



Ticagrelor with aspirin or alone in high-risk patients after coronary intervention: Rationale and design of the TWILIGHT study

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Background Dual antiplatelet therapy (DAPT) is necessary to prevent thrombosis yet increases bleeding after percutaneous coronary intervention (PCI) with drug-eluting stents (DES). Antiplatelet monotherapy with a potent P2Y₁₂ receptor antagonist may reduce bleeding while maintaining anti thrombotic efficacy compared with conventional DAPT.

Methods TWILIGHT is a randomized, double-blind placebo-controlled trial evaluating the comparative efficacy and safety of antiplatelet monotherapy versus DAPT in up to 9000 high-risk patients undergoing PCI with DES. Upon enrollment after successful PCI, all patients will be treated with open label low-dose aspirin (81-100 mg daily) plus ticagrelor (90 mg twice daily) for 3 months. Event-free patients will then be randomized in a double-blind fashion to low-dose aspirin versus matching placebo with continuation of open-label ticagrelor for an additional 12 months. The primary hypothesis is that a strategy of ticagrelor monotherapy will be superior with respect to the primary endpoint of bleeding academic research consortium type 2, 3 or 5, while maintaining non-inferiority for ischemic events compared with ticagrelor plus ASA.

Conclusions TWILIGHT is the largest study to date that is specifically designed and powered to demonstrate reductions in bleeding with ticagrelor monotherapy versus ticagrelor plus ASA beyond 3 months post-procedure in a high-risk PCI population treated with DES. The trial will provide novel insights with respect to the potential role of ticagrelor monotherapy as an alternative for long-term platelet inhibition in a broad population of patients undergoing PCI with DES. (*Am Heart J* 2016;182:125-34.)

Background

The current therapeutic paradigm for preventing thrombosis after percutaneous coronary intervention (PCI) with drug-eluting stents (DES) includes dual antiplatelet therapy (DAPT) with aspirin and an inhibitor of the platelet P2Y₁₂ receptor.^{1,2} The clinical rationale and evidence base supporting this approach comprises

randomized studies showing significant reductions in near-term adverse events with DAPT compared with aspirin monotherapy or anticoagulant-containing regimens.³ In contrast to these earlier trials, contemporary PCI is characterized by safer DES platforms, broader availability of more potent antiplatelet pharmacotherapy^{4,5} and a heightened awareness of bleeding as an important risk factor for post-PCI mortality.⁶⁻⁸

As a consequence novel therapeutic strategies, such as shorter DAPT durations or even antiplatelet monotherapy, have been proposed as safer alternatives with comparable efficacy to conventional DAPT, which itself differs according to the intensity of P2Y₁₂ inhibition agent. Regarding the former, a 3 to 6 month course of DAPT is associated with significant reductions in bleeding, non-cardiac death and perhaps all-cause mortality, compared with 12 months or longer.⁹⁻¹⁵ With respect to the latter, at least one randomized trial demonstrated substantial reductions in bleeding without incremental thrombotic risk by withdrawing aspirin in PCI patients with atrial fibrillation who were receiving warfarin.¹⁶ Coupling these approaches in concert with a potent P2Y₁₂ inhibitor, however, has not been examined in a large randomized fashion to date. This distinction is

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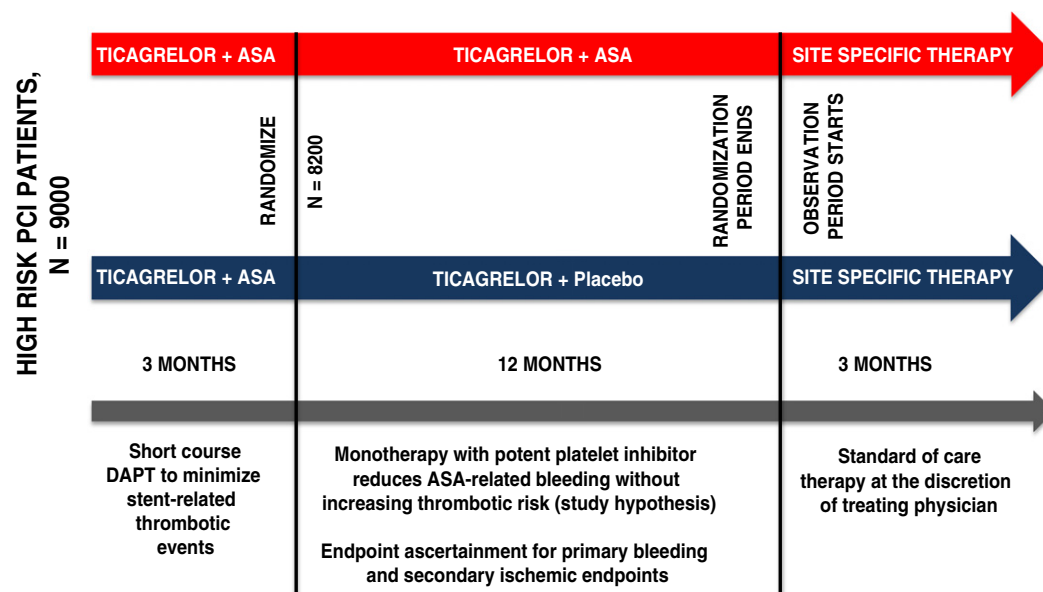
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Figure 1



