This supplement contains the following items:

1. Original protocol and final protocol with summary of changes.
2. Original statistical analysis plan and final statistical analysis plan with summary of changes.

STOPDAPT-2 ACS

ShorT and OPtimal duration of Dual AntiPlatelet Therapy-2

Study for patients with ACS

Protocol Version 1.1

＜Date of preparation: Nov 9, 2017 Ver.1.1＞

Document History

Version	Date of revised	Changes	Notes
Ver. 1.1	Nov 9, 2017	New Document based on STOPDAPT-2 protocol	N/A

STOPDAPT-2 ACS Study Overview
ShorT and OPtimal duration of Dual AntiPlatelet Therapy-2 study for patients with ACS

[Study to Evaluate the Safety of Reducing Dual Antiplatelet Therapy (DAPT) Duration to 1 Month for patients with acute coronary syndrome (ACS) after Implantation of Everolimus-eluting Cobalt-chromium Stent]

Study Overview: The cardiovascular/bleeding event rate at 12 months after stenting is evaluated in patients who have undergone percutaneous coronary intervention (PCI) under the setting of acute coronary syndrome (ACS) with the cobalt-chromium everolimus-eluting stent (CoCr-EES, Xience^{TM}) and randomly assigned to the 1-month (≥ 30 days and < 60 days) DAPT group or the 12-month (≥ 11 months and < 13 months) DAPT group (primary analysis).

In the 1-month DAPT group, clopidogrel (Plavix) monotherapy will be continued up to 5 years after DAPT discontinuation and in the 12-month DAPT group, aspirin monotherapy will be continued up to 5 years after DAPT discontinuation. The superiority of the clopidogrel monotherapy over the aspirin monotherapy with regard to cardiovascular/bleeding events and upper gastrointestinal examination events will be verified (secondary analysis).

- Study design: Multicenter, randomized, open-label, controlled study
- Primary endpoint: Composite of cardiovascular death, myocardial infarction (MI), stroke (ischemic and hemorrhagic), stent thrombosis (Definite stent thrombosis yet to develop into MI), and serious bleeding (TIMI Major/Minor) at 12 months
- Evaluation method of the primary endpoint: Non-inferiority of the Clopidogrel monotherapy after 1-month DAPT over the 12-month DAPT will be verified with regard to the primary endpoint at 12 months (primary analysis).

  In the 1-month DAPT group, clopidogrel monotherapy will be continued up to 5 years and in the 12-month DAPT group, aspirin monotherapy will be continued up to 5 years. The superiority of the clopidogrel monotherapy after 1-month DAPT over the aspirin monotherapy after 12-month DAPT with regard to the primary endpoint and upper gastrointestinal examination events will be verified (secondary analysis).
- Target sample size : 3000 patients including ACS patients enrolled in the STOPDAPT-2 study
- Principal Investigator:

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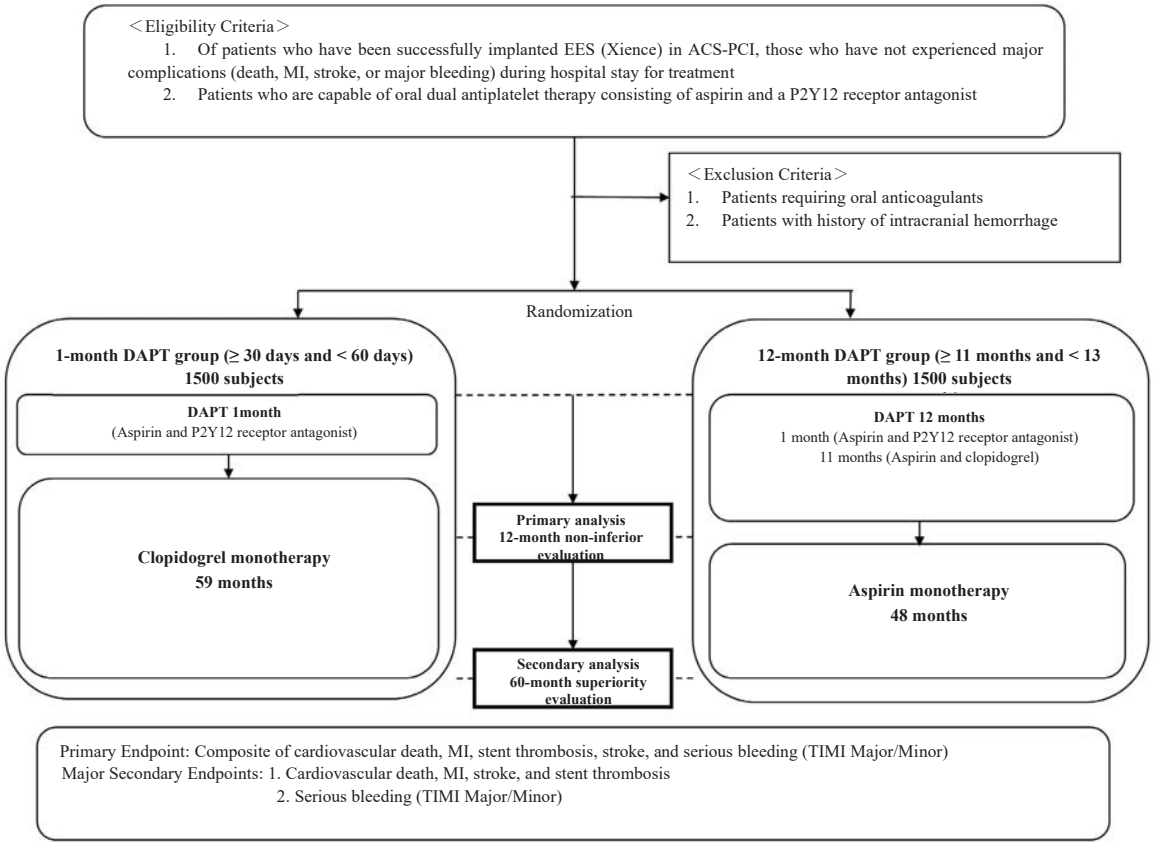
■ Study period: From study approval date to 5 years after the end of enrollment period and to finish major analysis (8 years from study approval date, planned)

■ Enrollment period: From study approval date to the earlier date of the enrollment of target number patients or 2 years from study approval date

Scheme


＜Eligibility Criteria＞
1. Of patients who have been successfully implanted EES (Xience) in ACS-PCI, those who have not experienced major complications (death, MI, stroke, or major bleeding) during hospital stay for treatment
2. Patients who are capable of oral dual antiplatelet therapy consisting of aspirin and a P2Y12 receptor antagonist
＜Exclusion Criteria＞
1. Patients requiring oral anticoagulants
2. Patients with history of intracranial hemorrhage
Randomization
1-month DAPT group (≥ 30 days and < 60 days) 1500 subjects
DAPT 1month
(Aspirin and P2Y12 receptor antagonist)
Clopidogrel monotherapy
59 months
12-month DAPT group (≥ 11 months and < 13 months) 1500 subjects
DAPT 12 months
1 month (Aspirin and P2Y12 receptor antagonist)
11 months (Aspirin and clopidogrel)
Aspirin monotherapy
48 months
Primary analysis
12-month non-inferior evaluation
Secondary analysis
60-month superiority evaluation
Primary Endpoint: Composite of cardiovascular death, MI, stent thrombosis, stroke, and serious bleeding (TIMI Major/Minor)
Major Secondary Endpoints: 1. Cardiovascular death, MI, stroke, and stent thrombosis
2. Serious bleeding (TIMI Major/Minor)

Index

List of Abbreviations (Common Examples)

Abbreviation	Description
ACS	Acute Coronary Syndrome
BMS	Bare-Metal Stent
BVS	Bioabsorbable Vascular Scaffold
CABG	Coronary Artery Bypass Graft
CoCr-EES	Cobalt-Chromium Everolimus-Eluting Stent
DAPT	Dual Anti-Platelet Therapy
DEB	Drug Eluting Balloon
DES	Drug Eluting Stent
ECG	Electrocardiogram
eGFR	estimated Glomerular Filtration Rate
LMCA	Left Main Coronary Artery
MI	Myocardial Infarction
PCI	Percutaneous Coronary Intervention
QCA	Quantitative Coronary Angiography
ST	Stent Thrombosis
TLR	Target Lesion Revascularization
TVF	Target Vessel Failure
TVR	Target Vessel Revascularization
UA	Unstable Angina

1. Study Objectives

The purpose of this study is to evaluate the safety of reducing DAPT duration to 1 month after implantation of the everolimus-eluting cobalt-chromium stent (CoCr-EES) in patients who presented as acute coronary syndrome (ACS).

2. Background and Rationale

The sirolimus-eluting stent and the paclitaxel-eluting stent, which are known as the first-generation drug-eluting stents (DESs), have already achieved remarkable results, as represented in reducing restenosis rate to 10% or less at 1 year after coronary stenting, so that DESs are currently used in the majority of PCI procedures.[1,2] On the other hand, even though the frequency is low, the problems of the first-generation DES (i.e., late adverse events, such as very late stent thrombosis and late restenosis at 1 year or later, which rarely occur in conventional bare-metal stents [BMSs]) have been pointed out.[3,4]

Since P2Y12 platelet receptor antagonists, when used in combination with aspirin for 1 month, have been indicated to significantly suppress the occurrence of stent thrombosis after BMS implantation, DAPT, in which aspirin and a P2Y12 platelet receptor antagonist are used in combination for 1 month after BMS implantation, has become a standard regimen.[5,6] At the same time, for fear of very late stent thrombosis, DAPT is frequently performed for 1 year or longer after DES implantation in clinical practice. In RESET (Randomized Evaluation of Sirolimus-eluting versus Everolimus-eluting stent Trial) conducted in clinical practice in Japan, 90% of the subjects had been on DAPT for 1 year or longer.[7] Moreover, in the package insert of the Everolimus-eluting stent (EES), currently the most extensively used DES in Japan, 1-year DAPT is recommended. However, serious hemorrhagic complications, such as cerebral hemorrhage, associated with a prolonged DAPT duration can bring disadvantages to patients, it is extremely important to clarify an optimal DAPT duration after DES procedure. Based on the results of large-scale observational studies and small-scale randomized controlled studies, DAPT for 6 months or longer[8-12] had no inhibitory effects on the onset of serious cardiovascular events. Furthermore, we have recently assessed the safety of a DAPT regimen for 3 months after CoCr-EES implantation in STOPDAPT (ShorT and OPtimal duration of Dual AntiPlatelet Therapy study after everolimus-eluting cobalt-chromium stent) study, using the RESET study, in which DAPT had been performed in 90% of subjects for 1 year or longer, as a historical control.[13] More recently, attempt to further reduce DAPT duration after DES procedure begins.

In Global LEADERS (A Clinical Study Comparing Two Forms of Anti-platelet Therapy After Stent Implantation: NCT01813435) study, the safety of a DAPT regimen with ticagrelor, a new P2Y12 platelet receptor antagonist for 1 month after DES procedure is under evaluation.[14] In addition, in LEADERS FREE (A Randomized Clinical Evaluation of the BioFreedom™ Stent: NCT01623180) study, the efficacy and safety of polymer-free DES (BioFreedom™) compared with BMS in 1-month DAPT regimen are proven in the subject group with a high bleeding risk.[15] These clinical studies are currently being conducted while monitoring safety, and have already completed patient recruitment, presumably generating no major safety concerns. Currently, 1-month DAPT regimen after BMS implantation is commonly used in clinical practice, producing no major problems. Based on a meta-analysis of recent clinical studies, it has also been reported that the use of CoCr-EES reduces the risk of early stent thrombosis by half compared to the use of BMS.[16] At least from a logical standpoint, there is no necessity to extend antiplatelet therapy after CoCr-EES implantation longer than after BMS implantation, and it is considered possible to use the same 1-month DAPT duration as after BMS implantation. On the other hand, for bleeding complication, it is clear that a prolonged DAPT duration increases bleeding complications compared to aspirin monotherapy.[10,16-18] We therefore started STOPDAPT-2 (NCT02619760), a multicenter, randomized, open-label, controlled study, in which DAPT is discontinued at 1 month after stenting in subjects who have undergone CoCr-EES procedure, which is considered to be associated with a lower risk of stent thrombosis than BMS, to compare incidences of cardiovascular events and bleeding events at 12 months after stenting between the 1-month DAPT group and the 12-month DAPT group.

Moreover in STOPDAPT-2, the superiority of clopidogrel monotherapy after 1-month DAPT over aspirin monotherapy after 12-month DAPT will be verified by comparing results of clopidogrel monotherapy continued up to 5 years after DAPT discontinuation in the 1-month DAPT group and aspirin monotherapy continued up to 5 years after DAPT discontinuation in the 12-month DAPT group.

In the current AHA/ACC or ESC guidelines, 12-month DAPT is standard recommendation for patients with ACS, though 6-month DAPT is recommended for stable coronary artery disease[19,20]. However, the rational of the longer DAPT duration for ACS patients was based only on the CURE study, which was performed more than 15 years ago[21,22]. We previously reported the incidence of ischemic events beyond 3 months after index PCI was not different between the acute myocardial infarction (AMI) patients and non-AMI patients in registry data[23]. Therefore, in contemporary clinical practice using 2nd generation DES, there is no solid rationale to recommend extended DAPT duration in patients with ACS. In the ongoing STOPDAPT-2 study,

the proportion of ACS cases is expected to be 30 to 40% of the entire study population, and the power is insufficient to evaluate safety of 1-month DAPT in ACS patients. Therefore, we designed the STOPDAPT-2 ACS study, in which we would enroll only ACS patients with the same protocol as the STOPDAPT-2, and analyze the safety of 1-month DAPT in ACS patients. We would combine the two studies to include the ACS patients enrolled in the STOPDAPT-2.

3. Study Method

In this study, the cardiovascular/bleeding event (primary endpoint) rate at 12 months after stenting will be evaluated in patients who have undergone PCI with CoCr-EES (DES) for ACS and randomly assigned to the 1-month DAPT group or the 12-month DAPT group (primary analysis).

In the 1-month DAPT group, clopidogrel monotherapy will be continued up to 5 years after DAPT discontinuation and in the 12-month DAPT group, aspirin monotherapy will be continued up to 5 years after DAPT discontinuation. The superiority of the clopidogrel monotherapy after 1-month DAPT over the aspirin monotherapy after 12-month DAPT with regard to the primary endpoint and upper gastrointestinal examination events will be verified (secondary analysis).

In this study, the genetic substudy to evaluate CYP2C19 polymorphism will not be performed, which was performed in STOPDAPT-2.

3.1 Inclusion Criteria

- Patients who have undergone PCI with the everolimus-eluting cobalt-chromium stent (CoCr-EES, Xience^{TM}) in the setting of ACS (STEMI, NSTEMI, or UA) and have not experienced major complications (death, MI, stroke, or major bleeding) during hospital stay for treatment
- Patients who are capable of oral dual antiplatelet therapy consisting of aspirin and a P2Y12 receptor antagonist

3.2 Exclusion Criteria

- Patients requiring oral anticoagulants

- Patients with medical history of intracranial hemorrhage
- Patients who have experienced serious complications (MI, stroke, and major bleeding) during hospital stay post-PCI
- Patients with DES other than Xience implanted in PCI performed at the time of enrollment.
- Patients with coronary bioabsorbable vascular scaffolds (BVS) implanted prior to or at the time of enrollment (including implantation cases in clinical trial)
- Patients confirmed to have no tolerability to clopidogrel before enrollment
- Patients requiring continuous administration of antiplatelet drugs (PDE3 inhibitors, prostaglandin preparations, etc.) other than aspirin and P2Y12 receptor antagonists (prasugrel, clopidogrel, and ticlopidine) at the time of enrollment

3.3 Patients Enrollment and Treatment Assignment

Enrollment and registration will be performed in database on web system during hospitalization after PCI in patients with ACS. The access to the database will be permitted to only the persons in charge having ID and password in each study participating facilities and they are permitted to access only the data of their facilities and not permitted to access to the data of other participating facilities.

All patients undergoing PCI in the study participating centers during registration period will be registered into PCI log page with information about the presence or absence of CoCr-EES implantation success and the presence or absence of other DES implantation than CoCr-EES after completion of planned staged-PCI. Among these patients, the patients who have successful implantation of one or more CoCr-EES and no implantation of DES other than CoCr-EES will be candidates participating current study and give the consent of participation. When patients give the consent of study participation, they will be randomly assigned into 1-month DAPT group or 12-month DAPT group after the confirmation of study exclusion criteria written in article 3.2. Adjustment factors of randomization is set to be only participating facilities.

Even when patient can be candidate but reject the participation of this study, patients background will be registered into screening log to grasp the characteristics of patients who don’t participate current study. Details will be written following article 4.1. Registration period is set to be 2 years.

4. Study Rule

4.1 Procedural Notes

In this study, ACS patients who have undergone PCI using CoCr-EES should be enrolled in a manner optimally close to consecutive cases.

- Patients with diagnosis of ACS at hospital admission will be enrolled during hospital stay after confirming stable condition without serious complication after PCI using CoCr-EES. Enrollment period is 2 years.
- If staged PCI is planned, enrollment should be performed after the completion of all PCI procedures. The final PCI procedure should be considered as the index procedure. In case of performing more than one procedure during the same admission period, diagnosis, lesion findings, or number of diseased vessel will be based on the condition at admission or 1st angiography. Therefore, in current STOPDAPT-2 ACS study, in the case of multivessel ACS and dividing PCI procedure into two or more, index procedure shall be the last procedure before discharge and subjects shall be treated with all lesions judged necessary for intervention during the hospitalization. (Patients with admission for ACS and planned to receive another PCI after hospital discharge should not be enrolled.)
- ACS is defined as one of following diagnosis treated within one week after onset; ST-segment elevation MI (STEMI), Non-ST-segment elevation MI (NSTEMI), or Unstable angina based on the Third universal definition of MI or 2014 AHA/ACC NSTE-ACS guideline.[24,25] Diagnosis of MI requires elevation of cardiac biomarkers.
- In the index PCI procedure, only Xience family (Xience V™, Xience Prime™, Xience Xpedition™, and Xience Alpine™) can be used, and BMS are allowed to be used in combination.
- Type and dose of aspirin should follow the clinical practice of each site.
- Type and dose of P2Y12 receptor antagonists within 1 month after procedure should be either clopidogrel 75 mg daily or prasugrel 3.75 mg daily, depending on the clinical practice of each site.
- Type and dose of P2Y12 receptor antagonists at 1 month or later after procedure should be clopidogrel 75 mg daily.
- It is allowed to reduce dose of P2Y12 receptor antagonist during the time course based on the clinical necessity, such as bleeding events.
- Patients confirmed to have no tolerability to clopidogrel before enrollment should not be enrolled. When patients have been found to have no tolerability to clopidogrel after

enrollment, it is allowed to change the drug to another P2Y12 receptor antagonist (prasugrel 3.75 mg daily or ticlopidine 200 mg daily).

- Patients requiring continuous administration of antiplatelet drugs other than aspirin and thienopyridine (PDE3 inhibitors, prostaglandin preparations, etc.) or oral anticoagulants at the time of enrollment should not be enrolled. It is allowed to start using these drugs during the follow-up period based on the clinical necessity.
- Although subjects are allowed to visit the doctor who has referred them to the site, the antiplatelet drug should be prescribed at the study site as possible. For subjects who have been referred from remote areas (i.e., other prefectures) and are unable to visit the site frequently, the site personnel may confirm medication adherence by phone.
- Subjects will visit the site at 1 month (≥ 30 days and < 60 days) post-PCI, aspirin will be discontinued and clopidogrel will be started in the 1-month DAPT group while aspirin/clopidogrel dual therapy will be started in the 12-month DAPT group.
- Subjects will visit the site at 12 months (≥ 11 months and < 13 months) post-PCI, clopidogrel will be continuously prescribed in the 1-month DAPT group while clopidogrel will be discontinued and only aspirin will be continuously prescribed in the 12-month DAPT group.
- To ensure that antiplatelet drug administration complies with the protocol, at the 1-month and 12-month visits post-PCI, the participating site's clinical research coordinator (CRC) or equivalent personnel will inform the outpatient doctor of the necessity of changing prescription and also confirm the prescription on the visit day comply with the protocol.
- When subjects visit the study site during the follow-up period, the investigator should interview subjects regarding the status of the following items since their previous visit and record it in their medical records: 1) whether they have been treated or hospitalized in other medical institutions, 2) whether they have undergone gastrointestinal endoscopy or experienced bleeding, 3) whether antiplatelet drugs have suspended, resumed, changed, or added, and 4) whether any other drugs have been changed.
- The initial enrollment should be performed by the participating site's investigator, while data entry should be performed by each site's CRC or outside CRC.
- After the start of enrollment at each site, all subjects who have successfully undergone CoCr-EES procedure should be registered in the screening log and the following data of each subject must be entered and reported: patient name, age, sex, height, weight, diagnosis, the presence or absence of hypertension, the presence or absence of diabetes mellitus (insulin, oral drugs, or diet), history of myocardial infarction, history of stroke (cerebral infarction or cerebral hemorrhage), creatinine level, presence or absence of dialysis, presence or absence of atrial fibrillation, oral anticoagulant therapy, history of PCI, history of the first-generation DES implantation, history of BVS implantation, history of heart failure, presence or absence

of peripheral vessel/aortic diseases, smoking status, presence or absence of multivessel treatment, number of target lesions, location of target lesion, number of implanted stent, size of implanted stent, major complication (MI, stroke, major bleeding) after index PCI procedure, presence or absence of tolerability to clopidogrel, administration of antiplatelet drugs other than aspirin and P2Y12 receptor antagonists, presence or absence of planned surgical operation, and planned DAPT duration.

- For the patient who is not enrolled in this study for exclusion criteria or disagreement etc. but whose information is collected in screening log, the fact of data collection mentioned above should be informed by word of mouth or written letter. Study content, URL address of current study showing the list of participating institutes and responsible person in each center, and contact information are open by notification of bulletin board in hospital ward and so on. Chance of rejecting to register screening log is secured.
- Follow-up coronary angiography should be performed according to the clinical practice of each site. When coronary arteriography is planned, presence or absence of recurrent angina symptoms and ischemic evaluation results should be described in the medical record prior to the coronary arteriography.
- When MI is suspected, quantitative troponin T measurement (qualitative measurement is acceptable in case quantitative measurement is not possible) and CK and CK-MB measurement should be performed before and after revascularization. After revascularization, measurement of the 3 parameters above should be continuously measured to determine their peak values. Measurement interval should be a maximum of every 6 hours.
- When MI is suspected, the following information should be described in the medical record wherever possible: presence or absence of ischemic symptoms, presence or absence of ECG changes (ST-T change, new left bundle branch block, and abnormal Q wave), presence or absence of decrease or abnormality in wall motion newly noted in image evaluation, and presence or absence of coronary artery thrombosis observed in coronary arteriography or autopsy.
- The presence or absence of recurrent angina symptoms and ischemic evaluation results should be described in the medical record at the time of target lesion revascularization (TLR).
- If PCI or coronary artery bypass grafting (CABG) is performed during the follow-up period, quantitative troponin T measurement (qualitative measurement is acceptable in case quantitative measurement is not possible) and CK and CK-MB measurement should be performed before the procedure, and within 48 hours post-PCI or within 72 hours post-CABG.

- If acute coronary syndrome, PCI, or CABG event has been observed, ECG before and after the treatment or procedure should be recorded and collected in hardcopy (photocopy is acceptable).

4.2 Required Tests

The following tests are required, and the adoption of other tests is subject to each site's standards.

At Enrollment：

- Blood tests
  - In this study, hemoglobin and hematocrit concentrations should be measured, because TIMI definition is used to rate hemorrhagic adverse events.
  - Hemoglobin and hematocrit concentrations should be measured also when a hemorrhagic adverse event is suspected during the follow-up period.
  - Test items：WBC, RBC, hemoglobin, hematocrit, Plt, creatinine, blood glucose、HbA1c, total cholesterol, HDL cholesterol, LDL cholesterol, triglyceride
  - In case the above blood tests performed within 1 month before the study enrollment, the blood tests are not required at enrollment.

4.3 Planned Follow-up Period

In this study, information described in "6. Items to be investigated" will be collected at enrollment, at 1 month, 12 months, 24 months, 36 months, 48 months, and 60months, and recorded on the electronic Case Report Form (eCRF).

5. Study Period

This study is planned to be carried out for 8 years from the beginning of enrollment to the scheduled completion of 60 months follow-up after PCI in the last enrolled patient and major study analysis. Though the enrollment period of this study is defined as within 2 years, the enrollment will be terminated when a total of 3000 ACS patients (including ACS patients in the STOPDAPT-2) are enrolled.

6. Items to be Investigated

6.1 Planned Follow-up Periods

The investigations in this study are performed at the following time points:

1) At enrollment
2) Follow-up at 1 month after procedure (At the outpatient visit in principle after at 30 days before at 60 days)
3) Follow-up at 12 months after procedure (At the outpatient visit in principle after at 335 days at before 395 days)
4) Follow-up at 24 months after procedure (At the outpatient visit in principle after at 700 days at before 760 days)
5) Follow-up at 36 months after procedure (At the outpatient visit in principle after at 1065 days at before 1125 days)
6) Follow-up at 48 months after procedure (At the outpatient visit in principle after at 1430 days at before 1490 days)
7) Follow-up at 60 months after procedure (At the outpatient visit in principle after at 1795 days at before 1855 days)

6.2 Observation Items

Observation items will be investigated at enrollment and at follow-up visit by various examinations and interview, etc. All results but the angiographic analysis will be recorded in the corresponding columns of the eCRF.

6.2.1 Observation Items at Enrollment/at Discharge

1. Enrollment data

Name of institute, date of enrollment, patient enrollment number, and name of the investigator.

2. Basic data

Age, sex, height, weight, date of hospitalization, blood pressure at hospitalization, and pulse rate at hospitalization.

3. Diagnosis of myocardial infarction (MI) or angina pectoris (select from below)

ST-elevation acute myocardial infarction (MI), Non ST-elevation acute MI, stable angina pectoris, unstable angina pectoris, asymptomatic myocardial ischemia, old myocardial ischemia, and coronary stenosis.

4. Additional information about ACS

Presence/Absence of ECG change, imaging evidence of new loss of viable myocardium or new regional wall motion abnormality, site of myocardial infarction, location of culprit lesion, time between onset and hospital arrival, time between hospital arrival and PCI (wire cross).

5. History of cardiac diseases

History of PCI, implantation history of bare metal stent, implantation history of 1st generation DES, implantation history of other DES, implantation history of BVS, history of CABG, history of myocardial infarction (MI), history of heart failure, history of stroke, history of atrial fibrillation, history of COPD, history of liver cirrhosis, history of malignant tumor, and history of hemorrhagic disease.

6. Complications

Complication of heart failure at hospitalization, heart failure (current or past history), carotid artery stenosis, arteriosclerosis obliterans, peripheral artery disease excluding carotid arteries or arteriosclerosis obliterans, aortic aneurism/dissection, diseases of the aorta/ peripheral vessels (all), diseases of the aorta/peripheral vessels (postoperative/planned to be treated), and dialysis.

7. Risk factors

Hypertension, Lipid abnormalities, smoking, diabetes mellitus, and family history of coronary diseases.

8. Concomitant medication

The presence or absence of anticoagulation therapy, and the presence or absence of other antiplatelet therapy than aspirin and thienopyridines.

9. Coronary angiographic findings

Procedure date of coronary angiography, stenotic lesions, number of branches affected, presence/absence of following lesions; unprotected left main lesion and chronic total occlusive (CTO) lesion, left ventricular ejection fraction, measurement method for left ventricular ejection fraction, mitral insufficiency, and evaluation method for mitral insufficiency.

10. Evaluation of Myocardial Ischemia

Myocardial Scintigraphy (positive or negative), Invasive FFR (positive or negative), and CT FFR (positive or negative).

11. PCI Baseline Observation

Per patient analysis: PCI procedure date, emergency procedure, target lesion segment, presence/absence of following treatments: treatment of unprotected left main coronary artery stenosis, treatment of CTO, treatment of ST-elevation acute MI culprit lesion, treatment of bifurcation lesion, treatment of 2 branches or more, treatment of 3 branches or more, treatment of in-stent restenosis lesion, and treatment of RCA ostial lesion, implanted stent diameter, and implanted stent length.

Per lesion analysis: target lesion, lesion classification (new lesion, residual lesion, lesion of in-stent-restenosis, lesion of restenosis except of stents), in-stent-restenosis pattern (BMS, Cypher, Taxus, Endeavor, Xience, Promus, Nobori, Resolute, other DES, and BVS [multiple choice allowed]), STEMI culprit lesion, ostial lesion, LMT distal bifurcation, unprotected LMT lesion, CTO lesion, severe calcified lesion, presence/absence of thrombus, lesion and proximal tortuousness, lesion and proximal bending (over an angle of 90 degrees), thrombus aspiration, stenting attempt, direct stenting, intervention before stenting (POBA, DEB, Cutting Balloon, Directional Coronary Atherectomy, Rotablator, aspiration, other, unknown), stenting (name of stent, diameter, length, expanding pressure, implanted site), post dilatation (balloon diameter, pressure), IVUS use, OCT use, bifurcation lesion, branch lesion, bifurcation type, bifurcation strategy, stent classification (only XIENCE, XIENCE and BMS)

12. Clinical laboratory tests

WBC, RBC, hemoglobin, hematocrit, Plt, creatinine, blood glucose, HbA1c, total cholesterol, HDL cholesterol, and triglyceride.

Before Index PCI: CK, CKMB, Troponin T or I: presence/absence of measurement, measured value (positive/negative or quantitative value), upper limit of normal if the tested in site other than participating institution.

After Index PCI: CK, CKMB, Troponin T or I: presence/absence of measurement, measured peak value (positive/negative or quantitative value), upper limited of normal of the institute.

13. Electrocardiogram (ECG) after procedure

14. Planned surgical operation

Presence or absence of planned surgical operation, detail of the surgical operation

15. Observation Items at Discharge

Discharge date and medication at discharge

Notes: Definition of observation items

1. Diabetes mellitus

Diabetes mellitus is defined as meeting either of 2 hour OGTT glucose level of ≥200 mg/dL, casual blood glucose level of ≥200 mg/dL, fasting blood glucose level of ≥126 mg/dL, or HbA1c ≥6.1% (JDS) or ≥6.5% (NGSP).

When the above tests have not been performed, patients who have been clinically diagnosed as diabetic or are treated with antidiabetic agents are defined as having diabetes.

