Prasugrel monotherapy after PCI with the SYNERGY stent in patients with chronic stable angina or stabilised acute coronary syndromes: rationale and design of the ASET pilot study

Norihiro Kogame[1,2], MD; Rodrigo Modolo[1,3], MD; Mariusz Tomaniak[4,5], MD; Rafael Cavalcante[6], MD, PhD; Fernando de Martino[7], MD, PhD; Joao Tinoco[8], MD; Expedito E. Ribeiro[9], MD, PhD; Roxana Mehran[10], MD; Carlos M. Campos[9], MD, PhD; Yoshinobu Onuma[4], MD, PhD; Pedro A. Lemos[9], MD, PhD; Patrick W. Serruys[11]*, MD, PhD

1. Department of Cardiology, Amsterdam University Medical Center, Amsterdam, the Netherlands; 2. Department of Cardiology, Toho University Medical Center, Ohashi Hospital, Tokyo, Japan; 3. Department of Internal Medicine, Cardiology Division, University of Campinas (UNICAMP), Campinas, Brazil; 4. Thoraxcenter, Erasmus University Medical Center, Rotterdam, the Netherlands; 5. First Department of Cardiology, Subdivision of Interventional Cardiology, Medical University of Warsaw, Warsaw, Poland; 6. Boston Scientific, Marlborough, MA, USA; 7. Department of Internal Medicine, Discipline of Cardiology, University of Triangulo Mineiro, Uberaba, MG, Brazil; 8. Unicor, Linhares, ES, Brazil; 9. Heart Institute (InCor), University of Sao Paulo, Sao Paulo, Brazil; 10. Icahn School of Medicine at Mount Sinai, New York, NY, USA; 11. Imperial College London, London, United Kingdom

A list of the study collaborators can be found in the Appendix paragraph.

GUEST EDITORS: Adnan Kastrati, MD; *Deutsches Herzzentrum, Munich, Germany*, and Alec Vahanian, MD, PhD; *Department of Cardiology, Hôpital Bichat-Claude Bernard, and University Paris VII, Paris, France*

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Introduction

The ASET (Acetyl Salicylic Elimination Trial) pilot study (NCT03469856) is designed to evaluate the hypothesis that a single antiplatelet therapy with prasugrel starting immediately after the procedure is feasible and safe in patients selected after successful percutaneous coronary intervention (PCI) with new-generation biodegradable polymer drug-eluting stent (DES) implantation.

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Methods

STUDY DESIGN

The ASET pilot study is designed as a multicentre, single-arm, open-label, proof-of-concept pilot trial. Based on previous pilot studies with similar designs, a sample of 200 patients will be enrolled from 12 centres in Brazil with a stopping rule based on the occurrence of definite stent thrombosis[1]. If more than three cases of definite stent thrombosis occur following the index procedure until three-month follow-up, the patient recruitment will be terminated. All potential patients must be consented prior to undergoing any study-specific procedures.

PATIENT SCREENING BEFORE INDEX PCI

Patients requiring PCI for chronic stable angina or stabilised acute coronary syndrome (ACS) and having a SYNTAX score <23 prior to revascularisation will be screened and considered eligible for the study **(Figure 1)**. Stabilised ACS fulfils the criteria of cardiac enzymes described in **Supplementary Appendix 1**. Inclusion and exclusion criteria are shown in **Supplementary Appendix 1** and **Supplementary Table 1**.

INDEX PCI

The patients will be loaded with standard dual antiplatelet therapy (DAPT: aspirin 300 mg and clopidogrel 600 mg, unless patients are on long-term therapy) at least two hours prior to the index PCI.

