Optimal Target of Activated Clotting Time During Percutaneous Coronary Intervention and Outcomes: The Randomized OPTIMAL-ACT Trial

NCT03772613

January 20, 2020

Optimal Target of Activated Clotting Time During Percutaneous Coronary Intervention and Outcomes: The Randomized OPTIMAL-ACT Trial

The **objective of this proposal** is to identify the optimal range of the activated clotting time (ACT) during percutaneous coronary intervention (PCI) that is associated with the lowest rates of adverse clinical events. The optimal ACT target during PCI has not previously been investigated in a prospective clinical trial, leaving uncertainty regarding the level of anticoagulation intensity during coronary revascularization procedures. The **primary research hypothesis** is that in the modern cardiac catheterization laboratory, where PCI procedural duration is relatively short and rates of intracoronary stenting and dual antiplatelet therapy use is high, lower ACT targets, as compared with higher ACT targets, will be associated with lower rates of bleeding while having similar rates of ischemic events.

Principal Investigator:

S. Michael Gharacholou, MD, MSc

Co-Investigators:

Peter M. Pollak, MD
Gary E. Lane, MD
Dilip P. Pillai, MD
Colleen S. Thomas, MS
Elizabeth R. Lesser, MS
Amy Swenson, RCIS
Cynthia Lynady,RCIS, RCES
Brad Karon, MD, PhD
Paula Santrach, MD
Leslie Donato, PhD
Mandeep Singh, MD

Rationale: For the past three decades, unfractionated heparin (UFH) has remained the mainstay of anticoagulation during invasive cardiac procedures(1-3) and has been the only available anticoagulant in interventional cardiology for many years (4). Advantages to UFH are related to availability, familiarity, low cost, point-of-care (POC) testing using the activated clotting time (ACT), and reversibility with protamine sulfate. Use of peri-procedural anticoagulation with UFH during percutaneous coronary intervention (PCI) is recommended to reduce thrombus formation on interventional devices and thrombotic complications during PCI(4-6).POC testing allows targeting ACT values to recommended ranges, gives fairly reproducible results, and ACT values increase linearly with UFH supplementation and decrease without additional UFH over time(7). However, despite guideline suggested use of ACT monitoring in UFH-treated patients undergoing PCI, there are limited and often conflicting data regarding the association of ACT target values and outcomes(6,8-10). Importantly, data for the relationship between ACT and outcomes are sparse in contemporary PCI practice that now includes the use of lower profile equipment, high rates of intracoronary stenting, transradial procedures, and dual antiplatelet therapy(10). Early small studies found low rates of ischemic complications with low and fixed dose heparin(11,12), while pooled data from clinical trial participants suggested lower ischemic event rates with higher ACT targets of 350 to 375 seconds, though at a cost of higher rates of bleeding(8). Other studies analyzing low risk patients from clinical trials have not observed an association between ACT levels and ischemic endpoints(9,10). Despite widespread use of ACT monitoring during PCI, uncertainty remains regarding the association between ACT cutoffs and outcomes in contemporary practice, largely related to lack of randomized trials evaluating the optimum ACT target and its relation with events. Practice guidelines conclude that despite the use of recommended ACT levels, often based on empiricism and ranges used in clinical trials of PCI, the utility of ACT in clinical practice remains uncertain (4).

The pOint-of-care PracTice to IMProve use of AnticoaguLation (OPTIMAL)-ACT trial is a prospective, randomized, investigator-initiated, trial to determine the optimal ACT target value in patients undergoing PCI. This will be the first prospective outcomes trial powered to identify the optimal ACT target range for reducing the rate of in-hospital bleeding (Bleeding Academic Research Consortium and EASY grading defined (Appendix I)). Different bleeding definitions will be used to account for shift in access site practice from femoral to radial, both here at Mayo Clinic Florida, and in the United States. In addition, the EASY grading scale is unique to transradial catheterization and complications related to bleeding may be more frequent among women (13). Rates of net adverse cardiovascular events (NACE) (defined as all-cause mortality, myocardial infarction (MI), stroke, or bleeding) would be identified as a primary safety endpoint in the trial. We aim to test the hypothesis that lower ACT target values, as compared to higher ACT target values, are associated with lower risk of bleeding without compromising efficacy as assessed by the primary safety endpoint. This finding would have significant implications for improving the safety of PCI by reducing bleeding complications.

A. Significance: The significance of the study proposal can be highlighted by 1) the recognition of the burden of coronary artery disease (CAD), 2) the widespread adoption and performance of PCI, and 3) the limited data regarding appropriate anticoagulation intensity during PCI. CAD causes 1 out of 6 deaths in the United States. Annually, over 600,000 patients suffer a coronary event, defined as a first hospitalized myocardial infarction or CAD-related death (14). Improvements in adherence to guideline-recommended therapies for patients with ischemic heart disease, including use of coronary revascularization procedures, have impacted the decline in deaths related to cardiovascular disease over the past several years. PCI is performed commonly in the United States with an estimated 490,000 procedures in 2010 alone (15). In patients with acute coronary syndromes, early revascularization with PCI has been

demonstrated to improve outcomes. As the technical success rates of PCI have continued to remain very high, there has been a renewed interest in delivering PCI safely and reducing complications. This evolution in contemporary PCI includes use of lower profile devices, smaller caliber intravascular sheaths, shorter procedural durations, and greater adoption of transradial catheterization. In addition, strategies to mitigate bleeding have garnered greater attention given the association of bleeding with adverse short and long-term outcomes. A fundamental aspect of current PCI practice involves the use of anticoagulants during the procedure to reduce the risk of thrombus formation on interventional devices (i.e., guiding catheters, wires) and reduce the risk of abrupt vessel closure. The intensity of anticoagulation to reduce thrombotic risk is, however, on balance with increased bleeding risk, which have led to recommendations on appropriate ACT targets during PCI (4). Despite these recommended ACT targets, bleeding events are observed in 1 out of 10 patients at currently recommended ACT target ranges (8). In addition, due to the limited evidence base, guidelines have also acknowledged that "the utility of measured ACT levels in current practice should be considered uncertain"(4). Despite the influential role of an ACT value on an operator's decision to intensify or reduce the level of anticoagulation in the patient, and thus directly impact the ischemic vs. bleeding risk-calculus, optimizing the dose of UFH during PCI has clinical equipoise. The current gaps in knowledge, therefore, underscores the need for a rigorous study of anticoagulation intensity during PCI to improve patient safety and advance scientific understanding of ACT monitoring. This has significant public health implications and tremendous potential to impact the current practice of PCI. In alignment with Mayo Clinic's commitment to improving the safety of patient care, the knowledge gap with regard to intensity of heparinization during PCI remains an important and unanswered question in interventional cardiology.