2. Dyslipidemia

Patients with total cholesterol ≥ 240 mg/dL or HDL cholesterol < 40 mg/dL, or patients who are treated with statins.

3. Evaluation of renal functions

The estimated glomerular filtration rate (eGFR) is calculated by using the equation fitted for Japanese people by the Japanese Society of Nephrology.

eGFR=194*Cr $^{-1.094}$*Age $^{-0.287}$ (*0.739 for females)

Terminal renal failure: e-GFR < 30 mL/min/1.73 mm^2

Chronic kidney disease: e-GFR < 60 mL/min/1.73 mm^2

4. Other items

Other items will be considered based on the clinical diagnosis described on the clinical record.

6.2.2 Angiographic Study

Not performed in this study

6.2.3 Follow-up at 1 month

At 1 month after enrollment, the following data will be recorded.

1. Death

Investigation method to determine the patient's death/survival, date of the last confirmation of death/survival, presence/absence of death, date of death, classification of cause of death, and cause of death.

2. Other events than death

Investigation method for other events than death, date of the last confirmation of other events than death, and presence/absence of other events than death.

3. Myocardial infarction (MI)

Presence/absence of MI, date of onset, status at onset, symptoms of ischemia, electrocardiographic change, ST-elevation MI, Q-wave MI, new hypokinesis by imaging evaluation, relationship with stent thrombosis, ARC classification, culprit lesion, angiography, treatment (PCI, CABG or medical therapy), and coronary thrombus.

Presence/absence of evaluation of the maximum values of cardiac enzymes, date of measurement of cardiac enzymes, CK, CK-MB, troponin T or I.

Before revascularization: CK, CK-MB, troponin T or I, measured value, and upper limits of normal at institute.

At peak value after revascularization: CK, CK-MB, troponin T or I, measured peak value, upper limits of normal at institute, measured peak value, and lethality.

4. ACS

Presence/absence of emergency hospitalization due to ACS, date of onset, ACS classification, relationship with stent thrombosis, identification of culprit lesion by angiography, lethality, and presence/absence of revascularization.

5. Definite stent thrombosis according to ARC definition

Presence/absence of stent thrombosis, date of onset, situation of onset, presence/absence of evaluation of the maximum values of cardiac enzymes, date of testing, CK, CK-MB, troponin T or I, presence/absence of Interim TVR trial, relationship with the surgical procedure, presence/absence of hemorrhagic complications before the onset of stent thrombosis, antiplatelet therapy (aspirin and thienopyridine drugs) at the onset of stent thrombosis, and lethality

6. Probable stent thrombosis according to ARC definition

Presence/absence of stent thrombosis, date of onset, and classification (unexplained death within 30days / MI in the target vessel area).

7. Possible stent thrombosis according to ARC definition

Presence/absence of stent thrombosis and date of onset.

8. Stroke

Presence/absence of stroke, date of onset, classification of stroke, and lethality.

9. Heart failure

Presence/absence of hospitalization due to heart failure, date of hospitalization, and presence/absence of coronary revascularization during hospitalization.

10. Ventricular fibrillation, persistent ventricular tachycardia

Presence/absence of hospitalization due to ventricular fibrillation or persistent ventricular tachycardia, date of hospitalization, and presence/absence of coronary revascularization during hospitalization.

11. Bleeding complication

Presence/absence of bleeding complication, date of onset, bleeding site, Nadir Hb, Nadir Ht, bleeding that requires blood transfusion, the amount of blood transfusion (units, MAP), drop in blood pressure, surgical hemostasis, TIMI classification, GUSTO classification, and BARC classification.

12. Gastrointestinal complication

Upper gastrointestinal endoscopy and upper gastrointestinal endoscopic treatment.

13. Surgery

Presence/absence of surgery, procedure date, general anesthesia, the name of surgery, and surgery area.

14. CABG

Presence/absence of CABG, procedure date, target vessel,

Before revascularization; CK, CK-MB, Troponin T or I: measured value, upper limits of normal at institute.

After revascularization; CK, CK-MB, Troponin T or I: measured value, upper limits of normal at institute.

15. Revascularization excluding TLR

Presence/absence of revascularization excluding TLR, procedure date, target vessel, revascularization method, non-TL TVR, and clinically driven revascularization.

Before revascularization; CK, CK-MB, Troponin T or I: measured value, upper limits of normal at institute.

After revascularization; CK, CK-MB, Troponin T or I: measured value, upper limits of normal at institute.

16. TLR

Presence/absence of TLR, procedure date, revascularization method, PCI devices, clinically driven revascularization, follow-up angiography, date of angiography, reason of angiography, the method of follow-up angiography, restenosis of main vessel, re-occlusion of main vessel, restenosis of side branch, and re-occlusion of side branch.

Before revascularization; CK, CK-MB, Troponin T or I: measured value, upper limits of normal at institute.

After revascularization; CK, CK-MB, Troponin T or I: measured value, upper limits of normal at institute.

17. Discontinuation of Medical Therapy

Final confirmation date of thienopyridine administration status, final thienopyridine administration status, discontinuation of thienopyridine, the discontinuation date, the reason of discontinuation, alternative agent, restart administration of thienopyridine, restart date, final confirmation date of aspirin administration status, final aspirin administration status, discontinuation of aspirin, the discontinuation date, the reason of discontinuation, alternative agent, restart administration of aspirin, restart date, and DAPT discontinuation and switching to thienopyridine monotherapy in 1 month DAPT arm (only after 1 month).

6.2.4 12 months follow-up

At 12 months after enrollment, in addition to the observation items of “6.2.3 1 month follow-up”,

17. Discontinuation of Medical Therapy

DAPT discontinuation in 12 months DAPT arm, and switching to aspirin monotherapy (only after 12 months) should be recorded.

6.2.5 24 months follow-up

At 24 months after enrollment, same observation items with "6.2.4 12months follow-up" should be recorded.

6.2.6 36 months follow-up

At 36 months after enrollment, same observation items with "6.2.4 12months follow-up" should be recorded.

6.2.7 48 months follow-up

At 48 months after enrollment, same observation items with "6.2.4 12months follow-up" should be recorded.

6.2.8 60 months follow-up

At 60 months after enrollment, same observation items with "6.2.4 12months follow-up" should be recorded.

6.2.9 Study termination and discontinuation

If this study discontinued or early terminated, last contact date to the subject and the reasons of the discontinuation will be recorded on the electronic Case Report Form (eCRF). The reason of the early termination should be recorded.

7. Endpoint

7.1 Primary Endpoint

Analyzed population will be a combined group of the patients with ACS enrolled in preceding STOPDAPT-2 (NCT02619760) and the patients enrolled in current study (STOPDAPT-2 ACS).

The primary endpoint of primary analysis in current study is the composite of cardiovascular death, myocardial infarction (MI, excluding MI within 2 days after index PCI), stroke (ischemic and hemorrhagic), stent thrombosis (definite stent thrombosis yet to develop into MI), and severe bleeding (TIMI Major/Minor) at 12 months. Non-inferiority of 1-month DAPT group will be verified compared with 12-month DAPT group.

The primary endpoint for the secondary analysis is the composite of cardiovascular death, MI, stroke (ischemic or hemorrhagic), stent thrombosis (definite stent thrombosis yet to develop into MI), and severe bleeding (TIMI Major/Minor) at 60 months. Superiority of 1-month DAPT

group will be verified compared with 12-month group.

As a descriptive analysis, event incidence from 1 month to 12 months or from 12-month to 60 months will be compared between 1-month DAPT group and 12-month DAPT group by a landmark analysis.

7.2 Secondary endpoints

7.2.1 Major Secondary Endpoint

In this study, the following major secondary endpoints will be evaluated

- 12-month observation
  - Cardiovascular death/ MI/ stroke/ definite ST
  - Major bleeding (TIMI Major/ Minor)
- 60-month observation
  - Cardiovascular death/ MI/ stroke/ definite ST
  - Major bleeding (TIMI Major/ Minor)
  - Upper gastrointestinal endoscopy / upper gastrointestinal endoscopic treatment

7.2.2 Other Secondary Endpoints

In this study, the following secondary endpoints will be also evaluated at 12 months and at 60 months observation

- Death / MI
- Death
- Cardiovascular death/ MI
- Cardiovascular death
- MI
- Stroke
- ST (ARC definition)
- TLF
- TVF
- MACE
- Any TLR
- Clinically-driven TLR

- Non-TLR
- CABG
- Any TVR
- Any revascularization
- Bleeding complications
- Gastrointestinal bleeding
- Gastrointestinal complaints

8. Determination of Sample size

8.1 Sample Size Required to Assess Safety in the Primary Endpoint and Evaluation Method

The primary endpoint of this clinical study is the composite of cardiovascular death, MI (excluded periprocedural MI within 2 days of the index PCI), stroke, stent thrombosis, and serious bleeding and primary analysis is non-inferiority analysis of 1 month DAPT group against 12 month DAPT group about incidence rate of primary endpoint up to the 12-month observation point. The following hypothesis was employed to calculate a required sample size.

In the pooled analysis including RESET and NEXT study[7,26], the 1-year incidence rate of the primary endpoint observed in the 533 ACS subjects treated with CoCr-EES was 5.5%.

The sample size was calculated using the following hypothesis:

True value:	5.5%
Non-inferior margin:	1.5 on the hazard ratio scale by the Cox model
Power:	80%
One-sided alpha:	0.025
Randomization ratio:	1:1

On the above hypothesis, in order to demonstrate non-inferiority of 1 month DAPT to 12 months DAPT on primary endpoint, a sample size of 2676 patients in both arms will be required. Taking into consideration of dropout cases, we plan to enroll a total of 3000 ACS patients including the patients already enrolled in STOPDAPT-2 (NCT02619760).

8.2 Power Evaluation of Secondary analysis

The cumulative incidence rate at 60 months of composite endpoint including cardiovascular death, MI, stroke, stent thrombosis, and severe bleeding for ACS patients treated with CoCr-EES was assumed to be 15.7% from 3-year event rate of RESET/NEXT study. At first non-inferiority test will be performed with 1.5 in hazard ratio scale as non-inferiority margin like primary analysis. In this non-inferiority test, power would be 99.9% with 0.025 as one-sided alpha value. When non-inferiority of 1-month DAPT against 12-month DAPT will be proven, additionally superiority evaluation will be performed. On the hypothesis that the clopidogrel monotherapy after 1-month DAPT lead to decrease of 25% risk (HR 0.75) compared with the aspirin monotherapy after 12-month DAPT, the power of secondary analysis would be 80% with 0.05 as two-sided alpha value.

9. Subgroup analysis

In this study, patients with different backgrounds are expected to receive the treatment. For this reason, subgroup analyses for diabetes, multiple vessel lesions, etc. will be performed, as well as the analysis including all the patients.

9.1 Pre-specified Subgroup

Per Patient：

- Diabetes
- Insulin-treated diabetes
- Age (≥75/<75)
- Hemodialysis
- e-GFR < 30, Non-HD
- Anticoagulation
- Bleeding disease history
- STEMI
- ACS
- Emergency procedure
- LMCA
- 2 vessel PCI
- 3 vessel PCI

- Total stent length category
- On-label /off -label

Per Lesion：

- Bifurcation
- LMCA
- Multiple overlapping stent
- ISR of BMS and DES
- CTO
- STEMI
- ACS
- Emergency procedure
- Ostial RCA
- Small Vessel

Notes: definition of lesions

- Overlapping stent is dealt with as 1 lesion.
- When a stent is implanted in the left anterior descending coronary artery overlapped on another stent implanted for the left main coronary artery stenosis, these are considered to be two lesions in the left main coronary artery and in the left anterior descending coronary artery, respectively.
- Ostial lesion of the left anterior descending coronary artery that is not accompanied by significant stenosis in the left main coronary artery, but was stented from the left main trunk crossing over a circumflex branch, this is dealt with as one lesion at the ostium of the left anterior descending coronary artery instead of a left main trunk lesion.
- Bifurcation lesion is considered to be one lesion together with the side branch.
- Any lesion having a side branch of ≥ 2.2 mm in diameter by visual evaluation is defined as a bifurcation lesion.
- Any lesion localized within 3 mm from the ostium is defined as an ostial lesion.
- On-label lesion is defined as a de novo lesion of ≤ 32 mm in length and 2.25-3.75 mm in lumen that has not been treated before. However, lesions responsible for a recent myocardial infarction, ostial lesions, bifurcation lesions, thrombotic lesions and highly calcified lesions are not defined as on-label lesions.
- Any lesion that does not meet the criteria for on-label lesion is defined as an off-label lesion.

10. Genetic Analysis Substudy

In STOPDAPT-2 ACS, the genetic substudy to evaluate CYP2C19 polymorphism will not be performed, which was performed in STOPDAPT-2.

11. Other Necessary Issues

11.1 Ethical concerns/Obtainment of informed consent

11.1.1 Protection of patients' rights

Compliance with the Declaration of Helsinki
Study investigators should carry out this study according to either of "the latest version of the Declaration of Helsinki" or "Ethical Guidelines for Clinical Studies (Public Notice of the Ministry of Health, Labor, and Welfare amended on December 22, 2014, revised on February 28, 2017)" that maximizes the protection of patients.

11.1.2 Explanation to the patient

11.1.2.1 For the patients enrolled into study and assigned by protocol

Prior to enrollment, the investigator should give the patient the information document approved by the Ethics Committee with verbal explanation of details of the content. After the explanation, the consent form attached to the information document should be filled in with required data and be signed. The consent form completed with all required data should be duplicated in two copies. One copy will be kept by the patient and another copy by the investigator. The original copy will be stored in the each participating centers.

Investigators should obtain patients' consent again if study protocol will require major modification influencing the judgment of study participation and site ethical committee will decide there is need to reobtain patients' consent.

11.1.2.2 For the patients corresponding to inclusion criteria and not enrolled into study

As mentioned above in 4.1 “Procedural Notes”, for the academic purpose of comparison of patients background between patients enrolled and not-enrolled into study after implantation of Xience^{TM} stents, the data of not-enrolled patients are also collected as screening log. Collected items are mentioned in article 4.1, all of them are preexisting information on medical records, and additional tests are unnecessary to record screening log. This log shall be input with patients’ name for the need of management in each participating centers, cannot be viewed from another participating center, and anonymized when the database will be integrated (see article 11.1.3, anonymization with correspondence table in each participating centers). For the patients whose data shall be input in screening log, the fact of data collection should be informed by word of mouth or written letter. Contact information are open by notification and chance of rejecting to register screening log is secured.

11.1.2.3. Notification and Opening to Public of Research

For the enrolled patients, contents of research shall be informed by the information document. For the patients without enrollment but with registration to screening log, the fact of data collection, contact information of each participating centers and address of current research shall be informed by word of mouth or letter.

In each participating centers, contents of research, collected items, URL address of research and list of participating centers and persons in charge shall be open in public in wards etc.

11.1.3 Privacy Issues

The clinical record, test data, records regarding the patient’s informed consent, etc. will be stored at each medical institute. These records will be disclosed when requested for audit, but the confidentiality will be protected. Moreover, these records should be stored so as to be retrieved when necessary.

All the staff involved in this study has the duty of confidentiality as data handlers and should have the maximum efforts to protect patients’ personal information. Collected data will be accumulated in database on the web with access limitation and the data manager in each participating center will not be allowed to browse the data of other centers. Moreover, while the

number assigned to the patient on the clinical chart at each institute will be used as the Patient ID Number, this number will be automatically encrypted when entered on the web. Therefore, the patient's number on the clinical chart is not transmitted from the participating institute to the Central Administration Office and the Data Center. Patient ID Number and patients' name will be seen only from the each participating center.

For identification of the patient and inquiry to each institute, the encrypted patient ID number will be used. Central Administration Office will check the consistency between data of eCRF and actual clinical recording if participating center approve, and the privacy data will be protected.

Though there is possibility that accumulated data will be utilized for secondary use or provided for study participating centers, the data will be managed with anonymous manner and will be provided for the only people whose utilization will be approved by the study administration office.

11.1.4 Evaluation and Management for Patients' Burden and Expected Risk and Benefit.

This study was performed based on the hypothesis that the risk of stent thrombosis in 1-month DAPT group is not excessive compared with 12-month DAPT group that is equal to current daily practice, as previously mentioned in section 2 "Background and Rationale". Moreover the diminished risk of bleeding will be expected for 1-month DAPT group. For 12-month DAPT group, the treatment will not be changed from current treatment guideline and the risk of embolic and bleeding event will be equal to current practice. Appropriate monitoring for occurrence of stent thrombosis will be planed and its report will be informed to study participation centers every appropriate time. When the risk difference of stent thrombosis will become as large as the definitive difference of causal relationships, the Safety Evaluation Committee will consider the discontinuation of current study and action to minimize the risk will be taken.

11.1.5 Management for serious adverse event

11.1.5.1 Definition of serious adverse event

Adverse event is defined as all disease or its sign that is unfavorable or unintentional, occurred to patients regardless the causality with this study. Among adverse event, serious adverse event is defined as one of following characteristics; 1. Fatal, 2. Threatening patients' life, 3. Requiring

prolonged hospitalization for treatment, 4. Related to permanent or severe impairment or organ malfunction, 5. Related to congenital abnormality of descendants. Expected serious adverse events in the current study are 1. Death, 2. Myocardial infarction, 3. Stroke or cerebral vascular disease, 4. Stent thrombosis, 5. Bleeding complication, 6. Coronary revascularization, 7. Other conditions requiring hospitalization.

11.1.5.2 Management for serious adverse event

Compensation for health damages associated with this study will be done only when it is obligated by legal liability. Compensation for health damages, which is caused by the medical intervention itself and not associated with the clinical study, will be deliberated by each institute. Due to the implementation of the study, adverse events occur, and if the health damages have occurred in the subject, research investigators, physicians are taken promptly to appropriate medical treatment and other best measures. Medical fees of the patients participating in the study are refunded by medical insurances. Although the compensation such as leave compensation and medical attention shall not be performed, when it is obligated by legal liability, it shall be covered by clinical research insurance. Health damages not associated with this study, caused by clinical practice. Health damages, which is caused by the medical intervention itself and not associated with the clinical study, will be deliberated by each institute.

When serious adverse events evidently associated with current study will be occurred, participating center shall report them to study administration office and follow article 11.4 “Discontinuation of the Study and the role of safety evaluation committee” mentioned later, discontinuation of study will be considered.

11.1.6 Compensation for health damages

As for the healthy damage by the side effect of pharmaceutical products to use in this study, pharmaceutical products of incorporated administrative agency Pharmaceuticals and Medical Devices Agency may be relieved primarily by a side effect damage relief system (it is said with "a damage relief system" as follows), The study subject who received health damage can demand payment from the medical supplies medical equipment synthesis system.

About this study, doctors responsible for the study join clinical study insurance as a person insured in all people engaged in this study for this study and compensation of the health damage

to have a causal association that occurred to the study subject.

When a physical disability occurs to the study subject due to a clinical study within one year after during the study period or the end, this insurance pays the insurance reimbursement to the damage of study doctors bearing legal compensation responsibility. In addition, a study responsibility doctor and the study allotment doctor join medical doctor liability insurance for compensation responsibility due to a medical activity.

11.1.7 Handling of Treatment Costs

All the examinations and treatments regarding this study will be basically within the range of daily clinical practice. Therefore, medical fees of the patients participating in the study are refunded by Japanese health insurances system.

11.2 Approval of Protocol

This study shall be conducted after the protocol is assessed and approval by the ethical committee in each participating site or equivalent organization.

11.3 Revision of the Protocol

If amendments of the protocol are required after implementation of the protocol, this should be communicated from the Central Administration Office to each institute interrupting the study. After the amended protocol is examined, the results of examination will be submitted to the ethical committee of each participating institute for its approval.

11.4 Discontinuation of the Study and the role of safety evaluation committee

The study in principle shall be continued until the target number of subjects is registered and the evaluation for all the subjects is completed. However, when any adverse events that are clearly related to this study occur, the independent safety evaluation committee shall discuss whether the study should be continued. Observation period of this study is as long as 60 months, and when primary analysis at the time of 12-month follow-up will be conducted, composite endpoints and also individual endpoints shall be evaluated and the safety evaluation committee will be held at the time and judge whether the continuation of study is appropriate or not.

11.5 Discontinuation of the Study

If this study must be discontinued for a reason that occurred during the study, the principal investigator, after discussing with study managers, should promptly report the discontinuation of the study and its reason to the Ethics Committee of each institute by written form.

11.6 Termination of the Study

When enrollment of all the patients is completed, the principal investigator should notify the completion of enrollment to the investigator of each institute, and each institute terminates the enrollment. Moreover, when the completion of follow-up of all the patients is verified, the principal investigator should notify the completion of follow-up of the patients to the investigator of each institute. The investigator of each institute should submit the study completion report to the chief of the medical research group of affiliation.

11.7 Restoration and disclosure of the study data

The principal investigator and study administration office shall restore the study data until at least 10 years after publication of the main paper of current study. The restoration plan shall observe the provision of article 7 (2) in the rules about fair research activities provided by Kyoto University. Investigators shall disclose the study data if necessary in case of doubt about research papers of current study.

11.8 Definitive Rating of Endpoints

11.8.1 Clinical Endpoints - Clinical Events Committee (CEC)

Clinical Events Committee (CEC) will carry out the definitive rating of all the clinical endpoints, and vascular and hemorrhagic adverse events.

11.8.2 Angiography Core Laboratory

Angiographic endpoints (pathological findings and qualitative analysis) will be rated by

Angiography Core Laboratory.

11.9 Report to the President of Research Center

When investigators earn the truth or information damaging or nearly damaging ethical appropriateness or scientific rationality of current study, safety report should be handed to the president of research center without delay. And when investigators earn the truth or information damaging or nearly damaging adequateness of study performance or reliability of study result, deviation report should be handed to the president of research center without delay. Progress of study should be annually reported and discontinuation or termination of study should be also reported. Published papers or presentation in scientific sessions as a result of study should be handed and reported through electronic application system in ethical committee in the manner of PDF.

11.10 Information Opening to the Public

This study is planned to be registered in study registry of Japanese University Hospital Medical Information Network (UMIN) and U.S. National Institutes of Health (NIH, ClinicalTrial.gov) and the information will be open to the public.

11.11 Study monitoring and inspection

11.11.1 Study monitoring

To secure the adequateness of study performance, monitoring of study progress or observance of study protocol shall be performed. Especially for 3 years after enrollment begins (until all study patients spend one year after enrollment), more strict monitoring shall be required for evaluation of safety. Central monitoring shall be continuously performed with the database on web about the progress of study and the occurrence of stent thrombosis more frequently than monthly, and reported to the persons in charge of participating facilities with E-mail. Additionally, onsite monitoring including the check of consent forms or the direct inspection of clinical record or original sources shall be performed for the selected participating facilities. All registered cases will be checked onsite for the required facilities and 10 registered cases will be checked onsite for the selected 15 facilities as samples.

11.11.2 Inspection

Primary investigator, if necessary, should appoint inspector and perform the inspection to secure the reliability of study outcomes. Inspectors should be those persons who do not work about study progress and monitoring and perform the inspection about observance of study protocol.

11.12 Study device and drug descriptions

The drugs associated with current study (aspirin [buffarin™ etc.], clopidogrel [Plavix™ etc.] and prasugrel [effient™]) and the devices associated with current study (Xience™ series, [Xience V™, Xience Prime™, Xience Xpedition™, Xience Alpine™]) are already approved by PMDA and sold in the Japanese market. The package inserts of these drugs and devices are handed at the application of this study to ethical committee.

11.13 Coping with consultation from Study Participants

To cope with consultations from study participants, following contact point will be set.

Kyoto University, Graduate School of Medicine, Cardiovascular Medicine
54 Shogoin Kawahara-cho, Sakyo-ku, Kyoto 606-8507, Japan
Tel: +81-75-751-4255 Fax：+81-75-751-3299
Responsible person: Takeshi Kimura,
Person in charge: Hirotoshi Watanabe, hwatanab@kuhp.kyoto-u.ac.jp

12. Definition of Endpoints

12.1 Death

As classified by Academic Research Consortium (ARC) [27]

- **Cardiac Death**
  Any death due to proximate cardiac cause (e.g. MI, low-output failure, fatal arrhythmia), unwitnessed death and death of unknown cause, all procedure related deaths including those related to concomitant treatment. All deaths are considered cardiac unless an unequivocal non-cardiac cause can be established. Specifically,

any unexpected death even in subjects with coexisting potentially fatal non-cardiac disease (e.g. cancer, infection) should be classified as cardiac.

- **Vascular Death**
  Death due to non-coronary vascular causes such as cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular cause.

- **Non-cardiovascular Death**
  Any death not covered by the above definitions such as death caused by infection, malignancy, sepsis, pulmonary causes, accident, suicide or trauma.

12.2 Myocardial Infarction: MI

As classified by Academic Research Consortium (ARC): However, the sensitivity is too high for the evaluation with Troponin of the peri-procedural MI, thus CKMB will be used.

- **Preprocedural Adjudication of MI**
  Myocardial Infarction (MI) is defined by the ARC criteria. However, periprocedural MI will be evaluated by CKMB, because the evaluation by troponin is too sensitive.

- **Baseline MI evaluation**
  ECG showing ST elevation, development of new abnormal Q-wave, clinical symptoms specific to MI, troponin or CK-MB values exceeding the standard values
- **Periprocedural MI**
  - Occurrence of any of the following events within 48 hours after PCI procedure will be judged as MI.
    - CK-MB ≥ **3 times Upper Reference Limit (URL)** (CK-MB value exceeding URL before procedure is not considered as a new MI, but as MI at enrollment.)
    - Abnormal ECG (new Q-wave, left bundle branch block)
  - Occurrence of troponin ≥ **5 times URL** or CK-MB ≥ **5 times URL** within 72 hours after CABG procedure accompanied by any of the following criteria will be judged as MI. (CK-MB value exceeding URL before procedure is not considered as a new MI, but as MI at enrollment.)
    - Abnormal ECG (new Q-wave, left bundle branch block)

        - New occlusion of coronary autografts or grafts
        - Reduction in living myocardium confirmed by diagnostic imaging
- **Spontaneous MI**
    - Occurrence of any of the following events at > 48 hours after PCI or > 72 hours after CABG will be judged as MI. MI caused by revascularization procedures, such as TLR and TVR, is defined as periprocedural MI.
        - Abnormal ECG (new Q-wave, left bundle branch block)
        - Troponin or CK-MB value **> URL** (CK-MB value exceeding URL before procedure is not considered as a new MI, but as MI at enrollment.)
- **Sudden Death**
    - When death occurred before blood sampling for biomarker measurements or while biomarkers appeared to be increasing, MI will be judged according to the following criteria:
        - Clinical symptoms suggesting ischemia that are accompanied by one of the following:
            - New ST elevation or left bundle branch block
            - Thrombus determined by angiography or at autopsy
- **Reinfarction**
    - When after onset of MI stable or decreasing values are confirmed in 2 biomarker measurements, but 20% increase 3 to 6 hours is observed after the second measurement.
        - If biomarkers are increasing or have not yet reached the peak, data are insufficient to diagnose reinfarction.

Electrocardiographic Classification:

- **Classification based on Q-wave**
    - **Q-wave MI (QMI)**
        - Development of abnormal Q-waves confirmed in 2 or more contiguous leads with or without elevation in cardiac enzymes.
    - **Non-Q-wave MI (NQMI)**
        - All MIs not classified as Q-wave.
- **Classification based on ST segment。**
    - **ST-elevation myocardial infarction (MI)（STEMI）**

        - New or presumably new elevation of ST segment at J point in 2 or more contiguous leads. Cut-off point is ≥ 0.2 mV in V1, V2 and V3 leads and ≥ 0.1 mV in other leads.
    - **Non-ST elevation myocardial infarction (MI)（NSTEMI）**
        - MI that is not STEMI

Determination by Infarction Size:

- **Major Infarction**
    - CK-MB level is ≥ 10 times the upper limit of normal (ULN) (or CK level is ≥ 10 times ULN in case CK-MB level is not measurable).
        - Even if the above conditions are not met, fatal MI is determined as large infarction.
- **Minor Infarction**
    - All types of MI other than the major infarction

- **Classification of MI Size Based on the ARC Classification**
    - Increase in the cardiac enzyme (CK-MB, Tn, and total CK) levels ≥ 10 times ULN
    - Increase in the cardiac enzyme (CK-MB, Tn, and total CK) levels ≥ 5 times, < 10 times ULN
    - Increase in the cardiac enzyme (CK-MB, Tn, and total CK) levels ≥ 3 times, < 5 times ULN
    - Increase in the cardiac enzyme (CK-MB, Tn, and total CK) levels < 3 times ULN
    - Increase in the troponin level; no increase in the CK-MB and total CK levels
    - Increase in the troponin level; no measurements of the CK-MB and total CK levels

  The cardiac enzymes should be prioritized in the order of CK-MB, Tn, and total CK.
- **Classification of MI Size Based on the CK-MB Level**
    - Increase in the cardiac enzyme (CK-MB) level ≥ 10 times ULN
    - Increase in the cardiac enzyme (CK-MB) level ≥ 5 times, < 10 times ULN
    - Increase in the cardiac enzyme (CK-MB) level ≥ 3 times, < 5 times ULN
    - Increase in the cardiac enzyme (CK-MB) level < 3 times ULN
    - Increase in the troponin level; no increase in the CK-MB level
    - Increase in the troponin level; no measurement of the CK-MB level

- **Classification of MI Size Based on the Troponin Level**
  - Increase in the cardiac enzyme (Tn) level ≥ 10 times ULN
  - Increase in the cardiac enzyme (Tn) level ≥ 5 times, < 10 times ULN
  - Increase in the cardiac enzyme (Tn) level ≥ 3 times, < 5 times ULN
  - Increase in the cardiac enzyme (Tn) level < 3 times ULN
  - Increase in the troponin level; no increase in the CK-MB level
  - Increase in the troponin level; no measurement of the CK-MB level

12.3 Revascularization

Classification:

- **Target Lesion Revascularization (TLR)**
  PCI performed in the target lesion (within 5 mm of the stent edges), or CABG performed for restenosis of the target lesion or for treatment of other complications
- **Target Vessel Revascularization (TVR)**
  PCI performed in the target vessel or revascularization by CABG, including TLR
- **Target Vessel Revascularization-Remote (TVR-Remote)**
  Revascularization of a non-target lesion in the target vessel
- **Non Target Vessel Revascularization (Non-TVR)**
  Any revascularization in a vessel other than the target vessel
- **Non Target Lesion Revascularization (Non-TLR)**
  Any revascularization in a lesion other than the target lesion
  Non-TLR = TVR-Remote + Non-TVR

Clinically indicated revascularization:

- The revascularization that meets the following criteria is considered as clinically indicated revascularization. Presence/absence of clinical findings is judged by the operator of the procedure before the revascularization.
  - Recurrence of angina pectoris, presumably related to the target vessel;
  - Objective signs of ischemia at rest or during exercise test (or equivalent), presumably related to the target vessel;
  - Signs of functional ischemia revealed by any invasive diagnostic test (e.g., Doppler flow velocity reserve [FVR], fractional flow reserve [FFR]);
  - Revascularization for ≥ 70% diameter stenosis even in the absence of the above-mentioned ischemic signs or symptoms.

