1. **Project Title:** Tailoring $P2Y_{12}$ Inhibiting Therapy in Patients requiring Oral Anticoagulation after undergoing Percutaneous Coronary Intervention: The Switching Anti-Platelet and Anti-Coagulant Therapy (SWAP-AC) – 2 Study

2. **Investigators:** Dominick J Angiolillo, MD, PhD, Francesco Franchi, MD, Fabiana Rollini, MD, Andrea Goosen, RN, Latonya Been, AAS

3. **Abstract:** The combination of aspirin plus a $P2Y_{12}$ receptor inhibitor, also known as dual antiplatelet therapy (DAPT), is the cornerstone of treatment for patients with coronary artery disease (CAD) undergoing percutaneous coronary intervention (PCI). However, a considerable number of patients undergoing PCI also have an indication to be on treatment with an oral anticoagulant (OAC). It is estimated that 10-15% of PCI patients also have an indication to be on OAC, raising concerns on their optimal antithrombotic treatment regimen. Studies have consistently shown dropping aspirin and maintaining a $P2Y_{12}$ inhibitor and OAC to be associated with reduces bleeding without any significant increase in ischemic events. Accordingly, current practice recommendations is to limit the use of aspirin to the peri-PCI period and maintain dual therapy with a $P2Y_{12}$ inhibitor and an OAC. Clopidogrel is the $P2Y_{12}$ inhibitor of choice in PCI patients requiring OAC. However, concerns have been raised based on the notion that a considerable number of patients may have inadequate response to clopidogrel, also known as high platelet reactivity (HPR) status, and thus be at risk for thrombotic complications. Although practice recommendations indicate that the use of potent $P2Y_{12}$ inhibitors (i.e., ticagrelor) may be considered in patients at increased thrombotic risk, they do not recommend

routine testing to identify patients with HPR status. Nevertheless, consensus recommendations do indicate that the selective use of tests to define HPR status is a reasonable option in selected cases such as PCI patients requiring OAC. The aim of this study is to assess the pharmacodynamic effects of different $P2Y_{12}$ inhibiting therapy (clopdiogrel vs ticagrelor) in patients at high risk for HPR identified according to the ABCD-GENE score in PCI treated patients also requiring OAC. Up to a total of up to 84 patients are planned to be prospectively enrolled in this investigation which will entail a series of comprehensive pharmacodynamic assessments to reach the study aim. Data will be collected and then entered into a secure database. For the scope of this study, the REDCap system will be used to store study related data, and all patients will be identified using a subject identifier. Telephone numbers, street addresses and email addresses may be used to contact the patient, however this information will not be stored in REDCap.

4. **Background:** The combination of aspirin plus a $P2Y_{12}$ receptor inhibitor, also known as dual antiplatelet therapy (DAPT), is the cornerstone of treatment for patients with coronary artery disease (CAD) undergoing percutaneous coronary intervention (PCI) [1]. However, a considerable number of patients undergoing PCI also have an indication to be on treatment with an oral anticoagulant (OAC) [2-5]. Most of these patients have atrial fibrillation (AF) [2-5]. Importantly, CAD and AF share common risk factors which explains why up to 40% of AF patients also have CAD [2-5]. Other indication to be on OAC include a history of deep venous thrombosis (DVT)/pulmonary embolism (PE), mechanical valves, and left ventricular thrombus [2-5]. It is estimated that 10-15% of PCI patients also have an indication to be on OAC, raising concerns on their optimal antithrombotic treatment regimen [2-5]. In fact, while PCI treated patients require DAPT