B. Specific Aims: Anticoagulation is routinely administered prior to performing PCI in interventional cardiology practice and intensity of anticoagulation is monitored using POC testing for the ACT. However, current target values were derived from older, case-control studies (6,16), and supported by post-hoc retrospective analysis from trials of antithrombotic therapies (9,10). In the modern era of high rates of dual antiplatelet therapy use, low profile devices, greater attention to access site management, and shorter procedural duration, the optimal ACT target for PCI remains unknown. The overall objective of this proposal is to identify the optimal range of the activated clotting time (ACT) during percutaneous coronary intervention (PCI) that is associated with the lowest rates of adverse clinical events. The optimal ACT target during PCI has not previously been investigated in a prospective clinical trial, leaving uncertainty regarding the level of anticoagulation intensity during coronary revascularization procedures. We hypothesize that in the modern cardiac catheterization laboratory, where PCI procedural duration is relatively short and rates of intracoronary stenting and dual antiplatelet therapy use is high, lower ACT targets, as compared with higher ACT targets, will be associated with lower rates of bleeding while having similar rates of ischemic events. The specific aims of this study are as follows:

B.1.1 Aim 1 (Primary)**:** The primary aim of this study of patients undergoing PCI is to compare the risk of bleeding in patients randomized to a low ACT target to those randomized to either a medium or high ACT target. We hypothesize that the risk of bleeding will be lower in those with a low ACT target compared to those with a medium ACT target as well as those with a high ACT target. See Figure 1 for ACT target ranges.

B.1.2 Aim 2 (Primary): We aim to estimate the incidence of both our primary study outcome (bleeding) and our primary safety endpoint (NACE) separately for those with a low, medium, and high ACT target.

B.1.3 Aim 3 (Primary): We aim to establish whether there is evidence of non-inferiority of a low ACT target compared to a high ACT target with respect to the proportion of patients undergoing

PCI with respect to NACE. We hypothesize that the rate of NACE is the same as or lower than that for patients with a high ACT target.

B.1.4 Aim 4 (Secondary): We aim to study the impact of sex, access-site (i.e., radial vs femoral), and concomitant use of glycoprotein (GP) IIb/IIIa inhibitors on the association of ACT target with bleeding. It has been shown that female sex is associated with higher ACT targets during PCI (17), and work from our group has shown an important observed interaction with myocardial infarction risk in women, but not men, with ACT targets >350 seconds(18). This observation of a potential differential sex-specific interaction has not previously been reported and requires validation in a prospective study. In addition, it has previously been shown that women appear to be at higher risk for developing forearm bleeding complications after transradial catheterization. The use of transradial PCI has steadily increased in the United States, though adoption of this technique remains lower than that observed in Canada and Europe. However, recent internal PCI data from the cardiac catheterization laboratory at Mayo Clinic Rochester has shown increasing utilization of the radial artery for PCI, now over 50%. At Mayo Clinic Florida, the percentage of radial access is over 70% and is considered the default access site for catheterization. It remains unknown whether ACT targets can be similarly interpreted for radial PCI, as these original targets were derived from studies in primarily transfemoral access cohorts with larger vascular access sheaths. Finally, the additional use of GP IIb/IIIa inhibitors in UFH-treated patients has been associated with higher rates of major and minor bleeding (9), thus lower ACT target values (i.e., 200-250 sec) are recommended in patients concomitantly treated with these agents. In the Mayo Clinic experience, there was no apparent interaction by GP IIb/IIIa inhibitor status when testing the association of ACT values to outcomes, however, baseline characteristics of groups receiving or not receiving these agents differed and residual confounding may have been present (18). The OPTIMAL-ACT trial will incorporate a pre-specified analysis with specific ACT targets in patients receiving GP IIb/IIIa inhibitors to better understand ACT targets and outcomes.

B.1.5 Aim 5 (Exploratory): We will explore the association of ACT targets with individual components of NACE and stent thrombosis for purposes of hypothesis generation.

C. Innovation/Experience: There are two innovative and unique aspects of this proposal. 1. This study will define the optimal ACT target during PCI. 2. Mayo Clinic (S. Michael Gharacholou, senior author) has published the largest non-randomized (observational) study on the relation of ACT and outcomes in the peer-reviewed literature(18). Our observations that ACT values were associated with unadjusted events, but were not independently associated with outcome after multivariable adjustment, offers credible background evidence for performing a prospective trial (18) 2. This study will incorporate an evidence-based algorithm for UFH supplementation and ACT sampling frequency to provide critical standardization to the process of intra-procedural anticoagulation. In addition, the study will be novel in formally defining the use of the ACT target as the value prior to first coronary device activation, which is recommended as it is a single, unique value, and unbiased as compared to peak ACT or closing ACT values which are greatly influenced by sampling frequency. ACT prior to device activation has been used as the primary predictor variable in retrospective analyses from previous antiplatelet trials (19-21), however, the extant literature is not consistent with use of pre-device ACT values.

D. Approach: Patients >18 years of age referred for coronary angiography with intent to perform revascularization, if clinically indicated, will be prospectively identified and eligible for participation. . Patients who undergo adjunctive intracoronary imaging or physiologic assessment of lesion severity that requires administration of UFH and ACT sampling prior to coronary vessel wiring may also be randomized. The following inclusion criteria for OPTIMAL-ACT are as follows:

Inclusion Criteria:

- Age>18
- Ability of subject to give appropriate consent
- Referred for coronary angiography with **possible** coronary revascularization or adjunctive invasive diagnostic testing (IVUS/OCT, FFR, or iFR)

