Title: TWILIGHT Study - Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention
PI Roxana Mehran
NCT Number NCT02270242
Date of protocol: 28-Mar-16

Drug Substance	Ticagrelor and Aspirin
Study Number	ISSBRIL0345
EudraCT No.	2014-005498-35
ClinicalTrials.gov ID	NCT02270242
Version Number	4.0
Date	28-Mar-2016

TWILIGHT Study

Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention

Funding Agency: **AstraZeneca**

Sponsor-Investigator/Academic Research Center (ARC): **The Office of Interventional Cardiovascular Research and Clinical Trials at Icahn School of Medicine at Mount Sinai**

PROTOCOL SYNOPSIS

Title of Study	TWLIGHT Study - Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention
Primary Investigator:	Roxana Mehran, MD, FACC, FACP, FCCP, FESC, FAHA, FSCAI Professor of Medicine and Director of Interventional Cardiovascular Research and Clinical Trials Icahn School of Medicine at Mount Sinai
Study Centers:	Approximately 100 sites in U.S., Canada, South America, Europe, and China
Study Design	Multicenter, prospective, blinded dual-arm study
Purposes	**Aim 1:** To determine the impact of ticagrelor alone versus ticagrelor plus aspirin in reducing clinically relevant bleeding among high-risk patients who had PCI with at least one drug-eluting stent. **Aim 2:** To determine the impact of ticagrelor alone versus ticagrelor plus aspirin in reducing ischemic adverse events at one year among high-risk patients undergoing PCI with at least one drug-eluting stent.
Enrollment and Patient Population	Up to 9000 high-risk patients who have undergone successful PCI with at least one locally approved drug eluting stent discharged on DAPT with aspirin and ticagrelor of at least 3 months intended duration.
Primary Objective	The primary objective of this study is to determine the impact of antiplatelet monotherapy with ticagrelor alone versus DAPT with ticagrelor plus aspirin for 12 months in reducing clinically relevant bleeding among high-risk patients undergoing PCI who have completed a 3-month course of aspirin plus ticagrelor.
Secondary Objectives	The secondary objective of this study is to determine the impact of antiplatelet monotherapy with ticagrelor alone versus DAPT with ticagrelor plus aspirin for 12 months in reducing major ischemic adverse events among high-risk patients undergoing PCI who have completed a 3-month course of aspirin plus ticagrelor.
Eligibility Criteria	High-risk patients who have undergone successful PCI with at least one locally approved drug eluting stent AND discharged on DAPT with aspirin and ticagrelor of at least 3 months intended duration will be eligible for the TWILIGHT study.

	Enrollment into the study will require meeting at least one clinical inclusion AND at least one angiographic inclusion AND none of the exclusion criteria. <u>Clinical Inclusion Criteria (MUST MEET AT LEAST ONE):</u> • Adult patients ≥ 65 years of age • Female gender • Troponin positive acute coronary syndrome • Established vascular disease defined as previous MI, documented PAD or CAD/PAD revascularization • Diabetes mellitus treated with medications (oral hypoglycemic, subcutaneous injection of insulin) • Chronic kidney disease defined as an estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73m^2 or creatinine clearance (CrCl) < 60 ml/min <u>Angiographic Inclusion Criteria (MUST MEET AT LEAST ONE):</u> • Multivessel coronary artery disease • Target lesion requiring total stent length >30 mm • Thrombotic target lesion(s) • Bifurcation lesions with Medina X,1,1 classification requiring at least 2 stents • Left main (≥50%) or proximal LAD (≥70%) lesion • Calcified target lesion(s) requiring atherectomy <u>Exclusion Criteria:</u> • Under 18 years of age • Contraindication to aspirin (listed in appendix D) • Contraindication to ticagrelor (listed in appendix E) • Planned surgery within 90 days • Planned coronary revascularization (surgical or percutaneous) within 90 days • Need for chronic oral anticoagulation • Prior stroke • Dialysis-dependent renal failure • Active bleeding or extreme-risk for major bleeding (e.g. acute gastrointestinal ulcer or history of chronic gastrointestinal ulceration, gastrointestinal pathology with a raised risk for bleeding, malignancies with a raised risk for bleeding) • Salvage PCI or STEMI presentation. • Liver cirrhosis • Life expectancy < 1 year • Unable or unwilling to provide informed consent • Women of child bearing potential (as defined in Section 4.2)

	• Fibrinolytic therapy within 24 hours of index PCI • Concomitant therapy with a strong cytochrome P-450 3A inhibitor or inducer • Platelet count < 100,000 mm^3 • Requiring ongoing treatment with aspirin ≥ 325 mg daily
Randomization	The eligibility for randomization for all enrolled subjects will be evaluated at the in-person 3-month study visit. Subjects with any of the following will not be randomized: • Refusal of randomization by subject or treating physician • Withdrawal of consent • Lost to follow-up • Death • Major bleeding (BARC Types 3b or greater) • Occurrence of an ischemic event after PCI such as myocardial infarction, definite or probable stent thrombosis, ischemic stroke, coronary revascularization with drug-eluting stent • No longer taking DAPT with aspirin and ticagrelor • Non physician-guided cessation of aspirin or ticagrelor of 5 consecutive days or greater. • Women of child bearing potential (as defined in Section 4.2) • Renal failure requiring dialysis • Current indication for oral anticoagulation or high dose aspirin
Statistical Methods	
Analysis for Primary Bleeding Endpoint	The analysis for the primary bleeding endpoint will be performed on the ITT population. The primary objective is to determine if ticagrelor monotherapy is superior to ticagrelor plus aspirin for the primary bleeding endpoint (BARC Types 2, 3 or 5 bleeding). The null hypothesis for this analysis is that the HR for the experimental group (H_0) = 1. The alternative hypothesis is that the HR for the experimental group (H_A) ≠ 1. A test of superiority at the two-sided 0.05 level will be performed using a Cox proportional hazard model that includes treatment group as a covariate. A point estimate and two-sided 95% CI for the relative risk as measured by the hazard ratio will be calculated based on the Cox proportional hazards model. Event rates will be estimated at one year and Kaplan-Meier curves will be plotted for the time from randomization to the first occurrence of confirmed BARC Type 2, 3 or 5 bleeding by treatment group. This analysis will be repeated in the per protocol (PP) cohort to support the primary results.

Analysis for Primary Ischemic Endpoint	The analysis for the primary ischemic endpoint will be performed on the PP cohort. The primary objective is to determine if ticagrelor monotherapy is non-inferior to ticagrelor plus aspirin for the primary ischemic endpoint (all-cause death, non-fatal myocardial infarction, or stroke). Event rates will be estimated at one year and Kaplan-Meier curves will be plotted for the time from randomization to the first occurrence of confirmed all-cause death, non-fatal myocardial infarction, or stroke or by treatment group. A test of non-inferiority at the one-sided 0.025 level will be performed. . . . Assuming an event rate of 8.0% in the control group, a sample size of 8200 will yield 80% power to exclude an absolute non-inferiority margin of 1.6%. If the upper limit of the 95% CI for the point estimate of the absolute risk difference between groups is less than or equal to 1.6% then the criteria for non-inferiority will be met. This non-inferiority margin translates to a relative risk of 20% assuming the observed event rate equals 8.0% in the control arm.
Statistical Methods	Unless otherwise stated, all hypothesis tests will be performed using two-sided tests at the 5% significance level. Continuous variables will be summarized using descriptive statistics including means and standard deviations if normally distributed or median with interquartile ranges for skewed distributions. Discrete variables will be summarized using absolute and relative frequencies.
Sample Size Parameters	A cumulative bleeding rate of 4.5% is anticipated between time of randomization and 1 year. Assuming a 2% loss to follow-up and non-compliance / cross-over rate of 4%, the current trial will require 8200 subjects to detect a relative reduction in bleeding of 28% with ticagrelor monotherapy with 80% power and a Type I error of 0.05. It is anticipated that approximately 8% - 10% of enrolled subjects will not be eligible for randomization and therefore 9000 subjects will be enrolled at the time of PCI.

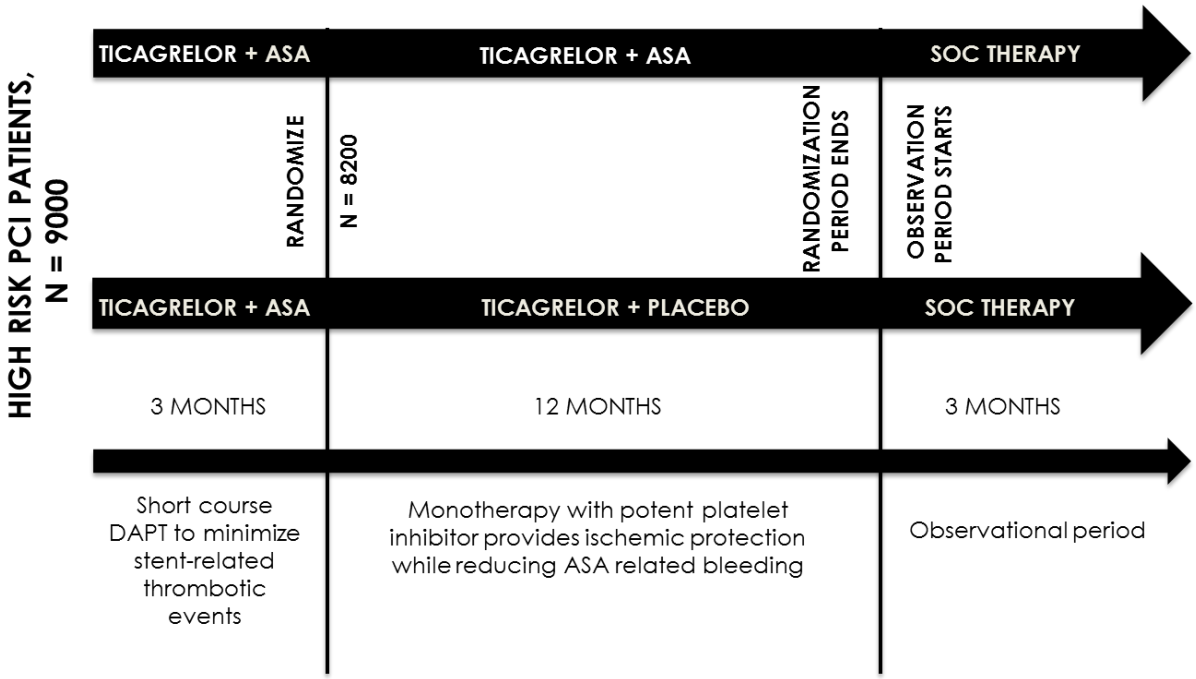

HIGH RISK PCI PATIENTS, N = 9000
TICAGRELOR + ASA
TICAGRELOR + ASA
SOC THERAPY
RANDOMIZE
N = 8200
RANDOMIZATION PERIOD ENDS
OBSERVATION PERIOD STARTS
TICAGRELOR + ASA
TICAGRELOR + PLACEBO
SOC THERAPY
3 MONTHS
12 MONTHS
3 MONTHS
Short course DAPT to minimize stent-related thrombotic events
Monotherapy with potent platelet inhibitor provides ischemic protection while reducing ASA related bleeding
Observational period

TABLE OF CONTENTS PAGE

LIST OF TABLES

PROTOCOL SIGNATURE PAGE

I have read this clinical investigation plan and appendices and agree to adhere to the requirements. I will provide copies of this clinical investigation plan and all pertinent information to the trial personnel under my supervision. I will discuss this material with them and ensure they are fully informed regarding the study drugs and the conduct of the trial.

