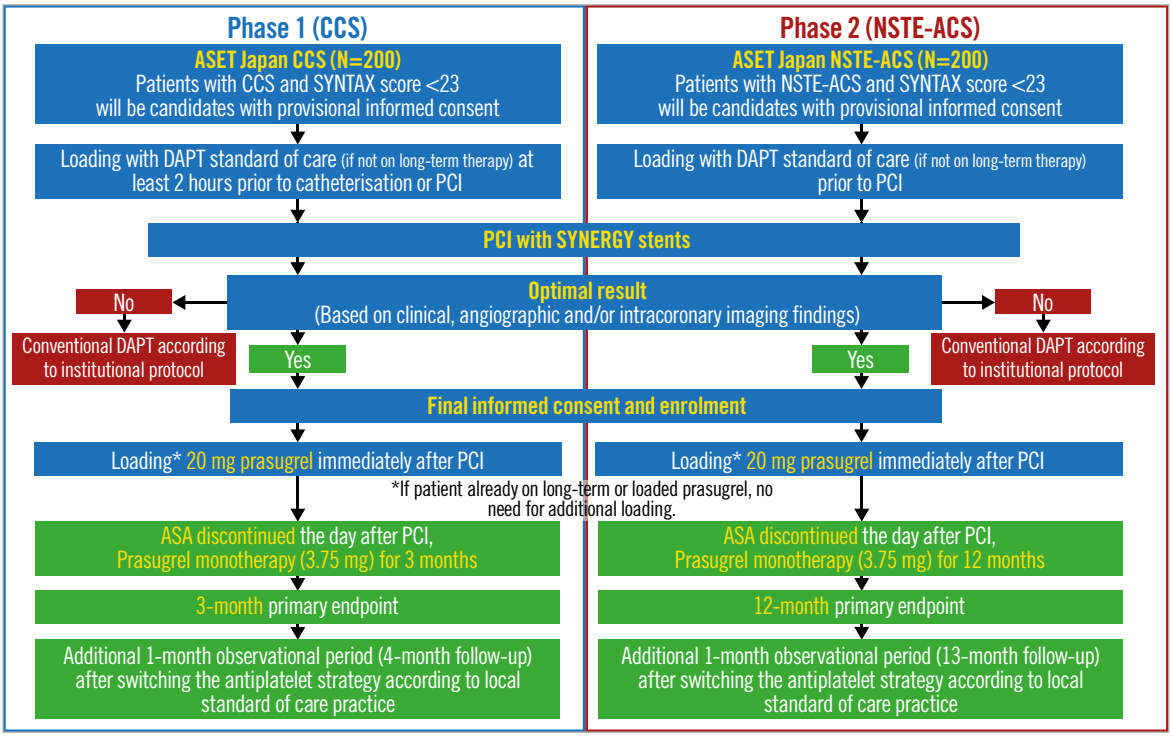

Figure 2. *Flowchart of the ASET Japan trial. ASA: acetylsalicylic acid; CCS: chronic coronary syndromes; DAPT: dual antiplatelet therapy; NSTE-ACS: non-ST-elevation acute coronary syndromes; PCI: percutaneous coronary intervention*

University). The study protocol has been registered at the Japanese Registry of Clinical Trials (identifier: jRCTs042200053).

PATIENT SCREENING

Patients requiring PCI for CCS or NSTE-ACS with an anatomical SYNTAX score <23 prior to revascularisation will be screened for enrolment in this trial. The anatomical SYNTAX score will be assessed onsite by trained investigators, and the results will be confirmed by an independent core lab. The inclusion and exclusion criteria are listed in **Table 2**. Cardiac enzymes and biomarkers must be sampled to detect acute MI prior to the index PCI. The criteria for cardiac enzymes and biomarkers are shown in **Supplementary Appendix 2**.

PCI PROCEDURE

All patients will be loaded with standard DAPT (aspirin 81 to 330 mg and clopidogrel 300 mg, prasugrel 20 mg, or ticagrelor 180 mg, unless patients are on long-term [≥5 days prior to the index PCI] therapy with prasugrel 3.75 mg as a Japanese standard maintenance dose), which according to local practice is at least two hours prior to their index PCI for CCS patients (Phase 1), and prior to their PCI procedure for NSTE-ACS patients (Phase 2). The use of glycoprotein IIb/IIIa inhibitors is regulated in Japan by the Pharmaceuticals and Medical Devices Agency (PMDA), and previous trials have demonstrated that abciximab does not reduce major coronary events, whilst significantly increasing bleeding and thrombocytopaenia[19].

The index PCI will be performed using a radial, brachial or femoral approach with the intention to achieve complete revascularisation in at least one stenosis with an angiographic diameter stenosis ≥50%, as identified by the local interventional cardiologist. Although not mandated, the radial approach will be strongly recommended. Periprocedural anticoagulation will be used at the operator's discretion according to local or international guidelines[20]. All target lesions must be exclusively treated with the SYNERGY stent (Boston Scientific), which elutes everolimus within three months from a 4 μm biodegradable poly(lactic-co-glycolic acid) (PLGA) coating that is located only on the abluminal side of 74 μm/79 μm/81 μm platinum-chromium struts (for the stent sizes ≤2.5 mm/3.0-3.5 mm/4.0 mm, respectively) and is resorbed within four months. These features have been introduced to improve early endothelialisation of stent struts, accelerate vessel healing, and reduce thrombotic events. The SYNERGY stent has been shown to have clinical safety and efficacy in a previous randomised trial[15]. The feasibility and safety of the SYNERGY stent with prasugrel monotherapy without aspirin were shown in the ASET study[17]. The potential advantage of uniform use of the SYNERGY stent is to facilitate the pooling of data with that of the ASET study in which the SYNERGY stent was also uniformly used. However, the potential disadvantage of this is that evidence stemming from this study will not be generalisable to other technologies.