TWILIGHT Study Schema.

clinically relevant because DAPT with aspirin (ASA) and clopidogrel does not confer maximal protection against ischemic events across the entire risk spectrum of PCI. Indeed, residual atherothrombotic risk remains substantial despite such therapy in several high-risk patient and lesion subsets, including those with diabetes mellitus (DM), renal dysfunction and multivessel disease.¹⁷⁻²² Treating these patients with an initial short-term DAPT duration to prevent early stent-related thrombosis followed by a sustained course of antiplatelet monotherapy using a potent P2Y₁₂ inhibitor alone may reduce ASA-related bleeding while maintaining anti-ischemic efficacy, thereby optimizing net clinical benefit. To test this hypothesis, we designed the TWILIGHT trial to examine the impact of ticagrelor monotherapy versus ticagrelor plus aspirin in reducing clinically relevant bleeding over one year in high-risk patients undergoing PCI with DES.

Methods

Study organization

The TWILIGHT study (ClinicalTrials.gov unique identifier NCT02270242) is a randomized, multicenter double-blind placebo controlled trial designed and sponsored by the Icahn School of Medicine at Mount Sinai and funded through an investigator-initiated grant by AstraZeneca. The trial will test the comparative efficacy and safety of two different antiplatelet strategies in high-risk patients undergoing PCI with DES (Figure 1). The executive and steering committees will be responsible for the medical, scientific, and operational conduct of the study. The executive

committee will be responsible for the integrity of data analysis and reporting of results. The study will adhere fully to the ethical principles of the Declaration of Helsinki, including the requirement for each subject's informed consent before initiating any study procedure.

Study objectives

The primary objective of TWILIGHT 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 with DES who have completed a 3-month course of DAPT with aspirin plus ticagrelor.

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

Study population – enrollment and randomization

The study will enroll 9000 high-risk patients 18 years of age or older undergoing PCI with at least one locally approved DES discharged on DAPT with aspirin and ticagrelor intended for at least 3 months duration. Enrollment into the study will require meeting at least one of the clinical inclusion criteria and one of the angiographic inclusion criteria but none of the exclusion criteria, as shown in Table I. These pre-specified criteria were chosen to enroll patients at high risk for either bleeding or ischemic complications after PCI. Most of

Table I. Study enrollment criteria

Inclusion criteria

Clinical criteria (Must meet at least one)

- 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 therapy or subcutaneous insulin)
- Chronic kidney disease defined as an estimated glomerular filtration rate < 60 mL/min per 1.73m^2 or creatinine clearance < 60 mL/min

Angiographic criteria (Must meet at least one)

- Multivessel coronary artery disease
- Target lesion requiring total stent length > 30 mm
- Thrombotic target lesion
- Bifurcation lesions with Medina X,1,1 classification requiring at least 2 stents
- Left main ($\geq 50\%$) or proximal LAD ($\geq 70\%$) lesion
- Calcified target lesion(s) requiring atherectomy

Exclusion criteria

- Under 18 years of age
- Contraindication to aspirin
- Contraindication to ticagrelor
- 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. active peptic ulcer disease, 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
- Fibrinolytic therapy within 24 hours of index PCI
- Concomitant therapy with a strong cytochrome P-450 3 A inhibitor or inducer
- Platelet count $< 100,000$ mm³
- Requiring ongoing treatment with aspirin ≥ 325 mg daily

MI, Myocardial infarction; PAD, peripheral arterial disease; CAD, coronary artery disease; LAD, left anterior descending artery; PCI, percutaneous coronary intervention; STEMI, ST segment elevation myocardial infarction.

these factors are included in validated risks scores for either bleeding, ischemic or both types of complications after PCI.^{23,24} Enrollment into the study will require providing written informed consent after the qualifying PCI and prior to receiving any study-related medications. Consent will also be obtained to collect vital status at the end of the extended scheduled follow-up.

Study treatment, follow-up and randomization

Protocol-mandated therapy includes an open-label phase for the first 3 months after PCI and a blinded phase from month 3 to 15. An additional 3 months of observation will start upon completion of all protocol-mandated therapy,

extending from month 15 to 18, during which time details on medication changes and any adverse events will be collected. The open-label phase includes a 3-month course of open-label ticagrelor at a dose of 90 mg twice daily and enteric-coated (EC) ASA at a dose of 81–100 mg daily starting at the time of discharge from index PCI. Of note, all other peri-procedural medications are left to the discretion of the treating physician and are not dictated by the study protocol. Protocol-mandated therapy, therefore, starts at the time of discharge from index PCI.

After 3 months from enrollment, patients will return for an in-person visit to assess for ischemic or bleeding events, medication status and randomization eligibility (Table II).

Table II. Randomization ineligibility criteria at 3 months

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

PCI, Percutaneous coronary intervention; BARC, Bleeding academic research consortium.