for the prevention of arterial thrombotic complications, they must also maintain OAC for cardioembolic protection [2-5]. However, the use of triple antithrombotic therapy (DAPT+OAC) significantly enhances the risk of bleeding complications [2-5]. Importantly, increased bleeding in PCI patients is associated with adverse prognosis, including mortality [6-7]. These observations have set the foundations for a number of studies in PCI patients also requiring OAC assessing antithrombotic treatment regimens associated with reduced bleeding while preserving efficacy [2-5]. Aspirin has been identified as a key contributor to bleeding complications, mostly gastrointestinal [8]. On this background a number of studies have tested withdrawal of aspirin therapy and maintaining alternative antithrombotic agents as a strategy to reduce bleeding [8]. Studies have consistently shown dropping aspirin and maintaining a $P2Y_{12}$ inhibitor and OAC to be associated with reduces bleeding without any significant increase in ischemic events [9-13]. Accordingly, current practice recommendations is to limit the use of aspirin to the peri-PCI period and maintain dual therapy with a $P2Y_{12}$ inhibitor and an OAC [14,15]. Clopidogrel is currently the $P2Y_{12}$ inhibitor of choice in patients undergoing PCI requiring OAC [14,15]. However, concerns have been raised based on the notion that a considerable number of patients may have inadequate response to clopidogrel, also known as high platelet reactivity (HPR) status, and thus be at potential risk for thrombotic complications [16,17]. Although practice recommendations indicate that the use of more potent $P2Y_{12}$ inhibitors (i.e., ticagrelor) may be considered in patients at increased thrombotic risk, they do not recommend routine testing to identify patients with HPR status [14,15]. Nevertheless, consensus recommendations do indicate that the selective use of tests to define HPR status is a reasonable option in selected cases such as

PCI patients requiring OAC [17]. Most recently a scoring system called ABCD-GENE has been developed which allows to readily identify patients with HPR status with high accuracy [18]. In particular, this scoring system integrates clinical (age, body mass index, chronic kidney disease, and diabetes mellitus) and genetic (CYP2C19 alleles) variables. Patients with a high ABCD-GENE score (≥10) have an increased risk of HPR and adverse ischemic events [18]. However, data on the impact on platelet inhibitory effects associated with tailored selection of $P2Y_{12}$ inhibiting agents in this setting remains unexplored.

5. **Specific Aims:** The aim of the Switching Anti-Platelet and Anti-Coagulant Therapy (SWAP-AC) – 2 Study is to assess the pharmacodynamic effects of different $P2Y_{12}$ inhibiting therapy (clopdiogrel vs ticagrelor) according to the ABCD-GENE score in PCI treated patients also requiring OAC.

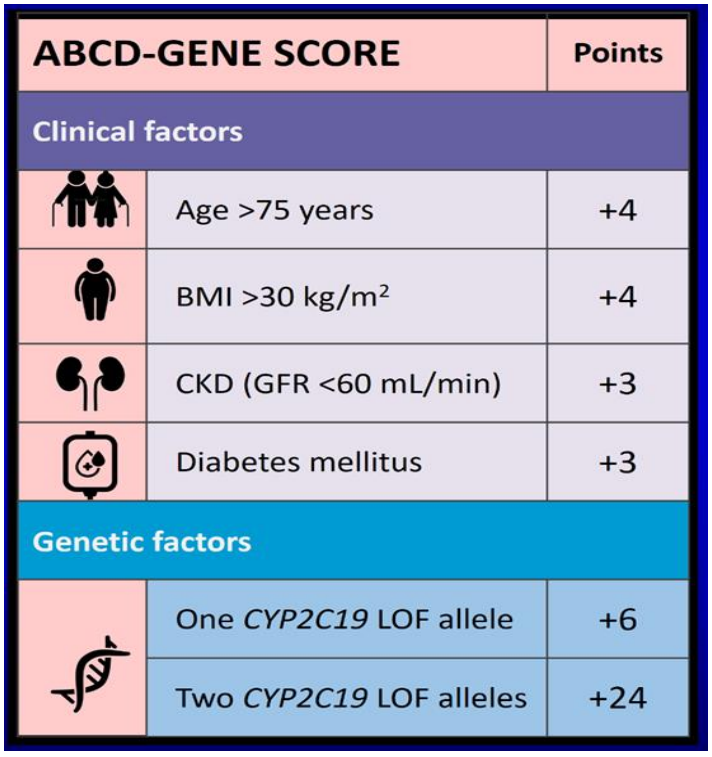
6. **Research Plan:**

Study design

This will be a prospective study conducted in any patients with CAD, including those with Acute Coronary Syndrome (ACS) undergoing PCI who have an indication to be treated with an OAC. Patients undergoing PCI treated with DAPT during the peri-PCI period and also require OAC as part of their standard of care will be identified. The study will be performed at the Division of Cardiology of University of Florida Health, Jacksonville, Florida (site PI: Dominick Angiolillo, MD, PhD) and at St. Antonius Hospital in Nieuwegein, The Netherlands (site PI: Jurrien M. ten Berg, MD, PhD).