The investigator should perform the procedure to achieve optimal stent implantation according to local standards of care by angiography including quantitative coronary angiography (QCA) and/or findings from intracoronary imaging (intravascular ultrasound [IVUS], optical coherence tomography [OCT], or optical frequency domain imaging [OFDI]). An optimal immediate

Table 2. Inclusion and exclusion criteria of the ASET Japan trial.

For CCS patients (Phase 1)
1. Inclusion criteria for CCS patients
All candidates must meet the following inclusion criteria:
1. Successful PCI with optimal acute stent implantation of one or more SYNERGY stent(s).
2. SYNERGY stent implantation was performed to treat:
a) at least one *de novo* lesion with ≥50% diameter stenosis determined by visual assessment in at least one native coronary artery with a vessel size between 2.25 mm and 5.0 mm in diameter.
b) non-acute coronary disease, with normal cardiac biomarker values prior to the PCI procedure, and evidence of myocardial ischaemia by symptoms or non-invasive/invasive testing.
c) patients with anatomical SYNTAX score <23 prior to PCI
3. Patient has provided written informed consent as approved by the ethics committee of the respective clinical site.
2. Exclusion criteria for CCS patients
Candidates will be ineligible for enrolment if any of the following conditions apply:
1. ≤20 years of age.
2. Unable to give informed consent.
3. Females of child-bearing potential unless negative pregnancy test at screening and willing to use effective contraception for the duration of treatment with study medication.
4. Females who are breastfeeding at time of enrolment.
5. Patients concomitantly receiving any other non-study stent for the same procedure.
6. Patients with planned PCI or surgical intervention to treat any cardiac or non-cardiac condition.
7. Previous PCI with any non-SYNERGY stents in the last 6 months.
8. Current (same hospitalisation) or previous (within 12 months) acute coronary syndrome.
9. Patients with the following lesion characteristics prior to PCI: saphenous or arterial graft, in-stent (re)stenosis.
10. History of definite stent thrombosis.
11. Concomitant cardiac valve disease requiring invasive therapy.
12. Atrial fibrillation or other indication for oral anticoagulant therapy.
13. Known allergy to aspirin or prasugrel or diagnosed lactose intolerance.
14. Acute heart failure.
15. Active myocarditis.
16. Cardiomyopathy.
17. Patient in haemodialysis.
18. Treatment in the last 10 days or requirement for ongoing treatment with a strong CYP3A4 inhibitor or inducer.
19. History of stroke or transient ischaemic cerebrovascular accident.
20. History of intracranial haemorrhage or other intracranial pathology associated with increased bleeding risk.
21. Haemoglobin <10 g/dL or other evidence of active bleeding.
22. Peptic ulceration documented by endoscopy within the last 3 months unless healing proven by repeat endoscopy.
23. Any other condition deemed by the investigator to place the patient at excessive risk of bleeding with prasugrel.
24. Participation in another trial with an investigational drug or device.
25. Comorbidity associated with life expectancy <1 year.
26. Assessment that the subject is not likely to comply with the study procedures or have complete follow-up.
27. Known drug or alcohol dependence within the past 12 months as judged by the investigator.
CCS: chronic coronary syndrome; PCI: percutaneous coronary intervention
For NSTE-ACS patients (Phase 2)
1. Inclusion criteria
For NSTE-ACS patients
1. Patients with diagnosed non-ST-elevation acute coronary syndrome.
2. Patients with anatomical SYNTAX score <23 prior to PCI.
3. Patient provided written informed consent as approved by the ethics committee of the respective clinical site.
Post-PCI for NSTE-ACS patients
1. Patient is free of angina symptoms at the end of PCI procedure.
2. Successful PCI with optimal acute stent implantation of one or more SYNERGY stent(s).
3. SYNERGY stent implantation was performed to treat at least one *de novo* lesion with ≥50% diameter stenosis determined by visual assessment in at least one native coronary artery with a vessel size between 2.25 mm and 5.0 mm in diameter.

Table 2. Inclusion and exclusion criteria of the ASET Japan trial. (cont'ed)