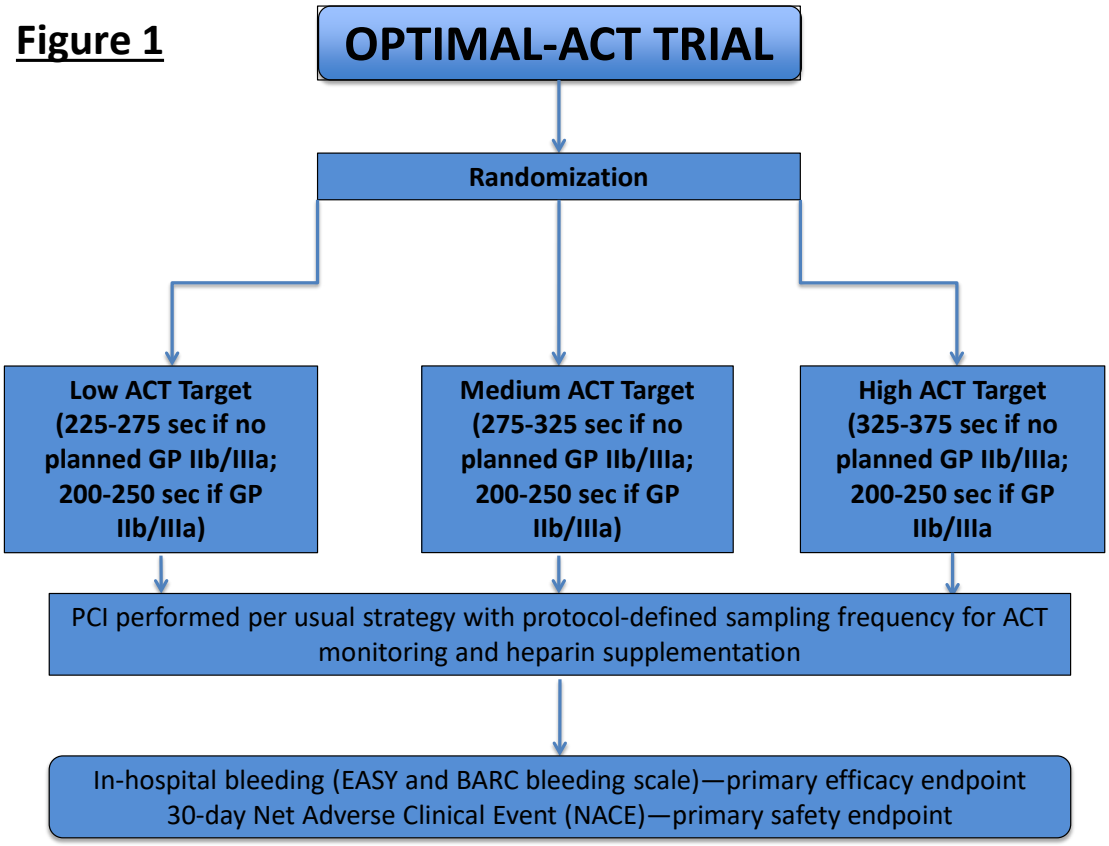
Specific exclusions would include patients receiving low-molecular weight heparin at treatment doses with last dose within 6 hours of coronary angiography (patients on low-molecular weight heparin (LMWH) for venous thromboembolism prophylaxis would be eligible), upstream treatment with GP IIb/IIIa inhibitors within the previous 72 hours, use of warfarin or a novel oral anticoagulant at the time of the procedure, patients being bridged with LMWH in the peri-procedural setting, PCI performed within the proceeding 30 days, need for rotational atherectomy, and planned use of bivalirudin as the procedural anticoagulant. If the operator was uncertain as to whether bivalirudin would be used, the patient would be eligible for screening and randomization. In the event that bivalirudin was selected to support the PCI procedure, the patient would be excluded from the OPTIMAL-ACT trial and recommendations would be for dosing bivalirudin per the manufacturer's instructions with ACT monitoring as used in the REPLACE-2 trial (22), which included ACT value 5 minutes after initial bolus and if <225 sec, an additional bolus of 0.3 mg/kg if needed. The following exclusion criteria for OPTIMAL-ACT are as follows:
Exclusion Criteria:

- Receipt of LMWH at treatment dose (not DVT prophylaxis dose) within 6 hours of coronary angiography
- Prior GP IIb/IIIa use within the previous 72 hours
- Use of warfarin (vitamin K antagonist) or direct oral anticoagulant
- Patients on LMWH bridging strategy
- PCI within prior 30 days
- Planned use of bivalirudin as the procedural anticoagulant
- Rotational atherectomy
- Excimer laser coronary angioplasty
- Chronic total occlusions
- Patients with active bleeding disorders or bleeding diathesis
- Patients with ST-segment elevation myocardial infarction
- Patient with clinical evidence of cardiogenic shock (defined as SBP<90 mmHg for ≥30 min OR support to maintain SBP ≥90 mmHg AND evidence of end-organ hypoperfusion (urine output <30 mL/h or cool extremities)
- Chronic kidney disease stage 4/5 (GFR 30 mL/min)

Patients would be randomized to one of three ACT target groups (Figure 1). Patients will undergo randomization (1:1:1) to either low ACT target, medium ACT target, or high ACT target using a software automatic program (insert information on SDMS). ACT target ranges would be modified based on intended or provisional use of GP IIb/IIIa inhibitors. Target ranges for the OPTIMAL-ACT trial were based on both review of practice guideline recommendations, including the uncertainty expressed in the guidelines regarding ACT values and outcomes (4), and consensus agreement by study interventional cardiologists regarding clinical equipoise in the target ranges studied. . PCI would be performed per routine clinical practice and selection of adjunctive oral antiplatelet therapies would be at the discretion of the operator and in accordance with clinical practice guidelines (4). Patients would be observed post PCI for