12.4 Stent Thrombosis

Based on the ARC definition, Stent thrombosis is classified into definite, probable and possible according to the "probability", and into acute, subacute late and very late according to timing of the onset.

- **Definite Stent Thrombosis**
  - Angiographic confirmation of stent thrombosis*:
    - The presence of a thrombus† that originates in the stent segment (including 5 mm of the stent edges) is revealed by angiography, and presence of at least one of the following criteria within a 48-hour time window is observed:
      - Acute onset of ischemic symptoms at rest
      - New ECG changes that suggest acute ischemia
      - Typical rise and fall in cardiac biomarkers (refer to definition of spontaneous MI)
      - Nonocclusive thrombus
        - Intracoronary thrombus is defined as a noncalcified filling defect (spheric, ovoid, or irregular) or lucency surrounded by contrast material (on 3 sides or within a coronary stenosis) seen in multiple projections, or persistence of contrast material within the lumen, or a visible embolization
      - Occlusive thrombus
        - TIMI 0 or TIMI 1 intrastent or proximal to a stent up to the most adjacent downstream side branch or main branch
  - Pathological confirmation of stent thrombosis:
    - Evidence of recent thrombus within the stent determined at autopsy or via examination of tissue retrieved following thrombectomy
- **Probable Stent Thrombosis**
  - When the following cases occurred after intracoronary stenting:
    - Any unexplained death within the first 30 days after procedure‡
    - Irrespective of the time after the index procedure, any MI in the territory of the implanted stent in the absence of any other obvious cause such as angiography or other lesions
- **Possible Stent Thrombosis**
  - Any unexplained death from 30 days after intracoronary stenting

* The incidental angiographic documentation of stent occlusion in the absence of clinical signs is not considered to be a confirmed stent thrombosis (silent occlusion)

† Intracoronary thrombus

- **Acute Stent Thrombosis**
  0-24 hours post stent implantation (Time 0 is defined as the time of removal of the guiding catheter).
- **Subacute Stent Thrombosis**
  > 24 hours-30 days post stent implantation
- **Late Stent Thrombosis ***
  > 30 days-1 year post stent implantation
- **Very Late Stent Thrombosis ***
  > 1 year post stent implantation

* Including "primary" as well as "secondary" stent thrombosis after stented segment revascularization.

12.5 Surgery

- Including endoscopic surgeries and therapies
- Including CABG
- Excluding percutaneous intravascular treatments
- Including aortic aneurysm stent graft procedure
- Excluding tooth extraction

12.6 Bleeding/Hemorrhagic Complications

Bleeding/Hemorrhagic Complications will be evaluated using the TIMI, GUSTO and BARC definitions [28-30]

TIMI bleeding classification[28]:

Bleeding is classified by the Thrombosis in Myocardial Infarction (TIMI). Measurement of hemoglobin and hematocrit values at baseline is required for the severity rating.

- **Major Bleeding**

- When any of the following criteria is met.
  - Intracranial hemorrhage
  - Decrease in hemoglobin to ≥ 5 g/dL decrease in the hemoglobin concentration
  - Absolute drop in hematocrit to ≥ 15% (Baseline – Onset of the event)

- **Minor Bleeding**
  - When blood loss is observed, and any of the following criteria is met:
    - Decrease in hemoglobin to ≥ 3 g/dL
    - Decrease in hematocrit to ≥ 10% (Baseline – Onset of the event)
  - When no blood loss is observed, but any of the following criteria is met:
    - Decrease in hemoglobin to ≥ 4 g/dL
    - Decrease in hematocrit to ≥ 12% (Baseline – Onset of the event)

- **Minimal Bleeding**
  - Any clinically overt sign of hemorrhage that is associated with a fall in hemoglobin to < 3 g/dL.
    (Microscopical urine occult blood and fecal occult blood are not defined as Minimal bleeding.)

GUSTO bleeding classification[29]:

Severe Bleeding

- Life-threatening bleeding
- Intracranial hemorrhage
- Hemorrhage or bleeding that causes drop in blood pressure and requires interventions, such as infusion, blood transfusion, administration of a hypertensor, surgical interception.

Moderate Bleeding

- Bleeding that requires blood transfusion but does not meet criteria for severe bleeding

BARC bleeding classification[30]:

Bleeding is classified based on definitions by the Bleeding Academic Research Consortium (BARC). Measurement of hemoglobin concentration is required for severity rating.

- **Type 0:** No bleeding
- **Type 1:** Bleeding that is not medically significant and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a health care professional.

- **Type 2 :** Any overt sign of hemorrhage that should be treated and does not fit the criteria for Types 3, 4, or 5, but does meet at least one of the following criteria: (1) requiring non-surgical, medical intervention by a health care professional, (2) leading to hospitalization or increased level of care, (3) prompting evaluation.
- **Type 3 :**
    - Type 3a
        - Overt bleeding plus hemoglobin drop of 3-5 g/dL
        - Transfusion with overt bleeding
    - Type 3b
        - Overt bleeding plus hemoglobin drop of ≥ 5 g/dL
        - Cardiac tamponade
        - Bleeding requiring surgical intervention (excluding dental/nasal/skin/haemorrhoid)
        - Bleeding requiring intravenous vasoactive drugs
    - Type 3c
        - Intracranial hemorrhage
        - Intraocular bleeding compromising vision
- **Type4:** CABG-related bleeding
    - Perioperative intracranial hemorrhage within 48 hours
    - Reoperation following closure of sternotomy for the purpose of controlling bleeding
    - Transfusion of ≥ 5 units of whole blood or concentrated red blood cell within 48 hours
    - Chest tube output ≥ 2 L within 24 hours
- **Type5:** Fatal bleeding
    - Type 5a
      Probable Fatal bleeding: no autopsy or imaging confirmation, but clinically suspicious
    - Type 5b
      Definite fatal bleeding: overt bleeding or autopsy or imaging confirmation

12.7 Composite Endpoint

Composite endpoint of secondary endpoints will be defined as follows:

- **TLF: Target Lesion Failure**

Cardiac death, myocardial infarction (MI) of target vessels, Clinically-indicated TLR

- **TVF:Target Vessel Failure**
  Cardiac death, MI or Clinically-indicated TVR。
- **MACE :Major Adverse Cardiac Events**
  Cardiac death, MI or Clinically-indicated TVR

12.8 Stroke or Cerebrovascular Accident

Acute onset of a neurological deficit that persists for at least 24 hours and is the result of a disturbance of the cerebral circulation due to ischemia or hemorrhage. Deficits that last ≤ 24 hours are due to transient ischemic neurological attack and are not classified in this category.

12.9 Classification of Angina

- **Braunwald Classification of Unstable Angina[31]**
  - **Class I：** New onset of severe or accelerated angina: Patients with new onset (< 2 months in duration) exertional angina pectoris that is severe or frequent (> 3 episodes/day) or patients with chronic stable angina who develop accelerated angina (angina distinctly more frequent, severe, longer in duration, or precipitated by distinctly less exertion than previously) but who have not experienced pain at rest during the preceding 2 months.
  - **Class II：** Angina at rest, subacute: Patients with 1 or more episodes of angina at rest during the preceding month but not within the preceding 48 hours
  - **Class III：** Angina at rest, acute: Patients with 1 or more episodes of angina at rest within the preceding 48 hours

- **Canadian Cardiovascular Society (CCS) Classification of Stable Angina[32]**
  - **Class I：** Ordinary physical activity does not cause angina, such as walking or climbing stairs. Angina occurs with strenuous, rapid or prolonged exertion at work or recreation.
  - **Class II：** Slight limitation of ordinary activity. Angina occurs on walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, or in cold, in wind, under emotional stress or only during the few hours after awakening. Angina occurs on walking more than two blocks on the level and climbing more than one flight of ordinary stairs at a normal pace and in normal condition.

- **Class III**：Marked limitation of ordinary physical activity. Angina occurs on walking one to two blocks on the level and climbing one flight of stairs in normal conditions and at a normal pace.
- **Class IV**：Inability to carry on any physical activity without discomfort – angina symptoms may be present at rest.

13. Study Organization

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13.8 Clinical Events Committee (CEC) members

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Yutaka Furukawa	Kobe City Medical Center General Hospital

13.9 Participating institutes

Open in public on the Web pages
https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr_view.cgi?recptno=R000022290
Total 132 centers in Japan

13.10 Study Sponsor

Abbott Vascular Japan, Co., Ltd.
The study sponsor participated in the discussion for preparation of the study protocol, but is not involved in the implementation of the study, data collection, event fixation and statistical analysis. However, approval of the study sponsor should be obtained for presentation in scientific meetings and submission of papers. The study sponsor has a non-exclusive right to use all the information or data obtained in this study.

14. Authorship

Main paper： Takeshi Kimura

For other sub-analyses than those described above, topics proposed from the institutes are selected in order of the number of enrolled patients.

15. References

1) Moses JW, Leon MB, Popma JJ, et al. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. N Engl J Med. 2003;349:1315-23.

2) Stone GW, Ellis SG, Cox DA, et al. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. N Engl J Med. 2004;350:221-31.

3) Kimura T, Morimoto T, Nakagawa Y, et al. Very late stent thrombosis and late target lesion revascularization after sirolimus-eluting stent implantation: five-year outcome of the j-Cypher Registry. Circulation. 2012;125:584-91.

4) Raber L, Magro M, Stefanini GG, et al. Very late coronary stent thrombosis of a newer-generation everolimus-eluting stent compared with early-generation drug-eluting stents: a prospective cohort study. Circulation. 2012;125:1110-112.

5) Schoming A, Neumann FJ, Kastrati A, et al. A randomized comparison of antiplatelet and anticoagulant therapy after the placement of coronary-artery stents. N Engl J Med. 1996;334:1084-89.

6) Leon MB, Baim DS, Popma JJ, et al. A clinical trial comparing three antithrombotic-drug regimens after coronary-artery stenting. Stent Anticoagulation Restenosis Study Investigators. N Engl J Med. 1998;339:1665-71.

7) Kimura T, Morimoto T, Natsuaki M, et al. Comparison of everolimus—eluting and sirolimus-eluting coronary stents: 1-year outcomes from the Randomized Evaluation of Sirolimus-eluting Versus Everolimus-eluting stent Trial (RESET). Circulation 2012;126:1225-36.

8) Kimura T, Morimoto T, Nakagawa Y, et al. Antiplatelet therapy and stent thrombosis after sirolimus-eluting stent implantation. Circulation. 2009;119:987-95.

9) Gwon HC, Hahn JY, Park KW, et al. Six-month versus 12-month dual antiplatelet therapy after implantation of drug-eluting stents: the Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting (EXCELLENT) randomized, multicenter study. Circulation. 2012;125:505-13.

10) Valgimigli M, Campo G, Monti M, et al. Short- Versus Long-term Duration of Dual Antiplatelet Therapy After Coronary Stenting: A Randomized Multicentre Trial. Circulation. 2012;125(16):2015-26.

11) Colombo A, Chieffo A, Frasheri A, et al. Second-generation drug-eluting stent implantation followed by 6- versus 12-month dual antiplatelet therapy: the SECURITY randomized clinical trial. J Am Coll Cardiol. 2014;64(20):2086-97.

12) Gilard M, Barragan P, Noryani AA, et al. 6- versus 24-month dual antiplatelet therapy after implantation of drug-eluting stents in patients nonresistant to aspirin: the randomized, multicenter ITALIC trial. J Am Coll Cardiol. 2015;65(8):777-86

13) Natasuaki M, Morimoto T, Yamamoto E, et al. One-year outcome of a prospective trial stopping dual antiplatelet therapy at 3 months after everolimus-eluting cobalt-chromium stent implantation: ShortT and OPtimal duration of Dual AntiPlatelet Therapy after everolimus-eluting cobalt-chromium stent (STOPDAPT) trial. Cardiovasc Interv and Ther. 2015 Epub ahead of pirnt, DOI: 10.1007/s12928-015-0366-9

14) US National Institutes of Health, ClinicalTrials.gov. GLOBAL LEADERS: A Clinical Study Comparing Two Forms of Anti-platelet Therapy After Stent Implantation. http://clinicaltrials.gov/ct2/show/study/NCT01813435. Updated May 18, 2015. Accessed May 20, 2015.

15) Urban P, Meredith IT, Abizaid A, et al. Polymer-free drug-coated coronary stents in patients at high bleeding risk. N Engl J Med. 2015;373(21):2038-47.

16) Palmerini T, Biondi-Zoccai G, Della Riva D, et al. Stent thrombosis with drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis. Lancet 2012;379(9824):1393-402

17) Tada T, Natsuaki M, Morimoto T, et al. Duration of dual antiplatelet therapy and long-term clinical outcome after coronary drug-eluting stent implantation: landmark analyses from the CREDO-Kyoto PCI/CABG Registry Cohort-2. Circulation. Cardiovascular interventions 2012;5(3):381-91

18) Toyoda K, Yasaka M, Iwade K, et al. Dual antithrombotic therapy increases severe bleeding events in patients with stroke and cardiovascular disease: a prospective, multicenter, observational study. Stroke. 2008;39:1740-5.

19) Valgimigli M, Bueno H, Byrne RA, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. doi: 10.1093/eurheartj/ehx419. [Epub ahead of print]

20) Bittl JA, Baber U, Bradley SM, et al. Duration of Dual Antiplatelet Therapy: A Systematic Review for the 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2016;68(10):1116-39.

21) Yusuf S, Zhao F, Mehta SR, et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med. 2001;345(7):494-502.

22) Mehta SR, Yusuf S, Peters RJ, et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. Lancet. 2001;358(9281):527-33.

23) Yamaji K, Natsuaki M, Morimoto T, et al. Long-Term Outcomes After Coronary Stent Implantation in Patients Presenting With Versus Without Acute Myocardial Infarction (an Observation from Coronary Revascularization Demonstrating Outcome Study-Kyoto Registry Cohort-2). Am J Cardiol. 2015;116(1):15-23.

24) Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. Circulation. 2012;126(16):2020-35.

25) Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;130(25):2354-94.

26) Natsuaki M, Kozuma K, Morimoto T, et al. Final 3-Year Outcome of a Randomized Trial Comparing Second-Generation Drug-Eluting Stents Using Either Biodegradable Polymer or Durable Polymer: NOBORI Biolimus-Eluting Versus XIENCE/PROMUS Everolimus-Eluting Stent Trial. Circ Cardiovasc Interv. 2015;8(10):e002817.

27) Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115:2344-51.

28) Rao AK, Pratt C, Berke A, et al. Thrombolysis in Myocardial Infarction (TIMI) trial: phase I: hemorrhagic manifestations and changes in plasma fibrinogen and the fibrinolytic system in patients treated with recombinant tissue plasminogen activator and streptokinase. J Am Coll Cardiol. 1988;11:1-11.

29) The GUSTO investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. N Engl J Med 1993;329:673-82.

30) Mehran R, Rao SV, Bhatt DL et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation. 2011;123:2736-47.

31) Braunwald E. Unstable angina: a classification. Circulation 1989;80:410-14.

32) Campeau L. Letter: grading of angina pectoris. Circulation. 1976;54:522-3.

STOPDAPT-2 ACS

ShorT and OPtimal duration of Dual AntiPlatelet Therapy-2 study for the patients with ACS

Protocol Version 3.3

＜Date of preparation: Nov 9, 2017 Ver.1.1＞
＜Date of preparation: Dec 27, 2017 Ver.1.2＞
＜Date of preparation: Apr 24, 2018 Ver.1.3＞
＜Date of preparation: January 9, 2018 Ver.2.1＞
＜Date of preparation: August 6, 2019 Ver.3.1＞
＜Date of preparation: April 26, 2020 Ver.3.2＞
＜Date of preparation: April 6, 2020 Ver.3.3＞

Document History

Version	Date of revised	Changes	Notes
Ver. 1.1	Nov 9, 2017	New Document based on STOPDAPT-2 protocol	N/A
Ver. 1.2	Dec 27, 2017	Modification of background and rationale (2), Description about newer P2Y12 inhibitors (4.1, 11.12), modification in ethical issue (11.1, 11.10)	IRB check
Ver 1.3	Apr 24, 2018	Addition of Xience Sierra™ (4.1), renewal of participating centers (13.10).	Reaction to the approval of new device
Ver 2.1	Jan 9, 2019	Application as a "specified clinical research" in Japan, addition of detail of inspection (11.11.2), and renewal of research organization (13.4, 13.8, 13.9) and participating centers (13.10)	Transition to specified clinical research in Japan
Ver 3.1	Aug 6, 2019	Extension of enrollment period (3.3, 5), Addition of observational items at enrollment and discharge (6.2.1), changes in the secondary endpoints (7.2.2), description of hierarchical testing (7.3), change of planned number of patients to be enrolled, recalculation of the statistical power (8), and change in the subgroups to be analyzed (9)	Addition of items to be collected and solution for the event rate lower than anticipated. Modification of analytical items, and extension of enrollment period due to slow recruitment.
Ver 3.2	April 26, 2020	Update of the participating center (13.10)	
Ver 3.3	April 6, 2021	The added subgroup (9.1) and the change of company name; Abbott Vascular Japan to Abbott Medical Japan (13.11, 13.12)	The final check of statistical analysis plan and the company name change.

STOPDAPT-2 ACS Study Overview
ShorT and OPtimal duration of Dual AntiPlatelet Therapy-2 study for patients with ACS

[Study to Evaluate the Safety of Reducing Dual Antiplatelet Therapy (DAPT) Duration to 1 Month for patients with acute coronary syndrome (ACS) after Implantation of Everolimus-eluting Cobalt-chromium Stent]

Study Overview: The cardiovascular/bleeding event rate at 12 months after stenting is evaluated in patients who have undergone percutaneous coronary intervention (PCI) under the setting of acute coronary syndrome (ACS) with the cobalt-chromium everolimus-eluting stent (CoCr-EES, Xience^{TM}) and randomly assigned to the 1-month (≥ 30 days and < 60 days) DAPT group or the 12-month (≥ 11 months and < 13 months) DAPT group (primary analysis).

In the 1-month DAPT group, clopidogrel (Plavix) monotherapy will be continued up to 5 years after DAPT discontinuation and in the 12-month DAPT group, aspirin monotherapy will be continued up to 5 years after DAPT discontinuation. The superiority of the clopidogrel monotherapy over the aspirin monotherapy with regard to cardiovascular/bleeding events and upper gastrointestinal examination events will be verified (secondary analysis).

- Study design: Multicenter, randomized, open-label, controlled study
- Primary endpoint: Composite of cardiovascular death, myocardial infarction (MI), stroke (ischemic and hemorrhagic), stent thrombosis (Definite stent thrombosis yet to develop into MI), and serious bleeding (TIMI Major/Minor) at 12 months
- Evaluation method of the primary endpoint: Non-inferiority of the Clopidogrel monotherapy after 1-month DAPT over the 12-month DAPT will be verified with regard to the primary endpoint at 12 months (primary analysis).

  In the 1-month DAPT group, clopidogrel monotherapy will be continued up to 5 years and in the 12-month DAPT group, aspirin monotherapy will be continued up to 5 years. The superiority of the clopidogrel monotherapy after 1-month DAPT over the aspirin monotherapy after 12-month DAPT with regard to the primary endpoint and upper gastrointestinal examination events will be verified (secondary analysis).
- Target sample size : 4100 patients including ACS patients enrolled in the STOPDAPT-2 study

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■ Clinical Study Managers:

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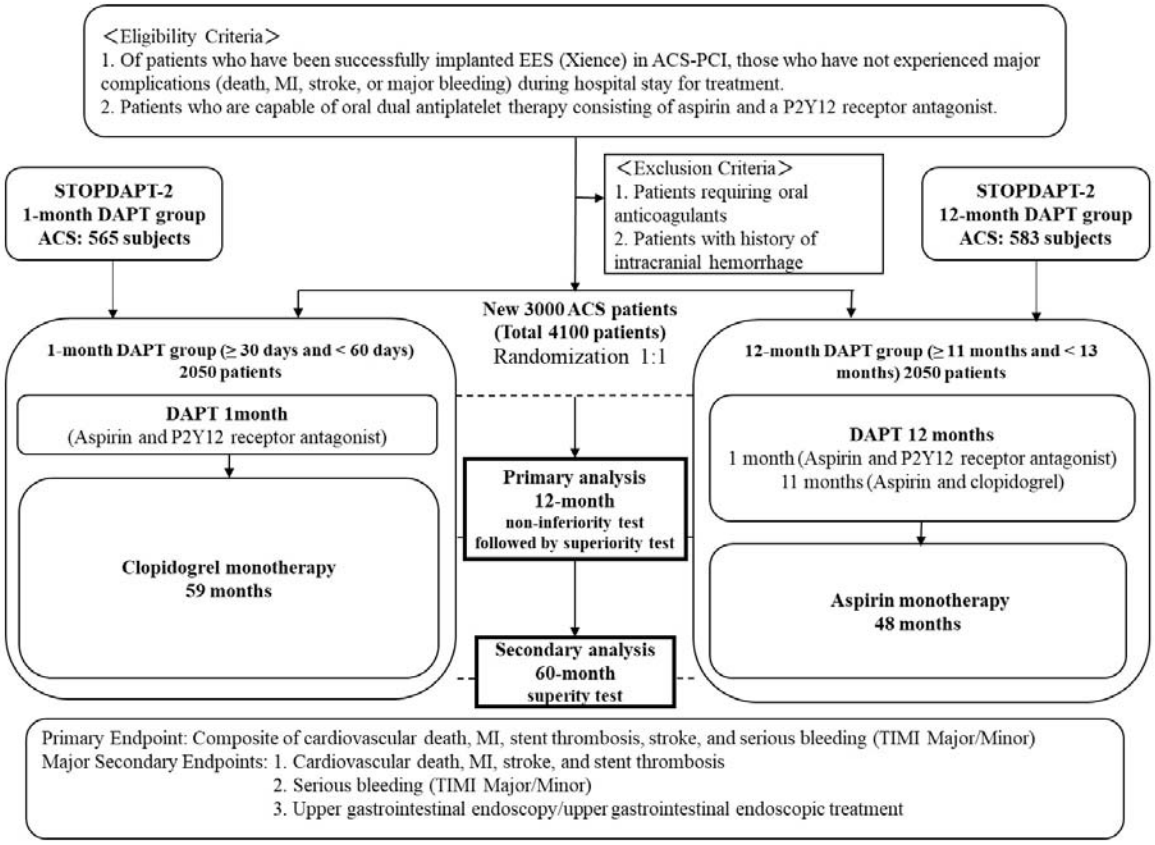
Toshiaki Toyota	Department of Cardiovascular Medicine, Kyoto University
Toshikazu Jinnai	Otsu Redcross Hospital

■ Study period: From study approval date to 5 years after the end of enrollment period and to finish major analysis (8 years from study approval date, planned)

■ Enrollment period: From study approval date to the earlier date of the enrollment of target number patients or 2 years and 3 months from study approval date

Scheme


<Eligibility Criteria>
1. Of patients who have been successfully implanted EES (Xience) in ACS-PCI, those who have not experienced major complications (death, MI, stroke, or major bleeding) during hospital stay for treatment.
2. Patients who are capable of oral dual antiplatelet therapy consisting of aspirin and a P2Y12 receptor antagonist.
<Exclusion Criteria>
1. Patients requiring oral anticoagulants
2. Patients with history of intracranial hemorrhage
STOPDAPT-2
1-month DAPT group
ACS: 565 subjects
STOPDAPT-2
12-month DAPT group
ACS: 583 subjects
New 3000 ACS patients
(Total 4100 patients)
Randomization 1:1
1-month DAPT group (≥ 30 days and < 60 days)
2050 patients
DAPT 1month
(Aspirin and P2Y12 receptor antagonist)
Clopidogrel monotherapy
59 months
12-month DAPT group (≥ 11 months and < 13 months) 2050 patients
DAPT 12 months
1 month (Aspirin and P2Y12 receptor antagonist)
11 months (Aspirin and clopidogrel)
Aspirin monotherapy
48 months
Primary analysis
12-month
non-inferiority test
followed by superiority test
Secondary analysis
60-month
superity test
Primary Endpoint: Composite of cardiovascular death, MI, stent thrombosis, stroke, and serious bleeding (TIMI Major/Minor)
Major Secondary Endpoints: 1. Cardiovascular death, MI, stroke, and stent thrombosis
2. Serious bleeding (TIMI Major/Minor)
3. Upper gastrointestinal endoscopy/upper gastrointestinal endoscopic treatment

Index

List of Abbreviations (Common Examples)

Abbreviation	Description
ACS	Acute Coronary Syndrome
BMS	Bare-Metal Stent
BVS	Bioabsorbable Vascular Scaffold
CABG	Coronary Artery Bypass Graft
CoCr-EES	Cobalt-Chromium Everolimus-Eluting Stent
DAPT	Dual Anti-Platelet Therapy
DEB	Drug Eluting Balloon
DES	Drug Eluting Stent
ECG	Electrocardiogram
eGFR	estimated Glomerular Filtration Rate
LMCA	Left Main Coronary Artery
MI	Myocardial Infarction
PCI	Percutaneous Coronary Intervention
QCA	Quantitative Coronary Angiography
ST	Stent Thrombosis
TLR	Target Lesion Revascularization
TVF	Target Vessel Failure
TVR	Target Vessel Revascularization
UA	Unstable Angina

1. Study Objectives

The purpose of this study is to evaluate the safety of reducing DAPT duration to 1 month after implantation of the everolimus-eluting cobalt-chromium stent (CoCr-EES) in patients who presented as acute coronary syndrome (ACS).

2. Background and Rationale

The sirolimus-eluting stent and the paclitaxel-eluting stent, which are known as the first-generation drug-eluting stents (DESs), have already achieved remarkable results, as represented in reducing restenosis rate to 10% or less at 1 year after coronary stenting, so that DESs are currently used in the majority of PCI procedures.[1,2] On the other hand, even though the frequency is low, the problems of the first-generation DES (i.e., late adverse events, such as very late stent thrombosis and late restenosis at 1 year or later, which rarely occur in conventional bare-metal stents [BMSs]) have been pointed out.[3,4]

Since P2Y12 platelet receptor antagonists, when used in combination with aspirin for 1 month, have been indicated to significantly suppress the occurrence of stent thrombosis after BMS implantation, DAPT, in which aspirin and a P2Y12 platelet receptor antagonist are used in combination for 1 month after BMS implantation, has become a standard regimen.[5,6] At the same time, for fear of very late stent thrombosis, DAPT is frequently performed for 1 year or longer after DES implantation in clinical practice. In RESET (Randomized Evaluation of Sirolimus-eluting versus Everolimus-eluting stent Trial) conducted in clinical practice in Japan, 90% of the subjects had been on DAPT for 1 year or longer.[7] Moreover, in the package insert of the Everolimus-eluting stent (EES), currently the most extensively used DES in Japan, 1-year DAPT is recommended. However, serious hemorrhagic complications, such as cerebral hemorrhage, associated with a prolonged DAPT duration can bring disadvantages to patients, it is extremely important to clarify an optimal DAPT duration after DES procedure. Based on the results of large-scale observational studies and small-scale randomized controlled studies, DAPT for 6 months or longer[8-12] had no inhibitory effects on the onset of serious cardiovascular events. Furthermore, we have recently assessed the safety of a DAPT regimen for 3 months after CoCr-EES implantation in STOPDAPT (ShorT and OPtimal duration of Dual AntiPlatelet Therapy study after everolimus-eluting cobalt-chromium stent) study, using the RESET study, in which DAPT had been performed in 90% of subjects for 1 year or longer, as a historical control.[13] More recently, attempt to further reduce DAPT duration after DES procedure begins.

In Global LEADERS (A Clinical Study Comparing Two Forms of Anti-platelet Therapy After Stent Implantation: NCT01813435) study, the safety of a DAPT regimen with ticagrelor, a new P2Y12 platelet receptor antagonist for 1 month after DES procedure is under evaluation.[14] In addition, in LEADERS FREE (A Randomized Clinical Evaluation of the BioFreedom™ Stent: NCT01623180) study, the efficacy and safety of polymer-free DES (BioFreedom™) compared with BMS in 1-month DAPT regimen are proven in the subject group with a high bleeding risk.[15] These clinical studies are currently being conducted while monitoring safety, and have already completed patient recruitment, presumably generating no major safety concerns. Currently, 1-month DAPT regimen after BMS implantation is commonly used in clinical practice, producing no major problems. Based on a meta-analysis of recent clinical studies, it has also been reported that the use of CoCr-EES reduces the risk of early stent thrombosis by half compared to the use of BMS.[16] At least from a logical standpoint, there is no necessity to extend antiplatelet therapy after CoCr-EES implantation longer than after BMS implantation, and it is considered possible to use the same 1-month DAPT duration as after BMS implantation. On the other hand, for bleeding complication, it is clear that a prolonged DAPT duration increases bleeding complications compared to aspirin monotherapy.[10,16-18] We therefore started STOPDAPT-2 (NCT02619760), a multicenter, randomized, open-label, controlled study, in which DAPT is discontinued at 1 month after stenting in subjects who have undergone CoCr-EES procedure, which is considered to be associated with a lower risk of stent thrombosis than BMS, to compare incidences of cardiovascular events and bleeding events at 12 months after stenting between the 1-month DAPT group and the 12-month DAPT group.