For NSTE-ACS patients (Phase 2)
2. Exclusion criteria
Candidates will be ineligible for enrolment if any of the following conditions apply:
1. ≤20 years of age.
2. Unable to give informed consent.
3. Females of child-bearing potential unless negative pregnancy test at screening and willing to use effective contraception for the duration of treatment with study medication.
4. Females who are breastfeeding at time of enrolment.
5. Patients concomitantly received any other non-study stent at the same procedure.
6. Patients with planned PCI or surgical intervention to treat any cardiac or non-cardiac condition.
7. Previous PCI with any non-SYNERGY stents in the last 6 months.
8. Patient with following lesion characteristics prior to PCI: saphenous or arterial graft, in-stent (re)stenosis.
9. History of definite stent thrombosis.
10. Concomitant cardiac valve disease requiring invasive therapy.
11. Known allergy to aspirin, prasugrel or diagnosed lactose intolerance.
12. Atrial fibrillation or other indication for oral anticoagulant therapy.
13. History of stroke or transient ischaemic cerebrovascular accident.
14. History of intracranial haemorrhage or other intracranial pathology associated with increased bleeding risk.
15. Acute heart failure.
16. Active myocarditis.
17. Cardiomyopathy.
18. Patient in haemodialysis.
19. Haemoglobin <10 g/dL or other evidence of active bleeding.
20. Haemodynamic instability or cardiogenic shock.
21. Recurrent or ongoing chest pain refractory to medical treatment.
22. Life-threatening arrhythmias or cardiac arrest.
23. Mechanical complications of myocardial infarction.
24. Recurrent dynamic ST-T wave changes, particularly with intermittent ST-elevation.
25. Peptic ulceration documented by endoscopy within the last 3 months unless healing proven by repeat endoscopy.
26. Any other condition deemed by the investigator to place the patient at excessive risk of bleeding with prasugrel.
27. Participation in another trial with an investigational drug or device.
28. Comorbidity associated with life expectancy <1 year.
29. Assessment that the subject is not likely to comply with the study procedures or have complete follow-up.
30. Known drug or alcohol dependence within the past 12 months as judged by the investigator.
ACS: acute coronary syndrome; NSTE-ACS: non-ST-elevation acute coronary syndrome; PCI: percutaneous coronary intervention

coronary stent result is a combination of successful stent implantation with no significant residual diameter stenosis (<20%), no major edge dissection, no angiographic finding suggestive of thrombus, no major side branch occlusion, no post-procedure delay in contrast filling, and no major stent incomplete apposition[21]. Use of intracoronary imaging pre- and/or post-stent implantation for optimisation is left to the operator's discretion. After the index PCI, only if the angiographic and/or intravascular results are considered satisfactory in the operator's clinical judgement will the patient be enrolled in the study.

In cases of screening failure, the reasons why optimal stent implantation was not achieved need to be recorded.

ENROLMENT AND FOLLOW-UP

After achievement of optimal SYNERGY stent implantation, patients will be enrolled in the study and loaded with prasugrel 20 mg immediately in the cath lab to avoid further delays in loading and maintained on prasugrel 3.75 mg monotherapy once daily for 3 months in Phase 1, and for 12 months in Phase 2. This strategy of switching $P2Y_{12}$ inhibitors is in line with the international

consensus on switching therapies and is supported by pharmacodynamic studies[22,23]. Patients who were loaded with prasugrel preprocedure or have been on long-term prasugrel do not need additional loading. Aspirin will be discontinued the day after the index PCI.

In Phase 1, clinical follow-up with outpatient visits will be performed at 3 months and with telephone contacts at 1 and 4 months. In Phase 2, clinical follow-up will be performed with outpatient visits at 1 and 12 months and telephone contact at 3, 6, and 13 months. The 4- and 13-month telephone follow-ups are not related to the scientific purpose of this pilot study; this period is rather for observational assessment after switching the standard of care (aspirin alone, $P2Y_{12}$ inhibitor monotherapy, or DAPT). An assessment of angina status, cardiovascular drug use, and any serious adverse events will be recorded during clinical follow-up visits.

Optimal medical therapy with strict control of low-density lipoprotein cholesterol is strongly recommended along with optimisation of all medication therapy according to current guidelines[20]. The use of other medications (e.g., beta blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers) will also be recommended.

STUDY ENDPOINTS

The study endpoints are described in **Table 3**. The primary endpoint is a composite of cardiac death, target vessel MI (>48 hours post-PCI), defined as an MI case with evidence of myocardial necrosis in the vascular territory of a previously treated target vessel, or definite stent thrombosis occurring within 3 months of the index PCI in CCS patients or 12 months for NSTE-ACS patients. Inclusion in this trial occurs after the index procedure; hence, only MI occurring >48 hours after the index PCI will be taken into consideration as a primary endpoint. The primary bleeding endpoint is any BARC type 3 or 5 bleeding occurring within 3 months of the index PCI in CCS patients or 12 months for NSTE-ACS patients.

Secondary endpoints will include all-cause death, stroke (subclassified as ischaemic, haemorrhagic, or unknown), all MI, repeat revascularisation, definite/probable/possible stent thrombosis, BARC type 1-5 bleeding, and each individual component of the primary endpoint. The patient-oriented composite endpoint (PoCE) is defined as a composite of all-cause death, any stroke, any MI, or revascularisation. The device-oriented composite endpoint (DoCE) is defined as a composite of cardiovascular death, target vessel MI, or clinically driven target lesion revascularisation. Net clinical adverse events are defined as a composite of PoCE and BARC type 3 or 5 bleeding.

All deaths will be considered cardiac unless an undisputed noncardiac cause can be established. Spontaneous MI will be defined according to the Fourth Universal definitions[24]. Periprocedural MI (<48 hours post-PCI) will be defined according to the Society for Cardiovascular Angiography and Interventions (SCAI) 2013 definition[25]. Stent thrombosis will be defined according to the Academic Research Consortium (ARC)-2 definition[13]. BARC bleeding will be defined as previously reported[26]. Safety measures will assess any drug discontinuation rate and date.

Table 3. Endpoints of the ASET Japan trial.