Patients who are event-free at this time point and remain on ASA and ticagrelor will then be randomized in a double-blinded 1:1 fashion to either continuation of active ASA (81–100 mg) or matching placebo for an additional 12 months. All randomized patients will also continue open-label ticagrelor for an additional 12 months. Although patients experiencing non-life-threatening bleeding in the first 3 months after enrollment are not excluded from randomization, study medications may be discontinued without prejudice to further treatment if it is felt that ongoing participation will expose the patient to unnecessary risks. While these patients may represent the ideal candidates for a trial such as TWILIGHT, interval events can change this calculus thereby highlighting the need to re-examine equipoise surrounding randomization at the 3-month visit. Details surrounding other time points, procedures and type of follow-up throughout the trial are shown in Figure 2.

Adherence to study-provided medications will be calculated using the medication possession ratio via manual pill count at the in-person 9 and 15 month study visits. Each instance of DAPT cessation will be further classified according to the underlying mode and duration as previously defined: physician-guided permanent discontinuation, temporary surgical interruption or disruption due to bleeding or non-compliance.²⁵

Blinding and unblinding

The study has a double-blind design with aspirin and matching placebo. The patients, 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. An independent data safety monitoring board (DSMB) will monitor the data on a periodic basis. In the

event of a medical emergency, wherein knowledge of the investigational drug is critical to the patient's medical management, the blind for that subject may be broken by the treating physician.

Study endpoints

Primary and secondary bleeding and ischemic endpoints are shown in Table III.

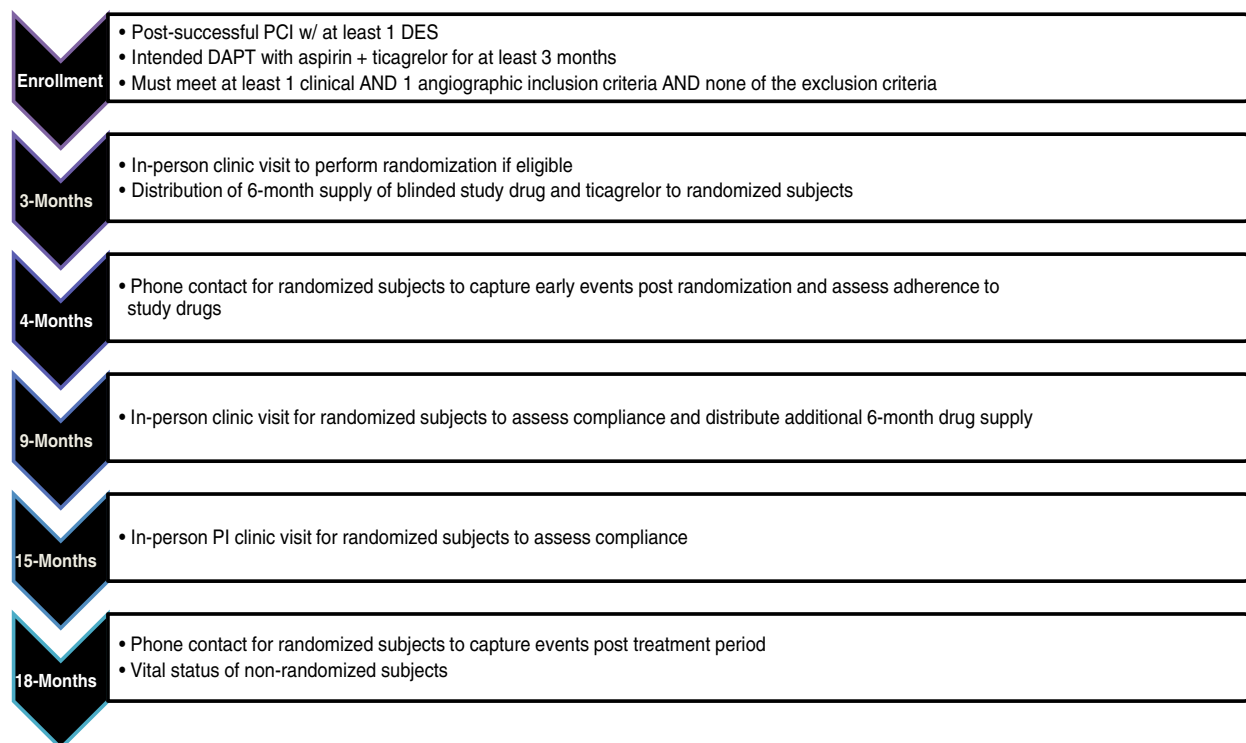
Primary endpoint. The primary bleeding outcome, which is also the primary endpoint of the trial, is the time to first occurrence of clinically relevant bleeding, defined as Bleeding Academic Research Consortium (BARC) Types 2, 3 or 5 bleeding²⁶ occurring between months 3 to 15. In brief, BARC types 2, 3 and 5 bleeds are defined as clinically overt hemorrhage requiring medical attention (type 2), requiring transfusion, surgical correction or associated with a hemoglobin drop of at least 3 g/dL (type 3) or fatal events (type 5). Previous studies have shown that non-fatal BARC type 2 and 3 bleeds are independently associated with increased mortality risk after PCI thereby justifying the inclusion of both within our primary endpoint.²⁷ The secondary bleeding outcomes include the time to first occurrence of: (i) BARC types 3 or 5 bleeding; (ii) Major or minor bleeding according to definitions from TIMI²⁸; (iii) Moderate or severe or life-threatening bleeding according to definitions from GUSTO²⁹; (iv) Major bleeding according to definitions from International Society of Thrombosis or Hemostasis (ISTH).³⁰

Key secondary endpoints. The key secondary outcome is the time to first occurrence of all-cause death, non-fatal myocardial infarction or stroke. Other secondary ischemic outcomes include the time to first occurrence of: (i) cardiovascular death, non-fatal myocardial infarction, ischemic stroke or clinically-driven revascularization (ii) cardiovascular death, non-fatal myocardial infarction or ischemic stroke; (iv) definite or probable stent thrombosis (v) cardiovascular death.