In this study, for antiplatelet therapy after the discontinuation of DAPT at 1 month, we will use clopidogrel, a P2Y12 receptor antagonist considered to be a key drug for stent thrombosis prophylaxis,[6] instead of the conventional aspirin monotherapy. Although aspirin is an inexpensive drug with a proven efficacy for preventing cardiovascular events in patients with coronary artery diseases, its side effects, such as gastrointestinal mucosal injury and gastrointestinal bleeding, are pointed out as a problem.[19] Based on the CAPRIE study results, it has been reported that clopidogrel monotherapy significantly suppressed cardiovascular events in patients with cardiovascular diseases compared to aspirin monotherapy.[20] It is known that a higher percentage of Japanese patients have resistance to the platelet aggregation inhibitory effect of clopidogrel attributable to CYP2C19 polymorphism. Even under such circumstances in Japan, clopidogrel monotherapy has been standard antiplatelet therapy in the cerebrovascular region, and recently there have been an increasing number of cases in which clopidogrel monotherapy is chosen after DAPT discontinuation in patients with coronary stent. To perform clopidogrel monotherapy after DAPT discontinuation in Japanese patients, it is necessary to

verify its effectiveness and safety, data of which, however, have been still insufficient. In the STOPDAPT-2, the superiority of clopidogrel monotherapy after 1-month DAPT over aspirin monotherapy after 12-month DAPT will be verified by comparing results of clopidogrel monotherapy continued up to 5 years after DAPT discontinuation in the 1-month DAPT group and aspirin monotherapy continued up to 5 years after DAPT discontinuation in the 12-month DAPT group.

In the current AHA/ACC or ESC guidelines, 12-month DAPT is standard recommendation for patients with ACS, though 6-month DAPT is recommended for stable coronary artery disease[21,22]. However, the rational of the longer DAPT duration for ACS patients was based only on the CURE study, which was performed more than 15 years ago[23,24]. We previously reported the incidence of ischemic events beyond 3 months after index PCI was not different between the acute myocardial infarction (AMI) patients and non-AMI patients in registry data[25]. Therefore, in contemporary clinical practice using 2nd generation DES, there is no solid rationale to recommend extended DAPT duration in patients with ACS. In the ongoing STOPDAPT-2 study, the proportion of ACS cases is expected to be 30 to 40% of the entire study population, and the power is insufficient to evaluate safety of 1-month DAPT in ACS patients. Therefore, we designed the STOPDAPT-2 ACS study, in which we would enroll only ACS patients with the same protocol as the STOPDAPT-2 and analyze the safety of 1-month DAPT in ACS patients. We would combine the two studies to include the ACS patients enrolled in the STOPDAPT-2.

3. Study Method

In this study, the cardiovascular/bleeding event (primary endpoint) rate at 12 months after stenting will be evaluated in patients who have undergone PCI with CoCr-EES (DES) for ACS and randomly assigned to the 1-month DAPT group or the 12-month DAPT group (primary analysis).

In the 1-month DAPT group, clopidogrel monotherapy will be continued up to 5 years after DAPT discontinuation and in the 12-month DAPT group, aspirin monotherapy will be continued up to 5 years after DAPT discontinuation. The superiority of the clopidogrel monotherapy after 1-month DAPT over the aspirin monotherapy after 12-month DAPT with regard to the primary endpoint and upper gastrointestinal examination events will be verified (secondary analysis).

In this study, the genetic substudy to evaluate CYP2C19 polymorphism will not be performed,

which was performed in STOPDAPT-2.

3.1 Inclusion Criteria

- Patients who have undergone PCI with the everolimus-eluting cobalt-chromium stent (CoCr-EES, Xience^{TM}) in the setting of ACS (STEMI, NSTEMI, or UA) and have not experienced major complications (death, MI, stroke, or major bleeding) during hospital stay for treatment
- Patients who are capable of oral dual antiplatelet therapy consisting of aspirin and a P2Y12 receptor antagonist

3.2 Exclusion Criteria

- Patients requiring oral anticoagulants
- Patients with medical history of intracranial hemorrhage
- Patients who have experienced serious complications (MI, stroke, and major bleeding) during hospital stay post-PCI
- Patients with DES other than Xience implanted in PCI performed at the time of enrollment.
- Patients with coronary bioabsorbable vascular scaffolds (BVS) implanted prior to or at the time of enrollment (including implantation cases in clinical trial)
- Patients confirmed to have no tolerability to clopidogrel before enrollment
- Patients requiring continuous administration of antiplatelet drugs (PDE3 inhibitors, prostaglandin preparations, etc.) other than aspirin and P2Y12 receptor antagonists (prasugrel, clopidogrel, and ticlopidine) at the time of enrollment

3.3 Patients Enrollment and Treatment Assignment

Enrollment and registration will be performed in database on web system during hospitalization after PCI in patients with ACS. The access to the database will be permitted to only the persons in charge having ID and password in each study participating facilities and they are permitted to access only the data of their facilities and not permitted to access to the data of other participating facilities.

All patients undergoing PCI in the study participating centers during registration period will be registered into PCI log page with information about the presence or absence of CoCr-EES

implantation success and the presence or absence of other DES implantation than CoCr-EES after completion of planned staged-PCI. Among these patients, the patients who have successful implantation of one or more CoCr-EES and no implantation of DES other than CoCr-EES will be candidates participating current study and give the consent of participation. When patients give the consent of study participation, they will be randomly assigned into 1-month DAPT group or 12-month DAPT group after the confirmation of study exclusion criteria written in article 3.2. Adjustment factors of randomization is set to be only participating facilities.

Even when patient can be candidate but reject the participation of this study, patients background will be registered into screening log to grasp the characteristics of patients who don't participate current study. Details will be written following article 4.1. Registration period is set to be 2 years 3 months and will be early finished if 3000 patients will be enrolled in this study.

4. Study Rule

4.1 Procedural Notes

In this study, ACS patients who have undergone PCI using CoCr-EES should be enrolled in a manner optimally close to consecutive cases.

- Patients with diagnosis of ACS at hospital admission will be enrolled during hospital stay after confirming stable condition without serious complication after PCI using CoCr-EES. Enrollment period is 2 years.
- If staged PCI is planned, enrollment should be performed after the completion of all PCI procedures. The final PCI procedure should be considered as the index procedure. In case of performing more than one procedure during the same admission period, diagnosis, lesion findings, or number of diseased vessel will be based on the condition at admission or 1st angiography. Therefore, in current STOPDAPT-2 ACS study, in the case of multivessel ACS and dividing PCI procedure into two or more, index procedure shall be the last procedure before discharge and subjects shall be treated with all lesions judged necessary for intervention during the hospitalization. (Patients with admission for ACS and planned to receive another PCI after hospital discharge should not be enrolled.)
- ACS is defined as one of following diagnosis treated within one week after onset; ST-segment elevation MI (STEMI), Non-ST-segment elevation MI (NSTEMI), or Unstable

angina based on the Third universal definition of MI or 2014 AHA/ACC NSTE-ACS guideline.[26,27] Diagnosis of MI requires elevation of cardiac biomarkers.

- In the index PCI procedure, only Xience family (Xience V™, Xience Prime™, Xience Xpedition™, Xience Alpine™, and Xience Sierra™) can be used, and BMS are allowed to be used in combination.
- Type and dose of aspirin should follow the clinical practice of each site.
- Type and dose of P2Y12 receptor antagonists within 1 month after procedure should be either clopidogrel 75 mg once daily, prasugrel 3.75 mg once daily, or ticagrelor 90mg twice daily, depending on the clinical practice of each site.
- Type and dose of P2Y12 receptor antagonists at 1 month or later after procedure should be clopidogrel 75 mg once daily.
- It is allowed to reduce dose of P2Y12 receptor antagonist during the time course based on the clinical necessity, such as bleeding events.
- Patients confirmed to have no tolerability to clopidogrel before enrollment should not be enrolled. When patients have been found to have no tolerability to clopidogrel after enrollment, it is allowed to change the drug to another P2Y12 receptor antagonist (prasugrel 3.75 mg once daily, ticagrelor 90mg twice daily, or ticlopidine 100 mg twice daily).
- Patients requiring continuous administration of antiplatelet drugs other than aspirin and thienopyridine (PDE3 inhibitors, prostaglandin preparations, etc.) or oral anticoagulants at the time of enrollment should not be enrolled. It is allowed to start using these drugs during the follow-up period based on the clinical necessity.
- Although subjects are allowed to visit the doctor who has referred them to the site, the antiplatelet drug should be prescribed at the study site as possible. For subjects who have been referred from remote areas (i.e., other prefectures) and are unable to visit the site frequently, the site personnel may confirm medication adherence by phone.
- Subjects will visit the site at 1 month (≥ 30 days and < 60 days) post-PCI, aspirin will be discontinued and clopidogrel will be started in the 1-month DAPT group while aspirin/clopidogrel dual therapy will be started in the 12-month DAPT group.
- Subjects will visit the site at 12 months (≥ 11 months and < 13 months) post-PCI, clopidogrel will be continuously prescribed in the 1-month DAPT group while clopidogrel will be discontinued and only aspirin will be continuously prescribed in the 12-month DAPT group.
- To ensure that antiplatelet drug administration complies with the protocol, at the 1-month and 12-month visits post-PCI, the participating site's clinical research coordinator (CRC) or equivalent personnel will inform the outpatient doctor of the necessity of changing prescription and also confirm the prescription on the visit day comply with the protocol.

- When subjects visit the study site during the follow-up period, the investigator should interview subjects regarding the status of the following items since their previous visit and record it in their medical records: 1) whether they have been treated or hospitalized in other medical institutions, 2) whether they have undergone gastrointestinal endoscopy or experienced bleeding, 3) whether antiplatelet drugs have suspended, resumed, changed, or added, and 4) whether any other drugs have been changed.
- The initial enrollment should be performed by the participating site's investigator, while data entry should be performed by each site's CRC or outside CRC.
- After the start of enrollment at each site, all subjects who have successfully undergone CoCr-EES procedure should be registered in the screening log and the following data of each subject must be entered and reported: patient name, age, sex, height, weight, diagnosis, the presence or absence of hypertension, the presence or absence of diabetes mellitus (insulin, oral drugs, or diet), history of myocardial infarction, history of stroke (cerebral infarction or cerebral hemorrhage), creatinine level, presence or absence of dialysis, presence or absence of atrial fibrillation, oral anticoagulant therapy, history of PCI, history of the first-generation DES implantation, history of BVS implantation, history of heart failure, presence or absence of peripheral vessel/aortic diseases, smoking status, presence or absence of multivessel treatment, number of target lesions, location of target lesion, number of implanted stent, size of implanted stent, major complication (MI, stroke, major bleeding) after index PCI procedure, presence or absence of tolerability to clopidogrel, administration of antiplatelet drugs other than aspirin and P2Y12 receptor antagonists, presence or absence of planned surgical operation, and planned DAPT duration.
- For the patient who is not enrolled in this study for exclusion criteria or disagreement etc. but whose information is collected in screening log, the fact of data collection mentioned above should be informed by word of mouth or written letter. Study content, URL address of current study showing the list of participating institutes and responsible person in each center, and contact information are open by notification of bulletin board in hospital ward and so on. Chance of rejecting to register screening log is secured.
- Follow-up coronary angiography should be performed according to the clinical practice of each site. When coronary arteriography is planned, presence or absence of recurrent angina symptoms and ischemic evaluation results should be described in the medical record prior to the coronary arteriography.
- When MI is suspected, quantitative troponin T measurement (qualitative measurement is acceptable in case quantitative measurement is not possible) and CK and CK-MB measurement should be performed before and after revascularization. After revascularization,

measurement of the 3 parameters above should be continuously measured to determine their peak values. Measurement interval should be a maximum of every 6 hours.

- When MI is suspected, the following information should be described in the medical record wherever possible: presence or absence of ischemic symptoms, presence or absence of ECG changes (ST-T change, new left bundle branch block, and abnormal Q wave), presence or absence of decrease or abnormality in wall motion newly noted in image evaluation, and presence or absence of coronary artery thrombosis observed in coronary arteriography or autopsy.
- The presence or absence of recurrent angina symptoms and ischemic evaluation results should be described in the medical record at the time of target lesion revascularization (TLR).
- If PCI or coronary artery bypass grafting (CABG) is performed during the follow-up period, quantitative troponin T measurement (qualitative measurement is acceptable in case quantitative measurement is not possible) and CK and CK-MB measurement should be performed before the procedure, and within 48 hours post-PCI or within 72 hours post-CABG.
- If acute coronary syndrome, PCI, or CABG event has been observed, ECG before and after the treatment or procedure should be recorded and collected in hardcopy (photocopy is acceptable).

4.2 Required Tests

The following tests are required, and the adoption of other tests is subject to each site's standards.

At Enrollment：

- Blood tests
  - In this study, hemoglobin and hematocrit concentrations should be measured, because TIMI definition is used to rate hemorrhagic adverse events.
  - Hemoglobin and hematocrit concentrations should be measured also when a hemorrhagic adverse event is suspected during the follow-up period.
  - Test items：WBC, RBC, hemoglobin, hematocrit, Plt, creatinine, blood glucose、HbA1c, total cholesterol, HDL cholesterol, LDL cholesterol, triglyceride
  - In case the above blood tests performed within 1 month before the study enrollment, the blood tests are not required at enrollment.

4.3 Planned Follow-up Period

In this study, information described in "6. Items to be investigated" will be collected at enrollment, at 1 month, 12 months, 24 months, 36 months, 48 months, and 60months, and recorded on the electronic Case Report Form (eCRF).

5. Study Period

This study is planned to be carried out for 8 years from the beginning of enrollment to the scheduled completion of 60 months follow-up after PCI in the last enrolled patient and major study analysis. Though the enrollment period of this study is defined as within 2 years and 3 months, the enrollment will be terminated when a total of 3000 ACS patients are enrolled in this study.

6. Items to be Investigated

6.1 Planned Follow-up Periods

The investigations in this study are performed at the following time points:

1) At enrollment
2) Follow-up at 1 month after procedure (At the outpatient visit in principle after at 30 days before at 60 days)
3) Follow-up at 12 months after procedure (At the outpatient visit in principle after at 335 days at before 395 days)
4) Follow-up at 24 months after procedure (At the outpatient visit in principle after at 700 days at before 760 days)
5) Follow-up at 36 months after procedure (At the outpatient visit in principle after at 1065 days at before 1125 days)
6) Follow-up at 48 months after procedure (At the outpatient visit in principle after at 1430 days at before 1490 days)
7) Follow-up at 60 months after procedure (At the outpatient visit in principle after at 1795 days at before 1855 days)

6.2 Observation Items

Observation items will be investigated at enrollment and at follow-up visit by various examinations and interview, etc. All results but the angiographic analysis will be recorded in the corresponding columns of the eCRF.

6.2.1 Observation Items at Enrollment/at Discharge

1. Enrollment data

Name of institute, date of enrollment, patient enrollment number, and name of the investigator.

2. Basic data

Age, sex, height, weight, date of hospitalization, blood pressure and pulse rate at the hospital arrival, cardiopulmonary arrest on arrival.

3. Diagnosis of myocardial infarction (MI) or angina pectoris (select from below)

ST-elevation acute myocardial infarction (MI), Non ST-elevation acute MI, stable angina pectoris, unstable angina pectoris, asymptomatic myocardial ischemia, old myocardial ischemia, and coronary stenosis.

4. Additional information about ACS

Presence/Absence of ECG change, imaging evidence of new loss of viable myocardium or new regional wall motion abnormality, site of myocardial infarction, location of culprit lesion, time between onset and hospital arrival, time between hospital arrival and PCI (wire cross), Killip classification, use of percutaneous circulatory support device (ECMO, Impella, IABP)

5. History of cardiac diseases

History of PCI, implantation history of bare metal stent, implantation history of 1st generation DES, implantation history of other DES, implantation history of BVS, history of CABG, history of myocardial infarction (MI), history of stent thrombosis, history of heart failure, history of stroke[1)], history of atrial fibrillation, history of COPD, history of liver cirrhosis, history of malignant tumor[2)], history of hemorrhagic disease[3)], chronic bleeding diathesis[4)], chronic use of oral NSAIDs and steroids, and recent major surgery or major trauma within 30 days prior to PCI.

[1)] Previous spontaneous intracranial hemorrhage (ICH), previous traumatic ICH within the past 12 months, presence of a brain arteriovenous malformation, moderate or severe ischemic stroke within the past 6 months, or other ischemic strokes.

[2] Additionally, we include active malignancy, which is defined as diagnosed within 12 months prior to PCI or ongoing malignant disease (excluding non-melanoma skin cancer).
[3] Requiring hospitalization or blood transfusion.
[4] e.g. von Willebrand disease, hemophilia, and so on, excluding thrombocytopenia.

6. Complications

Complication of heart failure at hospitalization, heart failure (current or past history), carotid artery stenosis, arteriosclerosis obliterans, peripheral artery disease excluding carotid arteries or arteriosclerosis obliterans, aortic aneurism/dissection, diseases of the aorta/ peripheral vessels (all), diseases of the aorta/peripheral vessels (postoperative/planned to be treated), and dialysis.

7. Risk factors

Hypertension, Lipid abnormalities, smoking, diabetes mellitus, and family history of coronary diseases.

8. Concomitant medication

The presence or absence of anticoagulation therapy, and the presence or absence of other antiplatelet therapy than aspirin and thienopyridines.

9. Coronary angiographic findings (initial angiography in the index hospitalization)

Procedure date of coronary angiography, stenotic lesions, number of branches affected, presence/absence of following lesions; unprotected left main lesion and chronic total occlusive (CTO) lesion, left ventricular ejection fraction, measurement method for left ventricular ejection fraction, mitral insufficiency, and evaluation method for mitral insufficiency.

10. Evaluation of Myocardial Ischemia

Myocardial Scintigraphy (positive or negative), Invasive FFR (positive or negative), and CT FFR (positive or negative).

11. PCI Baseline Observation (including all planned and staged procedure)

Per patient analysis: PCI procedure date, emergency procedure, target lesion segment, presence/absence of following treatments: treatment of unprotected left main coronary artery stenosis, treatment of CTO, stenting of the last remaining patent coronary artery, treatment of ST-elevation acute MI culprit lesion, treatment of bifurcation lesion, treatment of 2 branches or more, treatment of 3 branches or more, treatment of in-stent restenosis lesion, and treatment of RCA ostial lesion, implanted stent diameter, and implanted stent length.

Per lesion analysis: target lesion, lesion classification (new lesion, residual lesion, lesion of in-stent-restenosis, lesion of restenosis except of stents), in-stent-restenosis pattern (BMS, Cypher, Taxus, Endeavor, Xience, Promus, Nobori, Resolute, other DES, and BVS [multiple choice allowed]), STEMI culprit lesion, ostial lesion, LMT distal bifurcation, unprotected LMT lesion, CTO lesion, severe calcified lesion, presence/absence of thrombus, lesion and proximal tortuousness, lesion and proximal bending (over an angle of 90 degrees), thrombus aspiration, stenting attempt, direct stenting, intervention before stenting (POBA, DEB, Cutting Balloon, Directional Coronary Atherectomy, Rotablator, aspiration, other, unknown), stenting (name of stent, diameter, length, expanding pressure, implanted site), post dilatation (balloon diameter, pressure), IVUS use, OCT use, bifurcation lesion, branch lesion, bifurcation type, bifurcation strategy, stent classification (only XIENCE, XIENCE and BMS)

12. Clinical laboratory tests

WBC, RBC, hemoglobin, hematocrit, platelet counts, creatinine, blood glucose, HbA1c, total cholesterol, HDL cholesterol, and triglyceride.

Before Index PCI: CK, CKMB, Troponin T or I: presence/absence of measurement, measured value (positive/negative or quantitative value), upper limit of normal if the tested in site other than participating institution.

After Index PCI: CK, CKMB, Troponin T or I: presence/absence of measurement, measured peak value (positive/negative or quantitative value), upper limited of normal of the institute.

13. Electrocardiogram (ECG) after procedure

14. Planned surgical operation

Presence or absence of planned surgical operation, planned timing of the operation, detail of the surgical operation

15. Observation Items at Discharge

Discharge date and medication at discharge

Notes: Definition of observation items

1. Diabetes mellitus

Diabetes mellitus is defined as meeting either of 2 hour OGTT glucose level of ≥200 mg/dL, casual blood glucose level of ≥200 mg/dL, fasting blood glucose level of ≥126 mg/dL, or HbA1c ≥6.1% (JDS) or ≥6.5% (NGSP).

When the above tests have not been performed, patients who have been clinically diagnosed as

diabetic or are treated with antidiabetic agents are defined as having diabetes.

2. Dyslipidemia

Patients with total cholesterol ≥ 240 mg/dL or HDL cholesterol < 40 mg/dL, or patients who are treated with statins.

3. Evaluation of renal functions

The estimated glomerular filtration rate (eGFR) is calculated by using the equation fitted for Japanese people by the Japanese Society of Nephrology.

eGFR=194*Cr $^{-1.094}$*Age $^{-0.287}$ (*0.739 for females)

Terminal renal failure: e-GFR < 30 mL/min/1.73 mm^2

Chronic kidney disease: e-GFR < 60 mL/min/1.73 mm^2

4. High-risk features of stent-driven reccurent ischaemic events [21]

Followings are included as the high-risk features of stent-driven reccurent ischamemic events.

- Prior stent thrombosis on adequate antiplatelet therapy
- Stenting of the last remaining patent coronary artery
- Diffuse multivessel disease especially in diabetic patients
- Chronic kidney disease (eGFR<60ml/min)
- At least 3 stent implanted
- At least 3 lesions treated
- Bifurcation with two stents implanted
- Total stent length > 60mm
- Treatment of a CTO

5. ARC definition of high-bleeding risk (HBR) in patients undergoing percutaneous coronary intervention [28]

Following are the criteria of HBR defined in ARC definition. Patients are considered to be HBR if one major or two minor criteria are met

<Major criteria>

- Long term oral anticoagulation
- Severe or end-stage CKD (eGFR <30 ml/min)
- Hemoglobin <11 g/dL for both men and women
- Spontaneous bleeding requiring hospitalization and/or transfusion in the past 6 months or at any time if recurrent bleeding
- Moderate or severe thrombocytopenia (platelet count <100 x 10^9 per liter)

- Chronic bleeding diathesis
- Liver cirrhosis
- Active malignancy (excluding non-melanoma skin cancer) within the past 12 months
- Previous spontaneous ICH (at any time), previous traumatic ICH within the past 12 months, presence of a brain AV malformation, or moderate/severe ischemic stroke within the past 6 months
- Non-deferrable major surgery on DAPT
- Recent major surgery or major trauma within 30 days prior to PCI

<Minor criteria>

- Age ≥75 years
- Moderate CKD (eGFR 30-59 ml/min)
- Hemoglobin 11-12.9 g/dL for men and 11-11.9 g/dL for women
- Spontaneous bleeding requiring hospitalization and/or transfusion within the past 12 months not meeting the major criterion
- Chronic use of oral NSAIDs or steroids
- Any ischemic stroke at any time not meeting the major criterion

6. Other items

Other items will be considered based on the clinical diagnosis described on the clinical record.

6.2.2 Angiographic Study

Not performed in this study

6.2.3 Follow-up at 1 month

At 1 month after enrollment, the following data will be recorded.

1. Death

Investigation method to determine the patient's death/survival, date of the last confirmation of death/survival, presence/absence of death, date of death, classification of cause of death, and cause of death.

2. Other events than death

Investigation method for other events than death, date of the last confirmation of other events

than death, and presence/absence of other events than death.

3. Myocardial infarction (MI)

Presence/absence of MI, date of onset, status at onset, symptoms of ischemia, electrocardiographic change, ST-elevation MI, Q-wave MI, new hypokinesis by imaging evaluation, relationship with stent thrombosis, ARC classification, culprit lesion, angiography, treatment (PCI, CABG or medical therapy), and coronary thrombus.

Presence/absence of evaluation of the maximum values of cardiac enzymes, date of measurement of cardiac enzymes, CK, CK-MB, troponin T or I.

Before revascularization: CK, CK-MB, troponin T or I, measured value, and upper limits of normal at institute.

At peak value after revascularization: CK, CK-MB, troponin T or I, measured peak value, upper limits of normal at institute, measured peak value, and lethality.

4. ACS

Presence/absence of emergency hospitalization due to ACS, date of onset, ACS classification, relationship with stent thrombosis, identification of culprit lesion by angiography, lethality, and presence/absence of revascularization.

5. Definite stent thrombosis according to ARC definition

Presence/absence of stent thrombosis, date of onset, situation of onset, presence/absence of evaluation of the maximum values of cardiac enzymes, date of testing, CK, CK-MB, troponin T or I, presence/absence of Interim TVR trial, relationship with the surgical procedure, presence/absence of hemorrhagic complications before the onset of stent thrombosis, antiplatelet therapy (aspirin and thienopyridine drugs) at the onset of stent thrombosis, and lethality

6. Probable stent thrombosis according to ARC definition

Presence/absence of stent thrombosis, date of onset, and classification (unexplained death within 30days / MI in the target vessel area).

7. Possible stent thrombosis according to ARC definition

Presence/absence of stent thrombosis and date of onset.

8. Stroke

Presence/absence of stroke, date of onset, classification of stroke, and lethality.

9. Heart failure

Presence/absence of hospitalization due to heart failure, date of hospitalization, and presence/absence of coronary revascularization during hospitalization.

10. Ventricular fibrillation, persistent ventricular tachycardia

Presence/absence of hospitalization due to ventricular fibrillation or persistent ventricular tachycardia, date of hospitalization, and presence/absence of coronary revascularization during hospitalization.

11. Bleeding complication

Presence/absence of bleeding complication, date of onset, bleeding site, Nadir Hb, Nadir Ht, bleeding that requires blood transfusion, the amount of blood transfusion (units, MAP), drop in blood pressure, surgical hemostasis, TIMI classification, GUSTO classification, and BARC classification.

12. Gastrointestinal complication

Upper gastrointestinal endoscopy and upper gastrointestinal endoscopic treatment.

13. Surgery

Presence/absence of surgery, procedure date, general anesthesia, the name of surgery, and surgery area.

14. CABG

Presence/absence of CABG, procedure date, target vessel,

Before revascularization; CK, CK-MB, Troponin T or I: measured value, upper limits of normal at institute.

After revascularization; CK, CK-MB, Troponin T or I: measured value, upper limits of normal at institute.

15. Revascularization excluding TLR

Presence/absence of revascularization excluding TLR, procedure date, target vessel, revascularization method, non-TL TVR, and clinically driven revascularization.

Before revascularization; CK, CK-MB, Troponin T or I: measured value, upper limits of normal at institute.

After revascularization; CK, CK-MB, Troponin T or I: measured value, upper limits of normal at institute.

16. TLR

Presence/absence of TLR, procedure date, revascularization method, PCI devices, clinically driven revascularization, follow-up angiography, date of angiography, reason of angiography, the method of follow-up angiography, restenosis of main vessel, re-occlusion of main vessel, restenosis of side branch, and re-occlusion of side branch.

Before revascularization; CK, CK-MB, Troponin T or I: measured value, upper limits of normal at institute.

After revascularization; CK, CK-MB, Troponin T or I: measured value, upper limits of normal at institute.

17. Discontinuation of Medical Therapy

Final confirmation date of thienopyridine administration status, final thienopyridine administration status, discontinuation of thienopyridine, the discontinuation date, the reason of discontinuation, alternative agent, restart administration of thienopyridine, restart date, final confirmation date of aspirin administration status, final aspirin administration status, discontinuation of aspirin, the discontinuation date, the reason of discontinuation, alternative agent, restart administration of aspirin, restart date, and DAPT discontinuation and switching to thienopyridine monotherapy in 1 month DAPT arm (only after 1 month).

6.2.4 12 months follow-up

At 12 months after enrollment, in addition to the observation items of “6.2.3 1 month follow-up”,

17. Discontinuation of Medical Therapy

DAPT discontinuation in 12 months DAPT arm and switching to aspirin monotherapy (only after 12 months) should be recorded.

6.2.5 24 months follow-up

At 24 months after enrollment, same observation items with “6.2.4 12months follow-up” should be recorded.

6.2.6 36 months follow-up

At 36 months after enrollment, same observation items with “6.2.4 12months follow-up” should be recorded.

6.2.7 48 months follow-up

At 48 months after enrollment, same observation items with “6.2.4 12months follow-up” should be recorded.

6.2.8 60 months follow-up

At 60 months after enrollment, same observation items with “6.2.4 12months follow-up” should be recorded.

6.2.9 Study termination and discontinuation

If this study discontinued or early terminated, last contact date to the subject and the reasons of the discontinuation will be recorded on the electronic Case Report Form (eCRF). The reason of the early termination should be recorded.

7. Endpoint

7.1 Primary Endpoint

Analyzed population will be a combined group of the patients with ACS enrolled in preceding STOPDAPT-2 (NCT02619760) and the patients enrolled in current study (STOPDAPT-2 ACS).

The primary endpoint of primary analysis is the composite of cardiovascular death, myocardial infarction (MI, excluding MI within 2 days after index PCI), stroke (ischemic and hemorrhagic), stent thrombosis (definite stent thrombosis yet to develop into MI), and severe bleeding (TIMI Major/Minor) at 12 months. Non-inferiority of 1-month DAPT group will be firstly verified compared with 12-month DAPT group. Other analytical tests are described in following article 7.3 “Hierarchical testing for the primary and major secondary endpoints”.

The primary endpoint for the secondary analysis at 5-year is the composite of cardiovascular death, MI, stroke (ischemic or hemorrhagic), stent thrombosis (definite stent thrombosis yet to develop into MI), and severe bleeding (TIMI Major/Minor) at 60 months. Superiority of 1-month DAPT group will be verified compared with 12-month group.

As a descriptive analysis, event incidence from 1 month to 12 months or from 12-month to 60 months will be compared between 1-month DAPT group and 12-month DAPT group by a landmark analysis.

7.2 Secondary endpoints

7.2.1 Major Secondary Endpoint

In this study, the following major secondary endpoints will be evaluated

- 12-month observation
  - Major secondary cardiovascular composite endpoint
    as composite of cardiovascular death/ MI/ stroke/ definite ST
  - Major secondary bleeding endpoint
    as TIMI Major/ Minor bleeding
- 60-month observation
  - Major secondary cardiovascular composite endpoint
  - Major secondary bleeding endpoint
  - Upper gastrointestinal endoscopy/upper gastrointestinal endoscopic treatment

7.2.2 Other Secondary Endpoints

In this study, the following secondary endpoints will be also evaluated at 12 months and at 60 months observation

- Death
- Death from cardiac cause
- Death from cardiovascular cause
- Death from non-cardiovascular cause
- MI
- Large MI (CKMB>=10 times of upper limit of normal [ULN])
- Small MI (CKMB<10 times of ULN)
- MI without CKMB elevation
- MI without measurement of CKMB
- Stroke (ischemic/hemorrhagic)
- Ischemic stroke
- Hemorrhagic stroke
- Stent thrombosis (definite, probable, definite/probable in ARC definition)
- Bleeding (TIMI criteria, BARC criteria, and GUSTO criteria)
- Intracranial bleeding
- Gastrointestinal bleeding

- MACE (composite of death from cardiac cause. MI and clinically-driven TLR)
- Death / MI
- Cardiovascular death/ MI
- Any coronary revascularization
- Any TLR
- Clinically-driven TLR
- Non-TLR
- TLF
- TVF
- CABG

7.3 Hierarchical testing of primary endpoint and major secondary endpoints

The hypothesis tests for the endpoints shall be performed hierarchically in the following order.