Study endpoints.	
Primary ischaemic endpoints	
A composite of cardiac death, target vessel myocardial infarction (>48 hours post-PCI), and definite stent thrombosis up to 3 months for CCS patients (Phase 1) and up to 12 months for NSTE-ACS patients (Phase 2) after the index procedure.	
Primary bleeding endpoints	
The primary bleeding endpoint is any BARC type 3 or 5 bleeding up to 3 months for CCS patients, and 12 months for NSTE-ACS patients after the index PCI.	
Secondary endpoints	
1. All-cause death.	
2. Stroke	Ischaemic
	Haemorrhagic
	Unknown
3. All myocardial infarctions.	
4. Repeat revascularisation.	
5. Definite/probable/possible stent thrombosis.	
6. BARC type 1–5 bleedings and each individual component of the primary endpoint.	
7. Patient-oriented composite endpoints (PoCE).	
8. Device-oriented composite endpoints (DoCE).	
9. Net adverse clinical event (NACE).	

ACS: acute coronary syndrome; BARC: Bleeding Academic Research Consortium; CCS: chronic coronary syndrome; DoCE: device-oriented composite endpoint; NACE: net adverse clinical event; NSTE ACS: non-ST-elevation acute coronary syndrome; PCI: percutaneous coronary intervention; PoCE: patient-oriented composite events

CLINICAL EVENTS ADJUDICATION AND DATA SAFETY MONITORING

All events will be adjudicated by an independent clinical events committee. An independent DSMB will monitor the safety and efficacy of all the patients during enrolment and 3-month follow-up in CCS patients, and during enrolment and 12-month follow-up in NSTE-ACS patients, including the stopping rule based on the occurrence of definite stent thrombosis.

Discussion

Several randomised controlled trials have demonstrated the efficacy of potent $P2Y_{12}$ receptor inhibitor monotherapy following 1- or 3-month DAPT in CCS and ACS patients treated by PCI[27-30]. The characteristics of contemporary clinical trials of ticagrelor or clopidogrel monotherapy after PCI are summarised in **Supplementary Table 1**. The first-in-human ASET study was conducted in Brazil as a multicentre, single-arm, open-label trial and demonstrated the feasibility and safety of aspirin-free prasugrel monotherapy following PCI using the SYNERGY stent in low-risk patients with CCS or stabilised ACS[17]. Among the 201 enrolled patients, no stent thrombosis occurred with a high adherence to prasugrel (98.3%) during the 4-month follow-up period. The primary bleeding endpoint, defined as BARC type 3 or 5 bleeding,

occurred in one patient (0.5%). Currently at least 3 clinical trials, STOPDAPT-3, NEOMINDSET, and OPTICA, are exploring novel strategies of monotherapy using $P2Y_{12}$ receptor inhibitors **(Supplementary Table 2)**.

Limitations

With regard to limitations of the present study, firstly, the findings need to be considered as hypothesis-generating due to the single-arm design with a small sample size without formal sample size calculation. Secondly, only patients with optimal angiographic and/or intravascular results will be enrolled in the study. This is a potential issue in terms of generalising the ASET Japan results into practice. Finally, due to the protocol of the trial, some of the participants will be required to have a loading dose of $P2Y_{12}$ inhibitor twice. Although this strategy has been accepted in line with expert consensus, it potentially could affect the results.

Conclusions

With this "no DAPT" study, the investigators expect to demonstrate the feasibility and safety of prasugrel monotherapy just after stent deployment in selected Japanese patients with CCS and NSTE-ACS. Further randomised controlled trials are needed to evaluate the aspirin-free strategy compared with traditional DAPT following PCI.

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Conflict of interest statement

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Supplementary data

Supplementary Appendix 1. The history and recent trials of antiplatelet therapy.

Supplementary Appendix 2. Cardiac enzyme and biomarkers before the index PCI.

Supplementary Table 1. Characteristics of contemporary clinical trials of ticagrelor and clopidogrel monotherapy after percutaneous coronary intervention.

Supplementary Table 2. Characteristics of current clinical trials for prasugrel monotherapy after percutaneous coronary intervention.

Supplementary Figure 1. History of antiplatelet therapy after percutaneous coronary intervention.

Supplementary Figure 2. Gastrointestinal endoscopy showing gastric ulcer and the rate of gastrointestinal damage of aspirin and PL 2200 in a previous randomised trial.

Supplementary Figure 3. Kaplan-Meier curves of BARC 3 or 5 bleeding up to 30 days, from 31 days to 1 year, and from 1 year to end of follow-up by clinical presentation in the GLOBAL LEADERS trial.

The supplementary data are published online at: https://www.asiaintervention.org/ doi/10.4244/AIJ-D-22-00033

Supplementary data

Supplementary Appendix 1.

The history and recent trials of antiplatelet therapy.

DAPT is a combination of aspirin and a P2Y12 inhibitor, such as clopidogrel, ticagrelor or prasugrel. Historically, the first clinically utilised P2Y12 inhibitor was ticlopidine which replaced warfarin.[31,32] The history and recent trials of antiplatelet therapy are summarised in **Supplementary Figure 1**. The STARS trial compared the efficacy and safety of three anti-thrombotic regimens - aspirin alone, aspirin and warfarin, and aspirin and ticlopidine - after coronary artery stenting, and showed that the combination of aspirin and ticlopidine resulted in lower rates of stent thrombosis.[31] Furthermore, Colombo et al confirmed that anticoagulants could be safety omitted and replaced with a combination of aspirin and ticlopidine provided stents were optimally expanded.[33] At the time of the introduction of DAPT, it was considered that two drugs were needed to prevent acute vessel closure after stenting. In 2000, DAPT with the combination of clopidogrel and aspirin was shown to have superior safety and tolerability to the combination of aspirin and ticlopidine.[32]

Recently, more potent P2Y12 inhibitors, such as ticagrelor and prasugrel were introduced.[34,35] One in-vitro study suggested that aspirin failed to produce additional anti-aggregatory effects in the presence of strong P2Y12 blockade,[36] whilst pre-clinical data also show that the active metabolites of prasugrel cause strong inhibition of platelet activity which is independent of the presence or absence of aspirin.[37] The question remains as to whether single P2Y12 inhibitor therapy is potent enough to prevent acute thrombosis as well as late ischaemic events.