I will conduct the trial in accordance with the clinical investigation plan, Good Clinical Practice guidelines, World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects, as well as local regulations. I also accept respective revisions to the clinical investigation plan approved by authorized personnel of the ARCC and by regulatory authorities.

_____
Investigator Name (print)

_____
Investigator Name (signature)

_____
Date

_____
Institution Name (print)

LIST OF ABBREVIATIONS

The following abbreviations and special terms are used in this Clinical Study Protocol.

Abbreviation or special term	Explanation
AE	Adverse Event
ARC	Academic Research Center
ASA	Acetylsalicylic Acid (Aspirin)
BMI	Body Mass Index
BMS	Bare Metal Stent
CAD	Coronary Artery Disease
CEC	Clinical Events Committee
CRF	Case Report Form
DAPT	Dual Antiplatelet Therapy
DES	Drug Eluting Stent
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
FDA	Food and Drug Administration (U.S.)
FFR	Fractional Flow Reserve
ICF	Informed Consent Form
IND	Investigational New Drug Application (FDA)
IRB	Institutional Review Board
ISS	Investigator Sponsored Study
ITT	Intention-to-Treat (analysis dataset)
IVUS	Intravascular Ultrasound
IXRS	Interactive Voice/Web Response System
LAD	Left Anterior Descending (Coronary Artery)
MI	Myocardial Infarction
NSAID	Non-Steroidal Anti-Inflammatory Drug
NSTEMI	Non ST Elevation Myocardial Infarction
$P2Y_{12}$	The $P2Y_{12}$ protein is found mainly but not exclusively on the surface of blood platelets, and is an important regulator in blood clotting.
PAD	Peripheral Artery Disease
PCI	Percutaneous Coronary Intervention
PP	Per Protocol (analysis dataset)
SAE	Serious Adverse Event
STEMI	ST Elevation Myocardial Infarction

The following abbreviations and special terms describe other clinical protocols or academic bodies.

Abbreviation or special term	Explanation
BARC	Bleeding Academic Research Consortium
EXCELLENT	*Trial Name:* Efficacy of Xience/Promus versus Cypher in Reducing Late Loss after Stenting
GUSTO	Trial Name: Global Utilization of Streptokinase and TPA for Occluded Arteries
OPTIMIZE	*Trial Name:* Optimized Duration of Clopidogrel Therapy following Treatment with the Endeavor Zotarolimus-Eluting Stent in the Real World Clinical Practice
PLATO	*Trial Name:* Platelet Inhibition and Patient Outcomes Trial
PRODIGY	*Trial Name:* Synergy between Stent and Drugs to Avoid Ischemic Recurrences after Percutaneous Coronary Intervention
SYNTAX	*Trial Name:* TAXUS Drug-Eluting Stent versus Coronary Artery Bypass Surgery for the Treatment of Narrowed Arteries
TIMI	*Trial Name:* Thrombolysis in Myocardial Infarction

1. INTRODUCTION

Pharmacologic platelet inhibition with aspirin and a $P2Y_{12}$ inhibitor is a requirement in all patients undergoing percutaneous coronary intervention (PCI) with stenting. Such dual antiplatelet therapy (DAPT) is recommended by international guidelines, with duration varying according to clinical presentation (i.e. acute coronary syndrome) or type of stent implanted during PCI (bare metal vs. drug eluting)(1-3). The paradigm for DAPT is shifting to shorter durations, as evidenced by most recent ESC /EACTS Guidelines on myocardial revascularization giving a class Ib recommendation for 6 months of DAPT after DES (4).While clopidogrel is the most widely used $P2Y_{12}$ inhibitor, its efficacy is hampered by substantial variability in platelet inhibition that may be attributable to clinical, genetic and procedural parameters (5-8). Moreover, although the novel thienopyridine prasugrel has a more potent and consistent effect on platelet inhibition (9, 10), bleeding risk is significantly higher compared to clopidogrel in acute coronary syndrome (ACS) patients following PCI (11). In contrast, ticagrelor, an oral, reversible, direct-acting inhibitor of the adenosine diphosphate $P2Y_{12}$ receptor (12) has proven faster, greater and more consistent $P2Y_{12}$ inhibition than either clopidogrel or prasugrel (13-15). In the landmark Study of Platelet Inhibition and Patient Outcomes (PLATO) trial, ticagrelor significantly reduced death from vascular causes, myocardial infarction, or stroke, without significantly increasing overall major bleeding in patients presenting with acute coronary syndromes (16).

Along with the advent of more potent antiplatelet pharmacotherapy, stent technology has also advanced in a concordant fashion with the introduction of safer and less thrombogenic

platforms. These devices, compared to their older-generation counterparts, yield significant reductions in thrombotic events that are durable over the long term (17). As a consequence, classical paradigms favoring a minimum of DAPT duration of 1 year, particularly in elective patients, are being challenged as PCI safety continues to evolve and improve. Randomized comparisons of different DAPT durations such as the OPTIMIZE and the PRODIGY trials suggest no increased risk for thrombotic events after only 3-6 months of DAPT in PCI patients treated primarily with novel generation devices (18-22).

1.1 Research hypothesis

The overall hypothesis of the current study is that three months post-PCI of dual antiplatelet therapy with aspirin and ticagrelor, continued monotherapy with ticagrelor alone versus ticagrelor plus aspirin for an additional year will be superior with respect to bleeding and non-inferior with respect to ischemic events in high-risk patients undergoing elective or urgent PCI.

This hypothesis will be tested in the following two specific aims:

Aim 1: To determine the impact of ticagrelor alone versus ticagrelor plus aspirin in reducing clinically relevant bleeding among high-risk patients who had PCI.	**Hypothesis 1:** A DAPT strategy of ticagrelor + ASA for 3 months followed by ticagrelor alone for an additional 12 months will be superior to ticagrelor plus aspirin with respect to clinically relevant bleeding (BARC ≥ 2) in high-risk patients undergoing PCI.
Aim 2: To determine the impact of ticagrelor alone versus ticagrelor plus aspirin in reducing ischemic adverse events at one year among high-risk patients undergoing PCI	**Hypothesis 2:** A DAPT strategy of ticagrelor + ASA for 3 months followed by ticagrelor alone for an additional 12 months will be will be non-inferior to ticagrelor plus aspirin for with respect to ischemic adverse events at 1 year in high-risk patients undergoing PCI.

1.2 Rationale for conducting this study

Despite the trend and rationale for shorter DAPT durations following PCI, certain high-risk patients may derive additional benefit from potent and sustained platelet inhibition extending beyond 3 months after PCI. Defined by clinical and/or anatomic criteria, a short course of DAPT in such patients may provide sufficient protection against early stent-related thrombotic events while ongoing platelet inhibition may yield further reductions in systemic atherothrombosis. Among diabetics undergoing PCI, for example, Brar et al. previously demonstrated that the benefits of DAPT compared to antiplatelet monotherapy persisted irrespective of BMS or DES use, suggesting a systemic rather than stent-related effect (23). Analogously, results from the EXCELLENT trial suggested diabetics may derive additional benefit from prolonged DAPT (ASA + clopidogrel) compared to ASA alone (24). Findings from Dangas et al., which demonstrate a link between atherosclerosis and increased platelet

reactivity, provide a biological basis for potent platelet inhibition in high-risk patients characterized by diffuse vascular disease (25). These observations are clinically relevant as many patients undergoing elective or urgent PCI exhibit high-risk features, such as renal dysfunction, diabetes, peripheral arterial disease, that are associated with systemic atherosclerosis. Given the clear benefits of ticagrelor in the setting of high-risk ACS, it is plausible that ticagrelor alone will provide sufficient platelet inhibition to reduce thrombotic events compared to ticagrelor plus ASA among high-risk patients who have completed a requisite short course of DAPT.

Reduction in bleeding with ticagrelor alone while preserving of the anti-ischemic benefit associated with DAPT use would favor such a strategy in high-risk patients undergoing PCI.

Accordingly, the proposed study will examine the comparative safety and efficacy of a strategy of 3 month DAPT with ASA and ticagrelor followed by monotherapy using a potent agent (ticagrelor) compared to continued ASA and ticagrelor among high-risk patients undergoing PCI with DES. Our primary hypothesis is that, among such patients, use of ticagrelor alone will yield a significant reduction in clinically relevant bleeding while preserving anti-ischemic protection compared to the combination of ticagrelor and ASA.

1.3 Benefit/risk and ethical assessment

The potential benefits that subjects might realize by participating in this randomized trial is a reduction in clinically relevant bleeding for those who are randomly allocated to the placebo arm. Other benefits applicable to all subjects include close monitoring and surveillance for clinical events that will be performed by study personnel during the course of the trial.

The potential risks for subjects include an increased rate of thrombotic events for those who are randomized to the placebo arm and increased risk for bleeding in subjects randomized to the active treatment arm (low-dose ASA [81 mg – 100 mg]).

An independent data safety monitoring board will provide external oversight to ensure safety of all trial participants. In addition, subjects will be followed closely with periodic study contacts. Also, clinical equipoise exists for conducting a trial with this type of randomized comparison.

2. STUDY OBJECTIVES

2.1 Primary objective

The primary objective of this study is to determine the impact of antiplatelet monotherapy with ticagrelor alone versus DAPT with ticagrelor plus aspirin for 12 months in reducing clinically relevant bleeding among high-risk patients undergoing PCI who have completed a 3-month course of aspirin plus ticagrelor.

2.2 Secondary objective

The secondary objective of this study is to determine the impact of antiplatelet monotherapy with ticagrelor alone versus DAPT with ticagrelor plus aspirin for 12 months in reducing major ischemic adverse events among high-risk patients undergoing PCI who have completed a 3-month course of aspirin plus ticagrelor.