Patients will be recruited within the Cardiovascular services of each Institution. Patients will be screened by Cardiology Research staff, who will verify that all candidates meet inclusion and exclusion criteria. After providing written informed consent, patients will be stratified according to their ABCD-GENE score (using a cut-off of 10) into two cohorts: ABCD-GENE≥10 and ABCD-GENE< 10. The ABCD-GENE scoring system is described in Figure 1.

Figure 1. ABCD-GENE score



Patients will be screened during hospital stay after undergoing successful PCI. Results from blood tests performed within the last 30 days will be considered valid for screening. Patients will undergo genetic testing to identify CYP2C19 genetic status using the Spartan assay or central lab. Randomization will occur once genetic testing results become available, ideally prior to hospital discharge. However, for patients discharged

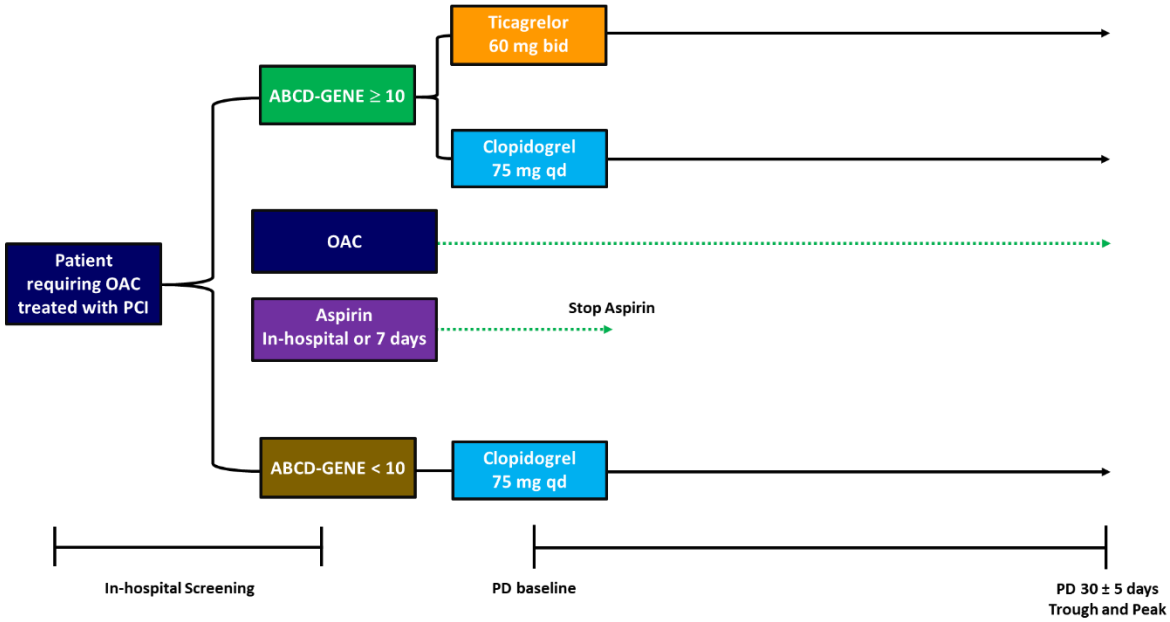
before having results available or over the weekend they will be allowed to return for their randomization within 3 days from test results. Patients with an ABCD-GENE≥10 score will be randomized in a 1:1 fashion to ticagrelor (60 mg/bid) or clopidogrel (75 mg/qd). Patients with an ABCD-GENE<10 will be treated with clopidogrel (75 mg/qd).

Since the choice of $P2Y_{12}$ inhibitor during the PCI procedure may vary (commercially available agents include clopidogrel, ticagrelor and prasugrel), the following recommendations will be made based on the agent chosen and the treatment assignment: a) patients assigned to clopidogrel and also treated with clopidogrel during PCI will continue with a 75 mg/qd maintenance dose for the duration of the study; b) patients assigned to clopidogrel but treated with ticagrelor or prasugrel during PCI will receive a 600 mg loading dose clopidogrel followed by a 75 mg/qd maintenance dose for the duration of the study; c) patients assigned to ticagrelor and also treated with ticagrelor during PCI will continue with ticagrelor 60 mg bid maintenance dose for the duration of the study; d) patients assigned to ticagrelor but treated with clopidogrel or prasugrel during PCI will be administered a 180 mg loading dose followed by a 60 mg bid for the duration of the study. Administration of randomized treatment will occur prior to hospital discharge as would occur per standard of care for administration of the next dose of $P2Y_{12}$ inhibiting therapy. The use of a loading dose when switching agent is in line with consensus recommendations for switching $P2Y_{12}$ inhibiting therapy [19]. The clopidogrel 600mg loading dose and 75 mg/qd maintenance dose regimen is in line with practice recommendations [1]. The ticagrelor 180 mg loading dose regimen is in line with practice guidelines; the 60 mg bid maintenance dose regimen was chosen in light of recent data that this dose provides platelet inhibitory effects not dissimilar from the 90 mg bid dosing

