Pharmacodynamic and pharmacokinetic profiles of switching between cangrelor and ticagrelor following ticagrelor pre-treatment:

The Switching Antiplatelet -5 (SWAP-5) study

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PROJECT SUMMARY

Cangrelor is an intravenous $P2Y_{12}$ inhibitor utilized as a bridge to achieve adequate platelet inhibition until oral $P2Y_{12}$ inhibitors achieve their full antiplatelet effects in patients undergoing coronary stenting. Although in this setting the potent oral $P2Y_{12}$ inhibitor ticagrelor 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. Despite the available evidence suggesting a lack of DDI with the use of ticagrelor in cangrelor treated patients, most data derive from studies in which ticagrelor was given at the time of initiation or during cangrelor infusion. To date, there is no data to fully rule out a DDI when ticagrelor is given prior to starting cangrelor infusion. The need for such investigation is underscored by the relatively high prevalence of pretreatment with ticagrelor in acute settings. The methodological approach for this assessment should rely on comprehensive pharmacodynamics (PD) investigations aimed to assess levels of $P2Y_{12}$ receptor inhibition, pharmacokinetic (PK) investigations to assess systemic levels of the drug/drug metabolite, and mechanistic investigations by assessment of levels of $P2Y_{12}$ receptor gene expression. The overarching aim of this investigation is to rule out a DDI when ticagrelor is administered prior to cangrelor infusion.

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 DDIs 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 particular patients with acute coronary syndromes (ACS), in whom the newer generation $P2Y_{12}$ inhibitors (i.e, prasugrel and ticagrelor) are recommended over clopidogrel [16-17]. 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 is such that drug is still systemically

available to bind with the $P2Y_{12}$ receptor after discontinuation of cangrelor infusion [3,4,8]. This was most recently demonstrated in the CANTIC (The Platelet Inhibition with CANgrelor and Crushed TICagrelor in STEMI Patients Undergoing Primary Percutaneous Coronary Intervention) study, which was the first study to rule out a DDI in the setting of patients presenting with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention, in which ticagrelor, administered as a crushed formulation, was given concomitantly with cangrelor without any apparent DDI [18]. Overall, based on these PD observations, according to FDA product label, ticagrelor can be administered at any time during cangrelor infusion or immediately after discontinuation [19].

STUDY RATIONALE

Despite the available evidence suggesting a lack of DDI with the use of ticagrelor in cangrelor treated patients, most data derive from studies in which ticagrelor was given at the time of initiation or during cangrelor infusion. To date there is no data to fully rule out a DDI when ticagrelor is given prior to starting cangrelor infusion. In fact, although a prior PD investigation demonstrated that ticagrelor given before cangrelor did not attenuate the PD effects of cangrelor, this study did not assess whether the PD effects of ticagrelor are preserved after discontinuing cangrelor infusion [8]. In another investigation, PD effects were studied in patients pretreated with ticagrelor with less than 1 hour from primary PCI or receiving ticagrelor in cath lab and treated with cangrelor [20]. At 30 min after end of infusion, platelet reactivity was within the therapeutic range for most patients and there were no differences between patients treated with ticagrelor prehospital or in the cath lab. Thus, the design of this study cannot rule-out a DDI due to several factors: the comparison was not randomized, at 30 min there is still residual effect of

cangrelor which warrants at least 60 minutes for complete wash-out of effects (thus not adequate to rule out a DDI), and 12.5% of patients had high platelet reactivity at this time point [20]. Moreover, in none of the above mentioned studies were pharmacokinetic (PK) assessments performed to characterize the impact, if any, of cangrelor on systemic levels of ticagrelor and its major metabolite (AR-C124910XX). Therefore, the lack of data to rule out a DDI between cangrelor and ticagrelor when the latter is administered prior to starting cangrelor infusion warrants dedicated prospective investigations. The need for such investigations is underscored by the relatively high prevalence of pretreatment with ticagrelor in acute settings [21,22]. Importantly, such acute settings represent desirable scenarios to use cangrelor. Of note, use of prehospital ticagrelor (i.e, pretreatment) in acute settings is endorsed by practice guidelines both in the United States and Europe [17]. Therefore, ruling out a DDI between cangrelor and ticagrelor when the latter is administered prior to starting cangrelor infusion would have important clinical implications for real-world practice. The methodological approach for this assessment should rely on comprehensive PD assessments aimed to evaluate levels of $P2Y_{12}$ receptor inhibition and thrombus formation, 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 ticagrelor is administered prior to cangrelor infusion. Comprehensive PK and PD assessments will be conducted to reach this study aim.