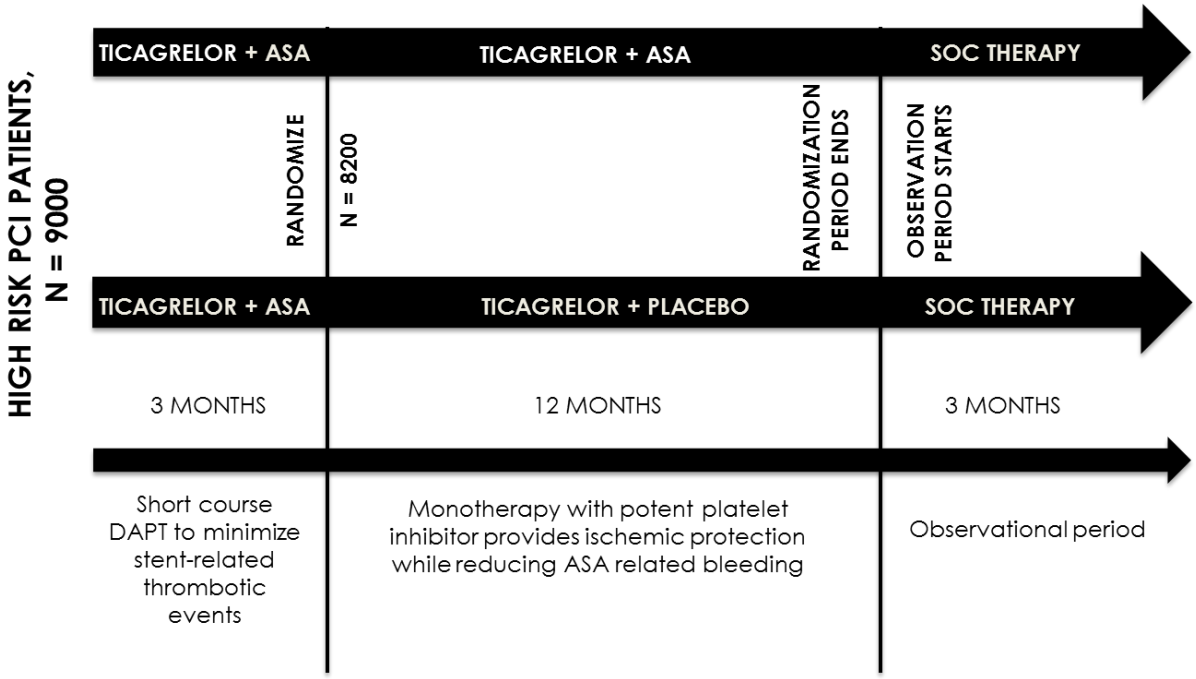
2.3 Exploratory objectives

Exploratory objectives include assessing the comparative safety and efficacy of the different DAPT regimens for individual components of the primary efficacy and secondary safety objectives.

3. STUDY PLAN AND PROCEDURES

3.1 Overall study design and flow chart

Figure 1 TWILIGHT Trial Design



3.2 Rationale for study design, doses and control groups

A randomized, double-blind study design was chosen as the most rigorous experimental approach to formally test the study hypotheses for the efficacy and safety of different DAPT regimens in high-risk patients undergoing PCI. Open label aspirin and ticagrelor per physician discretion will be given for the first 3 months after PCI. After 3 months, event-free subjects

will be randomized to placebo versus enteric-coated ASA for an additional 12 months. Open-label ticagrelor at a dose of 90 mg twice daily will be continued in all randomized subjects.

4. SUBJECT SELECTION CRITERIA

4.1 Inclusion criteria

High-risk patients who have undergone successful PCI with at least one locally approved drug eluting stent (DES) discharged on DAPT with aspirin and ticagrelor of at least 3 months intended duration will be eligible for the TWILIGHT study.

Enrollment into the study will require meeting at least one clinical inclusion AND at least one angiographic inclusion AND none of the exclusion criteria. A subject is considered enrolled if all these criteria are met and upon provision of informed consent.

Must meet AT LEAST ONE clinical inclusion criterion	**Must meet AT LEAST ONE angiographic inclusion criterion**
Adult patients ≥ 65 years of age Female gender Troponin positive acute coronary syndrome Established vascular disease defined as previous MI, documented PAD or CAD/PAD revascularization Diabetes mellitus treated with medications or insulin Chronic kidney disease defined as an estimated glomerular filtration rate (eGFR) <60 ml/min/1.73m^2 or creatinine clearance (CrCl) <60 ml/min	Multivessel coronary artery disease (CAD)* (see Section 16) Target lesion requiring total stent length >30 mm Thrombotic target lesion(s) Bifurcation lesion(s) with Medina X,1,1 classification requiring at least 2 stents (see Section 16) Left main (≥50%) or proximal LAD (≥70%) lesion Calcified target lesion(s) requiring atherectomy
*The diagnosis of multivessel CAD may be established with the angiogram performed at enrollment or an earlier angiogram. A vessel previously treated with either a stent or bypass graft may also be considered diseased for purposes of meeting the multivessel CAD angiographic inclusion criterion.	

4.2 Exclusion criteria

Subjects should not enter the study if any of the following exclusion criteria are met:

- Under 18 years of age
- Contraindication to aspirin, as listed in Appendix D
- Contraindication to ticagrelor, as listed in Appendix E
- Planned surgery within 90 days
- Planned coronary revascularization (surgical or percutaneous) within 90 days
- Need for chronic oral anticoagulation
- Prior stroke
- Dialysis-dependent renal failure
- Active bleeding or extreme-risk for major bleeding (e.g. acute gastrointestinal ulcer or history of chronic gastrointestinal ulceration, gastrointestinal pathology with a raised risk for bleeding, malignancies with a raised risk for bleeding)
- Salvage PCI or STEMI presentation.
- Liver cirrhosis
- Life expectancy < 1 year
- Unable or unwilling to provide informed consent
- Women of child bearing potential as defined below:
  A woman is considered of childbearing potential (WOBCP) following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
- Fibrinolytic therapy within 24 hours of index PCI
- Concomitant therapy with a strong cytochrome P-450 3A inhibitor or inducer
- Platelet count < 100,000 mm^3
- Requiring ongoing treatment with aspirin ≥325 mg daily

5. STUDY CONDUCT

5.1 Restrictions during the study

Enrolled subjects should remain on study-provided open-label ticagrelor plus open-label aspirin for the first three months after index PCI followed by study-provided open-label ticagrelor plus blinded study drug for 12 months after randomization.

Unless clinically indicated, non-steroidal anti-inflammatory drugs (NSAIDs) and additional $P2Y_{12}$ inhibitors (ticlopidine, prasugrel, clopidogrel) should not be taken by study participants during the course of the trial. In addition, ticagrelor should be administered with caution in patients with history of hyperuricemia or gouty arthritis.

5.2 Subject randomization and initiation of investigational product

5.2.1 Procedures for randomization

The eligibility for randomization for all enrolled subjects will be evaluated at the in-person 3-month study visit. Subjects with any of the following will not be randomized:

- Refusal of randomization by subject or treating physician
- Withdrawal of consent
- Lost to follow-up
- Death
- Major bleeding (BARC Types 3b or greater)
- Occurrence of an ischemic event after PCI such as myocardial infarction, definite or probable stent thrombosis, ischemic stroke, coronary revascularization with drug-eluting stent
- No longer taking DAPT with aspirin and ticagrelor
- Non physician-guided cessation of aspirin or ticagrelor of 5 consecutive days or greater.
- Women of child bearing potential (as defined in Section 4.2)
- Renal failure requiring dialysis
- Current indication for oral anticoagulation or high dose aspirin

Randomization will be performed within the EDC system among subjects eligible for randomization. The EDC will allocate the treatment group assignment for the subject and provide study site research personnel the appropriate bottle ID number(s).

Upon randomization at the conclusion of the in-person 3-month visit, the study site research personnel will provide a 6-month supply of blinded investigational product (aspirin or matching placebo) and open-label ticagrelor.

Enrolled subjects who do not meet eligibility for randomization will have completed their protocol required activities and therefore will not receive any further study-provided medications. Their treating physician will also be notified that the patient's protocol-mandated study activities have concluded. Further antiplatelet therapy will be at the discretion of the subject's treating physician in accordance with local standard of care. Vital status of these subjects will be determined at the 18-month time point.

Enrolled subjects who do not meet eligibility for randomization *prior to* the in-person 3-month visit will not be required to complete the 3-month in-person visit.

5.3 Procedures for handling subjects incorrectly enrolled or randomized on investigational product

Subjects who are incorrectly enrolled will be immediately withdrawn from the study. The subject and the treating physician will be notified. If the subject has already been randomized, the investigational drug (aspirin or matching placebo) will be discontinued and further treatment will be as per standard of care. Subjects will be advised to continue therapy with ticagrelor until seen by their treating physician.

Subjects who are provided the incorrect investigational drug (study drug bottle(s) were not provided according to EDC randomization instructions) may be identified during monitoring procedure and/or drug reconciliation. In this case, the subject will be informed immediately and requested to return with all dispensed investigational drugs. The subject will then be provided with the correct investigational drug according to the randomization instructions. In addition, a protocol deviation form will be completed.

5.4 Blinding and procedures for unblinding the study

5.4.1 Methods for ensuring blinding

This study has a double-blind design with aspirin and matching placebo. The subjects, study site research personnel, academic research center staff, and treating physicians involved in the treatment and/or clinical evaluation of the subjects will not be aware of treatments received. There will be an independent data safety monitoring board (DSMB) to monitor the data on a periodic basis. An independent statistician, not otherwise involved in the study, will prepare and provide the required reports to the DSMB as per the DSMB charter.

5.4.2 Methods for unblinding the study

In the event of a medical emergency, in which knowledge of the investigational drug is critical to the subject's medical management, the blind for that subject may be broken by the treating physician. The investigator should follow the instructions provided in the EDC to obtain the necessary treatment information or call the 24/7 TWILIGHT Medical Monitoring Hotline at 347-541-1376. As the active study drug in this trial is low-dose aspirin, in most instances the subject may be properly managed without the need for unblinding.

5.5 Treatments

5.5.1 Identity of investigational product

In this protocol, the investigational product is enteric coated aspirin (81 mg – 100 mg) tablets and matching aspirin-placebo tablets.

Table 1 Identity of Investigational Product

Investigational product	Dosage form and strength
Aspirin, EC	81 mg – 100 mg tablet, daily
Placebo for aspirin	tablet daily

5.5.2 Doses and treatment regimens

Study-provided medications including open-label ticagrelor at a dose of 90 mg twice daily plus open-label EC aspirin at a dose of 81mg – 100 mg daily will be dispensed to enrolled participants at the time of discharge and should be taken daily until the in-person 3-month study visit. Study-provided medications including open-label ticagrelor at a dose of 90 mg twice daily plus blinded study drug will be dispensed to randomized participants at the 3-month in-person visit and should be taken daily until end of study.