1. Non-inferiority test on the primary endpoint
2. Non-inferiority test for the major secondary cardiovascular composite endpoint
3. Superiority test for the major secondary bleeding endpoint
4. Superiority test for the primary endpoint

If non-inferiority of the 1-month DAPT group as compared with the 12-month DAPT group was met, we used a pre-specified hierarchical testing procedure with the use of a gatekeeping method to control for multiple comparisons; P values are presented with claim of significance. If statistical significance was not met in any test, P values would not be reported for this and subsequent outcomes; hazard ratios and 95% confidence intervals are presented without P values.

The non-inferiority margin is set to be 1.5 on the hazard ratio scale of the Cox proportional hazard model.

8. Determination of Sample size

8.1 Sample Size Required to Assess noninferiority in the Primary Endpoint in primary analysis (12 months after PCI)

The primary endpoint of this clinical study is the composite of cardiovascular death, MI (excluded periprocedural MI of the index PCI), stroke, stent thrombosis, and serious bleeding

and primary analysis is test for non-inferiority analysis of 1 month DAPT group against 12 month DAPT group about incidence rate of primary endpoint up to the 12-month observation point. The following hypothesis was employed to calculate a required sample size.

In the pooled analysis including RESET and NEXT study[7,29], the 1-year incidence rate of the primary endpoint observed in the 533 ACS subjects treated with CoCr-EES was 5.5%. Total 2,676 evaluable patients are required to prove non-inferiority of 1-month DAPT group against the 12-month DAPT group under the condition that unilateral α is 0.025 and power is 80% with a Cox hazard ratio scale of 1.5 as non-inferiority margin. We initially planned to enroll a total of 3,000 patients including the ACS patients already enrolled in original STOPDAPT-2 (NCT02619760). However, in 1,148 ACS patients enrolled in original STOPDAPT-2, the 1-year incidence rate of 12-month DAPT group was 4.0%, which was lower than the originally assumed event rate of 5.5%. We accordingly increased the sample size to maintain the power to detect the non-inferiority in the primary analysis.

The sample size was calculated using the following hypothesis:

True value:	4.0%
Non-inferior margin:	0.5 on the hazard ratio scale (2.0%: 50% of the true value)
Power:	90%
One-sided alpha:	0.025
Randomization ratio:	1:1

On the above hypothesis, in order to demonstrate non-inferiority of 1-month DAPT to 12 months DAPT on primary endpoint, a sample size of 2,018 patients in each arm, total 4,036 patients will be required. Taking into consideration of dropout cases, we plan to enroll a total of 4,100 ACS patients including the patients already enrolled in original STOPDAPT-2 (additional 3,000 ACS patients in current study).

Based on the observed incidence rate of 1,148 ACS patients in the preceding STOPDAPT-2 (the 1-year incidence rate of major secondary cardiovascular composite endpoint in is 3.0% and the incidence of major secondary bleeding endpoint is 1.5%), the total number of 4100 patients to be enrolled would provide

1) 80% power in the non-inferiority test for major secondary cardiovascular composite endpoints, and

2) 81% power in the superiority test for the major secondary bleeding endpoint under the assumption that the relative risk reduction of the 1-month group would be 60%.

8.2 Power Evaluation of Secondary analysis (60 months after index PCI)

The cumulative incidence rate at 60 months of composite endpoint including cardiovascular death, MI, stroke, stent thrombosis, and severe bleeding for ACS patients treated with CoCr-EES was assumed to be 15.7% from 3-year event rate of RESET/NEXT study. At first non-inferiority test will be performed with 1.5 in hazard ratio scale as non-inferiority margin like primary analysis. In this non-inferiority test, power would be 99.9% with 0.025 as one-sided alpha value. When non-inferiority of 1-month DAPT against 12-month DAPT will be proven, superiority test will be performed. On the hypothesis that the clopidogrel monotherapy after 1-month DAPT lead to decrease of 25% risk (HR 0.75) compared with the aspirin monotherapy after 12-month DAPT, the power of secondary analysis would be 95% with 0.05 as two-sided alpha value.

9. Subgroup analyses

In this study, patients with different backgrounds are expected to receive the treatment. For this reason, subgroup analyses for diabetes, multiple vessel lesions, etc. will be performed, as well as the analysis including all the patients.

9.1 Pre-specified Subgroups

Per Patient：

- Diabetes
- Age (≥ or <75 years)
- Sex (Female or Male)
- Severe CKD (eGFR<30 or HD)
- Prior MI and AMI at presentation of current study
- STEMI
- ACS
- Total stent length (>= or < 28mm)
- Number of target vessels (>= or < 2)
- Paris thrombotic/bleeding risk scores [30]
- CREDO-Kyoto thrombotic/bleeding risk scores [31]
- Study (STOPDAPT-2 ACS vs. the ACS patients in STOPDAPT-2)

10. Genetic Analysis Substudy

In STOPDAPT-2 ACS, the genetic substudy to evaluate CYP2C19 polymorphism will not be performed, which was performed in STOPDAPT-2.

11. Other Necessary Issues

11.1 Ethical concerns/Obtainment of informed consent

11.1.1 Protection of patients' rights

Compliance with the Declaration of Helsinki and Ethical guideline for clinical studies.
Study investigators should carry out this study according to either of "the latest version of the Declaration of Helsinki" and "Ethical Guidelines for Clinical Studies (Public Notice of the Ministry of Health, Labor, and Welfare amended on December 22, 2014, revised on February 28, 2017)" .

11.1.2 Explanation to the patient

11.1.2.1 For the patients enrolled into study and assigned by protocol

Prior to enrollment, the investigator should give the patient the information document approved by the Ethics Committee with verbal explanation of details of the content. After the explanation, the consent form attached to the information document should be filled in with required data and be signed. The consent form completed with all required data should be duplicated in two copies. One copy will be kept by the patient and another copy by the investigator. The original copy will be stored in the each participating centers.

Investigators should obtain patients' consent again if study protocol will require major modification influencing the judgment of study participation and site ethical committee will decide there is need to reobtain patients' consent.

11.1.2.2 For the patients corresponding to inclusion criteria and not enrolled into study

As mentioned above in 4.1 “Procedural Notes”, for the academic purpose of comparison of patients’ background between patients enrolled and not-enrolled into study after implantation of Xience^{TM} stents, the data of not-enrolled patients are also collected as screening log. Collected items are mentioned in article 4.1, all of them are preexisting information on medical records, and additional tests are unnecessary to record screening log. This log shall be input with patients’ name for the need of management in each participating center, cannot be viewed from another participating center, and anonymized when the database will be integrated (see article 11.1.3, anonymization with correspondence table in each participating centers). For the patients whose data shall be input in screening log, the fact of data collection should be informed by word of mouth or written letter. Contact information are open by notification and chance of rejecting to register screening log is secured.

11.1.2.3. Notification and Opening to Public of Research

For the enrolled patients, contents of research shall be informed by the information document. For the patients without enrollment but with registration to screening log, the fact of data collection, contact information of each participating centers and address of current research shall be informed by word of mouth or letter.

In each participating centers, contents of research, collected items, URL address of research and list of participating centers and persons in charge shall be open in public in wards etc.

11.1.3 Privacy Issues

The clinical record, test data, records regarding the patient’s informed consent, etc. will be stored at each medical institute. These records will be disclosed when requested for audit, but the confidentiality will be protected. Moreover, these records should be stored so as to be retrieved when necessary.

All the staff involved in this study has the duty of confidentiality as data handlers and should have the maximum efforts to protect patients’ personal information. Collected data will be accumulated in database on the web with access limitation and the data manager in each participating center will not be allowed to browse the data of other centers. Moreover, while the number assigned to the patient on the clinical chart at each institute will be used as the Patient ID Number, this number will be automatically encrypted when entered on the web. Therefore, the

patient's number on the clinical chart is not transmitted from the participating institute to the Central Administration Office and the Data Center. Patient ID Number and patients' name will be seen only from the each participating center.

For identification of the patient and inquiry to each institute, the encrypted patient ID number will be used. Central Administration Office will check the consistency between data of eCRF and actual clinical recording if participating center approve, and the privacy data will be protected.

Though there is possibility that accumulated data will be utilized for secondary use or provided for study participating centers, the data will be managed with anonymous manner and will be provided for the only people whose utilization will be approved by the study administration office.

11.1.4 Evaluation and Management for Patients' Burden and Expected Risk and Benefit.

This study was performed based on the hypothesis that the risk of stent thrombosis in 1-month DAPT group is not excessive compared with 12-month DAPT group that is equal to current daily practice, as previously mentioned in section 2 "Background and Rationale". Moreover the diminished risk of bleeding will be expected for 1-month DAPT group. For 12-month DAPT group, the treatment will not be changed from current treatment guideline and the risk of embolic and bleeding event will be equal to current practice. Appropriate monitoring for occurrence of stent thrombosis will be planed and its report will be informed to study participation centers every appropriate time. When the risk difference of stent thrombosis will become as large as the definitive difference of causal relationships, the Safety Evaluation Committee will consider the discontinuation of current study and action to minimize the risk will be taken.

11.1.5 Management for serious adverse event

11.1.5.1 Definition of serious adverse event

Adverse event is defined as all disease or its sign that is unfavorable or unintentional, occurred to patients regardless the causality with this study. Among adverse event, serious adverse event is defined as one of following characteristics; 1. Fatal, 2. Threatening patients' life, 3. Requiring prolonged hospitalization for treatment, 4. Related to permanent or severe impairment or organ malfunction, 5. Related to congenital abnormality of descendants. Expected serious adverse

events in the current study are 1. Death, 2. Myocardial infarction, 3. Stroke or cerebral vascular disease, 4. Stent thrombosis, 5. Bleeding complication, 6. Coronary revascularization, 7. Other conditions requiring hospitalization.

11.1.5.2 Management for serious adverse event

Compensation for health damages associated with this study will be done only when it is obligated by legal liability. Compensation for health damages, which is caused by the medical intervention itself and not associated with the clinical study, will be deliberated by each institute. Due to the implementation of the study, adverse events occur, and if the health damages have occurred in the subject, research investigators, physicians are taken promptly to appropriate medical treatment and other best measures. Medical fees of the patients participating in the study are refunded by medical insurances. Although the compensation such as leave compensation and medical attention shall not be performed, when it is obligated by legal liability, it shall be covered by clinical research insurance. Health damages not associated with this study, caused by clinical practice. Health damages, which is caused by the medical intervention itself and not associated with the clinical study, will be deliberated by each institute.

When serious adverse events evidently associated with current study will be occurred, participating center shall report them to study administration office and follow article 11.4 “Discontinuation of the Study and the role of safety evaluation committee” mentioned later, discontinuation of study will be considered.

11.1.6 Compensation for health damages

As for the healthy damage by the side effect of pharmaceutical products to use in this study, pharmaceutical products of incorporated administrative agency Pharmaceuticals and Medical Devices Agency may be relieved primarily by a side effect damage relief system (it is said with "a damage relief system" as follows), The study subject who received health damage can demand payment from the medical supplies medical equipment synthesis system.

About this study, doctors responsible for the study join clinical study insurance as a person insured in all people engaged in this study for this study and compensation of the health damage to have a causal association that occurred to the study subject.

When a physical disability occurs to the study subject due to a clinical study within one year after during the study period or the end, this insurance pays the insurance reimbursement to the damage of study doctors bearing legal compensation responsibility. In addition, a study responsibility doctor and the study allotment doctor join medical doctor liability insurance for compensation responsibility due to a medical activity.

11.1.7 Handling of Treatment Costs and economic load for participants

All the examinations and treatments regarding this study will be basically within the range of daily clinical practice. Therefore, medical fees of the patients participating in the study are refunded by Japanese health insurances system. Patients receiving PCI require attending a hospital at some frequency regardless of participation of this study and they do not need to increase frequency of attending a hospital for participation. Therefore, this study do not pay any reward for participating patients because the economic load for participants will not be increased.

11.2 Approval of Protocol

This study shall be conducted after the protocol is assessed and approval by the ethical committee in each participating site or equivalent organization.

11.3 Revision of the Protocol

If amendments of the protocol are required after implementation of the protocol, this should be communicated from the Central Administration Office to each institute interrupting the study. After the amended protocol is examined, the results of examination will be submitted to the ethical committee of each participating institute for its approval.

11.4 Discontinuation of the Study and the role of safety evaluation committee

The study in principle shall be continued until the target number of subjects is registered and the evaluation for all the subjects is completed. However, when any adverse events that are clearly related to this study occur, the independent safety evaluation committee shall discuss whether the study should be continued. Observation period of this study is as long as 60 months, and when primary analysis at the time of 12-month follow-up will be conducted, composite endpoints and also individual endpoints shall be evaluated and the safety evaluation committee will be held at

the time and judge whether the continuation of study is appropriate or not.

11.5 Discontinuation of the Study

If this study must be discontinued for a reason that occurred during the study, the principal investigator, after discussing with study managers, should promptly report the discontinuation of the study and its reason to the Ethics Committee of each institute by written form.

11.6 Termination of the Study

When enrollment of all the patients is completed, the principal investigator should notify the completion of enrollment to the investigator of each institute, and each institute terminates the enrollment. Moreover, when the completion of follow-up of all the patients is verified, the principal investigator should notify the completion of follow-up of the patients to the investigator of each institute. The investigator of each institute should submit the study completion report to the chief of the medical research group of affiliation.

11.7 Restoration and disclosure of the study data

The principal investigator and study administration office shall restore the study data until at least 10 years after publication of the main paper of current study. The restoration plan shall observe the provision of article 7 (2) in the rules about fair research activities provided by Kyoto University. Investigators shall disclose the study data if necessary in case of doubt about research papers of current study.

11.8 Definitive Rating of Endpoints

11.8.1 Clinical Endpoints - Clinical Events Committee (CEC)

Clinical Events Committee (CEC) will carry out the definitive rating of all the clinical endpoints, and vascular and hemorrhagic adverse events.

11.9 Report to the President of Research Center

When investigators earn the truth or information damaging or nearly damaging ethical appropriateness or scientific rationality of current study, safety report should be handed to the president of research center without delay. And when investigators earn the truth or information damaging or nearly damaging adequateness of study performance or reliability of study result, deviation report should be handed to the president of research center without delay. Progress of study should be annually reported and discontinuation or termination of study should be also reported. Published papers or presentation in scientific sessions as a result of study should be handed and reported through electronic application system in ethical committee in the manner of PDF.

11.10 Information Opening to the Public

This study is planned to be registered in study registry of Japanese University Hospital Medical Information Network (UMIN; UMIN000029981) and U.S. National Institutes of Health (NIH, ClinicalTrial.gov, NCT 03462498) and the information will be open to the public.

11.11 Study monitoring and inspection

11.11.1 Study monitoring

To secure the adequateness of study performance, monitoring of study progress or observance of study protocol shall be performed. Especially for 3 years after enrollment begins (until all study patients spend one year after enrollment), more strict monitoring shall be required for evaluation of safety. Central monitoring shall be continuously performed with the database on web about the progress of study and the occurrence of stent thrombosis more frequently than monthly, and reported to the persons in charge of participating facilities with E-mail. Additionally, onsite monitoring including the check of consent forms or the direct inspection of clinical record or original sources shall be performed for the selected participating facilities. All registered cases will be checked onsite for the required facilities and 10 registered cases will be checked onsite for the selected 15 facilities as samples.

11.11.2 Inspection

Primary investigator, if necessary, should appoint inspector and perform the inspection to secure the reliability of study outcomes. Inspectors should be those persons who do not work about

study progress and monitoring and perform the inspection about observance of study protocol. Detailed implementation method of inspection should follow the another statement on inspection, determined separately.

11.12 Study device and drug descriptions

The drugs associated with current study (aspirin [Buffarin™ etc.], clopidogrel [Plavix™ etc.], prasugrel [Effient™], ticagrelor [Brilinta™], ticlopidine [Panaldine™]) and the devices associated with current study (Xience™ series, [Xience V™, Xience Prime™, Xience Xpedition™, Xience Alpine™, Xience Sierra™]) are already approved by PMDA and sold in the Japanese market. The package inserts of these drugs and devices are handed at the application of this study to ethical committee.

11.13 Coping with consultation from Study Participants

To cope with consultations from study participants, following contact point will be set.

Kyoto University, Graduate School of Medicine, Cardiovascular Medicine
54 Shogoin Kawahara-cho, Sakyo-ku, Kyoto 606-8507, Japan
Tel: +81-75-751-4255 Fax：+81-75-751-3299
Responsible person: Takeshi Kimura,
Person in charge: Hirotoshi Watanabe, hwatanab@kuhp.kyoto-u.ac.jp

12. Definition of Endpoints

12.1 Death

As classified by Academic Research Consortium (ARC) [32]

- **Cardiac Death**
  Any death due to proximate cardiac cause (e.g. MI, low-output failure, fatal arrhythmia), unwitnessed death and death of unknown cause, all procedure related deaths including those related to concomitant treatment. All deaths are considered cardiac unless an unequivocal non-cardiac cause can be established. Specifically,

any unexpected death even in subjects with coexisting potentially fatal non-cardiac disease (e.g. cancer, infection) should be classified as cardiac.

- **Vascular Death**
  Death due to non-coronary vascular causes such as cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular cause.

- **Non-cardiovascular Death**
  Any death not covered by the above definitions such as death caused by infection, malignancy, sepsis, pulmonary causes, accident, suicide or trauma.

12.2 Myocardial Infarction: MI

As classified by Academic Research Consortium (ARC) [32]: However, the sensitivity is too high for the evaluation with Troponin of the peri-procedural MI, thus CKMB will be used.

- **Preprocedural Adjudication of MI**
  Myocardial Infarction (MI) is defined by the ARC criteria. However, periprocedural MI will be evaluated by CKMB, because the evaluation by troponin is too sensitive.

- **Baseline MI evaluation**
  ECG showing ST elevation, development of new abnormal Q-wave, clinical symptoms specific to MI, troponin or CK-MB values exceeding the standard values
- **Periprocedural MI**
  - Occurrence of any of the following events within 48 hours after PCI procedure will be judged as MI.
    - CK-MB ≥ **3 times Upper Reference Limit (URL)** (CK-MB value exceeding URL before procedure is not considered as a new MI, but as MI at enrollment.)
    - Abnormal ECG (new Q-wave, left bundle branch block)
  - Occurrence of troponin ≥ **5 times URL** or CK-MB ≥ **5 times URL** within 72 hours after CABG procedure accompanied by any of the following criteria will be judged as MI. (CK-MB value exceeding URL before procedure is not considered as a new MI, but as MI at enrollment.)
    - Abnormal ECG (new Q-wave, left bundle branch block)

        - New occlusion of coronary autografts or grafts
        - Reduction in living myocardium confirmed by diagnostic imaging
- **Spontaneous MI**
    - Occurrence of any of the following events at > 48 hours after PCI or > 72 hours after CABG will be judged as MI. MI caused by revascularization procedures, such as TLR and TVR, is defined as periprocedural MI.
        - Abnormal ECG (new Q-wave, left bundle branch block)
        - Troponin or CK-MB value **> URL** (CK-MB value exceeding URL before procedure is not considered as a new MI, but as MI at enrollment.)
- **Sudden Death**
    - When death occurred before blood sampling for biomarker measurements or while biomarkers appeared to be increasing, MI will be judged according to the following criteria:
        - Clinical symptoms suggesting ischemia that are accompanied by one of the following:
            - New ST elevation or left bundle branch block
            - Thrombus determined by angiography or at autopsy
- **Reinfarction**
    - When after onset of MI stable or decreasing values are confirmed in 2 biomarker measurements, but 20% increase 3 to 6 hours is observed after the second measurement.
        - If biomarkers are increasing or have not yet reached the peak, data are insufficient to diagnose reinfarction.

Electrocardiographic Classification:

- **Classification based on Q-wave**
    - **Q-wave MI (QMI)**
        - Development of abnormal Q-waves confirmed in 2 or more contiguous leads with or without elevation in cardiac enzymes.
    - **Non-Q-wave MI (NQMI)**
        - All MIs not classified as Q-wave.
- **Classification based on ST segment。**
    - **ST-elevation myocardial infarction (MI)（STEMI）**

        - New or presumably new elevation of ST segment at J point in 2 or more contiguous leads. Cut-off point is ≥ 0.2 mV in V1, V2 and V3 leads and ≥ 0.1 mV in other leads.
    - **Non-ST elevation myocardial infarction (MI)（NSTEMI）**
        - MI that is not STEMI

Determination by Infarction Size:

- **Major Infarction**
    - CK-MB level is ≥ 10 times the upper limit of normal (ULN) (or CK level is ≥ 10 times ULN in case CK-MB level is not measurable).
        - Even if the above conditions are not met, fatal MI is determined as large infarction.
- **Minor Infarction**
    - All types of MI other than the major infarction

- **Classification of MI Size Based on the ARC Classification**
    - Increase in the cardiac enzyme (CK-MB, Tn, and total CK) levels ≥ 10 times ULN
    - Increase in the cardiac enzyme (CK-MB, Tn, and total CK) levels ≥ 5 times, < 10 times ULN
    - Increase in the cardiac enzyme (CK-MB, Tn, and total CK) levels ≥ 3 times, < 5 times ULN
    - Increase in the cardiac enzyme (CK-MB, Tn, and total CK) levels < 3 times ULN
    - Increase in the troponin level; no increase in the CK-MB and total CK levels
    - Increase in the troponin level; no measurements of the CK-MB and total CK levels

  The cardiac enzymes should be prioritized in the order of CK-MB, Tn, and total CK.
- **Classification of MI Size Based on the CK-MB Level**
    - Increase in the cardiac enzyme (CK-MB) level ≥ 10 times ULN
    - Increase in the cardiac enzyme (CK-MB) level ≥ 5 times, < 10 times ULN
    - Increase in the cardiac enzyme (CK-MB) level ≥ 3 times, < 5 times ULN
    - Increase in the cardiac enzyme (CK-MB) level < 3 times ULN
    - Increase in the troponin level; no increase in the CK-MB level
    - Increase in the troponin level; no measurement of the CK-MB level

- **Classification of MI Size Based on the Troponin Level**
  - Increase in the cardiac enzyme (Tn) level ≥ 10 times ULN
  - Increase in the cardiac enzyme (Tn) level ≥ 5 times, < 10 times ULN
  - Increase in the cardiac enzyme (Tn) level ≥ 3 times, < 5 times ULN
  - Increase in the cardiac enzyme (Tn) level < 3 times ULN
  - Increase in the troponin level; no increase in the CK-MB level
  - Increase in the troponin level; no measurement of the CK-MB level

12.3 Revascularization

Classification:

- **Target Lesion Revascularization (TLR)**
  PCI performed in the target lesion (within 5 mm of the stent edges), or CABG performed for restenosis of the target lesion or for treatment of other complications
- **Target Vessel Revascularization (TVR)**
  PCI performed in the target vessel or revascularization by CABG, including TLR
- **Target Vessel Revascularization-Remote (TVR-Remote)**
  Revascularization of a non-target lesion in the target vessel
- **Non Target Vessel Revascularization (Non-TVR)**
  Any revascularization in a vessel other than the target vessel
- **Non Target Lesion Revascularization (Non-TLR)**
  Any revascularization in a lesion other than the target lesion
  Non-TLR = TVR-Remote + Non-TVR

Clinically indicated revascularization:

- The revascularization that meets the following criteria is considered as clinically indicated revascularization. Presence/absence of clinical findings is judged by the operator of the procedure before the revascularization.
  - Recurrence of angina pectoris, presumably related to the target vessel;
  - Objective signs of ischemia at rest or during exercise test (or equivalent), presumably related to the target vessel;
  - Signs of functional ischemia revealed by any invasive diagnostic test (e.g., Doppler flow velocity reserve [FVR], fractional flow reserve [FFR]);
  - Revascularization for ≥ 70% diameter stenosis even in the absence of the above-mentioned ischemic signs or symptoms.

12.4 Stent Thrombosis

Based on the ARC definition [32], Stent thrombosis is classified into definite, probable and possible according to the "probability", and into acute, subacute late and very late according to timing of the onset.

- **Definite Stent Thrombosis**
  - Angiographic confirmation of stent thrombosis*:
    - The presence of a thrombus† that originates in the stent segment (including 5 mm of the stent edges) is revealed by angiography, and presence of at least one of the following criteria within a 48-hour time window is observed:
      - Acute onset of ischemic symptoms at rest
      - New ECG changes that suggest acute ischemia
      - Typical rise and fall in cardiac biomarkers (refer to definition of spontaneous MI)
      - Nonocclusive thrombus
        - Intracoronary thrombus is defined as a noncalcified filling defect (spheric, ovoid, or irregular) or lucency surrounded by contrast material (on 3 sides or within a coronary stenosis) seen in multiple projections, or persistence of contrast material within the lumen, or a visible embolization
      - Occlusive thrombus
        - TIMI 0 or TIMI 1 intrastent or proximal to a stent up to the most adjacent downstream side branch or main branch
  - Pathological confirmation of stent thrombosis:
    - Evidence of recent thrombus within the stent determined at autopsy or via examination of tissue retrieved following thrombectomy
- **Probable Stent Thrombosis**
  - When the following cases occurred after intracoronary stenting:
    - Any unexplained death within the first 30 days after procedure‡
    - Irrespective of the time after the index procedure, any MI in the territory of the implanted stent in the absence of any other obvious cause such as angiography or other lesions
- **Possible Stent Thrombosis**
  - Any unexplained death from 30 days after intracoronary stenting

* The incidental angiographic documentation of stent occlusion in the absence of clinical signs is not considered to be a confirmed stent thrombosis (silent occlusion)

† Intracoronary thrombus

- **Acute Stent Thrombosis**
  0-24 hours post stent implantation (Time 0 is defined as the time of removal of the guiding catheter).
- **Subacute Stent Thrombosis**
  > 24 hours-30 days post stent implantation
- **Late Stent Thrombosis ***
  > 30 days-1 year post stent implantation
- **Very Late Stent Thrombosis ***
  > 1 year post stent implantation

* Including "primary" as well as "secondary" stent thrombosis after stented segment revascularization.

12.5 Surgery

- Including endoscopic surgeries and therapies
- Including CABG
- Excluding percutaneous intravascular treatments
- Including aortic aneurysm stent graft procedure
- Excluding tooth extraction

12.6 Bleeding/Hemorrhagic Complications

Bleeding/Hemorrhagic Complications will be evaluated using the TIMI, GUSTO and BARC definitions [33-35]

TIMI bleeding classification [33]:

Bleeding is classified by the Thrombosis in Myocardial Infarction (TIMI). Measurement of hemoglobin and hematocrit values at baseline is required for the severity rating.

- **Major Bleeding**

- When any of the following criteria is met.
  - Intracranial hemorrhage
  - Decrease in hemoglobin to ≥ 5 g/dL decrease in the hemoglobin concentration
  - Absolute drop in hematocrit to ≥ 15% (Baseline – Onset of the event)

- **Minor Bleeding**
  - When blood loss is observed, and any of the following criteria is met:
    - Decrease in hemoglobin to ≥ 3 g/dL
    - Decrease in hematocrit to ≥ 10% (Baseline – Onset of the event)
  - When no blood loss is observed, but any of the following criteria is met:
    - Decrease in hemoglobin to ≥ 4 g/dL
    - Decrease in hematocrit to ≥ 12% (Baseline – Onset of the event)

- **Minimal Bleeding**
  - Any clinically overt sign of hemorrhage that is associated with a fall in hemoglobin to < 3 g/dL.
    (Microscopical urine occult blood and fecal occult blood are not defined as Minimal bleeding.)

GUSTO bleeding classification [34]:

Severe Bleeding

- Life-threatening bleeding
- Intracranial hemorrhage
- Hemorrhage or bleeding that causes drop in blood pressure and requires interventions, such as infusion, blood transfusion, administration of a hypertensor, surgical interception.

Moderate Bleeding

- Bleeding that requires blood transfusion but does not meet criteria for severe bleeding

BARC bleeding classification [35]:

Bleeding is classified based on definitions by the Bleeding Academic Research Consortium (BARC). Measurement of hemoglobin concentration is required for severity rating.

- **Type 0:** No bleeding
- **Type 1:** Bleeding that is not medically significant and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a health care professional.

- **Type 2 :** Any overt sign of hemorrhage that should be treated and does not fit the criteria for Types 3, 4, or 5, but does meet at least one of the following criteria: (1) requiring non-surgical, medical intervention by a health care professional, (2) leading to hospitalization or increased level of care, (3) prompting evaluation.
- **Type 3 :**
    - Type 3a
        - Overt bleeding plus hemoglobin drop of 3-5 g/dL
        - Transfusion with overt bleeding
    - Type 3b
        - Overt bleeding plus hemoglobin drop of ≥ 5 g/dL
        - Cardiac tamponade
        - Bleeding requiring surgical intervention (excluding dental/nasal/skin/haemorrhoid)
        - Bleeding requiring intravenous vasoactive drugs
    - Type 3c
        - Intracranial hemorrhage
        - Intraocular bleeding compromising vision
- **Type4:** CABG-related bleeding
    - Perioperative intracranial hemorrhage within 48 hours
    - Reoperation following closure of sternotomy for the purpose of controlling bleeding
    - Transfusion of ≥ 5 units of whole blood or concentrated red blood cell within 48 hours
    - Chest tube output ≥ 2 L within 24 hours
- **Type5:** Fatal bleeding
    - Type 5a
      Probable Fatal bleeding: no autopsy or imaging confirmation, but clinically suspicious
    - Type 5b
      Definite fatal bleeding: overt bleeding or autopsy or imaging confirmation

12.7 Composite Endpoint

Composite endpoint of secondary endpoints will be defined as follows:

- **TLF: Target Lesion Failure**

Cardiac death, myocardial infarction (MI) of target vessels, Clinically-indicated TLR

- **TVF:Target Vessel Failure**
  Cardiac death, MI or Clinically-indicated TVR。
- **MACE :Major Adverse Cardiac Events**
  Cardiac death, MI or Clinically-indicated TVR

12.8 Stroke or Cerebrovascular Accident

Acute onset of a neurological deficit that persists for at least 24 hours and is the result of a disturbance of the cerebral circulation due to ischemia or hemorrhage. Deficits that last ≤ 24 hours are due to transient ischemic neurological attack and are not classified in this category.