REASERCH PLAN

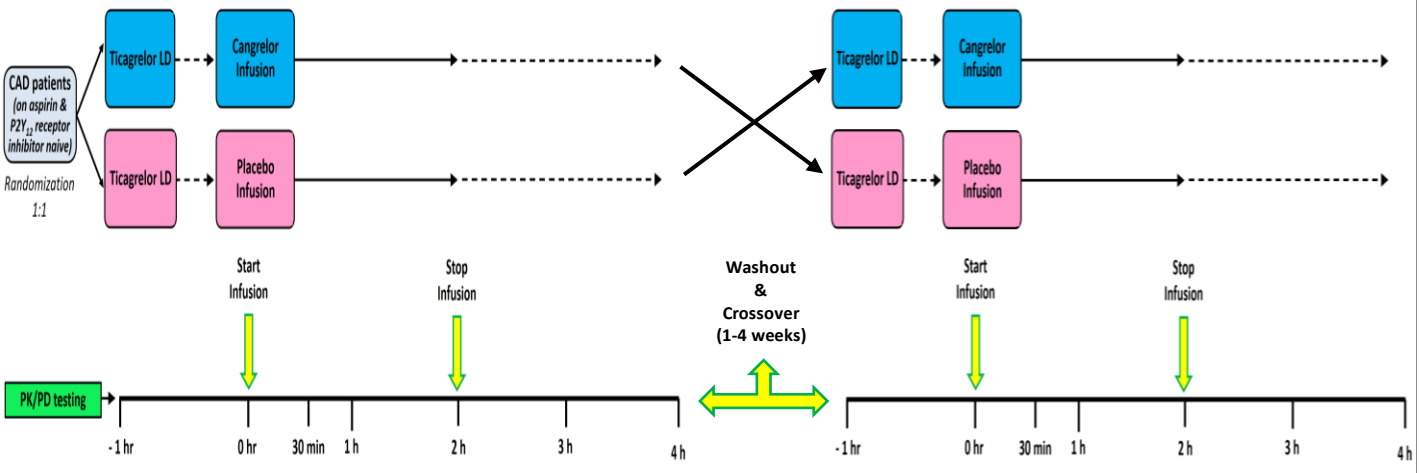
Study design

The Switching Antiplatelet Therapy-5 (SWAP-5) study will be a prospective, randomized, double-blind, placebo controlled, cross-over PK and PD investigation aimed to rule out a DDI when ticagrelor is administered prior to cangrelor infusion. Aspirin treated patients with known coronary artery disease will be considered eligible for the study. 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. 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.

Using a computer-based randomization system, patients will be randomized in a 1:1 fashion to one of the following treatment arms: a) ticagrelor loading dose followed after 1 hour by cangrelor bolus and infusion or b) ticagrelor loading followed after 1 hour by placebo infusion. In line with FDA recommendations, ticagrelor will be administered as a 180mg loading dose (two 90mg tablets) [23]. Cangrelor will be used at the FDA recommended dose using a 30 μg/kg bolus followed by 4 μg/kg/min infusion [19]. The duration of cangrelor/placebo infusion