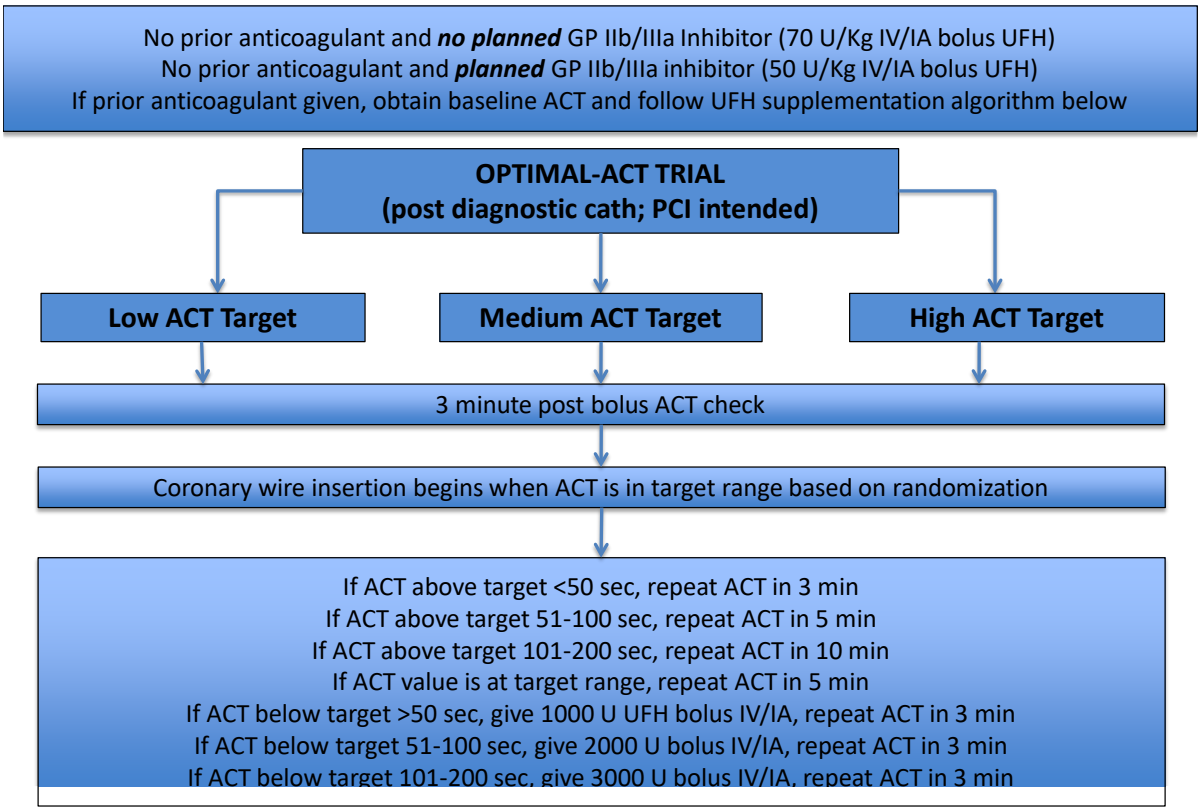
bleeding (primary endpoint), defined as BARC 1, 2,3 or 5 and EASY I-V (Appendix) and for NACE (i.e., ischemic events or bleeding as the primary safety endpoint). Follow-up would extend for 30-days post PCI for occurrence of the primary endpoint and primary safety endpoint. A dedicated telephone script will be used to contact the patient 30 days post-procedure. If the patient experienced a possible endpoint event and was treated at an outside facility, medical records will be obtained for review of whether the endpoint was met.

Figure 1



The ACT target algorithm closely mirrors practice guidelines for UFH supplementation and ACT monitoring (Figure 2)(4). The algorithm provides rigorous standardization to the process of ACT sampling and UFH supplementation to reduce the risk for bias in the study. Although there will be multiple ACT values for each PCI procedure, the use of the ACT value prior to device activation will be the "target" for the purposes of the trial. In the event that an ACT prior to device activation was not obtained, the ACT value closest to the time of initial device activation will be used and the procedure time between the ACT sample and device activation will be recorded.

Figure 2



The Hemochron Signature Elite (Hemochron® Jr.) whole blood microcoagulation system (International Technidyne Corporation, Edison, NJ) for ACT is the POC test performed in the cardiac catheterization laboratory at Mayo Clinic Florida. The ACT demonstrates linear correlation to the anticoagulation effects of heparin to 2.5 units/,L of blood. The device is intended for clinical use during *in vitro* diagnostic testing of whole blood for POC monitoring of anticoagulation intensity in UFH-treated patients undergoing medical procedures. The test result is automatically converted to a reference Celite® ACT value and both displayed and electronically recorded on the device. No other ACT assay system will be used for the OPTIMAL-ACT trial. Although some patients receive non-UFH anticoagulants, ACT is most commonly used to monitor patients receiving UFH and undergoing cardiac catheterization. The Mayo Clinic Department of Laboratory Medicine and Pathology oversees POC testing in the cardiac catheterization laboratories at Mayo Clinic Florida. For the OPTIMAL-ACT trial, collaborators from the Mayo Clinic Department of Laboratory Medicine and Pathology will be co-investigators to provide technical expertise regarding POC testing using ACT. Quality controls are outlined in an institutional Standard Operating Procedure document.

E. Preliminary Work: Data for the relationship between ACT and outcomes are sparse in contemporary PCI practice and guideline recommended targets for ACT during PCI were based on small studies in angioplasty alone settings (23) or proof-of-concept studies that did not report clinical outcomes (24). Table 1 summarizes the existing literature comprising the largest studies with regard to ACT target values and outcomes. These studies have primarily been derived from “lower-risk” populations in trials and are entirely post-hoc analyses, the exception being the registry based design of the Mayo Clinic experience by Rajpurohit et al (S.M. Gharacholou,

senior author), representing the largest study on this topic to date (18). However, the study is primarily limited in terms of drawing firm conclusions by its retrospective design.

Table 1. Summary of studies investigating association of ACT and outcomes

Study	Year	Study Design	Patients (n)	Rates of adjunctive therapies	ACT associated with ischemic/thrombotic events?	ACT associated with bleeding?	Comments
Bittl et al[6]	1998	Post hoc analysis of clinical trial comparing heparin with bivalirudin	4,098	Balloon angioplasty only study, no thienopyridine, no GP IIb/IIIa inhibition	Higher risk of abrupt vessel closure in heparin-treated patients at lower initial ACT No risk difference observed in bivalirudin treated patients	Bleeding requiring transfusion was not associated with initial ACT result, but was associated with peak ACT for both heparin and bivalirudin groups	ACT was only repeated if procedure>45 minutes or if patient developed intraprocedural ischemic complication (i.e, abrupt vessel closure) Multivariable adjustment not performed
Chew et al[8]	2001	Meta analysis of pooled data from 6 trials of GP IIb/IIIa inhibitors	5,216	Majority of patients were angioplasty alone (<8% stenting), no thienopyridine	Reduction in composite ischemic events with increasing ACT, with optimal ACT range of 350 sec-375 sec In subgroup of GP IIb/IIIa treated patients, there was no association between ACT and composite ischemic events across the ACT range of 275 sec to 375 sec	Peak ACT associated with bleeding, including higher rates of bleeding in patients additionally treated with GP IIb/IIIa inhibitors	Optimal ACT range did not vary when analyzed by procedural duration Multivariable adjustment not performed
Tolleson et al[9]	2003	Post hoc analysis of clnical trial comparing heparin with eptifibatide	2,064	High rates of dual antiplatelet therapy (97%) and coronary stenting (97%)	No association between ACT at time of device activation and ischemic events (p=0.43). No increased risk of ischemic complications at low ACT values (as low as 200 sec).	No association between ACT and major bleeding (p=0.9). Higher ACT values associated with bleeding among GP IIb/IIIa treated patients	The lowest rate of ischemic events were seen in the lowest ACT tertile, with similar observation among GP IIb/IIIa treated patients Lower-doses of weight-adjusted heparin used Lower profile vascular devices
Brener et al[10]	2004	Meta-analysis of pooled data from 4 trials	9,974	Clopidogrel (81%), GP IIb/IIIa inhibitors (89%), and coronary stents (93%)	No association between peak ACT and composite ischemic events (p=0.40))	Higher peak ACTs were associated with bleeding (p=0.01)	No interaction between ACT and ischemic or bleeding outcomes in cohorts of patients presenting with unstable angina or diabetes ACT data missing in 16% of patients
Rajpurohit et al[18]	2016	Mayo Clinic PCI Registry/DataMart	12,055	High rates of clopidogrel (98%) and coronary stenting (93%)	No association between ACT at time of device activation and ischemic or thrombotic events	No association between ACT at time of device activation and clinically overt bleeding	Largest study on topic to date Increasing ACT associated with MI risk in women at 1 year