regimen but with less side effects and more efficacious platelet inhibitory effects than clopidogrel, including after PCI [1,20]. All patients will maintain aspirin 81 mg /qd at least for the duration of hospital stay. Aspirin therapy will be discontinued at time of hospital discharge or at 7 days after PCI at the discretion of the treating physician in patients deemed to be at high ischemic risk, as per standard of care for patients requiring concomitant treatment with a $P2Y_{12}$ inhibitor and an OAC [14,15].

Assigned treatment will be maintained for 30±5 days. PD assessments will be conducted at 3 time points: i) baseline (while on standard of care DAPT therapy): day after PCI, ideally before the administration of the morning dose of $P2Y_{12}$ inhibiting therapy and OAC (trough levels of platelet reactivity); however, since patients may get discharged the same day of the PCI or may have already taken their daily dosing regimen, blood sampling will be allowed as this does not interfere with the study hypothesis; patients will continue to take their morning dose of aspirin and all other standard of care therapies; ii) 30±5 days after randomization: before (trough levels of platelet reactivity) and 2 hours after (trough levels of platelet reactivity) the administration of the morning doses of $P2Y_{12}$ inhibiting therapy and OAC (trough levels of platelet reactivity); patients will take all other standard of care therapies. Figure 2 illustrates the overall study design and a further breakdown of what will occur during the course of the study:

Figure 2. SWAP-AC-2 study design



- Patients will first be screened by research personnel to see if they are eligible for the study. Results from blood tests performed within the last 30 days which patients would have performed because of their stent procedure will be considered valid for screening purposes.
- If it is a woman of childbearing potential, a pregnancy test will be done. If the subject is found to be pregnant, their participation in this study will end.
- If they are eligible for the study based on the screening results, they will start the study procedures as outlined below:
    - Genetic test buccal swab. This swab is being done to determine CYP2C19 genetic status.
    - The physician will determine the ABCD-GENE score as described in Figure 1. This score is calculated by looking at the subject's CYP2C19 genetic

status and clinical information, including age, BMI, renal function, and diabetic status.

Patients with an ABCD-GENE<10 will be treated with clopidogrel (75 mg/qd). Patients with an ABCD-GENE≥10 score will be randomized in a 1:1 fashion to ticagrelor (60 mg/bid) or clopidogrel (75 mg/qd). Assigned treatment will be maintained for 30 +/- 5 days.

- Blood will be collected at two visits by inserting a needle into a vein or from a catheter in a vein. The first visit will be after the PCI ideally before the subject has taken their antithrombotic medications (baseline); however, since patients may get discharged the same day of the PCI or may have already taken their daily dosing regimen, blood sampling will be allowed as this does not interfere with the study hypothesis. The second visit will be 30 +/- 5 days later. At this visit there will be two blood draws: the first before the subject has taken their antithrombotic medication (trough) and second 2 hours after the subject has taken their antithrombotic medication (peak).

PD measures will include a multitude of assays aimed to assess various measures of platelet reactivity, including purinergic and non-purinergic signaling pathways, and thrombin generation, as described below. Although the study will have an open-label design, laboratory personnel will be blinded to treatment assignments. Compliance with antithrombotic therapies will be assessed by interview and pill counting. During study treatment, 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 will be collected. After completing the study, patients will resume an antithrombotic treatment regimen at the discretion of the treating physician.