Daily use of aspirin results in an increased risk of gastrointestinal damage and bleeding, which can lead to adverse cardiovascular and non-cardiovascular events.[38-42]

Previous randomised data reported rates of multiple erosions and/or ulcers on endoscopy of 42.2% in patients treated with 7-days of low-dose aspirin compared to 17.6% in those who treated with PL2200, which creates a non-covalent complex of aspirin-phosphatidylcholine **(Supplementary Figure 2)**.[40] In addition, it has also been shown that aspirin increases the risk of cerebral bleeding, especially in East Asian patients.[43] Ultimately, these findings suggest that aspirin has a significant role in increasing bleeding events. Furthermore, contemporary coronary intervention trials continue to demonstrate that a significant number of bleeding events occur within a month of PCI, especially in the ACS population. For example, the rate of BARC type 3 or 5 bleeding was 0.77% at 1-month compared to 0.76% between 1 and 12 months amongst patients with ACS receiving the experimental treatment in the GLOBAL LEADERS trial **(Supplementary Figure 3)**.[44] In the CREDO Kyoto Registry Cohort 3, the rate of BARC type 3 or 5 bleeding was 20.9% amongst the ACS cohort at 5 years; however, half of these events (11.1%) occurred within 30 days of PCI, suggesting that half of the critical bleeding events occurred in the early phase.[45] Elimination of aspirin from post procedure anti-platelet therapy regimes may therefore benefit patients by reducing bleeding without compromising the anti-ischaemic effect of P2Y12 inhibitor monotherapy.

Recent evidence of P2Y12 monotherapy

The GLOBAL LEADERS trial showed the safety of one-month DAPT followed by ticagrelor monotherapy amongst 15991 all comer patients undergoing PCI with biolimus A9-eluting stents for ACS or CCS.[27] The trial randomised patients to two anti-platelet regimens: the experimental strategy of one-month DAPT with aspirin and ticagrelor followed by 23 months of ticagrelor monotherapy versus the reference strategy of standard DAPT with aspirin plus either 12 months of clopidogrel (for patients with CCS) or ticagrelor (for patients with ACS), followed by 12 months of aspirin monotherapy. At 2-year follow-up, the incidence of

bleeding complications, defined as BARC type 3 or 5, was low and comparable between the experimental and control groups (2.1% versus 2.0%, P=0.77) **(Supplementary Figure 3)**;[26,44] however, in the GLASSY trial, which was a nested sub-study within the GLOBAL LEADERS trial using independent event adjudication, ticagrelor monotherapy after 1-month DAPT was neither non-inferior nor superior to conventional treatment in the prevention of ischaemic events. Furthermore, ticagrelor monotherapy did not reduce major bleeding risk compared with conventional treatment.[46]

The TWILIGHT and TICO trials showed that 3-months of DAPT followed by ticagrelor monotherapy was associated with a lower incidence of clinical bleeding events compared to ticagrelor plus aspirin, with no evidence of a higher risk of death, MI or stroke in patients with ACS and CCS who received newer generation DES.[28,29] The STOPDAPT-2 trial demonstrated the safety and feasibility of 1-month DAPT followed by clopidogrel monotherapy, compared with 12 months of DAPT with aspirin and clopidogrel among Japanese patients undergoing PCI with CoCr everolimus-eluting DES.[30] In contrast, in the STOPDAPT-2 ACS trial 1-month DAPT followed by clopidogrel monotherapy for 11 months failed to meet the criteria for noninferiority compared with 12-months DAPT for the composite ischaemic/bleeding endpoint among patients with ACS. These results raise the question as whether monotherapy with clopidogrel 75 mg per day is sufficient to prevent ischaemic events between 1 and 12 months compared to DAPT in ACS patients. Of note, when administered in combination with aspirin, reduced dose prasugrel (3.75 mg daily) decreased major adverse cardiovascular events (MACE) in ACS patients compared to clopidogrel 75 mg daily.[8] Hence it could be hypothesised that prasugrel monotherapy may be a better alternative to clopidogrel monotherapy due to its more potent platelet inhibition. The MASTER DAPT trial showed that 1-month DAPT in patients at high bleeding risk was non-inferior to standard anti-platelet regimens after PCI using the bioresorbable polymer coated

Ultimaster® sirolimus-eluting stent.[47] Similar results were seen in a meta-analysis, with a lower risk of major bleeding and net adverse clinical events with P2Y12 inhibitor monotherapy compared with DAPT after coronary stent deployment, especially in females.[48]

Prasugrel, a new-generation thienopyridine anti-platelet agent, is an irreversible oral P2Y12 receptor inhibitor that requires metabolic activation, shows less variability in platelet inhibition and has a faster onset of action than clopidogrel.[49] The ISAR-REACT 5 trial showed no significant difference in the composite primary endpoint of death, MI, stroke, or bleeding events (defined as BARC type 3-5 bleeding) between patients with ACS planned for an invasive strategy randomised to ticagrelor or prasugrel.[50] All these findings suggest that a specific and potent P2Y12 receptor inhibitor, such as prasugrel, used as monotherapy after DES implantation could reduce bleeding events when compared to DAPT without increasing ischaemic events.