will be 2 hours. After completing the first phase of the study, patients will undergo a 1-4 week wash-out period and then will cross-over to the alternative treatment in the second phase (i.e., patients assigned to treatment with cangrelor in the first phase will be assigned to placebo in the second phase and vice-versa). All patients will be on a background of aspirin therapy (81 mg daily maintenance dose). During each phase, PK and PD assessments will be conducted at 7 time points (total 14 time points): baseline (prior to ticagrelor loading dose; time -1 h); at start of cangrelor/placebo bolus and infusion (1 hour after ticagrelor loading dose); 30 minutes after cangrelor/placebo bolus; 1 hour after cangrelor/placebo bolus, 2 hours after cangrelor/placebo bolus (time of infusion discontinuation); 1 hour after discontinuation of cangrelor/placebo infusion; and 2 hours after after discontinuation of cangrelor/placebo infusion. Figure 1 illustrates the overall study design. The study will have a double-blind design. Patients, research staff and laboratory personnel will be blinded to treatment assignments. Masking and randomization of medications (cangrelor and placebo) will be performed by our institutional research pharmacy in line with prior investigations [18].

Figure 1. Overall study design



Study Population

Inclusion criteria:

- Patients with known coronary artery disease (defined as prior type I myocardial infarction, coronary revascularization, percutaneous or surgical, or presence of at least a 50% stenosis in any major epicardial vessel).
- Age > 18 years old
- On aspirin 81mg/qd for at least 1 month

Exclusion criteria:

- Inability to provide written informed consent
- Hemodynamic instability
- On treatment with a $P2Y_{12}$ receptor antagonist (ticlopidine, clopidogrel, prasugrel, ticagrelor) in past 30 days
- Known allergies to ticagrelor or cangrelor
- Considered at high risk for bleeding
- History of intracranial bleeding/hemorrhagic stroke
- On treatment with oral anticoagulant (Vitamin K antagonists, dabigatran, rivaroxaban, apixaban, edoxoban) within past 30 days
- Known platelet count $<80x10^6$/mL
- Known hemoglobin <10 g/dL
- Active bleeding
- Known end stage renal disease on hemodialysis
- Known severe hepatic dysfunction
- Acute or severe bronchial asthma or upper airway obstruction.
- Patients with sick sinus syndrome (SSS) or high degree AV block without pacemaker protection.
- Current treatment with drugs interfering with CYP3A4 metabolism (to avoid interaction with ticagrelor): Ketoconazole, itraconazole, voriconazole, clarithromycin, nefazodone, ritonavir, saquinavir, nelfinavir, indinavir, atazanavir, and telithromizycin.

- 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 a short venous catheter inserted into a forearm vein and collected in anticoagulated and serum tubes at each study time point for all PK/PD assessments. The first 2-4 mL of blood will be discarded to avoid spontaneous platelet activation.

Laboratory assessments will include:

1. VerifyNow PRU
2. Light transmittance aggregometry
3. Whole blood vasodilator-stimulated phosphoprotein (VASP)
4. Total Thrombus-Formation Analysis System (T-TAS)
5. PK
6. $P2Y_{12}$ 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 [18, 24-26]. 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) Light transmittance aggregometry (LTA): Platelet aggregation will be performed using LTA according to standard protocols. Blood will be collected in citrated (3.2%) tubes. LTA will be performed using platelet rich plasma (PRP) by the turbidimetric method in a 2-channel aggregometer (Chrono-Log 490 Model, Chrono-Log Corp., Havertown) as previously described [24-26]. Platelet agonists will include collagen (3µg/ml), ADP (20 µM) and TRAP (15 µM). PRP will be obtained as a supernatant after centrifugation of citrated blood at 1000 rpm for 10 minutes. The isolated PRP will be kept at 37° C before use. Platelet poor plasma (PPP) will be obtained by a second centrifugation of the blood fraction at 2800 rpm for 10 minutes. Light transmission will be adjusted to 0% with the PRP and to 100% for the PPP for each measurement. Curves will be recorded for 6 minutes and platelet aggregation will be determined as the maximal percent change (MPA) in light transmittance from baseline using PPP as a reference.