F. Statistical Considerations:

F1. Randomization and blinding: Patients will be randomized (1:1:1) to one of the three ACT target groups (low, medium, or high) using a dynamic minimization algorithm so as to optimize the likelihood that balance between the low, medium, and high ACT target groups will be

achieved with respect to sex (male or female) and glomerular filtration rate (30 to 59 ml/min/1.73m^2 or ≥60 ml/min/1.73m^2). The algorithm will be will be implemented in RAVE RTSM, a secure web-based interface, and accessed by the study coordinator or other appointed study personnel. Randomization will be conducted after the diagnostic portion of the procedure on only patients who will require ACT monitoring. Since eligible patients will require ACT monitoring during PCI, we will not conduct the study in a strictly blinded fashion. However, study participants will not be informed of their randomization assignment.

F2. Data collection and handling: Electronic case report forms along with a corresponding secure REDCap database will be created for data collection (29). Data to be collected will include baseline demographics, comorbidities, procedural variables, in-hospital events, NACE component, and adverse events.

F3: Definition of study outcomes: Study endpoints are summarized in Appendix II.
F3.1 Primary study endpoint: Our **primary study endpoint is bleeding** and is defined as either a Bleeding Academic Research Consortium (BARC) hemorrhage grade of 1, 2, 3, or 5 or an EASY hematoma scale grade of I-V from the time of PCI to the time the patient is discharged from the hospital.
F3.2 Primary safety endpoint: Our **primary safety endpoint is a composite of net adverse clinical events (NACE) and stent thrombosis**, as defined by the Academic Research Consortium, from the time of PCI to the time the patient is discharged from the hospital.
F3.2.1 NACE is the composite of all-cause mortality, myocardial infarction (MI), stroke, target lesion revascularization, and major bleeding within 30 days after PCI.
F3.2.2 MI will be defined as any two of the following 3 criteria: 1) chest pain for at least 20 minutes; 2) elevation of cardiac biomarkers, preferably troponin, above the laboratory upper limit of normal; and 3) new pathological Q wave on electrocardiogram.
F3.3.3 Stroke will have occurred if post-PCI neurological symptom is confirmed as a stroke by a consultant neurologist at Mayo Clinic with documentation on appropriate neuroimaging (CT or MRI).
F3.3.4 Major bleeding will be defined as BARC grade 3 or 5 or EASY grade ≥III.
F3.3.5 Target vessel revascularization will be defined as clinically driven revascularization, either by percutaneous or surgical means.
F3.3.6 Intra-procedural events would include both bleeding and thrombotic complications. Intra-procedural thrombus will be defined as a visible filling defect noted by the primary operator on the guiding catheter or intracoronary wire or device on selective angiogram.
F3.4 The study definition of non-inferiority will be defined based on the 95% confidence interval for the difference in proportions of patients with NACE in the low and high ACT target groups, $\Delta = p^L - p^H$, with a lower limit of Δ_L and an upper limit of Δ_U . Low ACT target will be considered to be non-inferior to high ACT target if one of the following holds, depending on the estimate p^H :

- $\Delta_U < 0.12$ if $p^H \geq 0.12$
- $\Delta_U < p^H$ if $0.04 < p^H < 0.12$
- $\Delta_U < 0.04$ if $p^H \leq 0.04$

Note that italicized version are the theoretical proportions and the estimates are not italicized.

F.4. Sample size determination: Recognizing the limitations of previously performed studies regarding ACT and risk of bleeding, including variability in definitions of bleeding, we estimate that the highest ACT target group will experience the in-hospital primary outcome at a rate of 25%, while the lowest ACT target will experience the in-hospital primary outcome at a rate of 5%. A **sample size of of 504 patients** was determined to ensure more than 80% power at the

two-sided overall 5% significance level with Bonferroni adjustment for multiple testing (*p* value ≤0.025 considered as statistically significant) to detect an absolute difference in in-hospital bleeding (Aim 1) between the low ACT target and the medium ACT target (ie. 5% vs. 15%) in addition to a 20% absolute difference between the low ACT target and the high ACT target (ie. 5% vs. 25%). The power was estimated on the the basis of 5000 simulations. Patients meeting eligibility criteria for the study and who consent for participation but that do not undergo randomization due to either not receiving intracoronary diagnostic imaging (IVUS/OCT) or physiologic testing (iFR/FFR) or PCI will be entered into the ACT registry and observed for clinical events, including 30-day outcomes. The reason these patients are not categorized as screen failures is because the final criterion for eligibility is receipt of PCI, a criterion that is not known until the coronary angiogram is performed which is after patients have signed informed consent. Because patients receive moderate sedation during their procedure as part of standard of care, ethical and scientific prudence dictates that informed consent be obtained prior to procedural start. True screen failures, therefore, are those subjects not meeting study inclusion or exclusion criteria. . Based on current lab practice patterns at our institution, it is anticipated that approximately 20% of patients who enroll in the study will not require ACT monitoring after the diagnostic portion of the procedure, therefore we intend to **consent up to 780 patients**. In 2016, there were 240 PCI procedures and 220 adjunctive coronary imaging/physiology procedures (Fractional Flow Reserve = 158, Intravascular Ultrasound = 59, Optical Coherence Tomography = 12) establishing the feasibility of performing the study and meeting patient accrual targets over an **18 - 24 month period**.