**Corresponding author: Cardiovascular Science Division of the NHLI within Imperial College of Science, Technology and Medicine, South Kensington Campus, London, SW7 2AZ, United Kingdom. E-mail: patrick.w.j.c.serruys@gmail.com*

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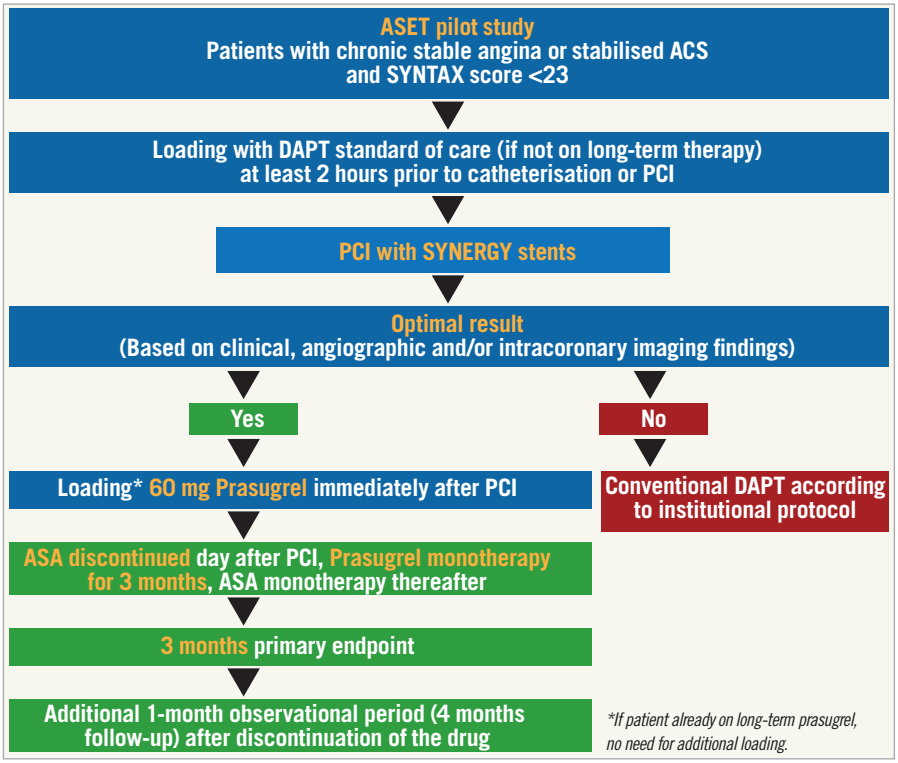

Figure 1. *Flow chart of the ASET pilot study. ACS: acute coronary syndromes; ASA: acetylsalicylic acid; DAPT: dual antiplatelet therapy; PCI: percutaneous coronary intervention*

The index PCI will be performed with the intention of achieving complete revascularisation of all vessels with at least 1.5 mm diameter showing a stenosis of 50% or more, as identified by the local interventional cardiologist. All target lesions must be exclusively treated with the SYNERGY™ stent (Boston Scientific, Marlborough, MA, USA).

The investigator should perform the procedure aiming to achieve optimal stent implantation according to local standard of care by angiography including quantitative coronary angiography and/or finding from intracoronary imaging (intravascular ultrasound or optical coherence tomography). Recommended criteria for optimal stent implantation are shown in **Supplementary Figure 1** and **Supplementary Table 2**[2].

ENROLMENT AND FOLLOW-UP

After achievement of optimal stent implantation, patients will be enrolled in the study and loaded with prasugrel 60 mg in the cath lab, in line with international consensus on switching therapies[3]. Prasugrel 10 mg once a day will be continued as monotherapy for three months. After three months, prasugrel will be replaced by aspirin monotherapy or DAPT, according to local standard of care. When switching from prasugrel back to aspirin monotherapy only, a loading dose of aspirin is recommended and must be given in the hospital at the time of the three-month follow-up visit. Clinical follow-up with an office visit will be performed at three months and telephone contacts at one and four months.

STUDY ENDPOINTS

The study endpoints are listed in **Table 1**. The primary ischaemic endpoint is a composite of cardiac death, target vessel myocardial infarction (MI) (>48 hours, i.e., without periprocedural MI having occurred within 48 hours after the index procedure) or definite

Table 1. Endpoints of the ASET pilot study.