Supplementary Appendix 2.

Cardiac enzyme and biomarkers before the index PCI.

In Phase 1, prior to the PCI procedure, the creatine kinase myocardial band (CK-MB) must be less than 2-times the upper limit of normal (<ULN). For patients showing elevated high-sensitivity cardiac troponin (hs-cTn) or troponin I or T (e.g. NSTE-ACS patients) at baseline (within 72h pre-PCI) an additional blood sample will have to be collected to confirm that hs-cTn or troponin I or T levels are stable (i.e. the value should be within 20% range of the value found in the first sample at baseline, or have dropped), and CK-MB and CK levels are within normal range. If hs-cTn or troponin I or T levels are stable or have dropped, the CK-MB and CK levels are within normal ranges, and the electrocardiogram (ECG) is normal, the patient may be included in the study.

In Phase 2, cardiac biomarkers must be sampled to confirm the elevation of cardiac troponin (I, T, or hs-cTn) prior to the PCI procedure. After the procedure, CK-MB or troponin is determined pre-discharge or within 6-8 hours post-procedure, whichever comes first. If cardiac enzymes or biomarkers are elevated (CK >2ULN with iso-enzyme CKMB, CKMB >3 ULN, or cTn/hs-cTn >35 ULN), serial measurements must be taken until a decline is noted. In any case of cardiac enzymes or biomarkers elevation (CK >2ULN with iso-enzyme CKMB, CKMB >3 ULN, or cTn/hs-cTn >35 ULN) at least two samples (with a preferred interval of 6 hours) should be obtained prior to discharge.

Supplementary Table 1. Characteristics of contemporary clinical trials of ticagrelor and clopidogrel monotherapy after percutaneous coronary intervention.

Study	Design	Study setting	Participants	Intervention	Stent type	Follow up duration	Primary endpoint
GLOBAL LEADERS (NCT01813435)	RCT open-label	130 sites in 18 countries	N = 15968 mean age 64.5 female 23.3% ACS 46.8%	ACS arm: 12 months DAPT (ticagrelor + aspirin) followed by 12 months aspirin monotherapy vs. 1 month DAPT (ticagrelor + aspirin) followed by 23 months ticagrelor monotherapy CCS arm: 12 months DAPT (clopidogrel + aspirin) followed by 12 months aspirin monotherapy vs. 1 month DAPT (ticagrelor + aspirin) followed by 23 months ticagrelor monotherapy	Biolimus A9-eluting stent	24 months	All-cause mortality, new Q wave MI
STOPDAPT-2 (NCT02619760)	RCT open-label	90 sites in Japan	N = 3045 mean age 68.6 female 22.0% ACS 38.0%	12 months vs. 1 month DAPT (clopidogrel or prasugrel + aspirin) followed by clopidogrel monotherapy	Durable polymer everolimus-eluting stent	12 months	NACE (Cardiovascular death, MI, definite stent thrombosis, stroke, major or minor bleeding[*])
SMART CHOICE (NCT02079194)	RCT open-label	33 sites in Korea	N = 2993 mean age 64 female 26.6% ACS 58.2%	12 months vs. 3 months DAPT followed by P2Y12 inhibitor monotherapy	Durable polymer everolimus-eluting stent	12 months	MACCE (All-cause death, MI, stroke)
TWILIGHT (NCT02270242)	RCT placebo-controlled	187 sites in 11 countries	N = 7119 mean age 65 female 23.8% ACS 64.8%	12 months vs. 3 months DAPT followed by ticagrelor monotherapy	2nd generation DES	12 months	BARC type 2,3 or 5 bleeding
TICO (NCT02494895)	RCT open-label	38 sites in Korea	N = 3056 mean age 61 female 20% ACS 100%	12 months vs. 3 months DAPT followed by ticagrelor monotherapy	Bioresorbable polymer sirolimus-eluting stent	12 months	Major bleeding defined as TIMI criteria[†], MACCE (death, MI, stent thrombosis, stroke, TVR)
PIONEER-IV (NCT04923191)	RCT single – blind (patient)	30 sites in Europa	N = 2540 All comer	1 month DAPT followed by ticagrelor monotherapy up to 12 months	Bioresorbable polymer sirolimus-eluting stent	36 months	POCE (all-cause death, any stroke, any myocardial infarction, any clinically and physiologically driven revascularisation)

Abbreviations: ACS; acute coronary syndrome, BARC; Bleeding Academic Research Consortium, CCS; chronic coronary syndrome, DAPT; dual antiplatelet therapy, DES; drug-eluting stent, MACCE; major adverse cardiac and cerebrovascular events, MI; myocardial infarction, NACE; net adverse clinical endpoints, PoCE; patient-oriented composite endpoint RCT; randomised controlled trial, TIMI; thrombolysis in myocardial infarction, TVR; target vessel revascularisation,