Power, sample size and statistical considerations

Power calculations are based on a superiority comparison for the primary bleeding endpoint of clinically relevant bleeding (BARC types 2, 3 or 5) between months 3 to 15. We anticipate a bleeding rate of 4.5%, comparable to the 4.2% incidence of BARC ≥ 2 bleeding reported by the DAPT trial between 12 and 30 months after PCI.³¹ 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% to 10% of enrolled subjects at the time of PCI will not be eligible for randomization at the 3-month in-person visit and therefore 9000 subjects will be enrolled. If the overall blinded event rate is lower than projected, the executive committee may recommend an increase in the sample or extend the duration of follow-up to maintain study power. Unless otherwise stated, all hypothesis tests will be performed using two-sided tests at the 5% significance level.

Figure 2



Time points at which study participants will be contacted and related activities.

Table III. Study endpoints

Primary endpoint: Time to first occurrence of clinically relevant bleeding, defined as Bleeding Academic Research Consortium (BARC) Types 2, 3 or 5 bleeding

Key Secondary endpoint: Time to first occurrence of all-cause death, non-fatal myocardial infarction or stroke

Other endpoints

- (i) BARC types 3 or 5 bleeding
- (ii) Major or minor bleeding according to definitions from TIMI
- (iii) Moderate or severe or life-threatening bleeding according to definitions from GUSTO
- (iv) Major bleeding according to definitions from International Society of Thrombosis or Hemostasis (ISTH)
- (v) Cardiovascular death, non-fatal myocardial infarction, ischemic stroke or clinically-driven revascularization
- (vi) Cardiovascular death, non-fatal myocardial infarction or ischemic stroke;
- (vii) Definite or probable stent thrombosis
- (viii) Cardiovascular death

In accordance with Food and Drug Administration guidance, analyses will be performed in both the intention to treat (ITT) and per-protocol cohorts as an ITT approach will avoid an over-optimistic estimate of efficacy for the superiority hypothesis of bleeding but may not be conservative for the non-inferiority ischemic outcome.³² The ITT cohort will be defined as those participants who were successfully randomized at the 3-month in person visit. Analyses in the ITT cohort will be censored at the time of death, last contact date or study end, whichever comes first. The per-protocol cohort will

include those randomized participants who completed all study-related contacts without any major protocol deviations. Analyses in the per-protocol cohort will be censored at the time of death, study end or date of study-related medication discontinuation +5 days, whichever comes first.

Analysis for the primary endpoint. Analyses for the primary bleeding endpoint will be performed using the intention to treat (ITT) principle, in which all randomized patients will be analyzed according to the random group assignment. Event rates will be estimated at one year and

Kaplan-Meier curves will be plotted from the time of randomization to the first occurrence of confirmed BARC type 2, 3 or 5 bleeding. A test of superiority at the two-sided 0.05 level will be performed using a Cox proportional hazards model that includes treatment group as a covariate. This analysis will be repeated in the per-protocol population to support the primary results.

Analysis for the key secondary endpoint. The primary objective of this analysis is to determine if ticagrelor monotherapy is non-inferior to ticagrelor plus aspirin for the key secondary endpoint (all-cause death, non-fatal myocardial infarction, or stroke), which will be assessed in the per protocol cohort. Event rates will be estimated at one year and Kaplan-Meier curves will be plotted from the time of randomization to the first occurrence of confirmed all-cause death, non-fatal myocardial infarction, or stroke. 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 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 margin of 20% assuming the observed event rate equals 8.0% in the control arm. This analysis will be repeated in the ITT cohort to support the primary results. Our assumption of an 8.0% event rate over 1 year for ischemic events is between the 5.0% and 11.0% MACE rates observed in the DAPT³¹ and PLATO⁵ trials, respectively, an estimate we justify based upon a study design that should enroll a population with an intermediate level of risk compared with these studies. As with bleeding events, if the overall blinded ischemic event rate is lower than projected, the executive committee may recommend an increase in the sample or extend the duration of follow-up to maintain study power.

Subgroup analyses

One-year event rates for the primary bleeding and secondary ischemic endpoints will be calculated in the following clinically relevant subgroups: age ≥ 65 years vs. < 65 years; race (white, non-white), female sex, geographic region (US vs. non-US), diabetes mellitus, chronic kidney disease ($\text{eGFR} < 60 \text{ mL/min per } 1.73\text{m}^2$), troponin (+) ACS, implanted stent length ($< 30 \text{ mm}$, $\geq 30 \text{ mm}$), body mass index ≥ 30 vs. < 30 ; history of prior MI, and presence or absence of multivessel disease. 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.