Primary ischaemic endpoint
Composite of cardiac death, target vessel myocardial infarction (>48 hours) or definite stent thrombosis at 3 months
Primary bleeding endpoint
BARC type 3 and 5 bleeding at 3 months
Secondary endpoints
All-cause death – Cardiac death Vascular death – Non-cardiovascular death
Stroke – Ischaemic – Haemorrhagic – Unknown
All myocardial infarctions
Repeat revascularisation
Definite/probable/possible stent thrombosis
BARC type 1-5 bleedings
Each individual component of the primary endpoint
BARC: Bleeding Academic Research Consortium

stent thrombosis at three months. The primary bleeding endpoint is any Bleeding Academic Research Consortium (BARC) type 3 and 5 bleeding at three months. Definitions of the study endpoints are described in **Supplementary Appendix 1**.

All endpoints will be independently adjudicated by the clinical events committee (CEC). An independent data safety and monitoring board (DSMB) will monitor the individual and collective safety of the patients in the study during the enrolment phase and up to three-month follow-up (primary endpoint).

Discussion

Regarding an aspirin-free strategy after DES implantation, currently two different types of evidence have been reported.

Firstly, in the AUGUSTUS trial, oral anticoagulation with a $P2Y_{12}$ inhibitor demonstrated reductions in bleeding events without any trade-off in ischaemic events compared to oral anticoagulation with aspirin in patients with atrial fibrillation who had an ACS or had undergone PCI[4].

Secondly, in the GLOBAL LEADERS trial, ticagrelor monotherapy following one-month DAPT failed to demonstrate superiority for a composite of all-cause mortality or new Q-wave MI at two years compared with aspirin monotherapy following 12-month DAPT[5]. However, two randomised controlled trials presented at ACC 2019, STOPDAPT-2[6] and SMART-CHOICE[7], showed that one- or three-month DAPT followed by $P2Y_{12}$ inhibitor monotherapy was superior for bleeding and non-inferior for the composite ischaemic endpoint to 12-month DAPT at one-year follow-up. Furthermore, the results of a large-scale RCT in a high-risk PCI population (the TWILIGHT study) are awaited[8].

When compared with these studies, the ASET pilot study is unique in that aspirin is completely eliminated from the antiplatelet regimen immediately after the procedure.

Limitations

The findings of the present study need to be considered as hypothesis-generating due to the single-arm design without formal sample size calculation.

Conclusion

Favourable results of the present study would justify a subsequent investigational phase testing the same treatment strategy and proof of concept in patients with non-ST-elevation myocardial infarction and ST-elevation myocardial infarction.

Impact on daily practice

The ASET pilot study challenges the concept of the additional synergistic effect of aspirin under monotherapy of a potent $P2Y_{12}$ inhibitor (ticagrelor or prasugrel) immediately after DES implantation. The study results could provide a scientific basis to perform a larger randomised trial that could have the impact of changing clinical practice regarding the use of antiplatelet therapy after coronary stenting.

Guest Editors

This paper was guest edited by Adnan Kastrati, MD; Deutsches Herzzentrum, Munich, Germany, and Alec Vahanian, MD, PhD; Department of Cardiology, Hôpital Bichat-Claude Bernard, and University Paris VII, Paris, France.

Funding

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Appendix. Study collaborators

Marie-Angèle Morel, BSc, *Cardialysis Clinical Trials Management and Core Laboratories, Rotterdam, the Netherlands*; Jan. J. Piek, MD, PhD, *Department of Cardiology, Amsterdam University Medical Center, Amsterdam, the Netherlands*; Joanna J. Wykrzykowska, MD, PhD, *Department of Cardiology, Amsterdam University Medical Center, Amsterdam, the Netherlands*.