12.9 Classification of Angina

- **Braunwald Classification of Unstable Angina** [36]
  - **Class I：** New onset of severe or accelerated angina: Patients with new onset (< 2 months in duration) exertional angina pectoris that is severe or frequent (> 3 episodes/day) or patients with chronic stable angina who develop accelerated angina (angina distinctly more frequent, severe, longer in duration, or precipitated by distinctly less exertion than previously) but who have not experienced pain at rest during the preceding 2 months.
  - **Class II：** Angina at rest, subacute: Patients with 1 or more episodes of angina at rest during the preceding month but not within the preceding 48 hours
  - **Class III：** Angina at rest, acute: Patients with 1 or more episodes of angina at rest within the preceding 48 hours

- **Canadian Cardiovascular Society (CCS) Classification of Stable Angina** [37]
  - **Class I：** Ordinary physical activity does not cause angina, such as walking or climbing stairs. Angina occurs with strenuous, rapid or prolonged exertion at work or recreation.
  - **Class II：** Slight limitation of ordinary activity. Angina occurs on walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, or in cold, in wind, under emotional stress or only during the few hours after awakening. Angina occurs on walking more than two blocks on the level and climbing more than one flight of ordinary stairs at a normal pace and in normal condition.

- **Class III**：Marked limitation of ordinary physical activity. Angina occurs on walking one to two blocks on the level and climbing one flight of stairs in normal conditions and at a normal pace.
- **Class IV**：Inability to carry on any physical activity without discomfort – angina symptoms may be present at rest.

13. Study Organization

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13.7 Study Monitoring members

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13.9 Clinical Events Committee (CEC) members

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Yutaka Furukawa	Kobe City Medical Center General Hospital

13.10 Participating institutes

Open in public on the Web pages
https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr_view.cgi?recptno=R000034230
Total 74 centers in Japan participate and enrolle one or more patients in this study at June 8, 2020.

13.11 Study Sponsor

Abbott Medical Japan, Co., Ltd.
The study sponsor is not involved in the implementation of the study, data collection, event fixation and statistical analysis. However, approval of the study sponsor should be obtained for presentation in scientific meetings and submission of papers. The study sponsor has a non-exclusive right to use all the information or data obtained in this study.

13.12 Conflicts of interest between researchers and research funding contributors

In this study, we conducted a research between Abbott Medical Japan, Co., Ltd. with the primary representative investigators, research doctors in participating centers, chief statistician and those who are obvious to benefit from conducting the clinical study. On the possibility of conflicts of interest with regard to the implementation and outcomes, these conflicts of interests shall be managed properly, and reviewed and approved by the Committee for Conflicts of Interest before this clinical research is conducted, in accordance with Conflict of Interest Management Standards and Conflicts of Interest Management Plan. In addition, Abbott Medical Japan, will make public the information on the provision of funds for research etc. according to the clinical

research law and related laws and regulations, by using the Internet etc.

In addition, researchers participating in this research include those having the following conflicts of interest with Abbott Medical Japan.

· Researchers who engaged in other clinical research, specific clinical research, post-marketing clinical trial, or post-marketing survey conducted with funds provided by Abbott Medical Japan.

· Researchers who received as an advisory or chairman's remuneration over 1 million yen from Abbott Medical Japan Company.

14. Authorship

Main paper： Takeshi Kimura

For other sub-analyses than those described above, topics proposed from the institutes are selected in order of the number of enrolled patients.

15. References

1) Moses JW, Leon MB, Popma JJ, et al. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. N Engl J Med. 2003;349:1315-23.

2) Stone GW, Ellis SG, Cox DA, et al. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. N Engl J Med. 2004;350:221-31.

3) Kimura T, Morimoto T, Nakagawa Y, et al. Very late stent thrombosis and late target lesion revascularization after sirolimus-eluting stent implantation: five-year outcome of the j-Cypher Registry. Circulation. 2012;125:584-91.

4) Raber L, Magro M, Stefanini GG, et al. Very late coronary stent thrombosis of a newer-generation everolimus-eluting stent compared with early-generation drug-eluting stents: a prospective cohort study. Circulation. 2012;125:1110-112.

5) Schoming A, Neumann FJ, Kastrati A, et al. A randomized comparison of antiplatelet and anticoagulant therapy after the placement of coronary-artery stents. N Engl J Med. 1996;334:1084-89.

6) Leon MB, Baim DS, Popma JJ, et al. A clinical trial comparing three antithrombotic-drug regimens after coronary-artery stenting. Stent Anticoagulation Restenosis Study Investigators. N Engl J Med. 1998;339:1665-71.

7) Kimura T, Morimoto T, Natsuaki M, et al. Comparison of everolimus—eluting and sirolimus-eluting coronary stents: 1-year outcomes from the Randomized Evaluation of Sirolimus-eluting Versus Everolimus-eluting stent Trial (RESET). Circulation 2012;126:1225-36.

8) Kimura T, Morimoto T, Nakagawa Y, et al. Antiplatelet therapy and stent thrombosis after sirolimus-eluting stent implantation. Circulation. 2009;119:987-95.

9) Gwon HC, Hahn JY, Park KW, et al. Six-month versus 12-month dual antiplatelet therapy after implantation of drug-eluting stents: the Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting (EXCELLENT) randomized, multicenter study. Circulation. 2012;125:505-13.

10) Valgimigli M, Campo G, Monti M, et al. Short- Versus Long-term Duration of Dual Antiplatelet Therapy After Coronary Stenting: A Randomized Multicentre Trial. Circulation. 2012;125(16):2015-26.

11) Colombo A, Chieffo A, Frasheri A, et al. Second-generation drug-eluting stent implantation followed by 6- versus 12-month dual antiplatelet therapy: the SECURITY randomized clinical trial. J Am Coll Cardiol. 2014;64(20):2086-97.

12) Gilard M, Barragan P, Noryani AA, et al. 6- versus 24-month dual antiplatelet therapy after implantation of drug-eluting stents in patients nonresistant to aspirin: the randomized, multicenter ITALIC trial. J Am Coll Cardiol. 2015;65(8):777-86

13) Natasuaki M, Morimoto T, Yamamoto E, et al. One-year outcome of a prospective trial stopping dual antiplatelet therapy at 3 months after everolimus-eluting cobalt-chromium stent implantation: ShortT and OPtimal duration of Dual AntiPlatelet Therapy after everolimus-eluting cobalt-chromium stent (STOPDAPT) trial. Cardiovasc Interv and Ther. 2015 Epub ahead of pirnt, DOI: 10.1007/s12928-015-0366-9

14) US National Institutes of Health, ClinicalTrials.gov. GLOBAL LEADERS: A Clinical Study Comparing Two Forms of Anti-platelet Therapy After Stent Implantation. http://clinicaltrials.gov/ct2/show/study/NCT01813435. Updated May 18, 2015. Accessed May 20, 2015.

15) Urban P, Meredith IT, Abizaid A, et al. Polymer-free drug-coated coronary stents in patients at high bleeding risk. N Engl J Med. 2015;373(21):2038-47.

16) Palmerini T, Biondi-Zoccai G, Della Riva D, et al. Stent thrombosis with drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis. Lancet 2012;379(9824):1393-402

17) Tada T, Natsuaki M, Morimoto T, et al. Duration of dual antiplatelet therapy and long-term clinical outcome after coronary drug-eluting stent implantation: landmark analyses from the CREDO-Kyoto PCI/CABG Registry Cohort-2. Circulation. Cardiovascular interventions 2012;5(3):381-91

18) Toyoda K, Yasaka M, Iwade K, et al. Dual antithrombotic therapy increases severe bleeding events in patients with stroke and cardiovascular disease: a prospective, multicenter, observational study. Stroke. 2008;39:1740-5.

19) Yahata H, Corley DA, Nakahata F, et al. aspirin and non-aspirin NSAIDs increase risk of colonic diverticular bleeding: a systematic review and meta-analysis. J Gastroenterol. 2014;49:992-1000.

20) Gent M, Beaumont D, Blanchard J, et al. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee. Lancet 1996;348:1329-39.

21) Valgimigli M, Bueno H, Byrne RA, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2018;39:213–260

22) Bittl JA, Baber U, Bradley SM, et al. Duration of Dual Antiplatelet Therapy: A Systematic Review for the 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2016;68(10):1116-39.

23) Yusuf S, Zhao F, Mehta SR, et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med. 2001;345(7):494-502.

24) Mehta SR, Yusuf S, Peters RJ, et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. Lancet. 2001;358(9281):527-33.

25) Yamaji K, Natsuaki M, Morimoto T, et al. Long-Term Outcomes After Coronary Stent Implantation in Patients Presenting With Versus Without Acute Myocardial Infarction (an Observation from Coronary Revascularization Demonstrating Outcome Study-Kyoto Registry Cohort-2). Am J Cardiol. 2015;116(1):15-23.

26) Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. Circulation. 2012;126(16):2020-35.

27) Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;130(25):2354-94.

28) Urban P, Mehran R, Colleran R, et al. Defining High Bleeding Risk in Patients Undergoing Percutaneous Coronary Intervention: A Consensus Document From the Academic Research Consortium for High Bleeding Risk. Circulation. 2019, in press, doi: 10.1161/CIRCULATIONAHA.119.040167.

29) Natsuaki M, Kozuma K, Morimoto T, et al. Final 3-Year Outcome of a Randomized Trial Comparing Second-Generation Drug-Eluting Stents Using Either Biodegradable Polymer or Durable Polymer: NOBORI Biolimus-Eluting Versus XIENCE/PROMUS Everolimus-Eluting Stent Trial. Circ Cardiovasc Interv. 2015;8(10):e002817.

30) Baber U, Mehran R, Giustino G, et al. Coronary Thrombosis and Major Bleeding After PCI With Drug-Eluting Stents: Risk Scores From PARIS. J Am Coll Cardiol. 2016;67(19):2224-2234

31) Natsuaki M, Morimoto T, Yamaji K, et al. Prediction of Thrombotic and Bleeding Events After Percutaneous Coronary Intervention: CREDO-Kyoto Thrombotic and Bleeding Risk Scores. J Am Heart Assoc. 2018;7(11):e008708

32) Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115:2344-51.

33) Rao AK, Pratt C, Berke A, et al. Thrombolysis in Myocardial Infarction (TIMI) trial: phase I: hemorrhagic manifestations and changes in plasma fibrinogen and the fibrinolytic system in patients treated with recombinant tissue plasminogen activator and streptokinase. J Am Coll Cardiol. 1988;11:1-11.

34) The GUSTO investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. N Engl J Med 1993;329:673-82.

35) Mehran R, Rao SV, Bhatt DL et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation. 2011;123:2736-47.

36) Braunwald E. Unstable angina: a classification. Circulation 1989;80:410-14.

37) Campeau L. Letter: grading of angina pectoris. Circulation. 1976;54:522-3.

STOPDAPT-2 ACS

ShorT and OPtimal duration of Dual AntiPlatelet Therapy-2

study for the patients with ACS

Statistical Analysis Plans

＜Date of preparation; 5th June, 2019 Ver 1.1>

1. Administrative Information

Title of the study; ShorT and OPtimal duration of Dual AntiPlatelet Therapy-2 study for patients with ACS
[Study to Evaluate the Safety of Reducing Dual Antiplatelet Therapy (DAPT) Duration to 1 Month for patients with acute coronary syndrome (ACS) after Implantation of Everolimus-eluting Cobalt-chromium Stent]
Trial registration number; NCT 03462498
Study protocol version; ver. 3.1
Version of current SAP; ver 1.1, 2019.6.5
SAP revisions;

Version	Date of revision	Major changes	Notes
Ver 1.1	June 5, 2019	New document	N/A

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2. Introduction

Background and rationale

See also study protocol article 2.

The sirolimus-eluting stent and the paclitaxel-eluting stent, which are known as the first-generation drug-eluting stents (DESs), have already achieved remarkable results, as represented in reducing restenosis rate to 10% or less at 1 year after coronary stenting, so that DESs are currently used in the majority of PCI procedures.[1,2] On the other hand, even though the frequency is low, the problems of the first-generation DES (i.e., late adverse events, such as very late stent thrombosis and late restenosis at 1 year or later, which rarely occur in conventional bare-metal stents [BMSs]) have been pointed out.[3,4]

Since P2Y12 platelet receptor antagonists, when used in combination with aspirin for 1 month, have been indicated to significantly suppress the occurrence of stent thrombosis after BMS implantation, DAPT, in which aspirin and a P2Y12 platelet receptor antagonist are used in combination for 1 month after BMS implantation, has become a standard regimen.[5,6] At the same time, for fear of very late stent thrombosis, DAPT is frequently performed for 1 year or longer after DES implantation in clinical practice. In RESET (Randomized Evaluation of Sirolimus-eluting versus Everolimus-eluting stent Trial) conducted in clinical practice in Japan, 90% of the subjects had been on DAPT for 1 year or longer.[7] Moreover, in the package insert of the Everolimus-eluting stent (EES), currently the most extensively used DES in Japan, 1-year DAPT is recommended. However, serious hemorrhagic complications, such as cerebral hemorrhage, associated with a prolonged DAPT duration can bring disadvantages to patients, it is extremely important to clarify an optimal DAPT duration after DES procedure. Based on the results of large-scale observational studies and small-scale randomized controlled studies, DAPT for 6 months or longer[8-12] had no inhibitory effects on the onset of serious cardiovascular events. Furthermore, we have recently assessed the safety of a DAPT regimen for 3 months after CoCr-EES implantation in STOPDAPT (ShorT and OPtimal duration of Dual AntiPlatelet Therapy study after everolimus-eluting cobalt-chromium stent) study, using the RESET study, in which DAPT had been performed in 90% of subjects for 1 year or longer, as a historical control.[13] More

recently, attempt to further reduce DAPT duration after DES procedure begins. In Global LEADERS (A Clinical Study Comparing Two Forms of Anti-platelet Therapy After Stent Implantation: NCT01813435) study, the safety of a DAPT regimen with ticagrelor, a new P2Y12 platelet receptor antagonist for 1 month after DES procedure was evaluated and although in primary analysis the study hypothesis was not statically proven, the effectiveness and feasibility of 1 month DAPT regimen were shown.[14] In addition, in LEADERS FREE (A Randomized Clinical Evaluation of the BioFreedom™ Stent: NCT01623180) study, the efficacy and safety of polymer-free DES (BioFreedom™) compared with BMS in 1-month DAPT regimen are proven in the subject group with a high bleeding risk.[15] Currently, 1-month DAPT regimen after BMS implantation is commonly used in clinical practice, producing no major problems. Based on a meta-analysis of recent clinical studies, it has also been reported that the use of CoCr-EES reduces the risk of early stent thrombosis by half compared to the use of BMS.[16] At least from a logical standpoint, there is no necessity to extend antiplatelet therapy after CoCr-EES implantation longer than after BMS implantation, and it is considered possible to use the same 1-month DAPT duration as after BMS implantation. On the other hand, for bleeding complication, it is clear that a prolonged DAPT duration increases bleeding complications compared to aspirin monotherapy.[10,16-18] We therefore started STOPDAPT-2 (NCT02619760), a multicenter, randomized, open-label, controlled study, in which DAPT is discontinued at 1 month after stenting in subjects who have undergone CoCr-EES procedure, which is considered to be associated with a lower risk of stent thrombosis than BMS, to compare incidences of cardiovascular events and bleeding events at 12 months after stenting between the 1-month DAPT group and the 12-month DAPT group.[19]

In this study, for antiplatelet therapy after the discontinuation of DAPT at 1 month, we will use clopidogrel, a P2Y12 receptor antagonist considered to be a key drug for stent thrombosis prophylaxis,[6] instead of the conventional aspirin monotherapy. Although aspirin is an inexpensive drug with a proven efficacy for preventing cardiovascular events in patients with coronary artery diseases, its side effects, such as gastrointestinal mucosal injury and gastrointestinal bleeding, are pointed out as a problem.[20] Based on the CAPRIE study results, it has been reported that clopidogrel monotherapy significantly suppressed cardiovascular events in patients with cardiovascular diseases compared to aspirin monotherapy.[21] It is known that a

higher percentage of Japanese patients have resistance to the platelet aggregation inhibitory effect of clopidogrel attributable to CYP2C19 polymorphism. Even under such circumstances in Japan, clopidogrel monotherapy has been standard antiplatelet therapy in the cerebrovascular region, and recently there have been an increasing number of cases in which clopidogrel monotherapy is chosen after DAPT discontinuation in patients with coronary stent. To perform clopidogrel monotherapy after DAPT discontinuation in Japanese patients, it is necessary to verify its effectiveness and safety, data of which, however, have been still insufficient. In the STOPDAPT-2, the superiority of clopidogrel monotherapy after 1-month DAPT over aspirin monotherapy after 12-month DAPT will be verified by comparing results of clopidogrel monotherapy continued up to 5 years after DAPT discontinuation in the 1-month DAPT group and aspirin monotherapy continued up to 5 years after DAPT discontinuation in the 12-month DAPT group.

In the current AHA/ACC or ESC guidelines, 12-month DAPT is standard recommendation for patients with ACS, though 6-month DAPT is recommended for stable coronary artery disease[21,22]. However, the rational of the longer DAPT duration for ACS patients was based only on the CURE study, which was performed more than 15 years ago[23,24]. We previously reported the incidence of ischemic events beyond 3 months after index PCI was not different between the acute myocardial infarction (AMI) patients and non-AMI patients in registry data[25]. Therefore, in contemporary clinical practice using 2nd generation DES, there is no solid rationale to recommend extended DAPT duration in patients with ACS. In the ongoing STOPDAPT-2 study, the proportion of ACS cases is expected to be 30 to 40% of the entire study population, and the power is insufficient to evaluate safety of 1-month DAPT in ACS patients. Therefore, we designed the STOPDAPT-2 ACS study, in which we would enroll only ACS patients with the same protocol as the STOPDAPT-2 and analyze the safety of 1-month DAPT in ACS patients. We would combine the two studies to include the ACS patients enrolled in the STOPDAPT-2.

Study Objectives

The purpose of this study is to evaluate the safety of reducing DAPT duration to 1

month after implantation of the everolimus-eluting cobalt-chromium stent (CoCr-EES) in patients who presented as acute coronary syndrome (ACS).

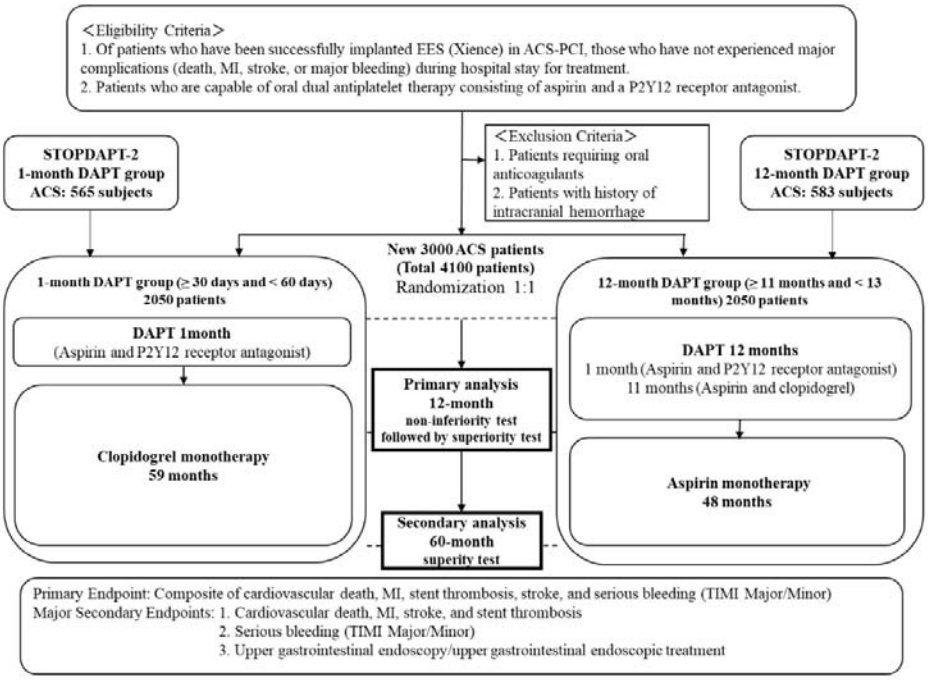
3. Study Methods

Trial design

STOPDAPT-2 ACS is a multicenter, randomized, open-label but blind for event assessor, controlled study, with parallel group.

ACS Patients with successful CoCr-EES implantation without any in-hospital complication are enrolled and made randomization into two groups, 1-month DAPT followed by clopidogrel monotherapy (experimental arm) or 12-month DAPT comprising of aspirin and clopidogrel (control arm). At 1-year after index PCI, we will assess the non-inferiority of the experimental arm against the control arm as primary analysis about the net clinical outcome, composite of death from cardiovascular death, myocardial infarction, definite stent thrombosis, stroke, and bleeding defined as TIMI major and minor criteria (primary outcome) [25].

After 1-year, we will follow the patient population to assess the long-term efficacy and safety. Patients in experimental arm will continue clopidogrel monotherapy and patients in control arm will discontinued DAPT and change into aspirin monotherapy. At 5-year after index PCI, we will assess the superiority of the experimental arm as secondary analysis. Allocation rate was made as 1:1 fashion.



Randomization

Randomization was performed centrally through the electronic data capture system, with a stochastic minimization algorithm to balance treatment assignment within the centers. Also see protocol article 3.3.

Sample size

See protocol article 8.1

The primary endpoint of this clinical study is the composite of cardiovascular death, MI (excluded periprocedural MI of the index PCI), stroke, stent thrombosis, and serious bleeding and primary analysis is test for non-inferiority analysis of 1 month DAPT group against 12 month DAPT group about incidence rate of primary endpoint up to the 12-month observation point. The following hypothesis was employed to calculate a required sample size.

In the pooled analysis including RESET and NEXT study[7,29], the 1-year incidence rate of the primary endpoint observed in the 533 ACS subjects treated with

CoCr-EES was 5.5%. Total 2,676 evaluable patients are required to prove non-inferiority of 1-month DAPT group against the 12-month DAPT group under the condition that unilateral α is 0.025 and power is 80% with a Cox hazard ratio scale of 1.5 as non-inferiority margin. We initially planned to enroll a total of 3,000 patients including the ACS patients already enrolled in original STOPDAPT-2 (NCT02619760). However, in 1,148 ACS patients enrolled in original STOPDAPT-2, the 1-year incidence rate of 12-month DAPT group was 4.0%, which was lower than the originally assumed event rate of 5.5%. We accordingly increased the sample size calculation to maintain the power to detect the non-inferiority in the primary analysis.

The sample size was calculated using the following hypothesis:

True value:	4.0%
Non-inferior margin:	0.5 on the hazard ratio scale (2.0%: 50% of the true value)
Power:	90%
One-sided alpha:	0.025
Randomization ratio:	1:1

On the above hypothesis, in order to demonstrate non-inferiority of 1-month DAPT to 12 months DAPT on primary endpoint, a sample size of 2,018 patients in each arm, total 4,036 patients will be required. Taking into consideration of dropout cases, we plan to enroll a total of 4,100 ACS patients including the patients already enrolled in original STOPDAPT-2 (additional 3,000 ACS patients in current study).

Based on the observed incidence rate of 1,148 ACS patients in the preceding STOPDAPT-2 (the 1-year incidence rate of major secondary cardiovascular composite endpoint in is 3.0% and the incidence of major secondary bleeding endpoint is 1.5%), the total number of 4100 patients to be enrolled would provide

1) 80% power in the non-inferiority test for major secondary cardiovascular composite endpoints, and

2) 81% power in the superiority test for the major secondary bleeding endpoint under the assumption that the relative risk reduction of the 1-month group would be 60%.

Framework

STOPDAPT-2 ACS is planned to prove the hypothesis of the non-inferiority about the incidence of the primary outcome of the experimental arm (1-month DAPT regimen) compared with the control arm (12-month DAPT) at one year after index PCI. The verifications for the endpoints of this research shall be performed hierarchically in the following order.

1. Non-inferiority test on the primary endpoint
2. Non-inferiority test of major secondary cardiovascular composite endpoint
3. Superiority test of major secondary bleeding endpoint
4. Superiority test for the primary endpoints

If non-inferiority of the 1-month DAPT group as compared with the 12-month DAPT group was met, we used a pre-specified hierarchical testing procedure with the use of a gatekeeping method to control for multiple comparisons; P values are presented with claim of significance. If statistical significance was not met in any test, P values would not be reported for this and subsequent outcomes; hazard ratios and 95% confidence intervals are presented without P values. The non-inferiority margin is set to be 1.5 on the hazard ratio scale of the Cox proportional hazard model.

Statistical interim analyses and stopping guidance

There was no plan to conduct statistical interim analysis. However, when any adverse events that are clearly related to this study occur, the independent safety evaluation committee shall discuss whether the study should be continued. Observation period of this study is as long as 60 months, and when primary analysis at the time of 12-month follow-up will be conducted, composite endpoints and also individual endpoints shall be evaluated, and the safety evaluation committee will be held at the time and judge whether the continuation of study is appropriate or not.

Timing of final analysis

The timing of primary analysis is planned at one-year and that of secondary

analysis is at 5-year.

Timing of outcome assessments

We set timing of outcome assessments as follows (protocol article 6.1)

1) At enrollment
2) Follow-up at 1 month after procedure (At the outpatient visit in principle after at 30 days before at 60 days)
3) Follow-up at 12 months after procedure (At the outpatient visit in principle after at 335 days at before 395 days)
4) Follow-up at 24 months after procedure (At the outpatient visit in principle after at 700 days at before 760 days)
5) Follow-up at 36 months after procedure (At the outpatient visit in principle after at 1065 days at before 1125 days)
6) Follow-up at 48 months after procedure (At the outpatient visit in principle after at 1430 days at before 1490 days)
7) Follow-up at 60 months after procedure (At the outpatient visit in principle after at 1795 days at before 1855 days)

4. Statistical Principles

Concealment of treatment allocation

Treatment allocation (experimental arm and control arm) will be concealed to study statistician and other analyzed in charge. We describe the anonymous treatment allocation (X arm and Y arm) in this section. For non-inferiority analyses, we conduct both analyses of X arm and Y arm as experimental arm.

Confidence intervals and P values

We set level of statistical significance (alpha) as 5%. We conduct all analyses in two-tailed except for non-inferiority analysis. We set one-tailed alpha 2.5% as significance level in non-inferiority analysis. We have no plan to conduct any adjustment about hazard ratio calculation. 95% confidence intervals will be reported by Wald statistics. See chapter 6 for detailed method of statistical analysis.

Adherence and protocol deviations

Whether participants receive assigned antiplatelet therapy or not were made at one-month and 12-month visit, and on web database, investigators input whether treatment is being performed according to the protocol or not, apart from the clinical events being tracked.
Moreover, to grasp temporary discontinuation or change of antithrombotic drug, investigators shall input the information about all discontinuation and restart of aspirin, P2Y12 inhibitors, and anticoagulation drug. From the data, we will depict the rate of persistent discontinuation rate of dual antiplatelet therapy. This rate was defined as discontinuation over 60 days of either aspirin or P2Y12 inhibitors from J-Cypher registry.[8]

Analysis populations

Population for Intention-to-treat analysis

The main analyses were performed for the full analysis set which included patients who received an allocated treatment and provided assessable endpoint data in the intention-to-treat population. Moreover, per-protocol and as-treated analysis will be conducted to avoid bias of open-label assigned group and confirm the consistency of non-inferiority as follows.[27,28]

Population for per-protocol analysis

This analysis included the patients in 1-month DAPT group receiving clopidogrel monotherapy without aspirin, and the patients in 12-month DAPT group receiving both aspirin and clopidogrel at 60-day after index PCI. Patients with oral anticoagulants use, use of other antiplatelet therapy, history of hemorrhagic stroke, and history of implantation of bioabsorbable vascular scaffolds were excluded according to the protocol defined exclusion criteria.

Population for as-treated analysis

In this analysis, regardless of randomly assigned group, 1) the patients receiving clopidogrel monotherapy without oral anticoagulants at 60-day were set as clopidogrel monotherapy group, and 2) the patients receiving both aspirin and

clopidogrel without anticoagulants at 60-day were set as aspirin plus clopidogrel group. We did not consider other exclusion criteria (history of hemorrhagic stroke, oral anticoagulants use, use of other antiplatelet therapy, history of implantation of bioabsorbable vascular scaffolds).

Population for sensitivity analysis (worst-case-scenario)

As a sensitivity analysis, we plan the analysis of worst-case-scenario assuming that patients lost to follow-up in the experimental arm had the primary endpoint event, while those in the control arm did not have the event. We will conduct the analysis with all assigned patients without withdrawal of consent.

5. Trial Population

Screening data, eligibility, and patient recruitment

The site investigators will make PCI-log to collect and screen the patients with one or more Cobalt-chromium everolimus-eluting (CoCr-EES) stents for the diagnosis of ACS. Among the patients in the log, the patients with other type of drug-eluting stents at index PCI or planed staged PCI procedure will be excluded and cannot be enrolled in the current study. Among the rest of patients (patients with CoCr-EES only and without planned procedure), patients who do not match any of exclusion criteria and are given informed consent will be registered as participants and assigned into one of the two treatment regimen. For the non-participants, we collect the information of the patients to explore the background of patients who are eligible to the study but do not participate (screening log). Collected items in the screening log are as follows; patient name, age, sex, height, weight, diagnosis, the presence or absence of hypertension, the presence or absence of diabetes mellitus (insulin, oral drugs, or diet), history of myocardial infarction, history of stroke (cerebral infarction or cerebral hemorrhage), creatinine level, presence or absence of dialysis, presence or absence of atrial fibrillation, oral anticoagulant therapy, history of PCI, history of the first-generation DES implantation, history of BVS implantation, history of heart failure, presence or absence of peripheral vessel/aortic diseases, smoking status, presence or absence of multivessel treatment, number of target lesions, location of target lesion, number of implanted stent, size of implanted stent, major complication (MI, stroke, major bleeding) after index

PCI procedure, presence or absence of tolerability to clopidogrel, administration of antiplatelet drugs other than aspirin and P2Y12 receptor antagonists, presence or absence of planned surgical operation, and planned DAPT duration (see protocol article 4.1).
Information to be included in the study flow are; the total number of patients in PCI-log, the total number of patients with CoCr-EES only and without planned staged PCI, the number of patients without participation and the breakdown of the reasons, the number of assigned patients, the numbers of patients with each treatment arm, the numbers of patients who withdraw the consent of participation in each arm, the number of patients included into analysis, and the percentage of patients with complete one-year follow-up.