5.5.3 Additional study drug

Open-label ticagrelor will be administered to all subjects regardless of randomization assignment.

5.5.4 Labeling

Each aspirin/placebo bottle will be labeled in black ink. This label will indicate the protocol number, blinded batch number, container number, blinded drug name, tablet quantity, storage conditions, directions for use and route of administration.

At the study site, the investigational product should be stored in a secure area according to local regulations. It is the responsibility of each site investigator to ensure that the investigational product is only dispensed to study subjects. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

The storage conditions for the subjects to follow will be included in the labeling on the bottles.

5.6 Concomitant and post-study treatment

There are no protocol specific concomitant treatments.

At the End of Study visit physicians caring for the patient will decide which antiplatelet medication the patient should receive as part of his/her ongoing clinical care. This medication(s) will be open label and obtained locally.

5.7 Treatment compliance

Study drug compliance will be assessed using manual pill count at the 9-month and 15-month in-person follow-up visits.

5.7.1 Accountability

Reconciliation between the quantity of shipped study drugs versus the allocation of study drugs via the EDC and versus distribution of study drug to subject will be monitored and reconciled.

5.8 Discontinuation of investigational product or study drug

Study-provided medications (open-label ticagrelor or blinded study drug) may require *temporary interruption* for the following reasons:

1. **Surgery or invasive procedure**: Study-provided medications should be resumed after surgery once the risk of bleeding is no longer considered prohibitive in the judgment of the treating physician. Minor surgeries and procedures, including but not limited to tooth extraction, colonoscopy and endoscopy, may be safely performed on low-dose aspirin and therefore do not require temporary interruption of blinded study drug. However, if deemed necessary and at the discretion of the treating physician, open-label ASA may be substituted for blinded study drug in the peri-operative period. Blinded study drug may then be restarted at the discretion of the treating physician after completing the mandatory course of open-label ASA.

2. **Balloon angioplasty or PCI with bare-metal stent**: In the event of coronary revascularization with balloon angioplasty alone or PCI with bare metal stent, blinded study drug may be temporarily interrupted for 2-4 weeks while patients receive open-label ASA at the discretion of the treating physician in accordance with local practice and standard of care. Blinded study drug may then be restarted at the discretion of the treating physician after completing the mandatory course of open-label ASA.

3. **Clinically Significant Bleeding**: Study-provided medications should be temporarily interrupted pending resolution of the acute bleeding episode and

may be restarted at the discretion of the treating physician if deemed clinically safe and in accordance with local practice and standard of care.

4. Details surrounding the date, duration and reason for each episode of temporary interruption should be entered in the appropriate section of the EDC.

Study-provided medications (open-label ticagrelor or blinded study drug) may require *permanent discontinuation* for the following reasons:

1. Patient decision: The patient is at any time free to discontinue treatment, without prejudice to further treatment.
2. Investigator's decision:
    a. Incorrectly enrolled patient in whom the inclusion/exclusion criteria violation would put the patient at undue risk
    b. Adverse Events felt to be related to either study medication for which Investigator feels continued treatment would put the patient at undue risk, such as severe or life-threatening bleeding, myocardial infarction, stent thrombosis, ischemic stroke or coronary revascularization with a DES.
3. Renal failure requiring dialysis
4. Chronic oral anticoagulation
5. Details surrounding the date, duration and reason for permanent discontinuation of study medication should be entered in the appropriate section of the EDC.
6. In the event of permanent discontinuation of either study medication, further antiplatelet therapy is at the discretion of and is to be provided by the patient's treating physician. Any remaining study-provided medication should be returned to the local site at the next scheduled follow-up visit. Although these patients will no longer receive study-related medication, follow-up will continue in all randomized patients until end of study

5.9 Withdrawal from study

Each enrolled subject shall remain in the trial until completion of the required follow-up period. However, a subject's participation in any clinical trial is voluntary and the subject has the right to withdraw at any time without penalty or loss of benefit. Conceivable reasons for discontinuation may include, but not be limited to, the following:

- Subject voluntary withdrawal
- Subject withdrawal by physician as clinically indicated
- Subject lost-to follow-up

The reason for subject discontinuation must be documented in the eCRF and source documents. The individual site Principal Investigators must also report all subject discontinuations to their IRB/EC as defined by their institution's procedure.

All data from evaluations and treatments performed prior to the withdrawal should be documented in the eCRFs. Source documents that pre-date the withdrawal should be submitted as required by the protocol. No data that post-dates the withdrawal will be collected.

Once a subject has withdrawn from the trial, no further follow-up contact will be performed. However, vital status may be obtained from public records. Medical therapy after stopping the study will be as prescribed by the subject's physician.

6. COLLECTION OF STUDY VARIABLES

6.1 Recording of data

The Investigator is responsible for maintaining complete and accurate documentation of the trial including but not limited to medical records, trial progress records, laboratory results, electronic case report forms, signed informed consent forms, investigational product accountability records, correspondence with the IRB or EC as well as trial monitors and sponsor, adverse event reports, and information regarding subject discontinuations.

The Investigator is required to maintain information in the subject's medical records which documents and corroborates data entered in the case report forms. As a minimum the subject record should contain:

- Medical history/physical exam documenting that subject meets inclusion/exclusion criteria
- Documentation of subject's consent and subject ID number in the trial
- Dated and signed notes from each subject visit
- Adverse events reported and their resolution or lack thereof including supporting documents such as hospital records, discharge summaries, catheterization reports, ECGs, etc.
- Record of protocol required medications during the trial
- Record of the subject's condition upon completion of or withdrawal from the trial

6.2 Data collection at enrollment and follow-up

Data collection commences after the subject has provided informed consent and has been enrolled in the study. Data collection, including subject demographic information, laboratory tests, and procedural data as well as follow-up visits or telephone contacts will be conducted

by an Investigator or site coordinator who has been trained on the protocol and electronic Case Report Forms (eCRFs).

Data required for analysis will be obtained as outlined in Table 1. After discharge from the hospital, each enrolled subject will be followed with a phone call at 1 month post enrollment and an in-clinic visit at 3 months post enrollment. Enrolled subjects who do not meet eligibility for randomization *prior to* the in-person 3-month visit will not be required to complete the 3-month in-person visit. Subjects who are randomized at 3 months post enrollment will be followed with a phone call at 4 months post enrollment and will return for additional in-clinic visits at 9 and 15 months post enrollment. A final follow-up phone call will be performed at 18 months post enrollment for randomized subjects. No further follow-up contact will be performed for subjects who did not meet eligibility for randomization at the 3 month visit; however, vital status may be obtained from medical or public records at 18 months post enrollment. A flow chart listing the planned visits and their timing can be found in appendix C).

Table 1 Schedule of Data Collection

Type of Data to be Collected	Enrollment	Post-Procedure or Discharge	1 Month (30d) (±7 days) Phone Call	3 Month (90d) (±14 days) Office Visit	4 Month (120d) (±7 days) Phone Call randomized	9 Month (270d) (± 30 days) Office Visit randomized	15 Month (450d) (± 30 days) Office Visit randomized	18 Month (540d) (± 14 days) Phone Call randomized
Eligibility Criteria	X			X				
Patient Informed Consent	X							
Physical Assessment	X							
Medical History/Risk Factors	X							
Cardiac Status	X							
Medications/Antiplatelets	X							
Clinical Tests* Lab tests, ECG	X			X		X	X	
Procedure Information	X							
DAPT Medication Status		X	X		X			X
Angina Status				X	X	X	X	X
Randomization– if eligible				X				
Dispense medication according to EDC		X		X		X		
Randomized Medications – reconciliation of provided medication						X	X	
Randomized Medications – subject self-reporting of compliance to medications				X	X	X	X	X
Adverse Events / Serious Adverse Events	X	X	X	X	X	X	X	X

*If performed, as per standard of care. Subject may be asked to provide an additional blood sample (10cc) for lipid profile testing if not already performed per standard of care.

6.2.1 Enrollment procedures

After successful PCI with implantation of at least one locally approved drug eluting stent and physician decision to treat subject with low–dose aspirin (81 mg – 100 mg) daily and ticagrelor 90 mg twice daily for 3 months, the investigator or designee will:

- Confirm inclusion/exclusion criteria
- Obtain written informed consent
- Obtain a complete medical history, including lab values for hemoglobin and creatinine as well as an ECG, if performed per standard of care. Subject may be asked to provide an additional blood sample (10cc) for lipid profile testing if not already performed per standard of care.
- Review concomitant medications taken within the last 30 days
- Instruct the subject to notify the investigator of any occurrence of adverse events
- Schedule next clinic visit at 3 months
- Dispense 3- month supply of study medications (open-label ticagrelor and EC aspirin)
- Instruct patients to return all study-provided medication at next in-person clinic visit

6.2.2 In-person follow-up procedure at 3 months

- Assess for adverse events including MI, unstable angina, stroke, and bleeding.
- Review concomitant medications with subject
- Counsel subject about importance of study drug compliance
- Assess for randomization eligibility , if applicable:
    - Randomize subject within EDC and obtain bottle numbers
    - Dispense study medication for next 6 months
    - Schedule next clinic visit at 9 months
- Instruct the subject and/or caregiver to notify the investigator of any occurrence of adverse events
- Instruct patients to return all study-provided medication at next in-person clinic visit

6.2.3 In-person follow-up procedure at 9 and 15 months (for randomized subjects)

- Assess for adverse events including MI, unstable angina, stroke, and bleeding.
- Review concomitant medications with subject
- Collect pill bottles, perform study medication accountability, and remind subject about importance of study drug compliance.
- Dispense study medication for next 6 months for those patients still taking study provided medications at the 9-month in-person visit. Patients who have permanently stopped study-provided medications prior to the 9-month in-person visit will continue to be followed but will not be provided additional study medication.
- Instruct the subject to notify the investigator of any occurrence of any adverse events.
- Schedule next clinic visit at 15 months
- Instruct patients to return all study-provided medication at next in-person clinic visit (only pertains to 9-month in-person clinic visit)

6.2.4 Phone-call follow-up contact at 1, 4 and 18 months post enrollment

- Assess for adverse events including MI, unstable angina, stroke, and bleeding.
- Review all medications and compliance with subject
- Instruct the subject to notify the investigator of any occurrence of adverse events

6.3 Efficacy and safety variables

The study site research personnel will collect data from the subjects during the follow-up contact for identification of the efficacy and safety variables, defined as the first occurrence of bleeding (efficacy variable) and all-cause death, myocardial infarction, stent thrombosis, or stroke (safety variables).

7. SAFETY

The Principal Investigator at each participating study site is responsible for ensuring that all staff involved in the study is familiar with the content of this section.

