# Pharmacodynamic and pharmacokinetic profiles on switching from cangrelor to prasugrel in patients with acute coronary syndrome undergoing percutaneous coronary intervention: The Switching Antiplatelet -6 (SWAP-6) study

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**PROJECT SUMMARY**

Cangrelor is an intravenous P2Y12 inhibitor utilized as a bridge to achieve adequate platelet inhibition until oral P2Y12 inhibitors achieve their full antiplatelet effects in patients undergoing coronary stenting. Although in this setting the potent oral P2Y12 inhibitor prasugrel is commonly utilized, there is very limited data on the optimal approach for switching between these therapies. In particular, ruling out a drug-drug interaction (DDI) is critical to this extent as the presence of a DDI would translate into reduced or abolished antiplatelet effects exposing these acute patients to an increased thrombotic risk. There is an unmet need to better elucidate pharmacodynamic profiles associated with the transition from cangrelor to prasugrel therapy. Of note, prasugrel has recently gone off patent and the availability of a generic formulation will favorably impact its use. Pharmacodynamic studies provide some support on the safety of administering prasugrel at the start of cangrelor infusion. However, the available data does not allow to rule out a DDI given that there was no comparator arm in which prasugrel was either given alone or at the end of cangrelor infusion. The methodological approach for this assessment should rely on comprehensive pharmacodynamics investigations aimed to assess levels of P2Y12 receptor inhibition, pharmacokinetic investigations to assess systemic levels of the drug/drug metabolite, and mechanistic investigations by assessment of levels of P2Y12 receptor gene expression. The overarching aim of this investigation is to rule out a DDI when cangrelor and prasugrel are concomitantly administered in patients undergoing coronary stenting.

**BACKGROUND**

Cangrelor is an intravenous adenosine triphosphate (ATP) analogue that directly and reversibly inhibits ADP binding to the adenosine diphosphate (ADP) $P2Y_{12}$ receptor subtype in a dose-dependent manner, achieving immediate potent platelet inhibition after a bolus dose [1,2]. The cangrelor binding site at the $P2Y_{12}$ receptor level has been subject to controversy and is not clearly defined [3,4]. Nonetheless, cangrelor is associated with high levels of receptor occupancy and prevents ADP binding. Cangrelor is promptly inactivated through dephosphorylation by ectonucleotidase and has a very short plasma half-life (3-6 minutes) [1-4]. Therefore, recovery of platelet function is rapid (~60 minutes) after discontinuation of cangrelor infusion [1-4].

Cangrelor was approved for clinical use based on the results of the CHAMPION (Cangrelor versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition) PHOENIX trial, which showed that cangrelor significantly reduced the rate of ischemic events, driven by a reduction in stent thrombosis and myocardial infarction, with no significant increase in severe bleeding in patients undergoing percutaneous coronary intervention (PCI) [5]. Given the different pharmacological properties of cangrelor and the oral $P2Y_{12}$ inhibitors, several studies have investigated the potential for drug-drug interaction (DDI) when these agents are concomitantly administered [6-12]. These potential DDI are concerning as they can result in reduced platelet inhibition and subsequent lack of protection from thrombotic complications in the peri-PCI period. In a study conducted in healthy volunteers, clopidogrel administration during cangrelor infusion was associated with an impaired antiplatelet effect of clopidogrel after cangrelor discontinuation [6]. This reflects the fact that clopidogrel active metabolite cannot bind to the $P2Y_{12}$ receptors if already largely occupied by cangrelor. In turn, the plasma concentrations of the unbound clopidogrel active metabolites fall rapidly to subtherapeutic levels

as a result of distribution to other compartments and systemic clearance. Therefore, after stopping cangrelor infusion, when receptors become available for binding, most of the active metabolite has already been eliminated from the circulation [6]. In contradistinction, clopidogrel's antiplatelet effects are not diminished when it is administered after cangrelor infusion, because of the very fast offset of action of cangrelor and subsequent availability of $P2Y_{12}$ receptors for binding by clopidogrel active metabolite [6]. Accordingly, across the CHAMPION clinical trial program, a clopidogrel loading dose (LD) was administered always immediately after discontinuation of cangrelor infusion [5,13-15].