Sub-studies

The impact of aspirin withdrawal on whole blood thrombogenicity will be examined in a physiologic sub-study using the validated ex-vivo Badimon perfusion

chamber.^{33,34} Blood thrombogenicity will be assessed at the time of randomization when patients are on maintenance DAPT with ASA and ticagrelor and then at 4 weeks after randomization. The expected results are that ticagrelor monotherapy will show similar antithrombotic effects to that of ASA + ticagrelor. Whole blood thrombus area will be quantified as previously described and compared between groups at 8 weeks post randomization. Additional potential sub-studies will examine changes in platelet function, serum lipids and whole blood coagulation on bleeding and ischemic endpoints.

Safety monitoring

An independent DSMB will monitor the study data on a periodic basis to evaluate interim results during the trial and determine reporting and stopping rules as specified in the DSMB charter and data monitoring plan. The DSMB members will not have primary affiliation with the study sponsor or the principal investigator of the trial. The data to be reviewed will consist of adjudicated and non-adjudicated major adverse cardiovascular events, 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. All final decisions regarding trial modifications rest with the Executive Committee.

Discussion

The primary hypothesis of TWILIGHT is that ticagrelor monotherapy will significantly reduce bleeding compared with ticagrelor plus aspirin in high-risk PCI patients treated with DES who have already completed a 3-month course of ticagrelor plus ASA. In this regard, TWILIGHT differs from most cardiovascular clinical trials wherein antiplatelet or antithrombotic therapy is added to existing standard of care to reduce thrombosis with bleeding usually considered a secondary or safety endpoint. Indeed, as the intervention in TWILIGHT is the active withdrawal of aspirin 3-months post-PCI, the efficacy measure in this study will be quantified by reductions in bleeding, an important distinction from conventional notions of safety and efficacy. Nevertheless, trials with designs that simplify or withdraw pharmacotherapy have been advocated by leading academic and regulatory authorities.³⁵ Moreover, the focus on bleeding as a primary endpoint is consistent with emerging data that hemorrhagic events may be associated with a comparable or even higher mortality risk to thrombotic events.³⁶

The relevance of bleeding notwithstanding, TWILIGHT will also challenge the current paradigm mandating the universal need for aspirin after PCI. While several placebo-controlled trials have examined the benefits of aspirin in both primary and secondary prevention

settings,^{37,38} analogous data with respect to PCI remain sparse. To date, only one modest-sized randomized controlled trial found that withdrawal of aspirin significantly reduced bleeding in patients with atrial fibrillation undergoing PCI while clopidogrel and warfarin were continued.¹⁶ Others have examined the potential for excess thrombosis in the absence of ASA after PCI. In a review of published late and very late stent thrombosis cases ($n = 161$), for example, Eisenberg et al found no episodes of ST in patients who discontinued ASA yet maintained P2Y₁₂ inhibitor therapy.³⁹ Kovacic et al reported similar findings from a large single-center registry.⁴⁰ While these studies suggest a limited role for ASA in most patients after PCI in the presence of ongoing P2Y₁₂ inhibition, conclusive inferences from these non-randomized data cannot be drawn. In contrast, TWILIGHT will extend these earlier observations to a large high-risk PCI population, thereby further clarifying the need, or lack thereof, for maintaining aspirin in the contemporary era of safe, newer-generation DES.

The TWILIGHT study design allows for the inclusion of stable CAD patients, a population in whom the safety and efficacy of ticagrelor versus clopidogrel has not been established. However, despite the lack of randomized evidence surrounding the use of ticagrelor in stable patients and practice guidelines that do not recommend ticagrelor in a non-ACS setting, studies involving “real-world” samples indicate that up to 14% of patients receiving ticagrelor after PCI present with stable symptoms.^{41,42} This practice pattern likely reflects the fact that certain subgroups of stable CAD patients, such as those with DM, prior MI and revascularization, continue to experience very high rates of thrombotic events despite treatment with ASA plus clopidogrel. As the primary objective of TWILIGHT is to examine the impact of ASA withdrawal after PCI with DES, not to evaluate the safety and efficacy of ticagrelor versus clopidogrel, we designed TWILIGHT to include those high-risk patients for whom a physician has already decided to discharge with ASA plus ticagrelor. In other words, study treatment commences upon discharge, not at the time of PCI and the study protocol does not dictate peri-procedural pharmacotherapy, which is at the discretion of the treating physician. Therefore, the profile of patients enrolled in TWILIGHT, at least with respect to ACS and non-ACS presentation, should reflect real-world preferences for ticagrelor and may vary across sites and regions. All drugs to be taken by TWILIGHT study participants (open-label ticagrelor, open-label aspirin and blinded study drug) are provided by the trial sponsor and distributed to sites upon activation. While this design might introduce a biased incentive towards enrolling patients in those countries with healthcare systems in which drug costs are partially borne by patients and/or third party payers, this concern is less relevant in nationalized or single-payer healthcare markets. Issues

of cost notwithstanding, all study investigators must abide by and attest to the ethical standards of good clinical practice, which stipulate that only those eligible patients meeting inclusion and exclusion criteria may be enrolled in the trial.