7.1 Definition of adverse events

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the

abnormal results of an investigation (e.g., laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

The term AE is used to include both serious and non-serious AEs.

7.2 Definitions of serious adverse event

A serious adverse event is an AE occurring during any study phase (i.e., run-in, treatment, wash-out, follow-up), that fulfills one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Results in a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

The severity and causality of SAEs (their relationship to all study treatments and/or procedures) will be assessed by the investigator(s) and communicated to the ARC.

7.2.1 Definition of suspected unexpected serious adverse reactions (SUSARs)

A SUSAR is a Suspected Unexpected Serious Adverse Reaction. To qualify as a SUSAR, the event must be:

- Serious
- Undesirable reaction to medicinal product
- Unexpected - NOT listed as a potential risk or reaction to the product as outlined in the protocol, informed consent document or literature.

7.3 Recording of adverse events or serious adverse events

7.3.1 Time period for collection of adverse events

All AEs related to bleeding and SAEs should be collected from the time the subject signs the informed consent through study exit.

7.3.2 Follow-up of unresolved adverse events

For ALL SAEs the subject's course must be monitored until the event has subsided or, in a case of permanent impairment, until the event stabilizes and the overall clinical outcome has been ascertained.

7.3.3 Information to be collected for each AE/SAE

- Description of AE/SAE
- The dates when the AE/SAE started and stopped
- Whether the AE/SAE is serious or not
- Investigator causality rating against the investigational product
- Action taken with regard to investigational product
- Whether the AE/SAE caused subject's withdrawal from study
- Outcome

In addition, the following variables will be collected for SAEs:

- Date the study site research personnel became aware of SAE
- Date when decision was made for meeting SAE criteria
- Criteria met leading to classification as SAE
- Date of hospitalization (if applicable)
- Date of discharge (if applicable)
- Date of death (if applicable)
- Probable cause of death (if applicable)
- Autopsy performed (if applicable)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 7.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE.

7.3.4 Adverse Events based on signs and symptoms

When collecting AEs, the recording of diagnoses (when possible) is preferred to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

7.3.5 Adverse Events based on examinations and tests

Deterioration as compared to baseline in laboratory values or vital signs should therefore only be reported as AEs if they fulfill any of the SAE criteria or are the reason for discontinuation of treatment with the investigational product.

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (e.g., anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

7.3.6 Disease progression or pre-existing conditions

Disease progression can be considered as a worsening of a subject's condition attributable to the disease for which the investigational product is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. For example, continued angina should be considered as disease progression and not an AE. Planned hospitalization for a pre-existing condition without serious deterioration in health, is not considered a serious adverse event.

7.3.7 Reporting of adverse events

AEs must be reported to the sponsor within 7 business days of the study site research personnel's knowledge of the event via the EDC.

SAEs must be reported to the sponsor immediately, but no later than 24 hours, of the study site research personnel's knowledge of the event via the EDC.

The ARC Safety Monitor will review all submitted SAEs for qualification as a Suspected Unexpected Serious Adverse Reactions (SUSARs). The ARC will further report SAEs determined to qualify as SUSARs to the local regulatory body (IRB/EC).

The ARC Safety Monitor will voluntarily inform the FDA, via a MedWatch/AdEERs form, and EudraVigilance, of any serious adverse events which qualify as SUSARs in accordance with reporting requirements.

A copy of the MedWatch/AdEERs report will be faxed or scanned and sent to the Principal Investigator of the applicable site for reporting according to the site's local regulatory body's reporting requirements.

8. ETHICAL AND REGULATORY REQUIREMENTS

8.1 Ethical conduct of the study

The trial will be conducted in compliance with the protocol, Good Clinical Practice guidelines, and World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects as well as local regulations, and applicable regional regulatory requirements.

The clinical investigation shall not begin until the required approvals/favorable opinions from the respective regulatory authority and ethics committee have been obtained. Any additional requirements imposed by the respective regulatory authority and/or ethics committee will also be followed, where specified.

8.2 Ethics and regulatory review

Institutional Review Board (IRB) or Ethics Committee (EC) approval for the protocol, informed consent form and other trial related documents will be obtained by the Principal Investigator at each investigational site prior to participation in this trial. The approval letter must be signed by the IRB/EC chairperson or authorized representative prior to the start of this trial and a copy must be provided to the ARC. In addition, the Investigator or designee will provide the ARC with all required documentation necessary for initial and ongoing trial approval at their site.

In accordance with the investigational site IRB/EC requirements, the Investigator will
(a) advise the IRB/EC of the progress of this trial on a regular basis until trial completion;
(b) obtain written IRB/EC approval at predetermined time points to continue the trial; and
(c) submit any amendments to the protocol as well as associated informed consent form changes and obtain written IRB/EC approval obtained prior to implementation.

8.3 Informed consent

All subjects must provide written informed consent in accordance with the site's IRB/EC, using an IRB/EC-approved informed consent form. All subjects are to be fully informed and trial conduct must be in accordance to the World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects.

Protocol-specific procedures or alterations of patient care must not be performed until the prospective subject has provided a signed informed consent. The informed consent will be in the prospective subject's native language and will contain non-technical language to describe the investigational procedures. The informed consent form should also include a clause that

ensures important new information will be provided to the subject throughout the clinical investigation.

After a review of the prospective subject's medical records to determine general eligibility, the investigator or authorized designee who has been trained on the protocol, will approach the prospective subject to explain the purpose and scope of the clinical trial, prospective risks, and benefits of participation. The prospective subject must be given the opportunity to ask questions about the trial and must be given sufficient time to decide to participate in the trial or not. Additional information requested by the prospective subject should be provided. Any coercion or undue improper influence on the prospective subject is to be avoided.

If the prospective subject agrees to participate, the informed consent form must be signed and personally dated by the prospective subject. The investigator or an authorized member of the research team who has witnessed the prospective subject's signature must also sign and date the informed consent, prior to enrollment of the prospective subject. A copy of the completed informed consent form must be provided to the subject. Local IRB/EC regulations regarding obtaining informed consent must be followed. The subject's medical record should have a notation regarding the signing of the informed consent.

The subject is to be made aware that their participation in the trial is voluntary, their legal rights will not be waived, and that they may withdraw from the trial at any time, without giving specific reason for doing so. The subject must also be informed that withdrawal from the trial will not affect their future treatment.

The investigator is responsible for the achievement of written consent from the prospective subject before they are included in the trial. All subjects must provide informed consent in accordance with the local IRB/EC requirements, using an IRB/EC-approved informed consent form.

8.4 Changes to the protocol and informed consent form

If the protocol or informed consent form (ICF) needs an amendment, the ARC is required to submit such amendment to the Regulatory Agencies and/or other regulating body in each participating country for approval. Approved protocol or ICF amendments will be provided to the Investigators by the ARC prior to implementing the amendment.

For administrative changes, the Principal Investigator is responsible for notifying the IRB/EC of the protocol or ICF amendment. For changes involving subject care or safety, the Principal Investigator is responsible for obtaining IRB/EC approval of the protocol or ICF amendment according to the instructions provided by the ARC with the protocol or ICF amendment.

Acknowledgement/approval by the IRB/EC of the protocol or ICF amendment must be documented in writing prior to implementation of the protocol or ICF amendment. Copies of this documentation must also be provided to the ARC.

8.5 Deviations from protocol

8.5.1 Compliance to protocol

No investigative procedures other than those defined in this clinical investigational plan will be undertaken on the enrolled subjects without the written agreement of the IRB/EC and ARC. It is the Investigator's responsibility to ensure that there are no deviations from the clinical investigational plan and full compliance with all established procedures of the IRB/EC is maintained. The Investigator will not deviate from the clinical investigational plan for any reason except in cases of medical emergencies, when the deviation is necessary to protect the life or physical well-being of the subject.

8.5.2 Procedures for recording, reporting, and analyzing protocol deviations

A deviation is an instance(s) of failure to follow, intentionally or unintentionally, the requirements of the protocol. All deviations must be reported to the ARC. The occurrence of clinical investigational plan deviations will be monitored by the ARC or designee. It is the Investigator's responsibility to inform their IRB/EC of clinical investigational plan deviations in accordance with their specific IRB/EC reporting policies and procedures.

In the event that an investigative site does not comply with the Investigator Agreement or clinical investigational plan, the ARC will notify the Investigator of the site’s non-compliance. Continued non-compliance may result in further escalation in accordance with the ARC’s standard procedures.

8.5.3 Corrective and preventative actions and principal investigator disqualification criteria

Protocol deviations and site/PI non-compliance will be closely monitored by the ARC and appointed study personnel. Identifying deviations and taking corrective actions at the earliest possible stage increases the potential for clinical trial success and reduces patient risk. The initiation of a corrective and preventative action (CAPA) to investigate and establish corrective actions may be required in some cases. The ARC reserves the right to close a clinical study site or replace a PI if non-compliance is observed.

8.6 Audits and inspections

In the event that an Investigator is contacted by a Regulatory Agency in relation to this trial, the Investigator will notify the ARC immediately. The Investigator and study site research personnel must be available to respond to reasonable requests and inspection queries made during the inspection process. The Investigator must provide the ARC with copies of all correspondence that may affect the review of this trial. The ARC will provide any needed assistance in response to regulatory inspections.

9. STUDY MANAGEMENT

9.1 Training

9.1.1 Training of Monitors

The ARC's monitors or designee will be trained to the protocol, randomization instructions, electronic case report forms, and study drug usage. The ARC or designee is responsible for the training. Training will be conducted in accordance with the ARC's and/or designee's standard procedures.

9.1.2 Training of study site research personnel

Participating investigators and study site research personnel will be trained during site initiation visits conducted by the Mount Sinai Clinical Coordinating Center or designee.

All training must be documented and must include or reference the revision of materials used for training, who was trained, the trainer and date of training. Original training records should be maintained at the site in the Regulatory Binder and copies should be dispensed to Mount Sinai Clinical Coordinating Center.

Site initiation/training involves a didactic session whereby the protocol, including screening procedures, clinical follow-up procedures, and study drug procedures are reviewed in detail along with investigator responsibilities.

In addition, the Mount Sinai Clinical Coordinating Center will assure that all participating investigators and study personnel are trained in the following:

- Protocol requirements, including patient screening requirements, inclusion/exclusion criteria, procedural requirements and subject follow-up requirements
- Study and personnel requirements
- Informed consent requirements
- Adverse event reporting
- Drug accountability procedures
- Electronic CRF completion
- Regulatory binder maintenance.