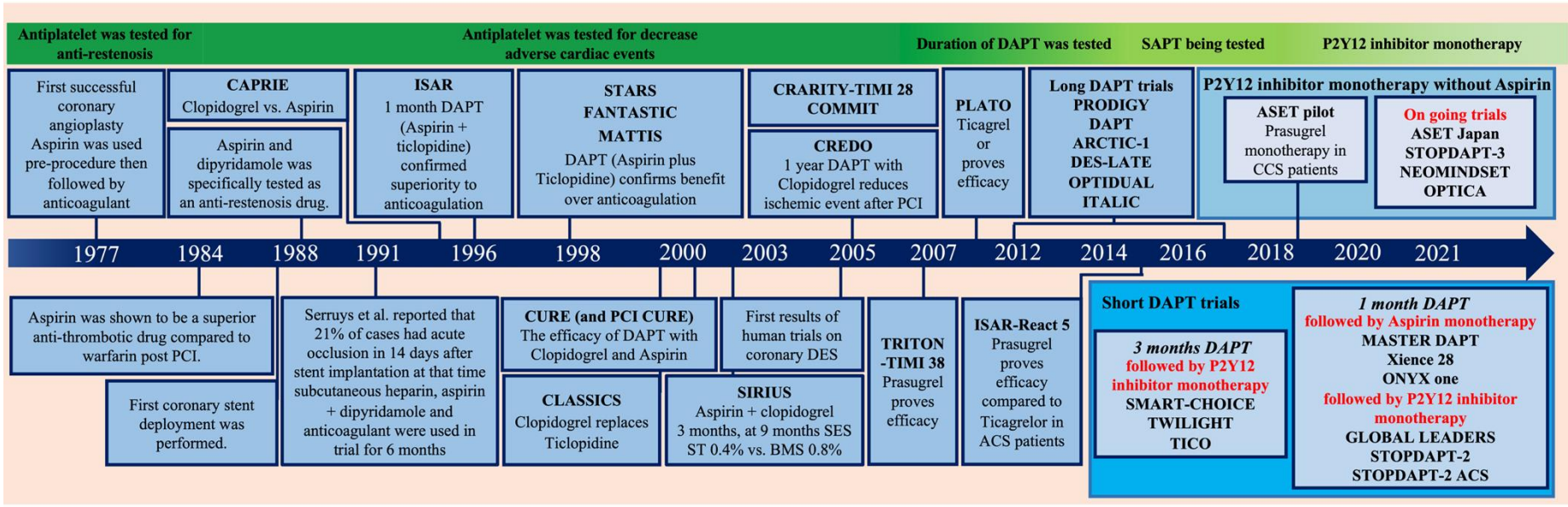
*Major or minor bleeding defined as TIMI major and minor bleeding

† Major bleeding is defined as: intracranial bleeding, haemorrhage with a haemoglobin decrease of at least 5 g/dL, or fatal bleeding that caused death within 7 days.

Supplementary Table 2. Characteristics of current clinical trials for prasugrel monotherapy after percutaneous coronary intervention.

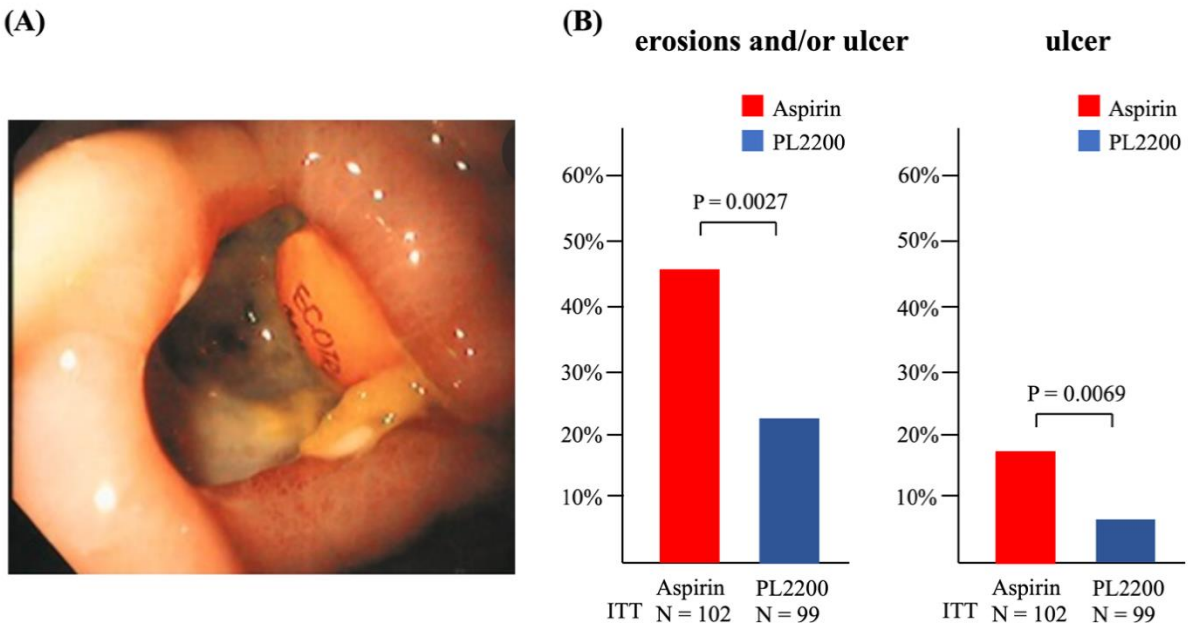
Study	Study type	Study setting	Participants	Antiplatelet therapy	Stent type	Follow up duration	Primary endpoint
ASET pilot NCT03469856	single arm multi-center open-label	9 sites in Brazil	N = 200 Mean age 59.5 CCS 100% female 35.3%	3 months prasugrel monotherapy vs. 3 months DAPT (aspirin + prasugrel)	bioresorbable polymer everolimus-eluting stent	3 months	cardiovascular death, target vessel MI, definite stent thrombosis, BARC type 3 or 5 bleeding
STOPDAPT3 NCT04609111	RCT multi-center open-label	51 sites in Japan	N = 3110 HBR or ACS patients	prasugrel monotherapy versus 1 month DAPT (aspirin + prasugrel)	durable polymer everolimus-eluting stent	1 month	BARC type 3 or 5 bleeding MACE (cardiovascular death, MI, ischaemic stroke, definite stent thrombosis)
OPTICA NCT04766437	RCT single-arm multi-canter	Dutch sites	N = 75 NSTE-ACS 100%	prasugrel monotherapy	any approved DES	12 months	all-cause mortality, MI, definite stent thrombosis, ischaemic stroke at 6 months after PCI BARC type 2, 3, or 5 bleeding
NEOMINDSET NCT04360720	RCT multi-center, parallel-group study	>35sites in Brazil	N = 3400 ACS 100%	ticagrelor alone or prasugrel alone vs. DAPT (aspirin + ticagrelor, or aspirin + prasugrel)	any approved DES	12 months	all-cause mortality, cerebrovascular accident, MI, urgent TVR), BARC type-2,3 or 5