Defining both the mandatory minimum and optimal durations of DAPT after PCI with DES represent areas of intense and active clinical investigation with over 30,000 patients enrolled in at least 10 randomized trials to date. With respect to the former current guidelines now stipulate at least 6 months of DAPT after PCI with DES^{43,44} yet clinical equipoise for much shorter courses, ranging between 1–3 months, may be found in recently completed and ongoing randomized studies.^{9,45} In the GLOBAL LEADERS trial, for example, patients randomized to the experimental arm will only receive one month of DAPT following PCI.⁴⁶ With respect to the latter, although a 12-month course of DAPT represents a historical standard for post-PCI pharmacotherapy, recent studies have examined durations beyond 12 months. For example, in a pooled analysis of 10 studies comparing different DAPT strategies by Palmerini et al, the prolonged DAPT arm varied from 12 months to 36 months.³⁶ Accordingly, while the 15-month course of DAPT that the conventional arm in TWILIGHT will receive is not necessarily standard in a historical context, it is consistent with the evolving paradigm towards refining the “optimal” DAPT duration after PCI.

Implicit within the TWILIGHT study design is that a 3-month course of DAPT is sufficient to mitigate early and largely stent-related thrombotic events, thereby providing a rationale to stop ASA at this time point. Nevertheless, several reports have highlighted the accentuated benefits of prolonging DAPT in ACS patients, findings that might challenge equipoise on the inclusion of such patients in TWILIGHT.^{47,48} In most studies such benefits were observed by comparing a strategy of clopidogrel plus ASA versus ASA alone, results that suggest thrombotic risk reduction in ACS patients is a function of ongoing P2Y₁₂ inhibition. In contrast all TWILIGHT participants will receive ticagrelor, which is both superior to clopidogrel and is the preferred P2Y₁₂ inhibitor for ACS patients. However, whether or not such ticagrelor-treated patients still require ASA is unknown and represents the primary objective to be addressed in TWILIGHT. Further evidence for equipoise on the inclusion of ACS patients may be found in the GLOBAL LEADERS trial as ticagrelor monotherapy in this trial will commence after only one month of DAPT. In the absence of ACS, recently reported prediction tools have identified a host of other clinical parameters, such as DM, prior MI or coronary revascularization, as reliable discriminators for identifying patients who might benefit from prolonged DAPT.^{49,50} Based upon the inclusion criteria for TWILIGHT we anticipate that most participants, even those with stable CAD, will be considered at

intermediate or high risk by these scales and therefore candidates for either more potent P2Y₁₂ inhibition or prolonged DAPT.

As with any clinical trial, the results of TWILIGHT will be generalizable to those high-risk PCI patients who may otherwise be candidates for enrollment. Within the context of TWILIGHT, however, the connotation 'high-risk' extends to not just bleeding risk, but both bleeding and ischemic complications. This distinction is meaningful as enrolling patients at high bleeding risk will increase the study's chance to meet its' primary bleeding endpoint. Nevertheless, the use of ticagrelor as background pharmacotherapy in all patients mandates a study population that is also at high risk for thrombosis. Such patients include those with troponin (+) ACS, one of the clinical inclusion criteria for trial enrollment. Other parameters, such as DM, prior coronary revascularization, bifurcation lesions and stent length > 30 mm have been previously linked with high thrombotic risk.⁵⁰⁻⁵² Acceptance of the trial results also requires testing the key secondary ischemic endpoint in a manner that might be acceptable to both lay and academic communities. Accordingly, the non-inferiority margin of 20% that the study is powered to detect is more stringent than^{9,45} or identical⁵³ to other large randomized studies comparing different antiplatelet strategies after PCI.

In conclusion, TWILIGHT will provide novel and clinically meaningful insights on the potential role of ticagrelor monotherapy versus ticagrelor plus ASA in reducing clinically relevant bleeding in a contemporary, high-risk PCI population. Findings from this trial may have major implications regarding the necessity of ASA in all patients after PCI and thereby offer a novel antiplatelet strategy to simultaneously lower bleeding risk while maintaining anti-ischemic efficacy.

Current status

The first patient was enrolled in TWILIGHT on 7/28/2015 and enrollment is expected to continue until 12/2017. At present 98 sites have been activated with a total enrollment of 2100 patients. The last patient visit is expected to occur in 3/2019.

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References

1. Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *Circulation* 2011;124(23):2574-609.
2. Hamm CW, Bassand JP, Agewall S, et al. ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *G Ital Cardiol* 2012;13(3): 171-228.
3. Yusuf S, Zhao F, Mehta SR, et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001;345(7):494-502.
4. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2007;357(20):2001-15.
5. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009;361(11):1045-57.
6. Mehran R, Pocock S, Nikolsky E, et al. Impact of bleeding on mortality after percutaneous coronary intervention results from a patient-level pooled analysis of the REPLACE-2 (randomized evaluation of PCI linking angiogram to reduced clinical events), ACUITY (acute catheterization and urgent intervention triage strategy), and HORIZONS-AMI (harmonizing outcomes with revascularization and stents in acute myocardial infarction) trials. *JACC Cardiovasc Imaging* 2011;4(6):654-64.
7. Rao SV, O'Grady K, Pieper KS, et al. Impact of bleeding severity on clinical outcomes among patients with acute coronary syndromes. *Am J Cardiol* 2005;96(9):1200-6.