9.2 Monitoring of the study

The ARC and/or designee will monitor the trial over its duration according to the pre-specified monitoring plan. The trial monitor will contact each site at appropriate intervals to review investigational data for accuracy and completeness and ensure compliance with the

clinical investigation plan. The trial monitor may request all documents and required records that are maintained by the Investigator/Site, including medical records (office, clinic, or hospital) for the subjects in this trial. Source documentation must be available to substantiate proper informed consent procedures, adherence to protocol procedures, adequate reporting and follow-up of adverse events, accuracy of data collected on case report forms, and study drug information. The Investigator and/or study site research personnel will be available for monitoring contact. If a site visit is required, it is expected that the Investigator/Site will provide the trial monitor with a suitable working environment for review of study-related documents.

9.2.1 Source data

The Investigator is responsible for maintaining complete and accurate documentation of the trial including but not limited to medical records, trial progress records, laboratory results, case report forms, signed informed consent forms, study drug accountability records, correspondence with the IRB/EC, the trial monitors, and the ARC, as well as adverse event reports and information regarding subject discontinuations.

The Investigator is required to maintain information in the subject's medical records which documents and corroborates data entered in the case report forms. As a minimum the subject record should contain:

- Medical history/physical exam documenting that subject meets inclusion/exclusion criteria
- Documentation of subject's consent and subject ID number in the trial
- Dated and signed notes from each subject visit
- Adverse events reported and their resolution or lack thereof including supporting documents such as hospital records, discharge summaries, catheterization reports, and ECGs.
- Record of protocol required medications during the trial
- Record of the subject's condition upon completion of or withdrawal from the trial

The Investigator and the associated institution will permit direct access to source data/documents for study-related monitoring, audits, IRB/EC review, and regulatory inspections.

Subjects providing informed consent agree to allow the ARC or designee access and copying rights to pertinent information in their medical records concerning their participation in this trial. The Investigator will obtain, as part of the informed consent, permission for trial monitors or regulatory authorities to review, in confidence, any records identifying the

subjects in this trial. This information may be shared with regulatory agencies; however, the ARC undertakes not to otherwise release the patient's personal and private information.

9.3 Study timetable and end of study

The trial is estimated to commence February 1st, 2015. The last subject follow-up at 18 months post-procedure is expected to occur in February 2018. The total expected duration of the trial is 36 months.

10. DATA MANAGEMENT

A computerized data entry and management system will be developed during the initial project months by an independent academic research center. A closed and password protected data entry system has been designed to ensure that only the responsible data entry person and the Data Management site supervisor can enter and/or edit data and this can be done only by using the programs and/or utilities available on the menu system. An audit trail will be created by date/time and user stamping. Range checks, review screens, and various error trapping routines are built into the system as quality control procedures. All possible relevant information on the forms is pre-coded. Specific instructions and explanation of choices will be provided for all data forms.

The statistical programmer will perform additional data checks, data cleaning, and variable coding to create analysis datasets using SAS. The programmer will also create a reporting system that generates study specific tables, listings, and figures, which will be run periodically to monitor study and data entry. As a final check on data integrity, the Director of Clinical Biometrics and study biostatistician will check these outputs against the raw data in order to resolve any discrepancies. The Biometrics lead, statistician, and statistical programmer will be responsible for working with the project staff to ensure the integrity of the data entry process.

11. EVALUATION AND CALCULATION OF VARIABLES

11.1.1 Primary Bleeding Endpoint

The primary bleeding endpoint of the present study is the time to first occurrence of clinically relevant bleeding, defined as Bleeding Academic Research Consortium (BARC) Types 2, 3 or 5 bleeding.

11.1.2 Secondary Bleeding Endpoints

Time to first occurrence of:

- Types 3 or 5 bleeding according to definitions from BARC
- Minor or major bleeding according to definitions from Thrombolysis in Myocardial Infarction (TIMI)

- Moderate or severe or life-threatening bleeding according to definitions from GUSTO
- Major bleeding according to definitions from International Society of Thrombosis or Hemostasis (ISTH)

11.1.3 Primary Ischemic Endpoint

The primary ischemic endpoint of the present study is the time to first occurrence of confirmed all-cause death, non-fatal myocardial infarction, or stroke.

11.1.4 Secondary Ischemic Endpoints

Time to first occurrence of:

- cardiovascular death, non-fatal myocardial infarction, ischemic stroke or clinically-driven revascularization
- cardiovascular death, non-fatal myocardial infarction or ischemic stroke
- definite or probable stent thrombosis
- cardiovascular death
- non-fatal myocardial infarction
- cardiovascular death, non-fatal myocardial infarction or definite or probable stent thrombosis
- ischemic stroke
- all-cause mortality

12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

The statistical analyses will be performed using SAS version 9.0 or greater and Stata versions 12.0 or greater.

12.1 Description of analysis sets

The Enrolled Population consists of all subjects who signed informed consent.

The intention-to-treat (ITT) population will consist of all subjects who have been randomized (i.e. when the subject number and allocated treatment are recorded in the EDC). Subjects will be analyzed in the treatment group assigned by the EDC.

The per-protocol population (PP) will consist of all randomized subjects without any major deviations from the protocol. The following deviations will lead to exclusion from the PP population

- Subjects not receiving the assigned treatment as allocated by the EDC or no treatment at all
- Non-compliance to study drug (aspirin or placebo) or ticagrelor. Non-compliance is defined as taking less than 80% of dispensed tablets based on manual pill bottle count at each study visit.

12.1.1 Efficacy analysis set

All analyses for the primary bleeding endpoint will be performed on the ITT and PP population. The primary analysis will be performed on the ITT population. This analysis will be repeated in the PP population to support the primary results.

The primary bleeding endpoint is the composite of BARC Types 2, 3 or 5 bleeding.

12.1.2 Safety analysis set

Analyses for the primary ischemic endpoint will be performed on the PP cohort. A secondary analysis for the primary ischemic endpoint will be performed in the ITT cohort.

12.2 Methods of statistical analyses

Unless otherwise stated, all hypothesis tests will be performed using two-sided tests at the 5% significance level. Continuous variables will be summarized using descriptive statistics including means and standard deviations if normally distributed or median with interquartile ranges for skewed distributions. Discrete variables will be summarized using absolute and relative frequencies.

Demographic and baseline characteristics will be summarized by randomized treatment group and for all randomized subjects combined. Baseline characteristics that will define subgroups of interest for the efficacy and safety analyses are:

- Age group (< 65, >= 65 years)
- Race (Caucasian, non-Caucasian)
- Gender (Male, Female)
- Geographic Region (US, non-US)
- Diabetes Mellitus (yes, no)
- Chronic Kidney Disease (yes, no)

- CAD Presentation (Stable, Unstable)
- PCI Status (Elective, Urgent)
- Stent length implanted (< 30 mm, >=30 mm)
- BMI (above median, below median)
- History of Prior MI (yes, no)
- Multivessel disease (yes, no)

Censoring: Subjects not experiencing any endpoint will be censored at time of death, last contact date (for subjects who withdraw consent or are lost to follow-up) or 365 days after randomization, whichever comes first.

Analysis for the Primary Bleeding Endpoint: This analysis will be performed on the ITT population. The primary objective is to determine if ticagrelor monotherapy is superior to ticagrelor plus aspirin for the primary efficacy endpoint (BARC Types 2, 3 or 5 bleeding). The null hypothesis for this analysis is that the HR for the experimental group (H_0) = 1. The alternative hypothesis is that the HR for the experimental group (H_A) ≠ 1. A test of superiority at the two-sided 0.05 level will be performed using a Cox proportional hazard model that includes treatment group as a covariate. A point estimate and two-sided 95% CI for the relative risk as measured by the hazard ratio will be calculated based on the Cox proportional hazards model. Event rates will be estimated at one year and Kaplan-Meier curves will be plotted for the time from randomization to the first occurrence of confirmed BARC Type 2, 3 or 5 bleeding by treatment group. This analysis will be repeated in the PP cohort to support the primary results.

Analysis for the Primary Ischemic Endpoint: The analysis for the primary ischemic endpoint will be performed on the PP cohort. The primary objective is to determine if ticagrelor monotherapy is non-inferior to ticagrelor plus aspirin for the primary safety endpoint (all-cause death, non-fatal myocardial infarction, or stroke). . A test of non-inferiority at the one-sided 0.025 level will be performed. Event rates will be estimated at one year and Kaplan-Meier curves will be plotted for the time from randomization to the first occurrence of confirmed all-cause death, non-fatal myocardial infarction, or stroke or by treatment group. Assuming an event rate of 8.0% in the control group, a sample size of 8200 will yield 80% to exclude a non-inferiority margin of 1.6%. If the upper limit of the 95% CI for the point estimate of the absolute risk difference is less than or equal to 1.6% then the criteria for non-inferiority will be met. This non-inferiority margin translates to a relative risk of 20% assuming the observed event rate equals 8.0% in the control arm.

Subgroup Analysis One year event rates for the primary efficacy and safety endpoints will be calculated in all subgroups described in section 12.2. Stratum-specific HRs and corresponding 95% CI will be calculated for each subgroup using a Cox proportional hazards

model. Formal interaction testing will be performed using the subgroup X treatment allocation as an additional term in the Cox model.

12.3 Determination of sample size

Power calculations are based on a superiority comparison for the primary efficacy endpoint of clinically relevant bleeding (BARC Types 2, 3 or 5) at 1 year from randomization (15 months after enrollment). Based on bleeding rates as shown in Table 3, a cumulative bleeding rate of 4.5% is anticipated between time of randomization and 1 year. This estimate is more conservative than rates shown in Table 3 as subjects sustaining a major hemorrhagic event in the first 3 months after PCI will not be randomized. Assuming a 2% loss to follow-up and non-compliance / cross-over rate of 4%, the current trial will require 8200 subjects to detect a relative reduction in bleeding of 28% with ticagrelor monotherapy with 80% power with a Type I error of 0.05. It is anticipated that approximately 8% - 10% of enrolled subjects will not be eligible for randomization and therefore 9000 subjects will be enrolled. Additional sample size estimates are provided in Table 4 assuming different control bleeding rates and risk reductions. References for the sample size estimates include Lakatos 1988, Biometrics volume 44 pages 229-241; and Lakatos 2002, Statistics in Medicine, Volume 21 pages 1969-1989.

Assuming a 1 year ischemic adverse event rate of 8% the current study will have 80% power to exclude a non-inferiority margin of 1.6% (upper limit of 95% CI for absolute risk difference).