Although cangrelor was approved based on a trial in which clopidogrel was used, in real-world clinical practice cangrelor is more commonly utilized in high-risk patients undergoing PCI, in whom the newer generation $P2Y_{12}$ inhibitors (i.e, prasugrel and ticagrelor) are recommended over clopidogrel [16,17,18]. Recommendations on how to transition from cangrelor to oral treatment with ticagrelor and prasugrel largely derive from pharmacodynamic (PD) studies [3,4,8,9]. Unlike that observed with clopidogrel, no interaction was shown when transitioning from cangrelor to ticagrelor, allowing for a more versatile use of ticagrelor with respect to timing of administration in relation to the start of cangrelor therapy [8]. The presence of an interaction between clopidogrel and cangrelor, but not between ticagrelor and cangrelor is probably the result of different half-lives of these drugs, as well as the different sites and types of binding to the $P2Y_{12}$ receptor [3,4,6-8,11,12]. Ticagrelor reversibly binds the $P2Y_{12}$ receptor at a site distinct from the ADP-binding site and has a half-life of 6-12 hours. Although it is unknown whether ticagrelor can bind with the $P2Y_{12}$ receptor during cangrelor infusion, its half-life (which exceeds that of the duration of cangrelor infusion) is such that drug is still systemically available to bind with the $P2Y_{12}$ receptor after discontinuation of cangrelor infusion [3,4,8].

Based on these observations, ticagrelor can be administered before, during, or after cangrelor infusion [3,4,8].

The transition from cangrelor to prasugrel is associated with transient recovery of platelet reactivity, in particular within 1 hour after cangrelor discontinuation, which could be explained by a DDI similar to that described for clopidogrel [9]. However, it was observed that recovery of platelet function was attenuated when prasugrel was administered 30 minutes before stopping the cangrelor infusion [9]. Accordingly, it is recommended that prasugrel be administered at the end of cangrelor infusion or 30 minutes prior to discontinuation of infusion [3,4,9]. However, recently the ExcelsiorLOAD2 (Impact of Extent of Clopidogrel-Induced Platelet Inhibition during Elective Stent Implantation on Clinical Event Rate - Advanced Loading Strategies) study showed that prasugrel 60 mg LD given at the start of a 2-hour infusion of cangrelor was associated with sufficient platelet inhibition post-cangrelor, with only rare cases of high platelet reactivity (HPR) [19]. Moreover, there were no differences with levels of platelet reactivity and HPR rates compared with those observed with ticagrelor, which was also given at the start of the cangrelor infusion. These observations may be attributed to relatively higher concentration and longer half-life of prasugrel's active metabolite compared with that of clopidogrel [20-23]. However, ExcelsiorLOAD2 was not powered to test the non-inferiority on PD effects between prasugrel and ticagrelor, but only for the comparison of prasugrel versus clopidogrel. Moreover, whether similar findings would be observed with longer infusions of cangrelor (e.g., up to 4 hours) is unknown. Therefore, although the PD results of this study provide some support on the safety of administering prasugrel at the start of cangrelor infusion, the trial design does not allow to rule out a DDI given that there was no comparator arm in which prasugrel was either given alone or at the end of cangrelor infusion [24]. Moreover, pharmacokinetic (PK) assessments,

pivotal to help elucidate a DDI, were not performed. Accordingly, recommendations on timing of prasugrel administration in cangrelor treated patients remain unchanged.

**STUDY RATIONALE**

Guidelines recommend the preferential use of new generation $P2Y_{12}$ inhibitors, including prasugrel, over clopidogrel in high-risk patients with coronary artery disease (CAD) undergoing PCI [16-18]. Since high-risk patients undergoing PCI is a setting in which cangrelor is frequently used, there is an unmet need to better elucidate PD profiles associated with the transition from cangrelor to prasugrel therapy. To date the uptake of the newer oral $P2Y_{12}$ inhibitors has been mostly limited by costs. However, prasugrel has recently gone off patent and the availability of a generic formulation will favorably impact its use. Moreover, to date PD studies assessing the transition from cangrelor to prasugrel have been conducted in patients with stable coronary artery disease, and current recommendations are based on assessments conducted in patients not undergoing PCI [9]. Importantly, acute coronary syndrome (ACS) and PCI are both known to affect PK and PD profiles of antiplatelet agents. Overall, these observations strongly underscore the need to conduct dedicated investigations to rule out a DDI when transitioning from cangrelor to prasugrel and to define the optimal approach for transitioning therapy in real-world high-risk patients, including ACS patients, undergoing PCI. The methodological approach for this assessment should rely on comprehensive PD assessments aimed to assess levels of $P2Y_{12}$ receptor inhibition, PK assessments to assess systemic levels of the drug/drug metabolite, and mechanistic assessments by measuring levels of $P2Y_{12}$ receptor gene expression. In particular, different levels of $P2Y_{12}$ receptor gene expression can modulate the PD effects of oral $P2Y_{12}$ receptor inhibitors at a given level of drug exposure defined by PK profiling.