8. Eikelboom JW, Mehta SR, Anand SS, et al. Adverse impact of bleeding on prognosis in patients with acute coronary syndromes. *Circulation* 2006;114(8):774-82.
9. Kim BK, Hong MK, Shin DH, et al. A new strategy for discontinuation of dual antiplatelet therapy: the RESET Trial (REal Safety and Efficacy of 3-month dual antiplatelet Therapy following Endeavor zotarolimus-eluting stent implantation). *J Am Coll Cardiol* 2012;60(15):1340-8.
10. Colombo A, Chieffo A, Frasieri A, et al. Second-Generation Drug-Eluting Stent Implantation Followed by 6- Versus 12-Month Dual Antiplatelet Therapy: The SECURITY Randomized Clinical Trial. *J Am Coll Cardiol* 2014;64(20):2086-97.
11. Varenhorst C, Jensen K, Jernberg T, et al. Duration of dual antiplatelet treatment with clopidogrel and aspirin in patients with acute coronary syndrome. *Eur Heart J* 2014;35(15):969-78.
12. Gilard M, Barragan P, Noryani AA, et al. Six-month versus 24-month dual antiplatelet therapy after implantation of drug eluting stents in patients non-resistant to aspirin: ITALIC, a randomized multicenter trial. *J Am Coll Cardiol* 2014.
13. Valgimigli M, Borghesi M, Tebaldi M, et al. Should duration of dual antiplatelet therapy depend on the type and/or potency of implanted stent? A pre-specified analysis from the PROlonging Dual antiplatelet treatment after Grading stent-induced Intimal hyperplasia study (PRODIGY). *Eur Heart J* 2013;34(12):909-19.
14. Gwon HC, Hahn JY, Park KW, et al. Six-month versus 12-month dual antiplatelet therapy after implantation of drug-eluting stents: the Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting (EXCELLENT) randomized, multicenter study. *Circulation* 2012;125(3):505-13.
15. Giustino G, Baber U, Sartori S, et al. Duration of Dual Antiplatelet Therapy After Drug-Eluting Stent Implantation: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *J Am Coll Cardiol* 2015;65(13):1298-310.
16. Dewilde WJ, Oirbans T, Verheugt FW, et al. Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial. *Lancet* 2013;381(9872):1107-15.
17. Kang SH, Park KH, Ahn HS, et al. Everolimus-eluting versus sirolimus-eluting coronary stents in patients with and without diabetes mellitus. *EuroIntervention* 2014;10(1):74-82.
18. Brar SS, Kim J, Brar SK, et al. Long-term outcomes by clopidogrel duration and stent type in a diabetic population with de novo coronary artery lesions. *J Am Coll Cardiol* 2008;51(23):2220-7.
19. Baber U, Bander J, Karajgikar R, et al. Combined and independent impact of diabetes mellitus and chronic kidney disease on residual platelet reactivity. *Thromb Haemost* 2013;110(1):118-23.
20. Baber U, Mehran R, Kirtane AJ, et al. Prevalence and Impact of High Platelet Reactivity in Chronic Kidney Disease: Results From the Assessment of Dual Antiplatelet Therapy With Drug-Eluting Stents Registry. *Circ Cardiovasc Interv* 2015;8(6):e001683.
21. Angiolillo DJ, Bernardo E, Capodanno D, et al. Impact of chronic kidney disease on platelet function profiles in diabetes mellitus patients with coronary artery disease taking dual antiplatelet therapy. *J Am Coll Cardiol* 2010;55(11):1139-46.
22. Morrow DA. Cardiovascular risk prediction in patients with stable and unstable coronary heart disease. *Circulation* 2010;121(24):2681-91.
23. Dangas GD, Claessen BE, Mehran R, et al. Development and validation of a stent thrombosis risk score in patients with acute coronary syndromes. *JACC Cardiovasc Interv* 2012;5(11):1097-105.
24. Rao SV, McCoy LA, Spertus JA, et al. An updated bleeding model to predict the risk of post-procedure bleeding among patients undergoing percutaneous coronary intervention: a report using an expanded bleeding definition from the National Cardiovascular Data Registry CathPCI Registry. *JACC Cardiovasc Interv* 2013;6(9):897-904.
25. Mehran R, Baber U, Steg PG, et al. Cessation of dual antiplatelet treatment and cardiac events after percutaneous coronary intervention (PARIS): 2 year results from a prospective observational study. *Lancet* 2013;382(9906):1714-22.
26. Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. *Circulation* 2011;123(23):2736-47.
27. Baber U, Dangas G, Chandrasekhar J, et al. Time-Dependent Associations Between Actionable Bleeding, Coronary Thrombotic Events, and Mortality Following Percutaneous Coronary Intervention: Results From the PARIS Registry. *JACC Cardiovasc Interv* 2016;9(13):1349-57.
28. Bovill EG, Terrin ML, Stump DC, et al. Hemorrhagic events during therapy with recombinant tissue-type plasminogen activator, heparin, and aspirin for acute myocardial infarction. Results of the Thrombolysis in Myocardial Infarction (TIMI), Phase II Trial. *Ann Intern Med* 1991;115(4):256-65.
29. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. The GUSTO investigators. *N Engl J Med* 1993;329(10):673-82.
30. Schulman S, Kearon C, Subcommittee on Control of Anticoagulation of the S, et al. Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost* 2005;3(4):692-4.
31. Mauri L, Kereiakes DJ, Yeh RW, et al. Twelve or 30 Months of Dual Antiplatelet Therapy after Drug-Eluting Stents. *N Engl J Med* 2014.
32. Guidance for Industry. *E9 Statistical Principles for Clinical Trials*. 1998.
33. Zafar MU, Ibanez B, Choi BG, et al. A new oral antiplatelet agent with potent antithrombotic properties: comparison of DZ-697b with clopidogrel a randomised phase I study. *Thromb Haemost* 2010;103(1):205-12.
34. Dangas G, Badimon JJ, Collier BS, et al. Administration of abciximab during percutaneous coronary intervention reduces both ex vivo platelet thrombus formation and fibrin deposition: implications for a potential anticoagulant effect of abciximab. *Arterioscler Thromb Vasc Biol* 1998;18(8):1342-9.
35. Pocock SJ, Gersh BJ. Do current clinical trials meet society's needs?: a critical review of recent evidence. *J Am Coll Cardiol* 2014;64(15):1615-28.
36. Palmerini T, Benedetto U, Bacchi-Reggiani L, et al. Mortality in patients treated with extended duration dual antiplatelet therapy after drug-eluting stent implantation: a pairwise and Bayesian network meta-analysis of randomised trials. *Lancet* 2015;385(9985):2371-82.
37. Final report on the aspirin component of the ongoing Physicians' Health Study. Steering Committee of the Physicians' Health Study Research Group. *N Engl J Med* 1989;321(3):129-35.
38. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002;324(7329):71-86.
39. Eisenberg MJ, Richard PR, Liberman D, et al. Safety of short-term discontinuation of antiplatelet therapy in patients with drug-eluting stents. *Circulation* 2009;119(12):1634-42.
40. Kovacic JC, Lee P, Karajgikar R, et al. Safety of temporary and permanent suspension of antiplatelet therapy after drug eluting stent implantation in contemporary "real-world" practice. *J Interv Cardiol* 2012;25(5):482-92.