Table 2 Bleeding Rates/Effect Sizes for Primary Endpoint Power Calculations

Basis for Proposed <u>Bleeding Event Rates</u> in TWILIGHT Power Calculations			
Study	**Study Type**	**Time Point**	**BARC ≥ 2 Rate**
DAPT	RCT	18 months	**~ 4.2%**
PARIS (unpublished data)	Registry		
Age > 65	Registry	1 year	8.6%
Diabetes Mellitus (on insulin) Diabetes Mellitus (orals)	Registry	1 year	8.3% 6.3%
Renal disease	Registry	1 year	13.2%
Vranckx et al., EHJ 2013	Post-hoc (TRACER)	500 days	14%
ADAPT-DES			
CrCl < 60 (Baber et al, TCT 2013)	Registry	1 year	10.0%
Rao et al., JACC Int 2013	NCDR CathPCI	In-hospital (women)	8.5%
Basis for Proposed <u>Effect Size</u> in TWILIGHT Power Calculations			

Study	Study Type	Comparators	Relative Bleeding Increase
Baigent et al., Lancet 2009	Pooled Data from Randomized trials	ASA vs. placebo/control	50% (1° prevention) 170% (2 ° prevention)
WOEST, Lancet 2013	RCT	ASA vs. placebo	~ 60%
CAPRIE, Lancet 1996	RCT	ASA vs. clopidogrel	~35% (GI hemorrhage)
Physician Health Study, NEJM 1989	RCT	ASA vs. Placebo	~35%
De Berardis et al., JAMA 2012	Cohort study	ASA vs. No ASA	55%
Seshasai et al., Archives Int Med 2012	Meta-analysis of 9 RCTs	ASA vs. Placebo	~31%
HOT Trial, Lancet 1998	RCT	ASA vs. Placebo	~ 80%

Table 3 Power and Sample Size Scenarios for Primary Superiority Endpoint of BARC ≥ 2 Bleeding

Control Bleeding Rate	Relative Risk Reduction	Total Randomized Sample Size	Total Sample Size (Enrolled + Randomized) with 8% loss after enrollment*	Total Sample Size (Enrolled + Randomized) with 10% loss after enrollment*
5%	30%	6400	7000	7111
5%	28%	7400	8040	8222
5%	26%	8030	9800	10000
4.5%	30%	7090	7706	7900
4.5%	28%	8200	8913	9111
4.5%	26%	9700	10500	10800
4.0%	30%	8000	8700	8888
4.0%	28%	9300	10100	10333
4.0%	26%	10900	11800	12111

We anticipate that ~10% of enrolled subjects will not be eligible or lost for randomization. Power calculations assume 2% loss to follow-up and 4% cross-over/non-compliance.

12.4 Data and safety monitoring board

The TWILIGHT study will be conducted under the auspices of an independent Data and Safety Monitoring Board (DSMB), whose activities will be described in a DSMB charter. DSMB members will not have primary affiliation with the study sponsor, the EDC supplier or

the principal investigator of the trial. Members of the Board will be determined prior to study enrollment.

The DSMB will review data and determine reporting and stopping rules as specified in the DSMB charter. The DSMB members will review safety data while maintaining the scientific integrity of the trial. The data to be reviewed will consist of adjudicated and non-adjudicated MACE, Bleeding, and other Serious Adverse Events and their incidence, in order to identify potential safety issues. Based on the safety data, the DSMB may recommend modifications to the protocol, suspension or termination of the trial, and advise the Executive Committee.

Members of the DSMB will meet or conference with steering group members before the trial starts to review the protocol, to determine the meeting schedule, the logistics of reporting the safety data and the stopping rules. Frequency of meetings can change during the study and will be determined by the DSMB and its charter.

All adverse events will be reported to the DSMB and reviewed on an on-going basis throughout the subject enrollment and follow-up period as specified in the DSMB charter to ensure the safety of subjects enrolled in this trial. The DSMB may request additional information as needed. Based on safety data, the DSMB may recommend that the Executive Committee modify or discontinue the trial. All final decisions, regarding trial modifications, however, rest with the Executive Committee.

13. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

13.1 Overdose

If an overdose on the study drug occurs in the course of the study, then investigators or other site personnel inform appropriate the ARC **within one day**, i.e., immediately but no later than **the end of the next business day** of when he or she becomes aware of it.

The ARC will work with the investigator to ensure that all relevant information is provided to the ARC.

13.2 Pregnancy

Due to the study enrollment criteria and proposed population, women of child bearing potential (as defined in Section 4.2) are excluded from participation in this study. In the unlikely event that pregnancy should occur during the course of the study, all outcomes of pregnancy should be reported to the ARC.

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15. APPENDIX A – DEFINITIONS FOR STUDY ENDPOINTS

15.1 Bleeding events

15.1.1 Bleeding Academic Research Consortium definition of bleeding

Clinically relevant bleeding is defined as any bleeding event that meets the BARC criteria types 2, 3 or 5.

Table 4 BARC Bleeding Definition, modified from Mehran et al (26)

Type	Definition
0	No evidence of bleeding.
1	Bleeding that is not actionable and patient does not have unscheduled studies, hospitalization or treatment by a health care professional
2	Any clinically overt sign of hemorrhage that is actionable but does not meet criteria for type 3, 4 or 5 bleeding. It must meet at least one of the following criteria: • requiring medical or percutaneous intervention guided by a health care profession, includes (but are not limited to) temporary/permanent cessation of a medication, coiling, compression, local injection • leading to hospitalization or an increased level of care • prompting evaluation defined as an unscheduled visit to a healthcare professional resulting in diagnostic testing (laboratory or imaging)
3	Clinical, laboratory and/or imaging evidence of bleeding with specific healthcare provider responses, as listed below:
3a	• Any transfusion with overt bleeding • Overt bleeding plus hemoglobin (Hb) drop ≥3 to <5g/dL* (provided Hb drop is related to bleeding)
3b	• Overt bleeding plus Hb drop ≥5g/dL* (Hb drop is related to bleed) • Cardiac tamponade • Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid) • Bleeding requiring intravenous vasoactive drugs
3c	• Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation; does include intraspinal). Subcategories: confirmed by autopsy, imaging or lumbar puncture

* Hemoglobin drop should be corrected for for intracurrent transfusion in which 1 unit of packed red blood cells or whole blood should be expected to increase hemoglobin by 1g/dL.

Type	Definition
	• Intraocular bleed compromising vision
4	CABG – Related Bleeding • Perioperative intracranial bleeding within 48 hours • Reoperation following closure of sternotomy for the purpose of controlling bleeding • Transfusion of ≥5 units of whole blood or packed red blood cells within a 48 hour period • Chest tube output ≥2L within a 24 hour period
5	Fatal Bleeding. Bleeding directly causes death with no other explainable cause. Categorized further as either definite or probable.
5a	Probable fatal bleeding is bleeding that is clinically suspicious as the cause of death, but the bleeding is not directly observed and there is no autopsy or confirmatory imaging.
5b	Definite fatal bleeding is bleeding that is directly observed (either by clinical specimen – blood, emesis, stool, etc. – or by imaging) or confirmed on autopsy.

15.1.2 Thrombolysis in Myocardial Infarction definition of bleeding

Table 5 TIMI Bleeding Definition(27)

Type	Definition
Non-CABG related bleeding	
Major	• Any intracranial bleeding (excluding microhemorrhages <10 mm evident only on gradient-echo MRI) • Clinically overt signs of hemorrhage associated with a drop in hemoglobin of ≥5 g/dL or a ≥15% absolute decrease in haematocrit • Fatal bleeding (bleeding that directly results in death within 7 days) **Life threatening** bleeding is a TIMI major bleeding event that meets any of the following criteria: • Symptomatic intracranial hemorrhage • Fatal bleeding • Leads to hypotension requiring inotropic agents • Requires surgical intervention for ongoing bleeding • Necessitates transfusion of 4 or more units of whole blood or packed red blood cells over a 48-hour period

Type	Definition
Minor	• Clinically overt (including imaging), resulting in hemoglobin drop of 3 to <5 g/dL or ≥10% decrease in haematocrit • No observed blood loss: ≥4 g/dL decrease in the haemoglobin concentration or ≥12% decrease in haematocrit • Any overt sign of hemorrhage that meets one of the following criteria and does not meet criteria for a major bleeding event: o Requiring intervention (medical practitioner-guided medical or surgical treatment to stop or treat bleeding, including temporarily or permanently discontinuing or changing the dose of a medication or study drug) o Leading to or prolonging hospitalization o Prompting evaluation (leading to an unscheduled visit to a healthcare professional and diagnostic testing, either laboratory or imaging)
Minimal	• Any overt bleeding event that does not meet the criteria above • Any clinically overt sign of haemorrhage (including imaging) associated with a <3 g/dL decrease in haemoglobin concentration or <9% decrease in haematocrit
Bleeding in the setting of CABG	
	• Fatal bleeding (bleeding that directly results in death) • Perioperative intracranial bleeding • Reoperation after closure of the sternotomy incision for the purpose of controlling bleeding • Transfusion of ≥5 U PRBCs or whole blood within a 48-h period; cell saver transfusion will not be counted in calculations of blood products. • Chest tube output >2 L within a 24-h period

15.1.3 Global Utilization of Streptokinase and TPA for Occluded Arteries (GUSTO) definition of bleeding

Table 6 GUSTO Bleeding Definition (28)

Type	Definition
Severe or life-threatening	Intracerebral bleeding or bleeding resulting in substantial hemodynamic compromise requiring treatment
Moderate	Any bleeding not meeting the requirements for severe / life-threatening bleeding that requires transfusion
Minor	Other bleeding not requiring transfusion or causing hemodynamic compromise

15.1.4 International Society on Thrombosis and Haemostasis definition of bleeding

The ISTH classification of major bleeding in non-surgical patients includes any one of the following:

- Fatal bleeding,
- Symptomatic bleeding in a critical area or organ such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome,
- Bleeding causing a fall in haemoglobin level of 2 g/dL (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells.(25)

15.2 Major Adverse Cardiovascular Events

Major adverse cardiovascular events (MACE) is the composite of cardiovascular death, non-fatal myocardial infarction, ischemic stroke, or clinically-driven revascularization. The definitions of the individual components of MACE are given below.

15.2.1 Death

All-cause death comprises several subclassifications (Table 7). In general, all deaths are considered cardiac unless an alternate cause is unequivocally established, even among subjects with serious noncardiac comorbidities.

Table 7 Classification of Death(29)

Cardiac death	Any death due to proximate cardiac cause (eg, MI, low-output failure, fatal arrhythmia), unwitnessed death and death of unknown cause, all procedure-related deaths including those related to concomitant treatment, will be classified as cardiac death.
Vascular death	Death caused by noncoronary vascular causes, such as cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm or other causes.
Noncardiovascular death	Any death not covered by the above definitions, such as death caused by infection, malignancy, sepsis, pulmonary causes, accident, suicide or trauma.