Study population

A total of 84 CAD patients will be recruited In particular, 42 patients with an ABCD-GENE≥10 will be included and randomized to ticagrelor (n=20) or clopidogrel (n=20), while 42 patients will be in the ABCD-GENE<10 cohort. Patients will need to meet the following study entry criteria:

Inclusion criteria:

- Age ≥ 18 years
- Willing and able to provide written informed consent
- Undergone successful PCI and treated with DAPT (aspirin plus a P2Y12 inhibitor) per standard of care
- On treatment with a novel oral anticoagulant (apixaban, dabigatran, edoxaban, or rivaroxaban) for any indication (dosing regimen will be according to standard of care and at the discretion of the treating physician)

Exclusion criteria:

- Any active bleeding or history of major bleeding
- Ischemic Stroke within 1 month
- Any history of hemorrhagic stroke, or intracranial hemorrhage
- Known non-cardiovascular disease that is associated with poor prognosis (e.g., metastatic cancer) or that increases the risk of an adverse reaction to study interventions.
- End-stage renal disease on hemodialysis

- Known severe liver dysfunction or any known hepatic disease associated with coagulopathy
- History of hypersensitivity or known contraindication to clopidogrel or ticagrelor.
- Systemic treatment with strong inhibitors of both CYP 3A4 and p-glycoprotein (e.g., systemic azole antimycotics, such as ketoconazole, and human immunodeficiency virus [HIV]-protease inhibitors, such as ritonavir), or strong inducers of CYP 3A4, i.e. rifampicin, rifabutin, phenobarbital, phenytoin, and carbamazepine
- Subjects who are pregnant, breastfeeding, or are of childbearing potential, and sexually active and not practicing an effective method of birth control (e.g. surgically sterile, prescription oral contraceptives, contraceptive injections, intrauterine device, double barrier method, contraceptive patch, male partner sterilization)
- Concomitant participation in another study with investigational drug
- Hemoglobin ≤9 mg/dL
- Platelet count $<80x10^6$/mL

Genetic Testing

Spartan RX point-of-care rapid genotyping: Spartan RX (Spartan Bioscience Inc., Ontario, Canada) is a point-of-care determining the CYP2C19 (*1,*2,*3,*17) allele status within 1 hour [21,22]. This test consists of four separate steps intended to be done in less than 8 minutes: acquisition of a buccal swab; insertion of the swab into the cartridge; insertion of the reaction solution into the device; and analysis of CYP2C19 genotype triggered by a button on the device. Patients are classified as having or not having a loss of function (LOF) allele status. In particular, patients may be carriers of one (heterozygotes) or two (homozygotes) LOF alleles (*2 or *3) which can be summarized as follows: heterozygotes (*1/*2, *1/*3, *2/*17, *3/*17) or homozygotes (*2/*2, *3/*3 or *2/*3).

Patients without a *2 or *3 LOF (*1/*1, *1/*17 or *17/*17) are defined as non-carriers of LOF alleles [21,22].

Laboratory assessments

Peripheral venous blood samples will be drawn through a short venous catheter inserted into a forearm vein and collected in citrate, EDTA, and serum tubes as appropriate for assessments. The first 2-4 mL of blood will be discarded to avoid spontaneous platelet activation. Blood sampling for PD will be performed at 3 time points as described above and shown in the study design section. The following tests will be performed to explore the pharmacodynamic effects of the tested strategies.

1. VerifyNow PRU
2. Light Transmittance Aggregometry (LTA)
3. Whole blood vasodilator-stimulated phosphoprotein (VASP)
4. Thrombus Formation Assay (Turbidimetric assay)
5. Total Thrombus-Formation Analysis System (T-TAS)

Laboratory assessments including VerifyNow PRU and LTA will be performed within 2 hours of sample collection. VASP and thrombus generation assessments will be performed on stored samples as final batch analysis. Samples will be stored under required refrigerated conditions at the Cardiovascular Research Center of the University of Florida-Jacksonville. Only laboratory staff will have access to the samples. Subject identity will be protected. In particular, samples will be de-identified and data coded. This information will be stored in locked filing cabinets or in computers with security passwords. All laboratory assessments with the exception of thrombin generation measures will be performed at the Cardiovascular Research Center of the University of

Florida-Jacksonville. Thrombus generation assessments will be performed at central core lab (Leeds Institute of Cardiovascular and Metabolic Medicine, University of Leeds, Leeds, UK).

Description of laboratory assays

1) VerifyNow (VN) PRU: The VN 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 [23-25]. The assay is based on microbead agglutination and uses specific reagents for the pathways of interest. The VN-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. 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). HPR is defined by PRU >208 [17].