## STUDY AIM

The aim of this investigation is to rule out a DDI when cangrelor and prasugrel are concomitantly administered in high-risk patients undergoing coronary stenting.

## REASERCH PLAN

### Study design

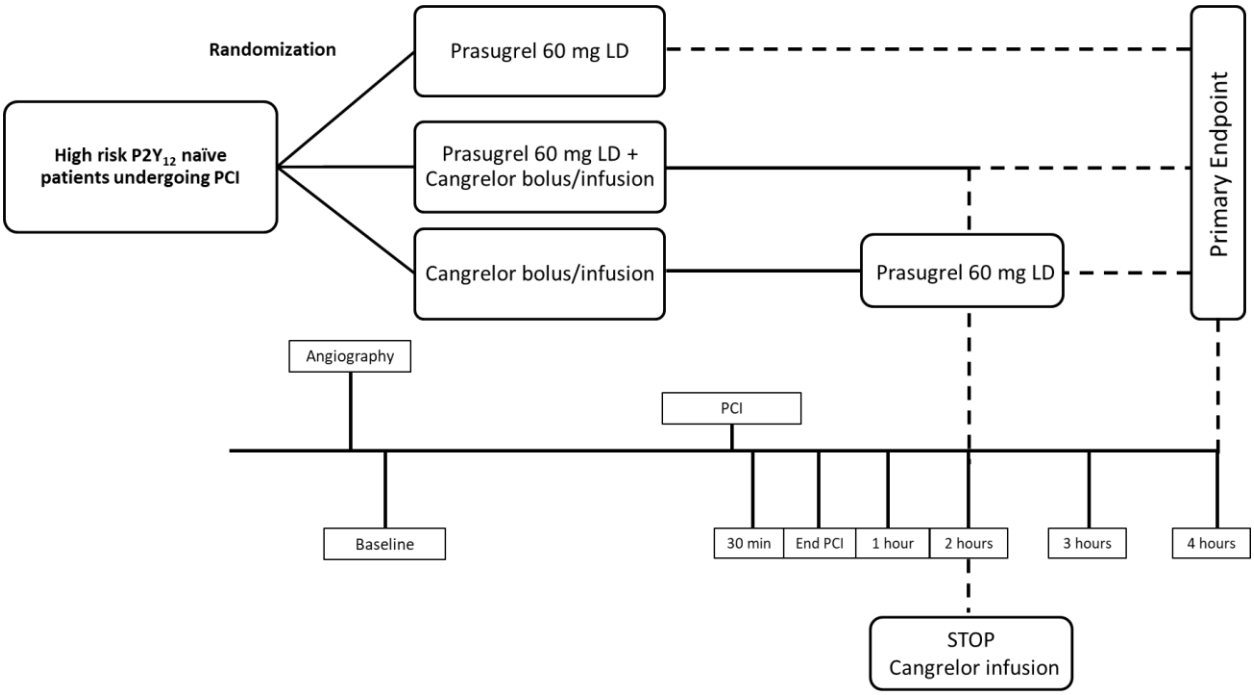
The Switching Antiplatelet Therapy-6 (SWAP-6) study will be a prospective, randomized, open label PD and PK study conducted in high-risk patients undergoing PCI. Patients presenting with a non-ST-segment elevation ACS (NSTE-ACS), including unstable angina (UA) and NSTE-myocardial infarction (NSTEMI), or with stable CAD but deemed at high risk undergoing an invasive management strategy as part of their standard of care will be screened. The study will be performed at the Division of Cardiology of University of Florida Health, Jacksonville, Florida. Patients will be screened by Cardiology Research staff, who will verify that all candidates meet inclusion and exclusion criteria, and obtain their written informed consent to participate in the study prior to undergoing their diagnostic invasive evaluation to define coronary anatomy. Results from blood tests performed within the last 90 days will be considered valid for screening purposes. If these are not available, a blood sample will be collected for the screening phase.