We also considered the implications of this samples size with the other primary aims. For purposes of estimating the incidence of our study endpoint and safety endpoint (Aim 2), a sample size of 504 with equal allocation to each of the three study arms would produce a two-sided 95% confidence interval with a width of 0.15 or less using the Wilson score method. This sample size would also ensure more than 80% power to show evidence of non-inferiority for our primary safety endpoint (NACE, Aim 3) in patients with a low ACT target compared to those with a high ACT target according to the above criteria (section F3.4) when the low and high ACT targets are the same with respect to NACE assuming the probability of NACE with a high ACT target is 12% or more. A review of the published literature had a median estimated rate of 12% for NACE (range 4% to 20% (Table 2).

Table 2.

Study	Hematoma Rate (%)	Major bleeding Rate (%)	NACE Rate (%)	Mean ACT range (sec)	Comments
Petroglou et al (25)	18	3	NR	147	Mostly diagnostic procedures, all radial cases, 5F sheaths, no high risk patients
Jolly SS (26)	3	3	4	NR	Acute coronary syndrome patients, strict bleeding definitions
Bertrand OF (27)	5	1	20	315	All radial cases

F5. Statistical analysis plans:
F5.1 Patient population for analysis: The primary analysis will include all randomized patients. Since patients will be randomized after the diagnostic portion of the procedure and the primary study outcome will be collected during their initial hospitalization after PCI, we anticipate negligible loss to follow-up and negligible imbalance between study arms. Analysis of the study aims will be conducted using an intent-to-treat approach, which means it will be an analysis including all randomized patients according to the group they were randomized regardless of whether or not the assigned ACT target was achieved.
F5.2 Primary analysis plan: Aim 1: The risk of in-hospital bleeding in the medium ACT target group and the high ACT target group will be compared to the risk of in-hospital bleeding in the low ACT target group using pair-wise chi-square tests (or Fisher's exact test). Relative risks and 95% confidence intervals will be reported. For these two tests of the primary study outcome, a two-sided p-value ≤ 0.025 will be considered statistically significant using the Bonferroni adjustment for multiple testing. This means that the overall two-sided level of significance for the trial will be 0.05. Aim 2: We will estimate the proportion of patients with each outcome (bleeding, NACE) along with 95% confidence intervals for the proportions using the Wilson score method separately for the three groups. Aim 3: We will create a 95% confidence interval for the difference in proportions of patients with NACE in the low and high ACT target groups using the Newcombe score method. This will be used to assess whether there is evidence of non-inferiority of low ACT target compared to high ACT target according to the definition in section F3.4.

F5.3 Secondary analysis plan: We will evaluate if associations between ACT target group (low, medium, high) and in-hospital bleeding are independent of sex, access site, and concomitant use of glycoprotein (GP) IIb/IIIa inhibitors (Aim 2) using a Cochran-Mantel-Haenszel test. For these pre-planned tests, a two-sided p-value≤0.0167 will be considered statistically significant using a Bonferroni adjustment for multiple testing. Descriptive summaries and relative risks will be reported as in the primary analysis, except stratified by each of the patient or procedure characteristics.

Baseline patient and procedure characteristics of the three groups will be reported as number and percentage for categorical variables and median and interquartile range for continuous variables. To evaluate the possibility of imbalance, we will make comparisons between the three randomized groups using a Kruskal-Wallis test for ordered or numeric variables and a chi-square test (or Fisher's exact test) for categorical variables. For those baseline characteristics with imbalance between groups, we will summarize the number and percentage as well as relative risk and 95% confidence intervals as was done with the pre-planned analyses of sex, access site, and concomitant use of glycoprotein (GP) IIb/IIIa inhibitors with stratification by the baseline characteristic. In addition, we will use a multivariable logistic regression model with in-hospital bleeding as our outcome measure and fixed effects for group (reference group = low ACT target), sex, access site, concomitant use of glycoprotein (GP) IIb/IIIa inhibitors, and any other baseline characteristics with evidence of potential imbalance between groups (p-value≤0.20) allowing no more than one variable for every 10 patients who experience in-hospital bleeding.

F5.4 Exploratory analysis plan: We will explore the association of ACT target with individual components of bleeding and NACE using a Cochran-Armitage trend test and report the number and percent of patients with each component separately for each group. Adjustment for multiple testing will be conducted using the Holm step-down method.

F5.5 Interim analysis plan: A blinded review of the study's overall incidence of the primary study outcome and the primary safety endpoint will be planned after 50% of patients have completed the study. If this review suggests that assumed incidence used to plan the study is much higher than the actual event rate then we may reestimate the sample size to ensure the study is adequately powered. Since the analysis will be conducted blind to group assignment this will not introduce statistical bias and adjustment to the study's significance level is not required...

Literature Cited

1. Bull MH, Huse WM, Bull BS. Evaluation of tests used to monitor heparin therapy during extracorporeal circulation. *Anesthesiology* 1975;43:346-53.
2. Gruntzig AR, Senning A, Siegenthaler WE. Nonoperative dilatation of coronary-artery stenosis: percutaneous transluminal coronary angioplasty. *NEJM* 1979;301:61-8.
3. Lopes RD, Peterson ED, Chen AY et al. Antithrombotic strategy in non-ST-segment elevation myocardial infarction patients undergoing percutaneous coronary intervention: insights from the ACTION (Acute Coronary Treatment and Intervention Outcomes Network) Registry. *JACC Int* 2010;3:669-77.
4. Levine GN, Bates ER, Blankenship JC et al. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention: 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:e574-651.
5. O'Gara PT, Kushner FG, Ascheim DD et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 2013;127:e362-425.
6. Bittl JA, Ahmed WH. Relation between abrupt vessel closure and the anticoagulant response to heparin or bivalirudin during coronary angioplasty. *Am J Cardiol* 1998;82:50P-56P.
7. Doherty TM, Shavelle RM, French WJ. Reproducibility and variability of activated clotting time measurements in the cardiac catheterization laboratory. *CCI* 2005;65:330-7.
8. Chew DP, Bhatt DL, Lincoff AM et al. Defining the optimal activated clotting time during percutaneous coronary intervention: aggregate results from 6 randomized, controlled trials. *Circulation* 2001;103:961-6.
9. Tolleson TR, O'Shea JC, Bittl JA et al. Relationship between heparin anticoagulation and clinical outcomes in coronary stent intervention: observations from the ESPRIT trial. *JACC* 2003;41:386-93.
10. Brener SJ, Moliterno DJ, Lincoff AM, Steinhubl SR, Wolski KE, Topol EJ. Relationship between activated clotting time and ischemic or hemorrhagic complications: analysis of 4 recent randomized clinical trials of percutaneous coronary intervention. *Circulation* 2004;110:994-8.
11. Koch KT, Piek JJ, de Winter RJ et al. Safety of low dose heparin in elective coronary angioplasty. *Heart* 1997;77:517-22.
12. Kaluski E, Krakover R, Cotter G et al. Minimal heparinization in coronary angioplasty--how much heparin is really warranted? *Amer J Cardiol* 2000;85:953-6.
13. Tizon-Marcos H, Bertrand OF, Rodes-Cabau J, et al. Impact of female gender and transradial coronary stenting with maximal antiplatelet therapy on bleeding and ischemic outcomes. Am Heart J 2009;157:740–745.
14. Go AS, Mozaffarian D, Roger VL et al. Executive summary: heart disease and stroke statistics-2014 update: a report from the American Heart Association. *Circulation* 2014;129:399-410.
15. Go AS, Mozaffarian D, Roger VL et al. Heart disease and stroke statistics-2014 update: a report from the American Heart Association. *Circulation* 2014;129:e28-e292.
16. Smith SC, Jr., Dove JT, Jacobs AK et al. ACC/AHA guidelines for percutaneous coronary intervention (revision of the 1993 PTCA guidelines)-executive summary: a report of the American College of Cardiology/American Heart Association task force on practice guidelines (Committee to revise the 1993 guidelines for percutaneous transluminal coronary angioplasty) endorsed by the Society for Cardiac Angiography and Interventions. *Circulation* 2001;103:3019-41.