Conflict of interest statement

R. Cavalcante is an employee of Boston Scientific. J.J. Piek is a consultant for Philips/Volcano and is a member of the advisory board of Abbott Vascular. R. Modolo has received institutional research funding from AstraZeneca, Bayer, Beth Israel Deaconess, Bristol-Myers Squibb/Sanofi, CSL Behring, Eli Lilly/Daiichi Sankyo, Medtronic, Novartis and OrbusNeich, and is a consultant to Boston Scientific, Abbott Vascular, Medscape, Siemens Medical Solutions, Regeneron Pharmaceuticals Inc. (no fees), Roivant Sciences Inc, and Sanofi. Y. Onuma is a member of the advisory board of Abbott Vascular. P.W. Serruys is a consultant to Volcano, and is a member of the advisory board of Abbott Vascular. The other authors have no conflicts of interest to declare. The Guest Editor A. Kastrati has no conflicts of interest to declare. The Guest Editor A. Vahanian is a consultant for Edwards Lifesciences.

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Supplementary data

Supplementary Appendix 1. Methods.

Supplementary Figure 1. Assessment of symmetric stent expansion with asymmetry index in a longitudinal IVUS image.

Supplementary Table 1. Inclusion and exclusion criteria.

Supplementary Table 2. Recommended criteria for optimal stent implantation.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-19-00131

Supplementary data

Supplementary Appendix 1. Methods

Criteria of cardiac enzymes

Stabilised ACS consists of unstable angina and only a few non-ST-elevation myocardial infarction (NSTEMI) fulfil the criteria of cardiac enzymes (creatine kinase myocardial band [CK-MB] or troponin). A standard 12-lead electrocardiogram (ECG) must be performed within 72 hours prior to the PCI to detect and exclude acute myocardial infarction. Cardiac enzymes must also be sampled prior to the PCI and all eligible patients must fulfil the following criteria of cardiac enzymes:

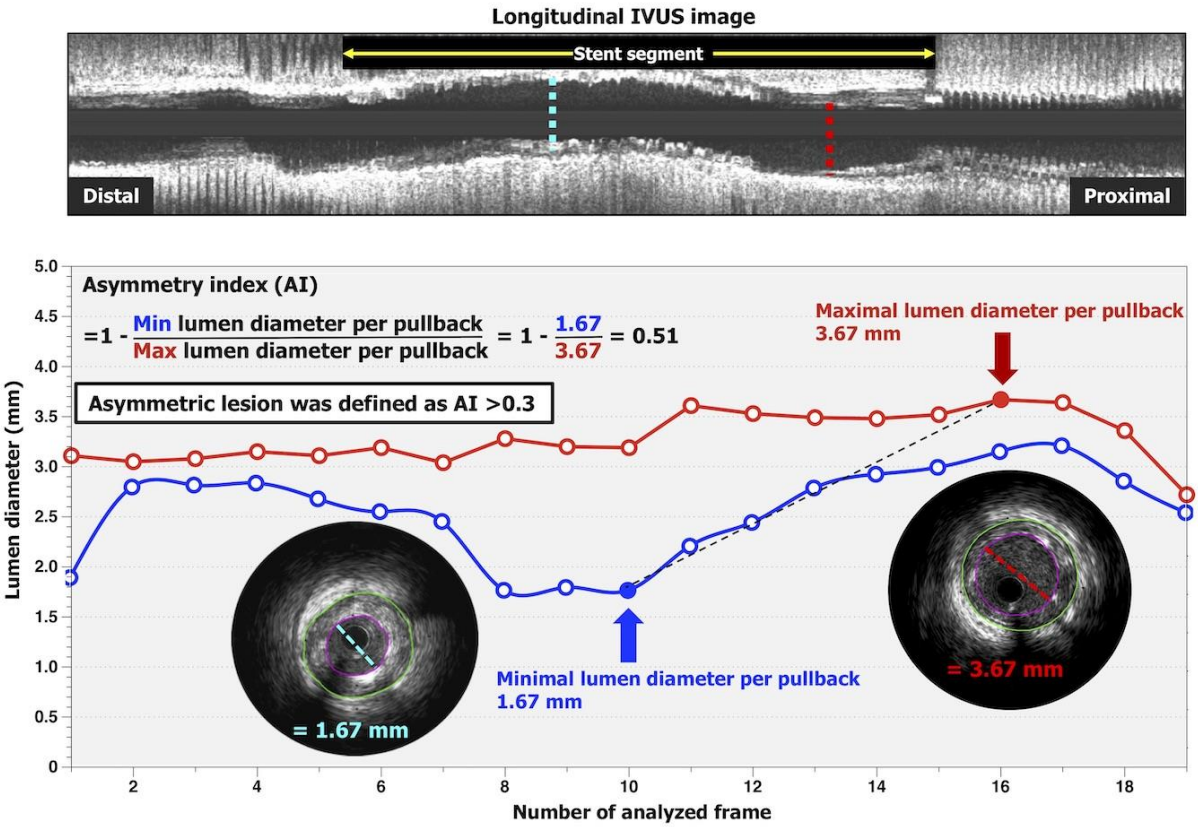
i. If CK-MB is sampled, the value of CK-MB must be less than two times the upper limit of normal (ULN).
ii. If the value of troponin is elevated more than the ULN at baseline (within 72 hours prior to the start of PCI) without any ST-T change and/or typical symptom, an additional blood sample will have to be collected prior to the PCI. If the second blood test shows either a stable level of troponin (less than 20% increase of the value of baseline troponin) or a dropped troponin level, normal range value of CK-MB and CK, and normal ECG, the patient may be enrolled in the study.