After undergoing invasive diagnostic evaluation of coronary anatomy, patients undergoing PCI will be considered eligible for randomization. Using a computer-based randomization system, patients will be randomized in a 1:1:1 fashion to one of the following treatment arms: a) prasugrel only administered at the start of PCI (group 1); b) cangrelor plus prasugrel concomitantly administered at the start of PCI (group 2); c) cangrelor administered at

the start of PCI plus prasugrel administered at the end of the cangrelor infusion (group 3). Prasugrel will be used in line with FDA recommendations using a 60mg LD followed by a 10mg daily maintenance dose started 24 hours after LD administration [25]. Cangrelor will be used at the FDA recommended dose using a 30 μg/kg bolus followed by 4 μg/kg/min infusion [26]. Study drugs will be administered before passing of the guidewire. The duration of cangrelor infusion will be 2 hours or until the end of PCI (whichever is longer). All patients will be on a background of aspirin therapy (325 mg loading dose followed by 81 mg daily maintenance dose). Patients will be managed according to standard of care. The interventional procedure will also be performed according to standard of care with choice of anticoagulant (heparin or bivalirudin) at the discretion of the operator. PK and PD assessments will be conducted at 7 time points: baseline, 30 minutes after administration of randomized treatment, end of PCI (defined as when the guide catheter is removed at procedure completion), 1 hour, 2 hours, 3 hours and 4 hours after administration of randomized treatment. Figure 1 illustrates the overall study design. In patients in which the infusion will be maintained for more than 2 hours (until the end of PCI), the 3-hour and 4-hour after time points will be collected 1 hour and 2 hours after stopping cangrelor, respectively.

Although the study will have an open-label design, laboratory personnel will be blinded to treatment assignments. During hospital stay, major adverse cardiac events (death, myocardial infarction, stroke, and urgent revascularization procedures), serious adverse events (bleeding and other adverse events), as well as non-serious adverse events considered to be study related will be collected. After completing the study, decisions on medical management, including the choice and duration of antiplatelet therapy will be at the discretion of the treating physician.

**Figure 1. Overall study design**




## Study Population

*Inclusion criteria:*

- Patients with NSTE-ACS (UA or NSTEMI) or high-risk patients with stable CAD undergoing PCI. NSTE-ACS will be defined as the presence of cardiac ischemic symptoms with ischemic changes (but not ST-segment elevation) on electrocardiogram with or without a positive troponin. However, normal electrocardiograms will be acceptable if the investigator will consider an ACS presentation likely. High-risk CAD will be defined at the discretion of the operator performing coronary intervention.
- Age between 18 and 75 years old

*Exclusion criteria:*

- Inability to provide written informed consent

- Age >75 years
- Weight <60 Kg
- ST-segment elevation myocardial infarction
- On treatment with a $P2Y_{12}$ receptor antagonist (ticlopidine, clopidogrel, prasugrel, ticagrelor) in past 7 days
- Known allergies to prasugrel or cangrelor
- Considered at high risk for bleeding
- History of ischemic or hemorrhagic stroke or transient ischemic attack
- On treatment with oral anticoagulant (Vitamin K antagonists, dabigatran, rivaroxaban, apixaban, edoxoban)
- Planned treatment with glycoprotein IIb/IIIa inhibitors (only bailout use allowed)
- Fibrinolytics within 24 hours
- Known platelet count $<80x10^6$/mL
- Known hemoglobin <10 g/dL
- Active bleeding
- Known end stage renal disease on hemodialysis
- Known severe hepatic dysfunction
- Intubated patients (prior to randomization)
- Pregnant females [women of childbearing age must use reliable birth control (i.e. oral contraceptives) while participating in the study]

*Blood sampling and Laboratory assessments*

Blood samples (10 mL) will be drawn through the arterial access sheet used for the PCI procedure for time points  while patient are in the cath lab (until the end of PCI); post-cath lab samples will be drawn through venous sampling. Samples will be collected in anticoagulated and serum tubes at each study time point for all PD and PK assessments. The first 2-4 mL of blood will be discarded to avoid spontaneous platelet activation.

Laboratory assessments will include the following:

1. VerifyNow PRU assay
2. VASP-PRI assay
3. Total Thrombus-Formation Analysis System (T-TAS)
4. PK
5. P2Y12 gene receptor level expression

*Description of laboratory assays*

*1) VerifyNow PRU:* The VerifyNow System is a turbidimetric based optical detection system which measures platelet induced aggregation as an increase in light transmittance (Accriva, San Diego, CA) and will be utilized according to manufacturer's instructions, as previously described [27-30]. The assay is based on microbead agglutination and uses specific reagents for the pathways of interest. The VerifyNow PRU assay, by combining ADP+PGE1, measures changes in platelet function specific to $P2Y_{12}$ receptor inhibitors. The assay is based upon the ability of activated platelets to bind fibrinogen. Fibrinogen-coated microparticles aggregate in proportion to the number of GP IIb/IIIa receptors expressed. Microbead aggregation is more rapid and reproducible if platelets are activated; therefore the reagents are incorporated into the assay channel to induce platelet activation without fibrin formation. Light transmittance increases as activated platelets bind and aggregate fibrinogen-coated beads. The instrument measures this change in optical signal and reports results in $P2Y_{12}$ Reaction Units (PRU).