15.2.2 Myocardial Infarction

Myocardial infarction is defined according to the third universal definition(30) and includes:

- Type 1: spontaneous MI
- Type 2: MI secondary to an ischemic imbalance
- Type 3: MI resulting in death when biomarker values are unavailable
- Type 4a. MI related to PCI
- Type 4b: MI related to stent thrombosis

- Type 5: MI related to CABG

Any one of the following criteria meets the diagnosis of MI:

- Detection of a rise and/or fall of cardiac biomarker values (preferably cardiac troponin) with at least one value above the 99th percentile URL and with at least one of the following:
    - Symptoms of ischemia
    - (Presumed) new significant ST-T wave changes or new LBBB
    - Development of pathological Q waves
    - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
    - Identification of an intracoronary thrombus by angiography or autopsy
- Cardiac death with symptoms suggestive of MI and presumed new ischemic ECG changes or new LBBB, but death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased
- PCI related MI is arbitrarily defined by elevation of cardiac biomarkers
    - (>5 x 99th percentile URL) in patients with normal baseline values or
    - > 20% if the baseline values are elevated and are stable or falling

In addition, one of the following is required

- symptoms suggestive of ischemia
- new ischemic ECG changes
- angiographic findings consistent with a procedural complication OR
- imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality

- Stent thrombosis associated with MI when detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/or fall of cardiac biomarker values with at least one value above the 99th percentile URL
- CABG related MI is arbitrarily defined by elevation of cardiac biomarkers >10 x 99th percentile URL in patients with normal baseline values, AND one of the following:

- New pathological Q waves or new LBBB
- Angiographic documented new graft or new native coronary artery occlusion, or
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

15.2.3 Stroke

Stroke is defined as an acute symptomatic episode of neurological dysfunction, more than 24 hours in duration in the absence of therapeutic intervention or death, due to cerebral, spinal or retinal tissue injury as evidenced by neuroimaging or lumbar puncture. It includes the following subclassifications:

- Ischemic stroke: infarction due to prolonged ischemia. Causes include (but are not limited to) arterial and venous thrombosis, embolism, and systemic hypoperfusion.
- Hemorrhagic stroke: caused by a non-traumatic intraperenchymal, intraventricular or subarachnoid hemorrhage
- Undetermined: stroke with insufficient information to determine ischemic or hemorrhagic cause

Transient ischemic attack (TIA) is a transient episode of neurological dysfunction (< 24 hours) caused by temporary cerebral, spinal or retinal ischemia with no evidence of acute infarction on neuroimaging.

15.2.4 Stent thrombosis

Stent thrombosis is classified according to the level of certainty and timing following PCI(29) (Table 8).

- Definite stent thrombosis: is highly specific and requires angiographic or pathological confirmation of stent thrombosis in or within 5 mm of the stent in the setting of at least one of the following criteria with a 48-hour time window
  - Acute ischemic symptoms at rest
  - New ischemic ECG changes
  - Typical rise and fall in cardiac biomarkers
- Probable stent thrombosis includes
  - Any unexplained death within the first 30 days following PCI

- Any MI at any time following PCI that is related to documented acute ischemia in the territory of the implanted stent, in the absence of angiographic/pathological confirmation of stent thrombosis and no other obvious cause

- Possible stent thrombosis
  - Any unexplained death after the first 30 days following PCI until the end of trial follow-up

Table 8 Timing of Stent Thrombosis

Acute	0-24 hours following PCI
Subacute	>24 hours to 30 days following PCI
Late	>30 days to 1 year following PCI
Very late	>1 year following PCI

15.2.5 Clinically driven revascularization

Clinically driven revascularization includes repeat PCI or CABG for recurrent or persistent symptomatic ischemia and can be defined according to the relationship to the index PCI (target lesion)(29):

- Target lesion revascularization, at the previously stented segment
- Non-target lesion, target vessel revascularization, of the previously treated vessel or its side branches AND
- Non-target vessel lesion revascularization, of a vessel other than the previously treated vessel

16. APPENDIX B - OTHER DEFINITIONS

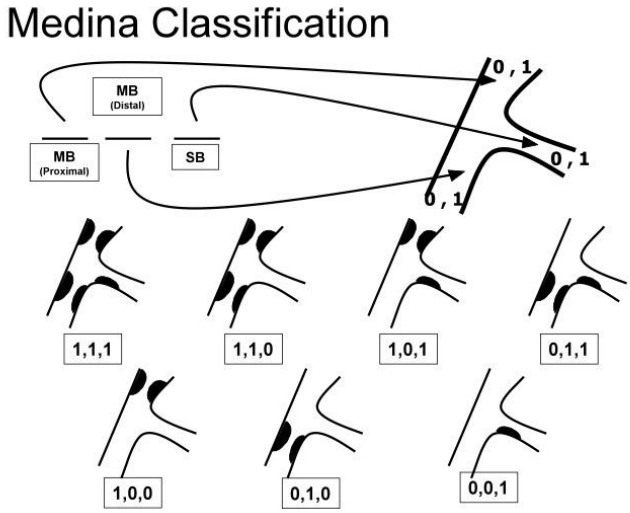
Coronary Artery Disease (CAD)

Multivessel (CAD), defined as significant disease in at least 2 major epicardial vessels or significant left main disease plus one major epicardial vessel. Significant coronary artery disease is defined as angiographic stenosis of at least 70% in a major epicardial vessel or at least 50% in the left main trunk. For intermediate stenosis in major epicardial vessels (50%-70%), an invasive hemodynamic assessment using fractional flow reserve (FFR) with values less than or equal to 0.8 will be considered significant. For intermediate left main lesions, a minimal lumen area by intravascular ultrasound (IVUS) less than 6.0 mm^2 will be considered significant.

Successful PCI

PCI is considered successful for lesions treated with stent implantation if the residual diameter stenosis based on visual estimation is less than or equal to 10% and the final TIMI flow grade is 3. PCI is considered successful for lesions treated without stent implantation if the residual diameter stenosis based on visual estimation is less than or equal to 30% and the final TIMI flow grade is 3.

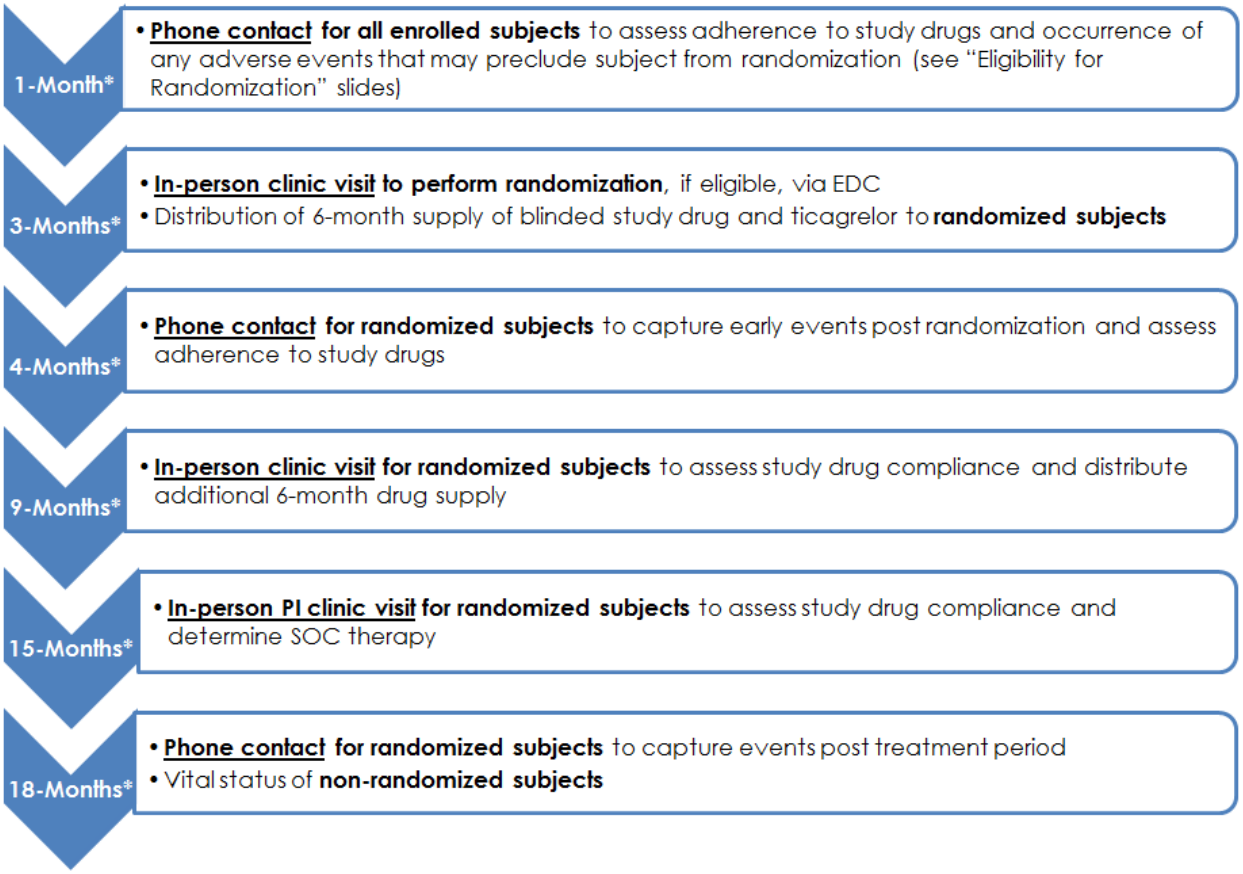
Medina Classification of Bifurcations



Indication for PCI according to National Cardiovascular Data Registry

17. APPENDIX C

Timeline Of In-Person Visits And Phone Calls



18. APPENDIX D

CONTRAINDICATIONS TO ASPIRIN

Hypersensitivity to ASA, salicylates, non-steroidal anti-inflammatory drugs (NSAIDs), analgesics, antipyretics or other ingredients in the product, excipients or component of the container.
Acute gastrointestinal ulcer, history of gastrointestinal ulcers
Hemorrhagic diathesis and severe active bleeding
Active or severe hepatic failure, renal failure requiring dialysis, or acute congestive heart failure
Patients with a history of asthma induced by the administration of salicylates or substances with a similar action, notably NSAIDs
Combination with methotrexate at doses of 15 mg/week or more
Last trimester of pregnancy and nursing women
Glucose-6-phosphate dehydrogenase (G6PD) deficiency

19. APPENDIX E

CONTRAINDICATIONS TO TICAGRELOR:

Hypersensitivity to the active substance or to any of the excipients
Active pathological bleeding
History of intracranial hemorrhage
Moderate to severe hepatic impairment
Co-administration of ticagrelor with strong CYP3A4 inhibitors (e.g., ketoconazole, clarithromycin, nefazodone, ritonavir, and atazanavir) is contraindicated, as co-administration may lead to a substantial increase in exposure to ticagrelor