Inclusion and exclusion criteria

In terms of exclusion criteria, first of all, the contraindications mentioned in the label of use of prasugrel are respected: evidence of active bleeding or haemoglobin <10 g/dL, and previous history of stroke or transient ischaemic cerebrovascular accident are contraindication and exclusion criteria. Also, patients not recommended in the label are excluded as follows: age ≥75 years and body weight <60 kg. The basic conditions are also respected as a prerequisite of implementing monotherapy with prasugrel (e.g., glomerular filtration rate below 60 mL/min, complex lesion characteristics including left main disease, chronic total occlusion, bifurcation lesion requiring a two-stent technique, saphenous or arterial graft disease, and severe calcification necessitating the use of a rotablator). Patients who require staged procedures will be excluded in order to avoid the heterogeneity of duration of pharmacological treatment between index and staged procedure. Patients with a history of ACS within 12 months before the index procedure will be excluded in order to avoid early discontinuation of DAPT in patients with ACS. Inclusion and exclusion criteria are shown in **Supplementary Table 1**.

Definitions of the study endpoints

All deaths will be considered cardiac unless an undisputed non-cardiac cause is present. Spontaneous MI will be defined according to third universal definitions. Periprocedural MI (<48 hours post PCI) will be defined according to the Society for Cardiovascular Angiography and Interventions (SCAI) 2013 definition. Stent thrombosis will be defined according to the Academic Research Consortium (ARC)-2 definition. BARC bleeding will be defined as previously reported.



Supplementary Figure 1. Assessment of symmetric stent expansion with asymmetry index in a longitudinal IVUS image.

The asymmetry index was calculated per stented segment as (1 – minimal lumen diameter/maximal lumen diameter). Minimal lumen diameter was the minimal value of the minimal lumen diameter throughout the stent segment (red arrow), maximal lumen diameter was the maximal value of the maximal lumen diameter throughout the stent segment (blue arrow). Therefore, the minimum lumen diameter and maximum lumen diameter could be derived from different cross-sections in the stent segment.

AI: asymmetry index

Supplementary Table 1. Inclusion and exclusion criteria.