3) 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 [18]. 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.

4) 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) [27]. 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.

4) Pharmacokinetic (PK) assay: Determination of plasma concentration of ticagrelor and its active metabolite (AR-C124910XX) will be assessed from blood samples taken at the same time points of PD analysis as previously described [28]. Blood samples for measurement of drug concentrations will be drawn through the same cannula used for PD sampling. The blood will be taken into lithium heparin tubes and placed on ice until centrifugation (2800 rpm, 4°C, 10 min) within 30 min of sampling to collect the plasma, which will be transferred to plain polypropylene tubes and frozen upright at or below -20°C until analysis. For ticagrelor and its active metabolite, the area under the plasma concentration vs. time curve from time 0 to the last measurable concentration (AUC0-t), maximum plasma concentration (Cmax), and time to Cmax (tmax) will be estimated.

5) $P2Y_{12}$ 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 [29].

In addition to specific assays described above, whole blood, serum and plasma samples will be stored for future analysis that may include genetic determinants of antiplatelet drugs response, alternative mRNAs, and biomarkers.

Study endpoints, sample size calculation and statistical analysis

The primary end point of the study will be the non-inferiority in PRU measured at 2 hours after discontinuation of cangrelor vs. placebo. We hypothesize that in patient receiving

cangrelor following a ticagrelor LD platelet inhibition assessed by PRU will be non-inferior compared to patients receiving ticagrelor LD followed by placebo infusion. 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 75 PRU, a sample size of 16 patients will allow for the 95% CI to stay within ± 45 PRU with a 95% power and alpha=0.05. Considering a 25% data attrition rate due to hemolysis, drop out or technical problems, 20 patients will need to be randomized in order to ensure complete available data for analysis. The sample size of this study was established according to results of previous PD investigations [18,30]. In line with previously reported investigations, 45 PRU was chosen for the noninferiority margin for the upper 95% CI limit of the difference [25, 31]. 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, PRI>50%, and LTA-ADP>59%, in line with consensus definitions [32].

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]. Treatment effects will be evaluated comparing the functional parameters observed in the overall patient population after cangrelor treatment with those achieved after placebo regardless of the sequence. All statistical comparisons of platelet function for the primary end point and exploratory end points with continuous variables will be conducted using a linear mixed-effect model with treatment group, sequence, period, and treatment-group-by-period as fixed effects, patient as a random effect, and baseline value of the corresponding

platelet function test as a covariate. The comparisons of rates of HPR will be conducted using the McNemar test.

Platelet reactivity results will be reported as least-square means (LSM) (95% confidence interval [CI]) for the above detailed analyses. LSM differences in PRU between groups and the corresponding 2-sided 95% CI for the difference will be obtained to assess non-inferiority based on the linear 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 superiority for all the analyses performed. Statistical analysis will be performed using SPSS version 25.0 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 ticagrelor. 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 1-8): we expect to randomize 2-3 subjects monthly and complete enrollment in 8 months (total: 20 subjects

randomized). Months 9 and 10 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 ticagrelor were dyspnea (13.8%), headache (6.5%), cough (4.9%), dizziness (4.5%), nausea (4.3%), and bradycardia (4.4%) principally. Infrequent events included intracranial hemorrhage (0.3%) and severe bradycardia requiring pacemaker insertion (0.9%) [33]. The most important adverse effect associated with the use of ticagrelor is bleeding. The risk of spontaneous bleeding with ticagrelor is 2.8% [32]. However, such bleeding prevalence occurred in the setting of a long-term (12 months) trial, while our study is limited to a single loading dose, thus reducing the risk of any side effect, in particular bleeding complications.

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 [34]. 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. Franchi (Principal Investigator) is a paid consultant for AstraZeneca pharmaceutical the maker of Ticagrelor, which is used in the study. Dr. Angiolillo (Sub-Investigator) is a consultant for Chiesi, the maker of cangrelor, and of AstraZeneca, the maker of ticagrelor

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