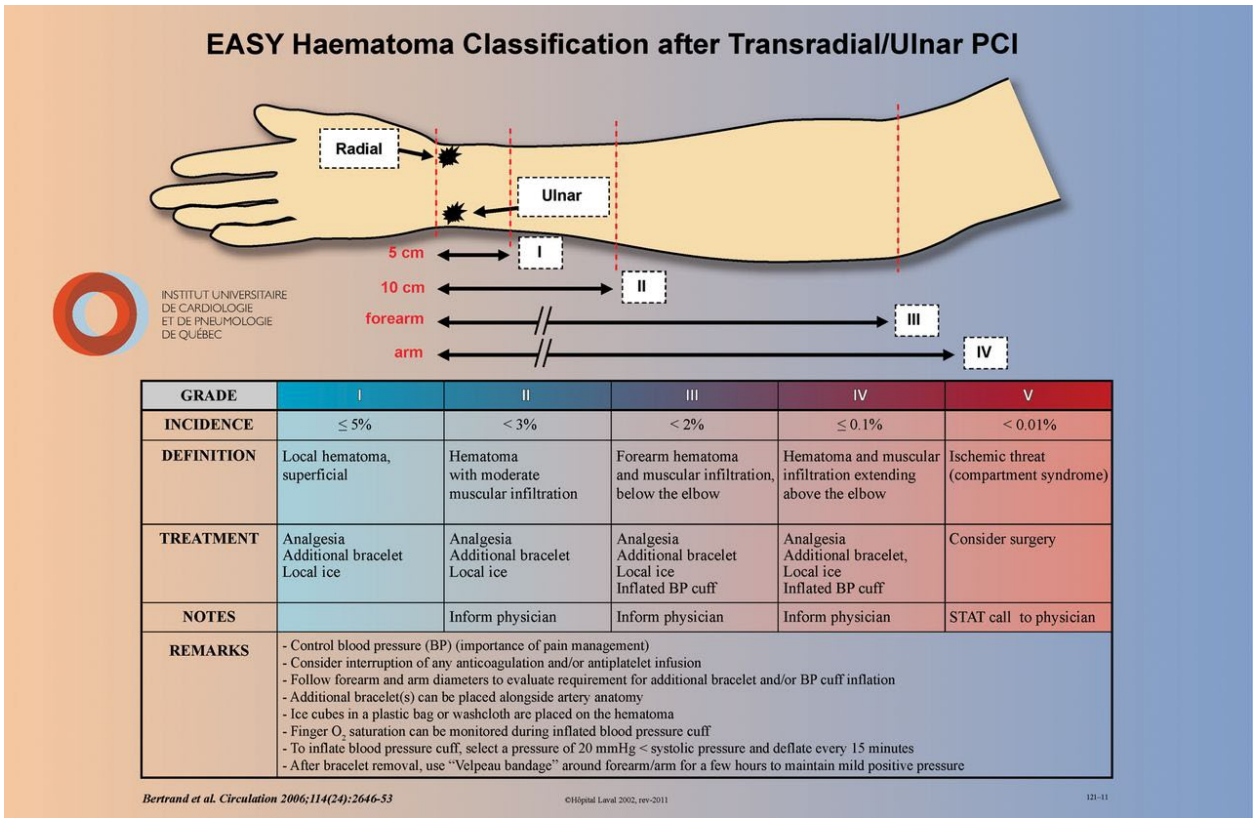
17. Bertrand OF, Rodes-Cabau J, Rinfret S et al. Impact of final activated clotting time after transradial coronary stenting with maximal antiplatelet therapy. *Am J Cardiol*. 2009;104:1235-40.
18. Rajpurohit N, Gulati R, Lennon RJ et al. Relation of activated clotting times during percutaneous coronary intervention to outcomes. Am J Cardiol 2015. PMID:26762725
19. Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) trial Investigators. Platelet glycoprotein IIb/IIIa receptor blockade and low-dose heparin during percutaneous coronary revascularization. *NEJM* 1997;336:1689-1696.
20. Evaluation of Platelet IIb/IIIa Inhibitor for Stenting (EPISTENT) trial Investigators. Randomised placebo-controlled and balloon-angioplasty-controlled trial to assess safety of coronary stenting with use of platelet glycoprotein-IIb/IIIa blockade. *Lancet* 1998;352:87-92.
21. Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy (ESPRIT) trial Investigators. Novel dosing regimen of eptifibatide in planned coronary stent implantation (ESPRIT): a randomised, placebo-controlled trial. *Lancet* 2000;356:2037-2044.
22. Lincoff AM, Bittl JA, Harrington RA et al. Bivalirudin and provisional glycoprotein IIb/IIIa blockade compared with heparin and planned glycoprotein IIb/IIIa blockade during percutaneous coronary intervention: REPLACE-2 randomized trial. *JAMA* 2003;289:853-63.
23. Popma JJ, Weitz J, Bittl JA, Ohman EM, Kuntz RE, Lansky AJ and King SB, 3rd. Antithrombotic therapy in patients undergoing coronary angioplasty. *Chest* 1998;114:728S-741S.
24. Ogilby JD, Kopelman HA, Klein LW and Agarwal JB. Adequate heparinization during PTCA: assessment using activated clotting times. *Cathet Cardiovasc Diagn* 1989;18:206-209.
25. Petroglou D, Didagelos M, Chalikias G, et al. Manual versus mechanical compression of the radial artery after transraial coronary angiography. J Am Coll Cardiol Intv 2018;11:1050-8.
26. Jolly SS, Yusuf S, Cairns J, et al. Radial versus femoral access for coronary angiography and intervention in patients with acute coronary syndromes (RIVAL): a randomised parallel group multicentre trial. Lancet 2011;377:1409-20.
27. Bertrand OF,De Larochelliere R, Rodes-Cabau J, et al. A randomized study comparing same-day home discharge and abciximab bolus only to overnight hospizalization and abciximab bolus and infusion after transradial coronary stent implantation. Circulation 2006;114:2636-2643.
28. Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding defintions for cardiovascular clinical trials. *Circulation* 2011;123:2736-2747
29. Harris PA, Taylor R, Thielke R, et al. A meta-data driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009;42:377-81.