Withdrawal/follow-up

When enrolled patients withdraw the consent of participation during follow-up, the data of the patients are excluded from the analysis totally. In such cases, details of withdrawal are recorded. If the enrolled patient becomes unable to be followed, it is censored at the time of the last trackable date and an event up to that point will be input and analyzed.

Baseline patient characteristics

Analyzed baseline characteristics are as follows. Please see protocol 6.2.1

1. Enrollment data

Name of institute, date of enrollment, patient enrollment number, and name of the investigator.

2. Basic data

Age, sex, height, weight, date of hospitalization, blood pressure and pulse rate at the hospital arrival, cardiopulmonary arrest on arrival.

3. Diagnosis of myocardial infarction (MI) or angina pectoris (select from below)

ST-elevation acute myocardial infarction (MI), Non ST-elevation acute MI, stable angina pectoris, unstable angina pectoris, asymptomatic myocardial ischemia, old myocardial ischemia, and coronary stenosis.

4. Additional information about ACS

Presence/Absence of ECG change, imaging evidence of new loss of viable myocardium or new regional wall motion abnormality, site of myocardial infarction, location of culprit lesion, time between onset and hospital arrival, time between hospital arrival and PCI (wire cross), Killip classification, use of percutaneous circulatory support device (ECMO, Impella, IABP)

5. History of cardiac diseases

History of PCI, implantation history of bare metal stent, implantation history of 1st generation DES, implantation history of other DES, implantation history of BVS, history of CABG, history of myocardial infarction (MI), history of stent thrombosis, history of heart failure, history of stroke*[1], history of atrial fibrillation, history of COPD, history of liver cirrhosis, history of malignant tumor*[2], history of hemorrhagic disease*[3], chronic bleeding diathesis*[4], chronic use of oral NSAIDs and steroids, and recent major surgery or major trauma within 30 days prior to PCI.

*[1] Previous spontaneous intracranial hemorrhage (ICH), previous traumatic ICH within the past 12 months, presence of a brain AV malformation, moderate or severe ischemic stroke within the past 6 months, or other ischemic strokes.

*[2] Additionally, input about malignancy diagnosed within 12 months prior to PCI or ongoing malignant disease (excluding non-melanoma skin cancer).

*[3] Requiring hospitalization or blood transfusion.

*[4] e.g. von Willebrand disease, hemophilia, and so on, excluding thrombocytopenia.

6. Complications

Complication of heart failure at hospitalization, heart failure (current or past history), carotid artery stenosis, arteriosclerosis obliterans, peripheral artery disease excluding carotid arteries or arteriosclerosis obliterans, aortic aneurism/dissection, diseases of the aorta/ peripheral vessels (all), diseases of the aorta/peripheral vessels (postoperative/planned to be treated), and dialysis.

7. Risk factors

Hypertension, Lipid abnormalities, smoking, diabetes mellitus, and family history of coronary diseases.

8. Concomitant medication

The presence or absence of anticoagulation therapy, and the presence or absence of other antiplatelet therapy than aspirin and thienopyridines.

9. Coronary angiographic findings (initial angiography in the index hospitalization)

Procedure date of coronary angiography, stenotic lesions, number of branches affected, presence/absence of following lesions; unprotected left main lesion and chronic total occlusive (CTO) lesion, left ventricular ejection fraction, measurement method for left ventricular ejection fraction, mitral insufficiency, and evaluation method for mitral insufficiency.

10. Evaluation of Myocardial Ischemia

Myocardial Scintigraphy (positive or negative), Invasive FFR (positive or negative), and CT FFR (positive or negative).

11. PCI Baseline Observation (including all planned and staged procedure)

Per patient analysis: PCI procedure date, emergency procedure, target lesion segment, presence/absence of following treatments: treatment of unprotected left main coronary artery stenosis, treatment of CTO, stenting of the last remaining patent coronary artery, treatment of ST-elevation acute MI culprit lesion, treatment of bifurcation lesion, treatment of 2 branches or more, treatment of 3 branches or more, treatment of in-stent restenosis lesion, and treatment of RCA ostial lesion, implanted stent diameter, and implanted stent length.

Per lesion analysis: target lesion, lesion classification (new lesion, residual lesion, lesion of in-stent-restenosis, lesion of restenosis except of stents), in-stent-restenosis pattern (BMS, Cypher, Taxus, Endeavor, Xience, Promus, Nobori, Resolute, other DES, and BVS [multiple choice allowed]), STEMI culprit lesion, ostial lesion, LMT distal bifurcation, unprotected LMT lesion, CTO lesion, severe calcified lesion, presence/absence of thrombus, lesion and proximal tortuousness, lesion and proximal bending (over an angle of 90 degrees), thrombus

aspiration, stenting attempt, direct stenting, intervention before stenting (POBA, DEB, Cutting Balloon, Directional Coronary Atherectomy, Rotablator, aspiration, other, unknown), stenting (name of stent, diameter, length, expanding pressure, implanted site), post dilatation (balloon diameter, pressure), IVUS use, OCT use, bifurcation lesion, branch lesion, bifurcation type, bifurcation strategy, stent classification (only XIENCE, XIENCE and BMS)

12. Clinical laboratory tests

WBC, RBC, hemoglobin, hematocrit, platelet counts, creatinine, blood glucose, HbA1c, total cholesterol, HDL cholesterol, and triglyceride.
Before Index PCI: CK, CKMB, Troponin T or I: presence/absence of measurement, measured value (positive/negative or quantitative value), upper limit of normal if the tested in site other than participating institution.
After Index PCI: CK, CKMB, Troponin T or I: presence/absence of measurement, measured peak value (positive/negative or quantitative value), upper limited of normal of the institute.

13. Electrocardiogram (ECG) after procedure

14. Planned surgical operation

Presence or absence of planned surgical operation, planned timing of the operation, detail of the surgical operation

15. Observation Items at Discharge

Discharge date and medication at discharge

Nominal variables are expressed as number and percentages. Continuous numbers are expressed as medina (IQR) or mean ±SD depending on its distribution.

6. Analysis

Data cleaning, and missing data

At first we will perform data cleaning and inquire participating facilities regarding obvious outliers. If the true value is unknown, treat it as missing data. An unknown

case of BMI is considered to be low BMI (BMI <25). For cases without hemoglobin or without platelet value, set as without anemia or without thrombocytopenia, respectively. Because the missing rate of ejection fraction tend to be relatively high, LVEF <40% is handled only when LVEF is measured.

Outcome definitions

The primary analysis is conducted to compare net clinical benefit between two groups during one-year after index PCI. The primary endpoint in current study is the composite of cardiovascular death, myocardial infarction (MI), stroke (ischemic and hemorrhagic), stent thrombosis (Definite stent thrombosis yet to develop into MI), and severe bleeding (TIMI Major/Minor) at 12 months. Non-inferiority of 1-month DAPT group will be verified compared with 12-month DAPT group.

The primary endpoint of follow-up analysis is the same as above, the composite of cardiovascular death, MI, stroke (ischemic or hemorrhagic), stent thrombosis (definite stent thrombosis yet to develop into MI), and severe bleeding (TIMI Major/Minor) at 60 months. Superiority of 1-month DAPT group will be verified compared with 12-month group.

In this study, the following major secondary endpoints will be evaluated

- 12-month observation
  - Major secondary cardiovascular composite endpoint:
    Cardiovascular death/ MI/ stroke/ definite ST
  - Major secondary bleeding endpoint:
    Bleeding with TIMI Major/ Minor criteria
- 60-month observation
  - Major secondary cardiovascular composite endpoint:
    Cardiovascular death/ MI/ stroke/ definite ST
  - Major secondary bleeding endpoint:
    Bleeding with TIMI Major/ Minor criteria
  - Upper gastrointestinal endoscopy / upper gastrointestinal endoscopic treatment

In this study, the following secondary endpoints will be also evaluated at 12 months and at 60 months observation

- Death
- Death from cardiac cause
- Death from cardiovascular cause
- Death from non-cardiovascular cause
- MI
- Large MI (CKMB>=10 times of upper limit of normal [ULN])
- Small MI (CKMB<10 times of ULN)
- MI without CKMB elevation
- MI without measurement of CKMB
- Stroke (ischemic/hemorrhagic)
- Ischemic stroke
- Hemorrhagic stroke
- Stent thrombosis (definite, probable, definite/probable in ARC definition)
- Bleeding (TIMI criteria, BARC criteria, and GUSTO criteria)
- Intracranial bleeding
- Gastrointestinal bleeding
- MACE (composite of death from cardiac cause. MI and clinically-driven TLR)
- Death / MI
- Cardiovascular death/ MI
- Any coronary revascularization
- Any TLR
- Clinically-driven TLR
- Non-TLR
- TLF
- TVF
- CABG

See also protocol article 7
MI and ST are defined as ARC study definition, Stroke is defined as neurological deficits lasting over 24 hours. Bleeding criteria is used according to TIMI bleeding but GUSTO or BARC classification is also used. See also protocol article 12.

Analysis methods

Background comparison

Background comparison are made with chi-square tests for nominal variable and ANOVA, Welch test or Wilcoxon test depending on its distribution and variance. Following analysis will be planed

1) Assigned patients vs eligible but not participating patients
2) 1-month DAPT group vs 12-month DAPT group

The ratio of participating patients and not-participating patients in each institutes will be calculated.
Proportion of patients on DAPT was calculated by the number of patients on DAPT divided by those in the cohorts in each arm.

Cumulative incidence and hazard ratio

Cumulative incidence rate
The calculation of cumulative incidence is made by Kaplan-Meier method and compared with Log-rank test.

Absolute risk reduction of cumulative incidence and 95% confidential interval
Absolute risk reduction (ARR) of the cumulative incidence is calculated with the event rate and its standard error output from the survival analysis.
When event rate (*EV1*) and its standard error (*SE1*) in experimental group 1 and event rate (*EV2*) and its standard error (*SE2*) in control group 2 are given,
Point estimate of ARR=*EV1*-EV2
Lower value of 95%CI of ARR= NORM.INV (0.025, (*EV1*-*EV2*), SQRT(*SE1*^2+*SE2*^2))
Lower value of 95%CI of ARR= NORM.INV (0.975, (*EV1*-*EV2*), SQRT(*SE1*^2+*SE2*^2))
Here, NORM.INV is the function of Excel™ (Microsoft, Washington, US).

Hazard ratio and 95% confidential interval

Hazard ratio is calculated with Cox proportional hazard model. P values for non-inferiority and superiority analyses are made with the beta estimate and its standard error of Cox hazard model as follows;

One-sided $P_{non\text{-}inferiority}=1-P_0$,
when $P_0 = NORM.DIST(LN(1.5), \beta, SE, TRUE)$

Two-sided $P_{superiority}=\begin{cases} if\ P_0 > 0.5, 2(1-P_0) \\ if\ P_0 \leq 0.5, 2P_0 \end{cases}$,

when $P_0 = NORM.DIST(0, \beta, SE, TRUE)$

Here, 1.5 is prespecified non-inferiority margin, β is beta estimate, and *SE* is standard error in output of Cox proportional hazard model. NORM.DIST and LN() are the function of Excel™ (Microsoft, Washington, US).

95% confidential interval (CI) of hazard ratio is calculated with Wald statistics as follows.
Lower border of 95%CI = EXP (NORM.INV(0.025, β, *SE*))
Upper border of 95%CI = EXP (NORM.INV(0.975, β, *SE*))
Here, β is beta estimate, and *SE* is standard error in output of Cox proportional hazard model. NORM.INV and EXP() are the function of Excel™ (Microsoft, Washington, US).

Adjustment of hazard ratio, mixed effect model with site as a random effect

Because current study is randomized control study, basically hazard ratio will be evaluated without any adjustment. But in case that some important background variables are different with statistically significance, we consider calculating hazard ratio with adjustment of the variables.
As for the adjustment of site effect, we will construct the mixed effect model with site as a random effect for the primary endpoint and confirm that the estimate of original analysis is similar or not to that from mixed effect.

Landmark analysis

We will conduct landmark analysis to evaluate incidence rate or hazard ratio beyond prespecified landmark point as for all endpoints. Because the assigned treatment between two groups will become gradually different during allowance period of 1-month (30-day to 60-day), we set landmark point as 30-day and 60-day after index PCI.

Subgroup analysis

Subgroup analysis will be made to compare the HR of experimental arm against control arm stratified by prespecified subgroups defined in protocol 9.1. Here, we will calculate the HRs stratified by subgroups and $P_{interaction}$ between presence and absence of the subgroup factor to explore the difference of effect.

Statistical software

JMP ver 14.0 (Watanabe H) and SAS version 9.4 (Morimoto T, both are produced by SAS Institute, Cary, North Carolina

References

1) Moses JW, Leon MB, Popma JJ, et al. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. N Engl J Med. 2003;349:1315-23.

2) Stone GW, Ellis SG, Cox DA, et al. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. N Engl J Med. 2004;350:221-31.

3) Kimura T, Morimoto T, Nakagawa Y, et al. Very late stent thrombosis and late target lesion revascularization after sirolimus-eluting stent implantation: five-year outcome of the j-Cypher Registry. Circulation. 2012;125:584-91.

4) Raber L, Magro M, Stefanini GG, et al. Very late coronary stent thrombosis of a newer-generation everolimus-eluting stent compared with early-generation drug-eluting stents: a prospective cohort study. Circulation. 2012;125:1110-112.

5) Schoming A, Neumann FJ, Kastrati A, et al. A randomized comparison of antiplatelet and anticoagulant therapy after the placement of coronary-artery stents. N Engl J Med. 1996;334:1084-89.

6) Leon MB, Baim DS, Popma JJ, et al. A clinical trial comparing three antithrombotic-drug regimens after coronary-artery stenting. Stent Anticoagulation Restenosis Study Investigators. N Engl J Med. 1998;339:1665-71.

7) Kimura T, Morimoto T, Natsuaki M, et al. Comparison of everolimus—eluting and sirolimus-eluting coronary stents: 1-year outcomes from the Randomized Evaluation of Sirolimus-eluting Versus Everolimus-eluting stent Trial (RESET). Circulation 2012;126:1225-36.

8) Kimura T, Morimoto T, Nakagawa Y, et al. Antiplatelet therapy and stent thrombosis after sirolimus-eluting stent implantation. Circulation. 2009;119:987-95.

9) Gwon HC, Hahn JY, Park KW, et al. Six-month versus 12-month dual antiplatelet therapy after implantation of drug-eluting stents: the Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting (EXCELLENT) randomized, multicenter study. Circulation. 2012;125:505-13.

10) Valgimigli M, Campo G, Monti M, et al. Short- Versus Long-term Duration of Dual Antiplatelet Therapy After Coronary Stenting: A Randomized Multicentre Trial. Circulation. 2012;125(16):2015-26.

11) Colombo A, Chieffo A, Frasheri A, et al. Second-generation drug-eluting stent implantation followed by 6- versus 12-month dual antiplatelet therapy: the SECURITY randomized clinical trial. J Am Coll Cardiol. 2014;64(20):2086-97.

12) Gilard M, Barragan P, Noryani AA, et al. 6- versus 24-month dual antiplatelet therapy after implantation of drug-eluting stents in patients nonresistant to aspirin: the randomized, multicenter ITALIC trial. J Am Coll Cardiol. 2015;65(8):777-86

13) Natsuaki M, Morimoto T, Yamamoto E, et al. One-year outcome of a prospective trial stopping dual antiplatelet therapy at 3 months after everolimus-eluting cobalt-chromium stent implantation: ShortT and OPtimal duration of Dual AntiPlatelet Therapy after everolimus-eluting cobalt-chromium stent (STOPDAPT) trial. Cardiovasc Interv and Ther. 2016;31(3):196-209

14) Vranckx P, Valgimigli M, Juni P, et al. Ticagrelor plus aspirin for 1 month, followed by ticagrelor monotherapy for 23 months vs aspirin plus clopidogrel or ticagrelor for 12 months, followed by aspirin monotherapy for 12 months after implantation of a drug-eluting stent: a multicentre, open-label, randomised superiority trial. Lancet 2018;392(10151):940-949.

15) Urban P, Meredith IT, Abizaid A, et al. Polymer-free drug-coated coronary stents in patients at high bleeding risk. N Engl J Med. 2015;373(21):2038-47.

16) Palmerini T, Biondi-Zoccai G, Della Riva D, et al. Stent thrombosis with drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis. Lancet 2012;379(9824):1393-402

17) Tada T, Natsuaki M, Morimoto T, et al. Duration of dual antiplatelet therapy and long-term clinical outcome after coronary drug-eluting stent implantation: landmark analyses from the CREDO-Kyoto PCI/CABG Registry Cohort-2. Circulation. Cardiovascular interventions 2012;5(3):381-91

18) Toyoda K, Yasaka M, Iwade K, et al. Dual antithrombotic therapy increases severe bleeding events in patients with stroke and cardiovascular disease: a prospective, multicenter, observational study. Stroke. 2008;39:1740-5.

19) Watanabe H, Domei T, Morimoto T, et al. Effect of 1-month dual antiplatelet therapy followed by clopidogrel vs 12-month dual antiplatelet therapy on cardiovascular and bleeding events in patients receiving PCI; The STOPDAPT-2 randomized clinical trial, JAMA 2019 in press, doi;XXX

20) Yahata H, Corley DA, Nakahata F, et al. aspirin and non-aspirin NSAIDs increase risk of colonic diverticular bleeding: a systematic review and meta-analysis. J Gastroenterol. 2014;49:992-1000.

20) Gent M, Beaumont D, Blanchard J, et al. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee. Lancet 1996;348:1329-39.

21) Valgimigli M, Bueno H, Byrne RA, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2018;39:213–260

22) Bittl JA, Baber U, Bradley SM, et al. Duration of Dual Antiplatelet Therapy: A Systematic Review for the 2016 ACC/AHA Guideline Focused Update on

Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2016;68(10):1116-39.

23) Yusuf S, Zhao F, Mehta SR, et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med. 2001;345(7):494-502.

24) Mehta SR, Yusuf S, Peters RJ, et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. Lancet. 2001;358(9281):527-33.

25) Rao AK, Pratt C, Berke A, et al. Thrombolysis in Myocardial Infarction (TIMI) trial: phase I: hemorrhagic manifestations and changes in plasma fibrinogen and the fibrinolytic system in patients treated with recombinant tissue plasminogen activator and streptokinase. J Am Coll Cardiol. 1988;11:1-11.

26) Natsuaki M, Kozuma K, Morimoto T, et al. Final 3-Year Outcome of a Randomized Trial Comparing Second-Generation Drug-Eluting Stents Using Either Biodegradable Polymer or Durable Polymer: NOBORI Biolimus-Eluting Versus XIENCE/PROMUS Everolimus-Eluting Stent Trial. Circ Cardiovasc Interv. 2015;8(10):e002817.

27) Mauri L, D'Agostino RB. Challenges in the Design and Interpretation of Noninferiority Trials. N Engl J Med. 2017;377:1357–1367.

28) Macaya F, Ryan N, Salinas P, Pocock SJ. Challenges in the Design and Interpretation of Noninferiority Trials: Insights From Recent Stent Trials. J Am Coll Cardiol. 2017;70:894–903.

STOPDAPT-2 ACS

ShorT and OPtimal duration of Dual AntiPlatelet Therapy-2 study for the patients with ACS

Statistical Analysis Plans

＜Date of preparation; 5th June, 2019 Ver 1.1>
＜Date of preparation; 6th April, 2021 Ver 2.1>

1. Administrative Information

Title of the study; ShorT and OPtimal duration of Dual AntiPlatelet Therapy-2 study for patients with ACS
[Study to Evaluate the Safety of Reducing Dual Antiplatelet Therapy (DAPT) Duration to 1 Month for patients with acute coronary syndrome (ACS) after Implantation of Everolimus-eluting Cobalt-chromium Stent]
Trial registration number; NCT 03462498
Study protocol version; ver. 3.3
Version of current SAP; ver 2.1, 2021.4.6
SAP revisions;

Version	Date of revision	Major changes	Notes
Ver 1.1	June 5, 2019	New document	N/A
Ver 2.1	April 6, 2021	Add descriptions about data screening, event adjudication, any other adverse events than study outcome measure, and how to display the p-value about secondary outcome analysis. Add the “studies” (STOPDAPT-2 or STOPDAPT-2 ACS) as the prespecified subgroup	Check before main analysis

Roles and responsibility:

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2. Introduction

Background and rationale

See also study protocol article 2.

The sirolimus-eluting stent and the paclitaxel-eluting stent, which are known as the first-generation drug-eluting stents (DESs), have already achieved remarkable results, as represented in reducing restenosis rate to 10% or less at 1 year after coronary stenting, so that DESs are currently used in the majority of PCI procedures.[1,2] On the other hand, even though the frequency is low, the problems of the first-generation DES (i.e., late adverse events, such as very late stent thrombosis and late restenosis at 1 year or later, which rarely occur in conventional bare-metal stents [BMSs]) have been pointed out.[3,4]

Since P2Y12 platelet receptor antagonists, when used in combination with aspirin for 1 month, have been indicated to significantly suppress the occurrence of stent thrombosis after BMS implantation, DAPT, in which aspirin and a P2Y12 platelet receptor antagonist are used in combination for 1 month after BMS implantation, has become a standard regimen.[5,6] At the same time, for fear of very late stent thrombosis, DAPT is frequently performed for 1 year or longer after DES implantation in clinical practice. In RESET (Randomized Evaluation of Sirolimus-eluting versus Everolimus-eluting stent Trial) conducted in clinical practice in Japan, 90% of the subjects had been on DAPT for 1 year or longer.[7] Moreover, in the package insert of the Everolimus-eluting stent (EES), currently the most extensively used DES in Japan, 1-year DAPT is recommended. However, serious hemorrhagic complications, such as cerebral hemorrhage, associated with a prolonged DAPT duration can bring disadvantages to patients, it is extremely important to clarify an optimal DAPT duration after DES procedure. Based on the results of large-scale observational studies and small-scale randomized controlled studies, DAPT for 6 months or longer[8-12] had no inhibitory effects on the onset of serious cardiovascular events. Furthermore, we have recently assessed the safety of a DAPT regimen for 3 months after CoCr-EES implantation in STOPDAPT (ShorT and OPtimal duration of Dual AntiPlatelet Therapy study after everolimus-eluting cobalt-chromium stent) study, using the RESET study, in which DAPT had been performed in 90% of subjects for 1 year or longer, as a historical control.[13] More recently, attempt to further reduce

DAPT duration after DES procedure begins. In Global LEADERS (A Clinical Study Comparing Two Forms of Anti-platelet Therapy After Stent Implantation: NCT01813435) study, the safety of a DAPT regimen with ticagrelor, a new P2Y12 platelet receptor antagonist for 1 month after DES procedure was evaluated and although in primary analysis the study hypothesis was not statically proven, the effectiveness and feasibility of 1 month DAPT regimen were shown.[14] In addition, in LEADERS FREE (A Randomized Clinical Evaluation of the BioFreedom™ Stent: NCT01623180) study, the efficacy and safety of polymer-free DES (BioFreedom™) compared with BMS in 1-month DAPT regimen are proven in the subject group with a high bleeding risk.[15] Currently, 1-month DAPT regimen after BMS implantation is commonly used in clinical practice, producing no major problems. Based on a meta-analysis of recent clinical studies, it has also been reported that the use of CoCr-EES reduces the risk of early stent thrombosis by half compared to the use of BMS.[16] At least from a logical standpoint, there is no necessity to extend antiplatelet therapy after CoCr-EES implantation longer than after BMS implantation, and it is considered possible to use the same 1-month DAPT duration as after BMS implantation. On the other hand, for bleeding complication, it is clear that a prolonged DAPT duration increases bleeding complications compared to aspirin monotherapy.[10,16-18] We therefore started STOPDAPT-2 (NCT02619760), a multicenter, randomized, open-label, controlled study, in which DAPT is discontinued at 1 month after stenting in subjects who have undergone CoCr-EES procedure, which is considered to be associated with a lower risk of stent thrombosis than BMS, to compare incidences of cardiovascular events and bleeding events at 12 months after stenting between the 1-month DAPT group and the 12-month DAPT group.[19]

In this study, for antiplatelet therapy after the discontinuation of DAPT at 1 month, we will use clopidogrel, a P2Y12 receptor antagonist considered to be a key drug for stent thrombosis prophylaxis,[6] instead of the conventional aspirin monotherapy. Although aspirin is an inexpensive drug with a proven efficacy for preventing cardiovascular events in patients with coronary artery diseases, its side effects, such as gastrointestinal mucosal injury and gastrointestinal bleeding, are pointed out as a problem.[20] Based on the CAPRIE study results, it has been reported that clopidogrel monotherapy significantly suppressed cardiovascular events in patients with cardiovascular diseases compared to aspirin monotherapy.[21] It is known that a higher

percentage of Japanese patients have resistance to the platelet aggregation inhibitory effect of clopidogrel attributable to CYP2C19 polymorphism. Even under such circumstances in Japan, clopidogrel monotherapy has been standard antiplatelet therapy in the cerebrovascular region, and recently there have been an increasing number of cases in which clopidogrel monotherapy is chosen after DAPT discontinuation in patients with coronary stent. To perform clopidogrel monotherapy after DAPT discontinuation in Japanese patients, it is necessary to verify its effectiveness and safety, data of which, however, have been still insufficient. In the STOPDAPT-2, the superiority of clopidogrel monotherapy after 1-month DAPT over aspirin monotherapy after 12-month DAPT will be verified by comparing results of clopidogrel monotherapy continued up to 5 years after DAPT discontinuation in the 1-month DAPT group and aspirin monotherapy continued up to 5 years after DAPT discontinuation in the 12-month DAPT group.

In the current AHA/ACC or ESC guidelines, 12-month DAPT is standard recommendation for patients with ACS, though 6-month DAPT is recommended for stable coronary artery disease[21,22]. However, the rational of the longer DAPT duration for ACS patients was based only on the CURE study, which was performed more than 15 years ago[23,24]. We previously reported the incidence of ischemic events beyond 3 months after index PCI was not different between the acute myocardial infarction (AMI) patients and non-AMI patients in registry data[25]. Therefore, in contemporary clinical practice using 2nd generation DES, there is no solid rationale to recommend extended DAPT duration in patients with ACS. In the ongoing STOPDAPT-2 study, the proportion of ACS cases is expected to be 30 to 40% of the entire study population, and the power is insufficient to evaluate safety of 1-month DAPT in ACS patients. Therefore, we designed the STOPDAPT-2 ACS study, in which we would enroll only ACS patients with the same protocol as the STOPDAPT-2 and analyze the safety of 1-month DAPT in ACS patients. We would combine the two studies to include the ACS patients enrolled in the STOPDAPT-2.

Study Objectives

The purpose of this study is to evaluate the safety of reducing DAPT duration to 1 month after implantation of the everolimus-eluting cobalt-chromium stent (CoCr-

EES) in patients who presented as acute coronary syndrome (ACS).

3. Study Methods

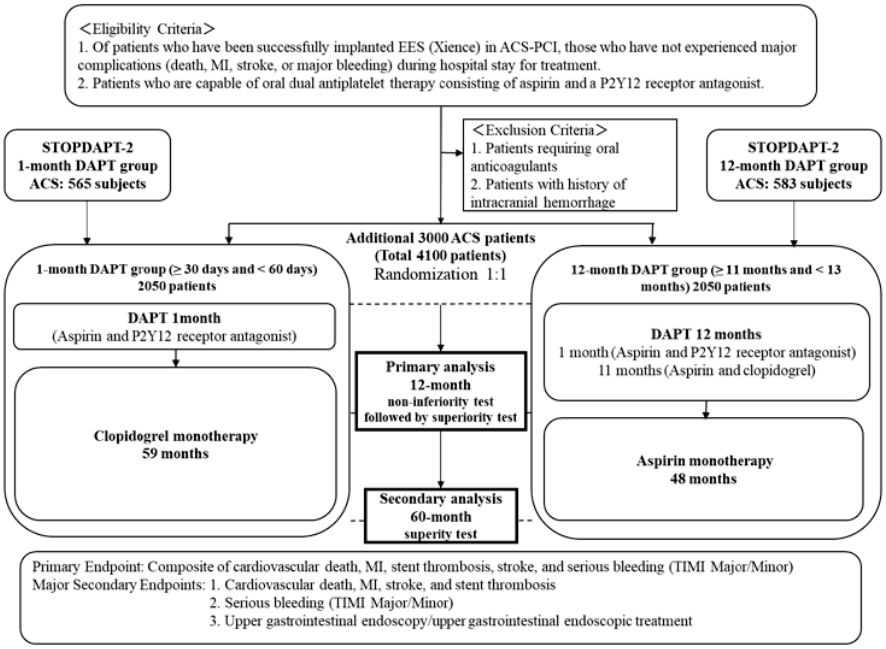
Trial design

STOPDAPT-2 ACS is a multicenter, randomized, open-label but blind for event assessor, controlled study, with parallel group.

ACS Patients with successful CoCr-EES implantation without any in-hospital complication are enrolled and made randomization into two groups, 1-month DAPT followed by clopidogrel monotherapy (experimental arm) or 12-month DAPT comprising of aspirin and clopidogrel (control arm). At 1-year after index PCI, we will assess the non-inferiority of the experimental arm against the control arm as primary analysis about the net clinical outcome, composite of death from cardiovascular death, myocardial infarction, definite stent thrombosis, stroke, and bleeding defined as TIMI major and minor criteria (primary outcome) [25].

After 1-year, we will follow the patient population to assess the long-term efficacy and safety. Patients in experimental arm will continue clopidogrel monotherapy and patients in control arm will discontinued DAPT and change into aspirin monotherapy. At 5-year after index PCI, we will assess the superiority of the experimental arm as secondary analysis. Allocation rate was made as 1:1 fashion.

The main analysis will be made in a total of 4100 patients including 1168 ACS patients enrolled in STOPDAPT-2 ACS.



Randomization

Randomization was performed centrally through the electronic data capture system, with a stochastic minimization algorithm to balance treatment assignment within the centers. Also see protocol article 3.3.