41. Fan W, Plent S, Prats J, et al. Trends in P2Y12 Inhibitor Use in Patients Referred for Invasive Evaluation of Coronary Artery Disease in Contemporary US Practice. *Am J Cardiol* 2016;117(9):1439-43.
42. Karve AM, Seth M, Sharma M, et al. Contemporary Use of Ticagrelor in Interventional Practice (from Blue Cross Blue Shield of Michigan Cardiovascular Consortium). *Am J Cardiol* 2015;115(11):1502-6.
43. Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines: An Update of the 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention, 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery, 2012 ACC/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease, 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction, 2014 AHA/ACC Guideline for the Management of Patients With Non-ST-Elevation Acute Coronary Syndromes, and 2014 ACC/AHA Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery. *Circulation* 2016;134:123-55.
44. Windecker S, Kolh P, Alfonso F, et al. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J* 2014;35(37):2541-619.
45. Feres F, Costa RA, Abizaid A, et al. Three vs twelve months of dual antiplatelet therapy after zotarolimus-eluting stents: the OPTIMIZE randomized trial. *JAMA* 2013;310(23):2510-22.
46. Vranckx P, Valgimigli M, Windecker S, et al. Long-term ticagrelor monotherapy versus standard dual antiplatelet therapy followed by aspirin monotherapy in patients undergoing biolimus-eluting stent implantation: rationale and design of the GLOBAL LEADERS trial. *EuroIntervention* 2015;11(7), http://dx.doi.org/10.4244/EIJY15M11_07.
47. Udell JA, Bonaca MP, Collet JP, et al. Long-term dual antiplatelet therapy for secondary prevention of cardiovascular events in the subgroup of patients with previous myocardial infarction: a collaborative meta-analysis of randomized trials. *Eur Heart J* 2016;37(4):390-9.
48. Yeh RW, Kereiakes DJ, Steg PG, et al. Benefits and Risks of Extended Duration Dual Antiplatelet Therapy After PCI in Patients With and Without Acute Myocardial Infarction. *J Am Coll Cardiol* 2015;65(20):2211-21.
49. Baber U, Mehran R, Giustino G, et al. Coronary Thrombosis and Major Bleeding After PCI With Drug-Eluting Stents: Risk Scores From PARIS. *J Am Coll Cardiol* 2016;67(19):2224-34.
50. Yeh RW, Secemsky EA, Kereiakes DJ, et al. Development and Validation of a Prediction Rule for Benefit and Harm of Dual Antiplatelet Therapy Beyond 1 Year After Percutaneous Coronary Intervention. *JAMA* 2016;315(16):1735-49.
51. Ong AT, Hoyer A, Aoki J, et al. Thirty-day incidence and six-month clinical outcome of thrombotic stent occlusion after bare-metal, sirolimus, or paclitaxel stent implantation. *J Am Coll Cardiol* 2005;45(6):947-53.
52. Suh J, Park DW, Lee JY, et al. The relationship and threshold of stent length with regard to risk of stent thrombosis after drug-eluting stent implantation. *JACC Cardiovasc Interv* 2010;3(4):383-9.
53. Schulz-Schupke S, Byrne RA, Ten Berg JM, et al. ISAR-SAFE: a randomized, double-blind, placebo-controlled trial of 6 vs. 12 months of clopidogrel therapy after drug-eluting stenting. *Eur Heart J* 2015;36(20):1252-63.