*2) Whole blood vasodilator-stimulated phosphoprotein (VASP):* VASP phosphorylation (VASP-P) is a marker of P2Y12 receptor signaling. VASP will be assessed the ELISA VASP-P kit (Biocytex Inc., Marseille, France) as previously described [31-33]. After a first step of parallel

whole blood sample activation with PGE1 and PGE1+ADP, platelets from the sample are lysed, allowing released VASP to be captured by an anti-human VASP antibody, which is coated in the microtiter plate. Then, a peroxidase-coupled anti-human VASP-P antibody binds to phosphorylated serine 239 antigenic determinant of VASP. The bound enzyme peroxidase is then revealed by its activity on TMB substrate over a predetermined time. After stopping the reaction, absorbance at 450 nm is directly related to the concentration of VASP-P contained in the sample.PGE1 increases VASP-P levels by stimulation of adenylate cyclase. Binding of ADP to P2Y12 leads to Gi-coupled inhibition of adenylate cyclase. Therefore, the addition of ADP to PGE1-stimulated platelets reduces PGE1-induced VASP-P levels. If P2Y12 receptors are successfully inhibited, addition of ADP will not reduce the PGE1-stimulated VASP-P levels. The platelet reactivity index (PRI) will be calculated after measuring VASP-P levels.

*3) Total Thrombus-Formation Analysis System (T-TAS):* T-TAS is an automated microchip flow chamber system for the quantitative analysis of the thrombus formation process under blood flow conditions. T-TAS allows measurement of thrombus formation using the PL-chip (Diapharma, West Chester Township, OH) [34]. The PL-chip contains 25 capillary channels (width 40 μm, depth 40 μm) coated with type I collagen and is specifically designed for quantitative analysis of platelet thrombus formation, including platelet adhesion and aggregation, granule secretion, and thrombus growth in the absence of coagulation and fibrinolysis systems. In measurements using the PL-chip, a blood sample collected in a hirudin containing blood sampling tube. The platelet aggregates gradually increase in size and, in the process, occlude the capillary, resulting in an increase in flow pressure. In the present study, total platelet-derived thrombogenicity is expressed as the area under the flow pressure curve for the first 10 min for the PL-chip tested at a

flow rate of 18 μL/min (PL18-AUC10). Low PL18-AUC10 reflect reduced thrombus growth and rapid breakdown of the thrombus.

*3) Pharmacokinetic (PK) assay*: Determination of prasugrel's active metabolite concentration in plasma will be performed using liquid chromatography with tandem mass spectrometry according to standard protocols as previously described [27,35]. Blood will be drawn into standard EDTA tubes and within 30 seconds a derivatizing agent (3'-methoxyphenacylbromide) will be added to capture and stabilize the active metabolite. The geometric mean area under the concentration-time curve through the sampling time of the last quantifiable prasugrel's active metabolite concentration (AUC[0-$t_{last}$]) will be calculated and the maximum observed plasma concentration (Cmax) and time to Cmax (Tmax) of Pras-AM will be recorded.

*4) $P2Y_{12}$ gene receptor level expression:* Gene expression in platelets will be performed using standard protocols. In particular, purified platelets are dissolved in Trizol reagent (Invitrogen) and total RNA will be extracted using RNA minipres kit (Zymos research) according to manufacturer's protocol. $P2Y_{12}$ mRNA expression will be measured with real-time PCR using SYBR green and specific primers as previously described [36].