Sample size

See protocol article 8.1

The primary endpoint of this clinical study is the composite of cardiovascular death, MI (excluded periprocedural MI of the index PCI), stroke, stent thrombosis, and serious bleeding and primary analysis is test for non-inferiority analysis of 1 month DAPT group against 12 month DAPT group about incidence rate of primary endpoint up to the 12-month observation point. The following hypothesis was employed to calculate a required sample size.

In the pooled analysis including RESET and NEXT study[7,29], the 1-year incidence rate of the primary endpoint observed in the 533 ACS subjects treated with CoCr-EES was 5.5%. Total 2,676 evaluable patients are required to prove non-inferiority

of 1-month DAPT group against the 12-month DAPT group under the condition that unilateral α is 0.025 and power is 80% with a Cox hazard ratio scale of 1.5 as non-inferiority margin. We initially planned to enroll a total of 3,000 patients including the ACS patients already enrolled in original STOPDAPT-2 (NCT02619760). However, in 1,148 ACS patients enrolled in original STOPDAPT-2, the 1-year incidence rate of 12-month DAPT group was 4.0%, which was lower than the originally assumed event rate of 5.5%. We accordingly increased the sample size calculation to maintain the power to detect the non-inferiority in the primary analysis.

The sample size was calculated using the following hypothesis:

True value:	4.0%
Non-inferior margin:	0.5 on the hazard ratio scale (2.0%: 50% of the true value)
Power:	90%
One-sided alpha:	0.025
Randomization ratio:	1:1

On the above hypothesis, in order to demonstrate non-inferiority of 1-month DAPT to 12 months DAPT on primary endpoint, a sample size of 2,018 patients in each arm, total 4,036 patients will be required. Taking into consideration of dropout cases, we plan to enroll a total of 4,100 ACS patients including the patients already enrolled in original STOPDAPT-2 (additional 3,000 ACS patients in current study).

Based on the observed incidence rate of 1,148 ACS patients in the preceding STOPDAPT-2 (the 1-year incidence rate of major secondary cardiovascular composite endpoint in is 3.0% and the incidence of major secondary bleeding endpoint is 1.5%), the total number of 4100 patients to be enrolled would provide
1) 80% power in the non-inferiority test for major secondary cardiovascular composite endpoints, and
2) 81% power in the superiority test for the major secondary bleeding endpoint under the assumption that the relative risk reduction of the 1-month group would be 60%.

Framework

STOPDAPT-2 ACS is planned to prove the hypothesis of the non-inferiority about the incidence of the primary outcome of the experimental arm (1-month DAPT

regimen) compared with the control arm (12-month DAPT) at one year after index PCI. The verifications for the endpoints of this research shall be performed hierarchically in the following order.

1. Non-inferiority test on the primary endpoint
2. Non-inferiority test of major secondary cardiovascular composite endpoint
3. Superiority test of major secondary bleeding endpoint
4. Superiority test for the primary endpoints

If non-inferiority of the 1-month DAPT group as compared with the 12-month DAPT group was met, we used a pre-specified hierarchical testing procedure with the use of a gatekeeping method to control for multiple comparisons; P values are presented with claim of significance. If statistical significance was not met in any test, P values would not be reported for this and subsequent outcomes; hazard ratios and 95% confidence intervals are presented without P values. The non-inferiority margin is set to be 1.5 on the hazard ratio scale of the Cox proportional hazard model.

Statistical interim analyses and stopping guidance

There was no plan to conduct statistical interim analysis, because the follow-up period of 12 months for primary analysis was short to do interim analysis and the subgroup analysis for ACS group in STOPDAPT-2 trial did not show the risk of trial. However, when any adverse events that are clearly related to this study occur, the independent safety evaluation committee shall discuss whether the study should be continued. Observation period of this study is as long as 60 months, and when primary analysis at the time of 12-month follow-up will be conducted, composite endpoints and also individual endpoints shall be evaluated, and the safety evaluation committee will be held at the time and judge whether the continuation of study is appropriate or not.

Timing of final analysis

The timing of primary analysis is planned at one-year and that of secondary analysis is at 5-year.

Timing of outcome assessments

We set timing of outcome assessments as follows (protocol article 6.1)

1) At enrollment
2) Follow-up at 1 month after procedure (At the outpatient visit in principle after at 30 days before at 60 days)
3) Follow-up at 12 months after procedure (At the outpatient visit in principle after at 335 days at before 395 days)
4) Follow-up at 24 months after procedure (At the outpatient visit in principle after at 700 days at before 760 days)
5) Follow-up at 36 months after procedure (At the outpatient visit in principle after at 1065 days at before 1125 days)
6) Follow-up at 48 months after procedure (At the outpatient visit in principle after at 1430 days at before 1490 days)
7) Follow-up at 60 months after procedure (At the outpatient visit in principle after at 1795 days at before 1855 days)

4. Statistical Principles

Concealment of treatment allocation

Treatment allocation (experimental arm and control arm) will be concealed to study statistician and other analyzed in charge. We describe the anonymous treatment allocation (X arm and Y arm) in this section. For non-inferiority analyses, we conduct both analyses of X arm and Y arm as experimental arm.

Confidence intervals and P values

We set level of statistical significance (alpha) as 5%. We conduct all analyses in two-tailed except for non-inferiority analysis. We set one-tailed alpha 2.5% as significance level in non-inferiority analysis. We have no plan to conduct any adjustment about hazard ratio calculation. 95% confidence intervals will be reported by Wald statistics. See chapter 6 for detailed method of statistical analysis.

Adherence and protocol deviations

Whether participants receive assigned antiplatelet therapy or not will be checked at one-month and 12-month visit, and on web database, investigators will input whether treatment is being performed according to the protocol or not, apart from the clinical events being tracked.
Moreover, to grasp temporary discontinuation or change of antithrombotic drug, investigators shall input the information about all discontinuation and restart of aspirin, P2Y12 inhibitors, and anticoagulation drug. From the data, we will depict the rate of persistent discontinuation rate of dual antiplatelet therapy. This rate was defined as discontinuation over 60 days of either aspirin or P2Y12 inhibitors from J-Cypher registry.[8]

Analytic population

The analytic population is pooled patients of the ACS patients enrolled in the STOPDAPT-2 and STOPDAPT-2 ACS. The following analyses and dataset were based on the analytic population.

Full analysis set for Intention-to-treat analysis

The main analyses will be performed for the full analysis set which included patients who received an allocated treatment and provided assessable endpoint data in the intention-to-treat population after the exclusion of patients declaring the withdrawal of the consent of study participation.
Moreover, for the first non-inferiority test of the primary endpoint (see chapter3. Framework), per-protocol analysis, as-treated analysis, and worst-case-scenario will be conducted to avoid the bias of open-label assigned group and confirm the consistency of non-inferiority. The definitions are as follows.[27,28]

Per-protocol set for per-protocol analysis

This analysis included the patients in 1-month DAPT group receiving clopidogrel monotherapy without aspirin, and the patients in 12-month DAPT group receiving both aspirin and clopidogrel at 60-day after index PCI. Patients with oral anticoagulants use, use of other antiplatelet therapy, history of hemorrhagic stroke,

and history of implantation of bioabsorbable vascular scaffolds were excluded according to the protocol defined exclusion criteria.

As treated set for as-treated analysis

In this analysis, regardless of randomly assigned group, 1) the patients receiving clopidogrel monotherapy without oral anticoagulants at 60-day were set as clopidogrel monotherapy group, and 2) the patients receiving both aspirin and clopidogrel without anticoagulants at 60-day were set as aspirin plus clopidogrel group. We did not consider other exclusion criteria (history of hemorrhagic stroke, oral anticoagulants use, use of other antiplatelet therapy, history of implantation of bioabsorbable vascular scaffolds).

5. Trial Population

Screening data, eligibility, and patient recruitment

The site investigators will make PCI-log to collect and screen the patients with one or more Cobalt-chromium everolimus-eluting (CoCr-EES) stents for the diagnosis of ACS. Among the patients in the log, the patients with other type of drug-eluting stents at index PCI or planed staged PCI procedure will be excluded and cannot be enrolled in the current study. Among the rest of patients (patients with CoCr-EES only and without planned procedure), patients who do not match any of exclusion criteria and are given informed consent will be registered as participants and assigned into one of the two treatment regimen. For the non-participants, we collect the information of the patients to explore the background of patients who are eligible to the study but do not participate (screening log). Collected items in the screening log are as follows; patient name, age, sex, height, weight, diagnosis, the presence or absence of hypertension, the presence or absence of diabetes mellitus (insulin, oral drugs, or diet), history of myocardial infarction, history of stroke (cerebral infarction or cerebral hemorrhage), creatinine level, presence or absence of dialysis, presence or absence of atrial fibrillation, oral anticoagulant therapy, history of PCI, history of the first-generation DES implantation, history of BVS implantation, history of heart failure, presence or absence of peripheral vessel/aortic diseases, smoking status, presence or absence of multivessel treatment, number of target lesions, location of target lesion, number of implanted stent, size of implanted stent, major complication

(MI, stroke, major bleeding) after index PCI procedure, presence or absence of tolerability to clopidogrel, administration of antiplatelet drugs other than aspirin and P2Y12 receptor antagonists, presence or absence of planned surgical operation, and planned DAPT duration (see protocol article 4.1).
Information to be included in the study flow are; the total number of patients in PCI-log, the total number of patients with CoCr-EES only and without planned staged PCI, the number of patients without participation and the breakdown of the reasons, the number of assigned patients, the numbers of patients with each treatment arm, the numbers of patients who withdraw the consent of participation in each arm, the number of patients included into analysis, and the percentage of patients with complete one-year follow-up.

Withdrawal/follow-up

When enrolled patients withdraw the consent of participation during follow-up, the data of the patients are excluded from the analysis totally. In such cases, details of withdrawal are recorded. If the enrolled patient becomes unable to be followed, it is censored at the time of the last trackable date and an event up to that point will be input and analyzed.

Baseline patient characteristics

Analyzed baseline characteristics are as follows. Please see protocol 6.2.1

1. Enrollment data

Name of institute, date of enrollment, patient enrollment number, and name of the investigator.

2. Basic data

Age, sex, height, weight, date of hospitalization, blood pressure and pulse rate at the hospital arrival, cardiopulmonary arrest on arrival.

3. Diagnosis of myocardial infarction (MI) or angina pectoris (select from below)

ST-elevation acute myocardial infarction (MI), Non ST-elevation acute MI, stable angina pectoris, unstable angina pectoris, asymptomatic myocardial ischemia, old myocardial ischemia, and coronary stenosis.

4. Additional information about ACS

Presence/Absence of ECG change, imaging evidence of new loss of viable myocardium or new regional wall motion abnormality, site of myocardial infarction, location of culprit lesion, time between onset and hospital arrival, time between hospital arrival and PCI (wire cross), Killip classification, use of percutaneous circulatory support device (ECMO, Impella, IABP)

5. History of cardiac diseases

History of PCI, implantation history of bare metal stent, implantation history of 1st generation DES, implantation history of other DES, implantation history of BVS, history of CABG, history of myocardial infarction (MI), history of stent thrombosis, history of heart failure, history of stroke*[1], history of atrial fibrillation, history of COPD, history of liver cirrhosis, history of malignant tumor*[2], history of hemorrhagic disease*[3], chronic bleeding diathesis*[4], chronic use of oral NSAIDs and steroids, and recent major surgery or major trauma within 30 days prior to PCI.

*[1] Previous spontaneous intracranial hemorrhage (ICH), previous traumatic ICH within the past 12 months, presence of a brain AV malformation, moderate or severe ischemic stroke within the past 6 months, or other ischemic strokes.

*[2] Additionally, input about malignancy diagnosed within 12 months prior to PCI or ongoing malignant disease (excluding non-melanoma skin cancer).

*[3] Requiring hospitalization or blood transfusion.

*[4] e.g. von Willebrand disease, hemophilia, and so on, excluding thrombocytopenia.

6. Complications

Complication of heart failure at hospitalization, heart failure (current or past history), carotid artery stenosis, arteriosclerosis obliterans, peripheral artery disease excluding carotid arteries or arteriosclerosis obliterans, aortic aneurism/dissection, diseases of the aorta/ peripheral vessels (all), diseases of the aorta/peripheral vessels (postoperative/planned to be treated), and dialysis.

7. Risk factors

Hypertension, Lipid abnormalities, smoking, diabetes mellitus, and family history of coronary diseases.

8. Concomitant medication

The presence or absence of anticoagulation therapy, and the presence or absence of other antiplatelet therapy than aspirin and thienopyridines.

9. Coronary angiographic findings (initial angiography in the index hospitalization)

Procedure date of coronary angiography, stenotic lesions, number of branches affected, presence/absence of following lesions; unprotected left main lesion and chronic total occlusive (CTO) lesion, left ventricular ejection fraction, measurement method for left ventricular ejection fraction, mitral insufficiency, and evaluation method for mitral insufficiency.

10. Evaluation of Myocardial Ischemia

Myocardial Scintigraphy (positive or negative), Invasive FFR (positive or negative), and CT FFR (positive or negative).

11. PCI Baseline Observation (including all planned and staged procedure)

Per patient analysis: PCI procedure date, emergency procedure, target lesion segment, presence/absence of following treatments: treatment of unprotected left main coronary artery stenosis, treatment of CTO, stenting of the last remaining patent coronary artery, treatment of ST-elevation acute MI culprit lesion, treatment of bifurcation lesion, treatment of 2 branches or more, treatment of 3 branches or more, treatment of in-stent restenosis lesion, and treatment of RCA ostial lesion, implanted stent diameter, and implanted stent length.

Per lesion analysis: target lesion, lesion classification (new lesion, residual lesion, lesion of in-stent-restenosis, lesion of restenosis except of stents), in-stent-restenosis pattern (BMS, Cypher, Taxus, Endeavor, Xience, Promus, Nobori, Resolute, other DES, and BVS [multiple choice allowed]), STEMI culprit lesion, ostial lesion, LMT distal bifurcation, unprotected LMT lesion, CTO lesion, severe calcified lesion, presence/absence of thrombus, lesion and proximal tortuousness, lesion and proximal bending (over an angle of 90 degrees), thrombus aspiration,

stenting attempt, direct stenting, intervention before stenting (POBA, DEB, Cutting Balloon, Directional Coronary Atherectomy, Rotablator, aspiration, other, unknown), stenting (name of stent, diameter, length, expanding pressure, implanted site), post dilatation (balloon diameter, pressure), IVUS use, OCT use, bifurcation lesion, branch lesion, bifurcation type, bifurcation strategy, stent classification (only XIENCE, XIENCE and BMS)

12. Clinical laboratory tests

WBC, RBC, hemoglobin, hematocrit, platelet counts, creatinine, blood glucose, HbA1c, total cholesterol, HDL cholesterol, and triglyceride.
Before Index PCI: CK, CKMB, Troponin T or I: presence/absence of measurement, measured value (positive/negative or quantitative value), upper limit of normal if the tested in site other than participating institution.
After Index PCI: CK, CKMB, Troponin T or I: presence/absence of measurement, measured peak value (positive/negative or quantitative value), upper limited of normal of the institute.

13. Electrocardiogram (ECG) after procedure

14. Planned surgical operation

Presence or absence of planned surgical operation, planned timing of the operation, detail of the surgical operation

15. Observation Items at Discharge

Discharge date and medication at discharge

Nominal variables are expressed as number and percentages. Continuous numbers are expressed as medina (IQR) or mean ±SD depending on its distribution.

6. Analysis

Data cleaning, and missing data

At first we will perform data cleaning and inquire participating facilities regarding obvious outliers. If the true value is unknown, treat it as missing data. An unknown

case of BMI is considered to be low BMI (BMI <25). For cases without hemoglobin or without platelet value, set as without anemia or without thrombocytopenia, respectively. Because the missing rate of ejection fraction tend to be relatively high, LVEF <40% is handled only when LVEF is measured.

In data cleaning, the systematic error (e.g. digits, or units) in each center will be appropriately screened. The error associated with different parameters will be checked (e.g. targeting SVG in the patient without prior CABG).

Outcome definitions

The primary analysis is conducted to compare net clinical benefit between two groups during one-year after index PCI. The primary endpoint in current study is the composite of cardiovascular death, myocardial infarction (MI), stroke (ischemic and hemorrhagic), stent thrombosis (Definite stent thrombosis yet to develop into MI), and severe bleeding (TIMI Major/Minor) at 12 months. Non-inferiority of 1-month DAPT group will be verified compared with 12-month DAPT group.

The primary endpoint of follow-up analysis is the same as above, the composite of cardiovascular death, MI, stroke (ischemic or hemorrhagic), stent thrombosis (definite stent thrombosis yet to develop into MI), and severe bleeding (TIMI Major/Minor) at 60 months. Superiority of 1-month DAPT group will be verified compared with 12-month group.

In this study, the following major secondary endpoints will be evaluated

- 12-month observation
  - Major secondary cardiovascular composite endpoint:
    Cardiovascular death/ MI/ stroke/ definite ST
  - Major secondary bleeding endpoint:
    Bleeding with TIMI Major/ Minor criteria
- 60-month observation
  - Major secondary cardiovascular composite endpoint:
    Cardiovascular death/ MI/ stroke/ definite ST

- Major secondary bleeding endpoint:
  Bleeding with TIMI Major/ Minor criteria
- Upper gastrointestinal endoscopy / upper gastrointestinal endoscopic treatment

In this study, the following secondary endpoints will be also evaluated at 12 months and at 60 months observation.

- Death
- Death from cardiac cause
- Death from cardiovascular cause
- Death from non-cardiovascular cause
- MI
- Large MI (CKMB>=10 times of upper limit of normal [ULN])
- Small MI (CKMB<10 times of ULN)
- MI without CKMB elevation
- MI without measurement of CKMB
- Stroke (ischemic/hemorrhagic)
- Ischemic stroke
- Hemorrhagic stroke
- Stent thrombosis (definite, probable, definite/probable in ARC definition)
- Bleeding (TIMI criteria, BARC criteria, and GUSTO criteria)
- Intracranial bleeding
- Gastrointestinal bleeding
- MACE (composite of death from cardiac cause. MI and clinically-driven TLR)
- Death / MI
- Cardiovascular death/ MI
- Any coronary revascularization
- Any TLR
- Clinically-driven TLR
- Non-TLR
- TLF
- TVF
- CABG

See also protocol article 7

MI and ST are defined as ARC study definition, Stroke is defined as neurological deficits lasting over 24 hours. Bleeding criteria is used according to TIMI bleeding but GUSTO or BARC classification is also used. See also protocol article 12.

As for any other adverse events not defined as outcome measure, if the participating centers spontaneously report, the number of events would be reported by the assigned DAPT group and statistical comparison is not scheduled.

Event Adjudication

Event adjudication will be made with blind fashion about assigned group. Based on the data recorded in EDC from each participating centers, at least two event adjudicators assess the clinical events. If the two members of the event judging committee agree, the event will be fixed to that opinion. If they do not agree, another event judge is added until at least two event judges agree. If there is not enough information, the event adjudicator can ask the participating facilities through the study administration office.

Analysis methods

Background comparison

Background comparison are made with chi-square tests for nominal variables and t-test or Wilcoxon rank sum test for continuous variables depending on its distribution. Following analysis will be planed.

1) Assigned patients vs eligible but not participating patients
2) 1-month DAPT group vs 12-month DAPT group

The ratio of participating patients and not-participating patients in each institute will be calculated.
Proportion of patients on DAPT was calculated by the number of patients on DAPT divided by those in the cohorts in each arm.

Cumulative incidence and hazard ratio

Cumulative incidence rate

The calculation of cumulative incidence is made by Kaplan-Meier method and compared with Log-rank test.

Absolute risk reduction of cumulative incidence and 95% confidential interval

Absolute risk reduction (ARR) of the cumulative incidence is calculated with the event rate and its standard error output from the survival analysis.

When event rate (*EV1*) and its standard error (*SE1*) in experimental group 1 and event rate (*EV2*) and its standard error (*SE2*) in control group 2 are given,

Point estimate of ARR=*EV1*-EV2

Lower value of 95%CI of ARR= NORM.INV (0.025, (*EV1*-*EV2*), SQRT(*SE1*^2+*SE2*^2))

Lower value of 95%CI of ARR= NORM.INV (0.975, (*EV1*-*EV2*), SQRT(*SE1*^2+*SE2*^2))

Here, NORM.INV is the function of Excel™ (Microsoft, Washington, US).

Hazard ratio and 95% confidential interval

Hazard ratio is calculated with Cox proportional hazard model. P values for non-inferiority and superiority analyses are made with the beta estimate and its standard error of Cox hazard model as follows;

One-sided $P_{\text{non-inferiority}}=1-P_0$,

when $P_0 = NORM.DIST(LN(1.5), \beta, SE, TRUE)$

Two-sided $P_{\text{superiority}}=\begin{cases} if\ P_0 > 0.5, 2(1-P_0) \\ if\ P_0 \leq 0.5, 2P_0 \end{cases}$,

when $P_0 = NORM.DIST(0, \beta, SE, TRUE)$

Here, 1.5 is prespecified non-inferiority margin, β is beta estimate, and *SE* is standard error in output of Cox proportional hazard model. NORM.DIST and LN() are the function of Excel™ (Microsoft, Washington, US).

95% confidential interval (CI) of hazard ratio is calculated with Wald statistics as follows.

Lower border of 95%CI = EXP (NORM.INV(0.025, β, SE))
Upper border of 95%CI = EXP (NORM.INV(0.975, β, SE))
Here, β is beta estimate, and SE is standard error in output of Cox proportional hazard model. NORM.INV and EXP() are the function of Excel™ (Microsoft, Washington, US).

Again, as for the primary outcome and major secondary outcomes, hierarchical tests will be planned as follows. See Chapter 3. Framework.
1. Non-inferiority test on the primary endpoint
2. Non-inferiority test of major secondary cardiovascular composite endpoint
3. Superiority test of major secondary bleeding endpoint
4. Superiority test for the primary endpoints
Here, P values are presented with claim of significance. If statistical significance was not met in any test, P values would not be reported for this and subsequent outcomes; hazard ratios and 95% confidence intervals are presented without P values.

As for the all other secondary outcomes, the hazard ratios and 95% confidence intervals will be presented without P values.

Worst-case-scenario analyses

As a sensitivity analysis, we plan the analysis of worst-case-scenario assuming that patients lost to follow-up in the experimental arm had the primary endpoint event, while those in the control arm did not have the event. We will conduct the analysis with all assigned patients without withdrawal of consent.

Adjustment of hazard ratio, mixed effect model with site as a random effect

Because current study is randomized control study, basically hazard ratio will be evaluated without any adjustment. But in case that some important background variables are different with statistically significance, we consider calculating hazard ratio with adjustment of the variables.

As for the adjustment of site effect, we will construct the mixed effect model with site as a random effect for the primary endpoint and confirm that the estimate of original analysis is similar or not to that from mixed effect.
These analyses were based on post-hoc and thus considered exploratory.

Landmark analysis

We will conduct landmark analysis to evaluate incidence rate or hazard ratio beyond prespecified landmark point as for all endpoints. Because the assigned treatment between two groups will become gradually different during allowance period of 1-month (30-day to 60-day), we set landmark point as 30-day and 60-day after index PCI.

Subgroup analysis

Subgroup analysis will be made to compare the HR of experimental arm against control arm stratified by prespecified subgroups defined in protocol 9.1. as well as ACS patients enrolled in STOPDAPT-2 and those in STOPDAPT-2 ACS. Here, we will calculate the HRs stratified by subgroups and $P_{interaction}$ between presence and absence of the subgroup factor to explore the difference of effect.

Exploratory analysis

It is possible that the background demographics are different between the ACS patients enrolled in STOPDAPT-2 and those in STOPDAPT-2 ACS. The background comparison will be also conducted between these two studies as well as subgroup analyses as described above

Statistical software

JMP version 15.2 and SAS version 9.4 (both are produced by SAS Institute, Cary, North Carolina)

References

1) Moses JW, Leon MB, Popma JJ, et al. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. N Engl J Med. 2003;349:1315-23.

2) Stone GW, Ellis SG, Cox DA, et al. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. N Engl J Med. 2004;350:221-31.

3) Kimura T, Morimoto T, Nakagawa Y, et al. Very late stent thrombosis and late target lesion revascularization after sirolimus-eluting stent implantation: five-year outcome of the j-Cypher Registry. Circulation. 2012;125:584-91.

4) Raber L, Magro M, Stefanini GG, et al. Very late coronary stent thrombosis of a newer-generation everolimus-eluting stent compared with early-generation drug-eluting stents: a prospective cohort study. Circulation. 2012;125:1110-112.

5) Schoming A, Neumann FJ, Kastrati A, et al. A randomized comparison of antiplatelet and anticoagulant therapy after the placement of coronary-artery stents. N Engl J Med. 1996;334:1084-89.

6) Leon MB, Baim DS, Popma JJ, et al. A clinical trial comparing three antithrombotic-drug regimens after coronary-artery stenting. Stent Anticoagulation Restenosis Study Investigators. N Engl J Med. 1998;339:1665-71.

7) Kimura T, Morimoto T, Natsuaki M, et al. Comparison of everolimus—eluting and sirolimus-eluting coronary stents: 1-year outcomes from the Randomized Evaluation of Sirolimus-eluting Versus Everolimus-eluting stent Trial (RESET). Circulation 2012;126:1225-36.

8) Kimura T, Morimoto T, Nakagawa Y, et al. Antiplatelet therapy and stent thrombosis after sirolimus-eluting stent implantation. Circulation. 2009;119:987-95.

9) Gwon HC, Hahn JY, Park KW, et al. Six-month versus 12-month dual antiplatelet therapy after implantation of drug-eluting stents: the Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting (EXCELLENT) randomized, multicenter study. Circulation. 2012;125:505-13.

10) Valgimigli M, Campo G, Monti M, et al. Short- Versus Long-term Duration of Dual Antiplatelet Therapy After Coronary Stenting: A Randomized Multicentre Trial. Circulation. 2012;125(16):2015-26.

11) Colombo A, Chieffo A, Frasheri A, et al. Second-generation drug-eluting stent implantation followed by 6- versus 12-month dual antiplatelet therapy: the SECURITY randomized clinical trial. J Am Coll Cardiol. 2014;64(20):2086-97.

12) Gilard M, Barragan P, Noryani AA, et al. 6- versus 24-month dual antiplatelet therapy after implantation of drug-eluting stents in patients nonresistant to aspirin: the randomized, multicenter ITALIC trial. J Am Coll Cardiol. 2015;65(8):777-86

13) Natsuaki M, Morimoto T, Yamamoto E, et al. One-year outcome of a prospective trial stopping dual antiplatelet therapy at 3 months after everolimus-eluting cobalt-chromium stent implantation: ShortT and OPtimal duration of Dual AntiPlatelet Therapy after everolimus-eluting cobalt-chromium stent (STOPDAPT) trial. Cardiovasc Interv and Ther. 2016;31(3):196-209

14) Vranckx P, Valgimigli M, Juni P, et al. Ticagrelor plus aspirin for 1 month, followed by ticagrelor monotherapy for 23 months vs aspirin plus clopidogrel or ticagrelor for 12 months, followed by aspirin monotherapy for 12 months after implantation of a drug-eluting stent: a multicentre, open-label, randomised superiority trial. Lancet 2018;392(10151):940-949.

15) Urban P, Meredith IT, Abizaid A, et al. Polymer-free drug-coated coronary stents in patients at high bleeding risk. N Engl J Med. 2015;373(21):2038-47.

16) Palmerini T, Biondi-Zoccai G, Della Riva D, et al. Stent thrombosis with drug-eluting and bare-metal stents: evidence from a comprehensive network meta-

analysis. Lancet 2012;379(9824):1393-402

17) Tada T, Natsuaki M, Morimoto T, et al. Duration of dual antiplatelet therapy and long-term clinical outcome after coronary drug-eluting stent implantation: landmark analyses from the CREDO-Kyoto PCI/CABG Registry Cohort-2. Circulation. Cardiovascular interventions 2012;5(3):381-91

18) Toyoda K, Yasaka M, Iwade K, et al. Dual antithrombotic therapy increases severe bleeding events in patients with stroke and cardiovascular disease: a prospective, multicenter, observational study. Stroke. 2008;39:1740-5.

19) Watanabe H, Domei T, Morimoto T, et al. Effect of 1-month dual antiplatelet therapy followed by clopidogrel vs 12-month dual antiplatelet therapy on cardiovascular and bleeding events in patients receiving PCI; The STOPDAPT-2 randomized clinical trial, JAMA 2019; 321(24): 2414-2427.

20) Yahata H, Corley DA, Nakahata F, et al. aspirin and non-aspirin NSAIDs increase risk of colonic diverticular bleeding: a systematic review and meta-analysis. J Gastroenterol. 2014;49:992-1000.

20) Gent M, Beaumont D, Blanchard J, et al. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee. Lancet 1996;348:1329-39.

21) Valgimigli M, Bueno H, Byrne RA, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2018;39:213–260

22) Bittl JA, Baber U, Bradley SM, et al. Duration of Dual Antiplatelet Therapy: A Systematic Review for the 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol.

2016;68(10):1116-39.

23) Yusuf S, Zhao F, Mehta SR, et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med. 2001;345(7):494-502.

24) Mehta SR, Yusuf S, Peters RJ, et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. Lancet. 2001;358(9281):527-33.

25) Rao AK, Pratt C, Berke A, et al. Thrombolysis in Myocardial Infarction (TIMI) trial: phase I: hemorrhagic manifestations and changes in plasma fibrinogen and the fibrinolytic system in patients treated with recombinant tissue plasminogen activator and streptokinase. J Am Coll Cardiol. 1988;11:1-11.

26) Natsuaki M, Kozuma K, Morimoto T, et al. Final 3-Year Outcome of a Randomized Trial Comparing Second-Generation Drug-Eluting Stents Using Either Biodegradable Polymer or Durable Polymer: NOBORI Biolimus-Eluting Versus XIENCE/PROMUS Everolimus-Eluting Stent Trial. Circ Cardiovasc Interv. 2015;8(10):e002817.

27) Mauri L, D'Agostino RB. Challenges in the Design and Interpretation of Noninferiority Trials. N Engl J Med. 2017;377:1357–1367.

28) Macaya F, Ryan N, Salinas P, Pocock SJ. Challenges in the Design and Interpretation of Noninferiority Trials: Insights From Recent Stent Trials. J Am Coll Cardiol. 2017;70:894–903.