Inclusion criteria
1. Successful PCI with optimal stent implantation of one or more SYNERGY stent(s). 2. SYNERGY stent implantation was performed to treat: a. Presence of one or more de novo lesion with diameter stenosis ≥50% by visual estimation in at least one native coronary artery with a reference vessel diameter ranging from 2.25 mm to 4.00 mm without left main stem involvement. b. Chronic stable angina or stabilised acute coronary syndromes with normal cardiac enzyme values prior to the index PCI, and evidence of myocardial ischaemia by symptoms or non-invasive 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. Under the age of 18 years or ≥75 years. 2. Patients weighing <60 kg. 3. Glomerular filtration rate <60 mL/min. 4. Previous PCI in the last 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 non-cardiac condition within next 6 months. 7. Concomitant cardiac valve disease requiring surgical therapy. 8. Following lesion characteristics: left main disease, chronic total occlusion, bifurcation lesion requiring two-stent treatment, saphenous or arterial graft lesion and severely calcified lesion requiring the use of a rotablator. 9. Patients concomitantly treated with any other non-study stent at the same procedure. 10. Previous history of definite stent thrombosis. 11. Previous history of stroke or transient ischaemic cerebrovascular accident. 12. Atrial fibrillation or other indication for oral anticoagulant therapy. 13. Haemoglobin <10 g/dL or other evidence of active bleeding. 14. Peptic ulceration documented by endoscopy within the last 3 months unless healing proven by repeat endoscopy. 15. Any other condition deemed by the investigator to place patient at excessive risk of bleeding with prasugrel. 16. Known allergy to aspirin, prasugrel or diagnosed lactose intolerance. 17. Treatment in the last 10 days or requirement for ongoing treatment with a strong CYP3A4 inhibitor or inducer. 18. 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. 19. Female who is breastfeeding at time of enrolment. 20. Participation in another trial with an investigational drug or stent. 21. Comorbidity associated with life expectancy less than one year. 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

Supplementary Table 2. Recommended criteria of optimal stent implantation.

Angiography including quantitative coronary angiography
Residual diameter stenosis <20% without edge dissection, thrombus, major side branch occlusion, no-reflow.
Intravascular ultrasound (IVUS) criteria (modified MUSIC criteria)
Stent deployment is suboptimal when at least one of the below IVUS findings is present: 1. Complete apposition against the vessel wall of the entire stent. 2. Adequate stent expansion: a) In case in-stent minimal lumen area (MLA) ≤5.5 mm^2, in-stent MLA ≥90% of the average reference lumen area or ≥100% of lumen area of the reference segment with the lowest lumen area; or b) In case in-stent MLA >5.5 mm^2, in-stent MLA ≥80% of the average reference lumen area or ≥90% of lumen area of the reference segment with the lowest lumen area. 3. Symmetric stent expansion defined by asymmetry index (1 – minimal lumen diameter per pullback / maximal lumen diameter per pullback) ≤0.3 **(Supplementary Figure 1)**.
OCT criteria[2]
Stent deployment is suboptimal when at least one of the below OCT findings is present: 1) Edge dissection: the presence of a linear rim of tissue with a width ≥200 μm and a clear separation from the vessel wall or underlying plaque that was adjacent (<5 mm) to a stent edge. 2) Reference lumen narrowing: lumen area <4.5 mm^2 in the presence of significant residual plaque adjacent to stent endings. 3) Malapposition: stent-adjacent vessel lumen distance >200 μm. 4) In-stent MLA <4.5 mm^2. 5) In-stent MLA <70% of the average reference lumen area. 6) Intrastent plaque/thrombus protrusion: tissue prolapsing between stent struts extending inside a circular arc connecting adjacent struts or intraluminal mass ≥500 μm in thickness, with no direct continuity with the surface of the vessel wall or highly backscattered luminal protrusion in continuity with the vessel wall and resulting in signal-free shadowing.

IVUS: intravascular ultrasound; MLA: minimum lumen area; OCT: optical coherence tomography