**Study endpoints, sample size calculation and statistical analysis**

The primary end point of the study will be the non-inferiority in PRU measured at 4 hours of cangrelor plus prasugrel concomitantly administered at the start of PCI versus prasugrel only administered at the start of PCI (group 2 vs. group 1). Non-inferiority will be assessed using a 95% confidence interval (CI) of the difference in mean PRU between the two arms. Under the assumption of 0 difference in mean PRU between group 1 and group 2 and a common standard

deviation of 50 PRU, a sample size of 22 patients per group will allow for the 95% CI to stay within ± 45 PRU with a 90% power and alpha=0.05. Considering a 25% data attrition rate due to GPI use, hemolysis, drop out or technical problems, 28 patients per group will need to be randomized in order to ensure complete available data for analysis. Considering the 3 arms of treatment up to 84 patients will need to be randomized. The sample size of this study was established according to results of previous PD investigations [28,37]. In line with previously reported investigations, 45 PRU was chosen for the noninferiority margin for the upper 95% CI limit of the difference [29,30]. Group 3 will be included in study design as this strategy represents current standard of care for the transition from cangrelor to prasugrel. However, the study will be powered to assess non inferiority of group 2 vs. group 1. Therefore, all other end points will be considered exploratory and will include the comparisons of PD and PK parameters, and $P2Y_{12}$ gene receptor level expression between all treatment arms at each time points, as well as the comparisons of rates of high on-treatment platelet reactivity (HPR). HPR will be defined as PRU>208 and PRI>50%, in line with consensus definitions [38].

Conformity to the normal distribution will be evaluated for continuous variables with the Kolmogorov-Smirnov test. For baseline characteristics, continuous variables will be expressed as mean ± SD or median [IQR]. One-way analysis of variance or Kruskal-Wallis test will be used to compare continuous variables. Chi-squared test will be used to compare categorical variables among groups. An analysis of covariance (ANCOVA) method with a general linear model, with treatment as the main effect and baseline values of platelet reactivity as a covariate, will be used to evaluate the primary end point as well as all between-group comparisons at each time point. Least-square mean (LSM) differences in PRU between group 1 and group 2 and the corresponding 2-sided 95% CI for the difference will be obtained to assess non-inferiority based

on the ANCOVA model. Given the exploratory nature of comparisons for secondary end points, correction for multiple comparisons will not be performed. A 2-tailed p value of <0.05 will be considered to indicate a statistically significant difference for all the analyses performed. Statistical analysis will be performed using SPSS version 22.0 software (SPSS Inc., Chicago, Illinois).

The safety population will include all randomized patients exposed to study medication. The PD population will include all patients with PD data and without a major protocol deviation thought to affect significantly the PD and PK of cangrelor or prasugrel. The PD population will be used for analysis of all primary and secondary end points. Erroneously treated patients (eg, those randomized to one treatment but actually given the other) will be accounted for based on the actual treatment received.

**Publication Strategy/Additional Information**

Subjects will be identified with a number and data collection sheets will all be stored in a locked area. Data will be kept for 6 years after enrollment ends to comply with HIPAA regulations. Patients will receive a handout with the names and telephone numbers of the doctors involved in the study. Study subjects will be identified first (months 1-17): we expect to randomize 5 subjects monthly and complete enrollment in 17 months (total: 84 subjects randomized). Months 18-20 will be implied for statistical analysis and manuscript preparation. Results will be presented at the first available major cardiovascular meeting (e.g. AHA, ACC, ESC), and final manuscript will be submitted to publication to one of major cardiovascular journals (e.g. JACC, Circulation, European Heart Journal).

**Possible Discomforts and Risk**

In clinical trials, the most common clinical side effect of cangrelor was bleeding. Severe/moderate bleeding occurred in 0.8% of patients receiving cangrelor, as compared to 0.6% of those receiving placebo. Other side effects include dyspnea (1.3%), worsening renal function (3.2% of patients with severe renal impairment), and hypersensitivity (0.05%) [5]. In clinical trials, the most common clinical side effects of prasugrel were blurred vision, dizziness, headache, nervousness; infrequent events included intracranial hemorrhage (0.79%) and severe neutropenia (< 0.1%). The most important adverse effect associated with the use of prasugrel is bleeding (2.4%) [39]. However, both cangrelor and prasugrel are standard of care therapies and would be potentially utilized as part of standard of care treatment in this study.

All clinical events described above, if they were to occur, as well as death, myocardial infarction, stroke, and urgent revascularization procedure with PCI or coronary artery bypass grafting will be recorded. Bleeding data will be collected using BARC definitions [40]. Clinical events will be evaluated by a local committee, comprised of 2 faculty members (2 cardiologists), not directly involved in the research. In the event of a report of a serious adverse event the local committee will meet and antiplatelet treatment management will be managed according to physician recommendation.

**Conflict of Interest**

Dr. Angiolillo (Sub-Investigator) is a consultant for Chiesi, the maker of cangrelor.

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