Appendix I

Bleeding Academic Research Consortium (BARC) Standard Bleeding Definition(26)

BARC 0	No bleeding
BARC 1	Non-actionable bleeding
BARC 2	Actionable bleeding, even if on imaging alone, that meets one of the following:1) requires non-surgical (medical) intervention by healthcare personnel; 2) leads to hospitalization or escalation in level of care; 3) prompts evaluation.
BARC 3a	Overt bleeding AND hemoglobin drop 3 to 5 g/dL OR blood transfusion
BARC 3b	Overt bleeding AND hemoglobin drop ≥5 OR cardiac tamponade, bleeding requiring surgical intervention for control, need for intravenous vasopressor
BARC 3c	Intracranial/intraspinal hemorrhage or intraocular hemorrhage with any visual impairment
BARC 4	CABG-related bleeding
BARC 5	Probable or definite fatal bleeding

EASY Hematoma Classification Scale



GRADE	I	II	III	IV	V
INCIDENCE	≤ 5%	< 3%	< 2%	≤ 0.1%	< 0.01%
DEFINITION	Local hematoma, superficial	Hematoma with moderate muscular infiltration	Forearm hematoma and muscular infiltration, below the elbow	Hematoma and muscular infiltration extending above the elbow	Ischemic threat (compartment syndrome)
TREATMENT	Analgesia Additional bracelet Local ice	Analgesia Additional bracelet Local ice	Analgesia Additional bracelet Local ice Inflated BP cuff	Analgesia Additional bracelet, Local ice Inflated BP cuff	Consider surgery
NOTES		Inform physician	Inform physician	Inform physician	STAT call to physician
REMARKS	- Control blood pressure (BP) (importance of pain management) - Consider interruption of any anticoagulation and/or antiplatelet infusion - Follow forearm and arm diameters to evaluate requirement for additional bracelet and/or BP cuff inflation - Additional bracelet(s) can be placed alongside artery anatomy - Ice cubes in a plastic bag or washcloth are placed on the hematoma - Finger O_2 saturation can be monitored during inflated blood pressure cuff - To inflate blood pressure cuff, select a pressure of 20 mmHg < systolic pressure and deflate every 15 minutes - After bracelet removal, use "Velpeau bandage" around forearm/arm for a few hours to maintain mild positive pressure				

Bertrand et al. Circulation 2006;114(24):2646-53

121-11

Appendix II

Optimal Target of Activated Clotting Time During Percutaneous Coronary Intervention and Outcomes: The OPTIMAL-ACT Trial

Study Endpoint Definitions:

Bleeding

-EASY hematoma classification after Transradial/Ulnar PCI

Type 1: less than 5cm in diameter from puncture site

Type 2: 5-10 cm in diameter from puncture site

Type 3: >10 cm in diameter but below the elbow limited to the forearm

Type 4:>10 cm in diameter and extends above the elbow

Type 5: any bleeding location with compartment syndrome (ischemic threat to the limb)

-BARC 2, 3, or 5 bleeding using BARC defined bleeding scale

BARC 0	No bleeding
BARC 1	Non-actionable bleeding
BARC 2	Actionable bleeding, even if on imaging alone, that meets one of the following:1) requires non-surgical (medical) intervention by healthcare personnel; 2) leads to hospitalization or escalation in level of care; 3) prompts evaluation.
BARC 3a	Overt bleeding AND hemoglobin drop 3 to 5 g/dL OR blood transfusion
BARC 3b	Overt bleeding AND hemoglobin drop ≥5 OR cardiac tamponade, bleeding requiring surgical intervention for control, need for intravenous vasopressor
BARC 3c	Intracranial/intraspinal hemorrhage or intraocular hemorrhage with any visual impairment
BARC 4	CABG-related bleeding
BARC 5	Probable or definite fatal bleeding

Net Adverse Clinical Events (composite of all-cause mortality, myocardial infarction, stroke, target lesion revascularization, or bleeding)

Stent thrombosis (ST) [1,2]:

Definite (ST): ACS with angiography or autopsy evidence of stent thrombosis.

Probable (ST): Unexplained death within 30 days of index procedure or acute myocardial infarction involving the target-vessel territory without angiographic confirmation.

Myocardial infarction: presence of 2 of the following: ischemic symptoms; elevation of cardiac troponin >99th percentile of lab upper reference range with typical rise and fall; ECG changes compatible with infarction. For cardiac troponin elevated prior to PCI due to myocardial infarction, the subsequent troponin would need to be increased by 20% or more than the previous value to be considered an endpoint event[3].

Stroke: Focal loss of neurological function caused by an ischemic or hemorrhagic insult, with residual symptoms lasting at least 24 hours, and confirmed on neuroimaging (CT or MRI) with final impression deemed as stroke by a consulting neurologist

Target lesion revascularization: repeated PCI of the stented segment

Intra-procedural thrombus: visible filling defect noted by the operator on the guiding catheter or intracoronary wire or device during selective angiography with or without adjunctive confirmation on alternative coronary imaging modality (IVUS/OCT)

References:

1. Cutlip DE, Windecker S, Mehran R, et al. Clinical end pints in coronary stent trials: a case for standardized definitions. Circulation.2007;115:2344-51.
2. Mauri L, Hsieh W, Massaro JM, et al. Stent thrombosis in randomized clinical trials of drug-eluting stents. N Engl J Med.2007;356:1020-9.
3. Yusuf S, et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med.2001;345:494-502.