Abbreviations: ACS; acute coronary syndrome, BARC; Bleeding Academic Research Consortium; CCS; chronic coronary syndrome, DAPT; dual antiplatelet therapy, DES; drug-eluting stent, HBR; high bleeding risk, MACE; major adverse cardiac event, MI; myocardial infarction, NSTE-ACS; non-ST elevation acute coronary syndrome, PCI; percutaneous coronary intervention, RCT; randomised controlled trial, TVR; target vessel revascularisation



Supplementary Figure 1. History of antiplatelet therapy after percutaneous coronary intervention.

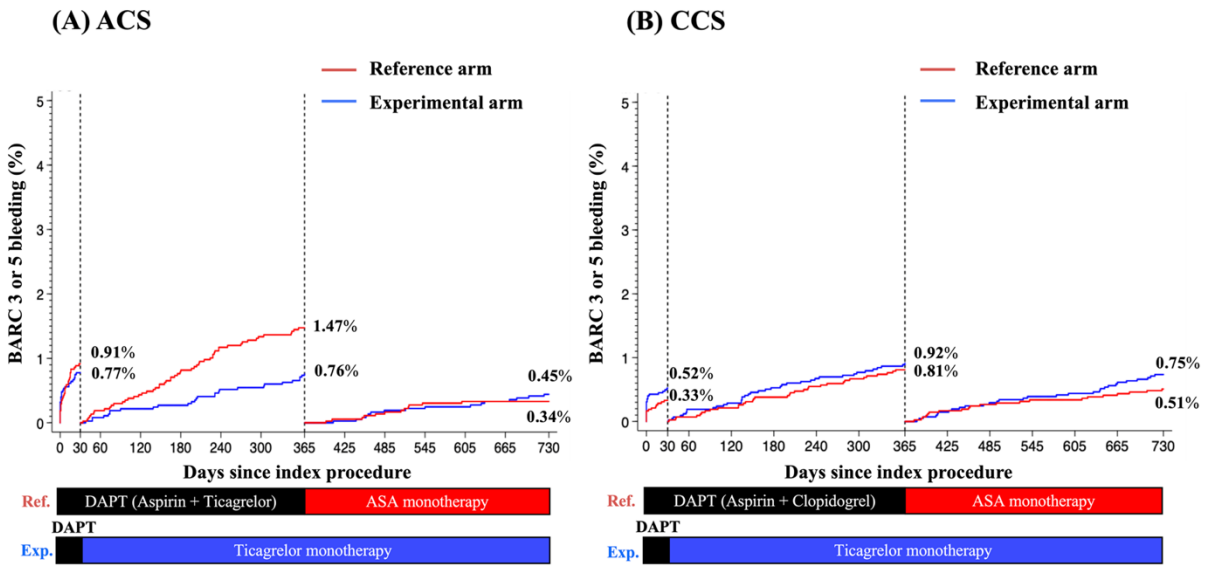
Abbreviations: ACS; acute coronary syndrome, BMS; bare-metal stent, CCS; chronic coronary syndrome, DAPT; dual antiplatelet therapy, DES; drug-eluting stent, NSTE-ACS; non-ST elevation acute coronary syndrome, PCI; percutaneous coronary intervention, SES; sirolimus-eluting stent, ST; stent thrombosis



Supplementary Figure 2. Gastrointestinal endoscopy showing gastric ulcer and the rate of gastrointestinal damage of aspirin and PL 2200 in a previous randomised trial.

(A) Gastrointestinal endoscopy showing a gastric ulcer and an aspirin tablet.[42]
(B) Data comparing upper gastrointestinal damage of aspirin and PL 2200, which creates a non-covalent complex of aspirin-phosphatidylcholine, in healthy subjects following 7 days of immediate release oral aspirin 325 mg once daily or PL2200. Percentage of subjects with gastrointestinal damage is significantly higher in the aspirin group. Left graph shows the percentage of subjects with erosions and/or ulcers. Right graph shows the percentage of subjects with ulcers. Bars, incidence ± 95% confidence interval.

Abbreviations: ITT; intent-to treat



Supplementary Figure 3. Kaplan-Meier curves of BARC 3 or 5 bleeding up to 30 days, from 31 days to 1 year, and from 1 year to end of follow-up by clinical presentation in the GLOBAL LEADERS trial. [44]
(A) Acute coronary syndrome
(B) Chronic coronary syndrome

Abbreviations: ASA; acetylsalicylic acid, ACS; acute coronary syndrome, BARC; bleeding academic research consortium, CCS; chronic coronary syndrome, DAPT; dual antiplatelet therapy