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 assessed using platelet-rich plasma (PRP) by the turbidimetric method in a 2-channel aggregometer (Chrono-Log 490 Model, Chrono-Log Corp., Havertown) [23-25]. Platelet agonists will include arachidonic acid (AA; 1 mM), collagen (3μg/ml), thrombin receptor activating peptide (TRAP;15 μM) and ADP (20 μM). LTA following 2 μg/ml collagen-related peptide + 5 μM ADP + 15 μM TRAP

(CAT) will also be used as agonist to assess the overall platelet-mediated thrombogenicity. 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 min. 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. HPR will be defined as MPA with 20 μM ADP > 59% [17].

3) VASP: VASP phosphorylation (VASP-P) is a marker of $P2Y_{12}$ receptor signaling. VASP will be assessed the ELISA VASP-P kit (Biocytex Inc., Marseille, France) as previously described [25]. 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 $P2Y_{12}$ leads to Gi-coupled inhibition of adenylate cyclase. Therefore, the addition of ADP to PGE1-stimulated platelets reduces PGE1-induced VASP-P levels. If $P2Y_{12}$ 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. HPR is defined by a PRI >50 [17].

4) Thrombus Formation Assay: A validated turbidimetric assay will be used to study fibrin clot formation, structure and lysis, as previously described [26]. Clot formation will be activated with thrombin (0.03u/ml) or tissue factor (10pM) after recalcification of citrated samples and the following parameters evaluated: 1) lag phase (seconds): time from start of reaction to beginning of clot formation, 2) clot formation time (seconds), representing the period from start of reaction to full clot formation, 3) clot final turbidity (maximum absorbance, measured in absorbance units), which is a measure of fibrin network density and 4) clot lysis time (seconds), assessed as time from full clot formation to 50% lysis, which is used to evaluate fibrinolysis potential [26].

5) 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/AR-chips (Diapharma, West Chester Township, OH) [17-18]. The PL/AR-chips 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/AR-chips, a blood sample collected in a hirudin and sodium citrate 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/AR-

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

Study endpoints, sample size calculation and statistical analysis

The primary end point of our study will be levels of platelet reactivity, measured as PRU using the VN system, of ticagrelor versus clopidogrel at 30 days after randomization in patients with an ABCD-Gene score ≥10. We hypothesize that ticagrelor 60 mg bid will lead to lower PRU compared with clopidogrel 75 mg qd. Based on previous studies [20], assuming a standard deviation of 55 and 80 PRU for ticagrelor and clopidogrel, respectively, a sample size of 17 patients per treatment group with valid primary end point data will be required to detect an absolute difference of 90 PRU between ticagrelor and clopidogrel with a 90% power and a 2-tailed alpha value of 0.05. Assuming a potential 25% in data attrition due to patient drop-out (e.g., due to side effects, unplanned use of parenteral antiplatelet therapies after randomization or withdrawal of consent) or invalid PD samples (e.g., due to hemolysis or technical reasons), a sample size of up to 21 patients per randomized group; 42 total will be randomized and an additional 42 in the control group. Thus, considering the 3 treatment arms, a total of up to 84 patients are expected to be enrolled to reach the sample size of patients with valid primary end point data required for the primary end point.

Additional exploratory end points will include the comparisons between clopidogrel-treated patients with ABCD-Gene score<10 and the other 2 arms, as well as comparisons between groups of rates of HPR. For baseline characteristics, categorical variables will be expressed as frequencies and percentages; continuous variables will be

presented as mean ± SD or median [IQR]. Continuous variables will be analyzed for normal distribution with the Kolmogorov-Smirnov test. Comparisons for the primary end point as well as for other intergroup comparisons of continuous variables will be performed with an analysis of covariance with a general linear model with baseline value of the corresponding platelet function test as a covariate. Intragroup comparisons will be performed using a mixed linear model. Comparisons for categorical variables, including rates of HPR will be performed with the Chi square test or Fisher exact test. A p-value < 0.05 will be considered statistically significant. Statistical analysis will be performed with SPSS version 25 software (SPSS Inc.). Data analysis will be performed at the University of Florida. Data transfer will occur in a HIPAA de-identified manner. Data from The Netherlands will arrive coded so that source of data can be easily known."

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

All patients who received at least 1 dose of study drug will be included in the safety population. Safety will be evaluated by assessment of adverse events (including bleeding and ischemic). Adverse events will be collected up to completion of the study. Bleeding events will be classified according to BARC (Bleeding Academic Research Consortium) criteria [27]. Stent thrombosis will be classified according to ARC (Academic Research Consortium) definitions [28]. MI, including peri-procedural MI, will be defined according to the universal definition [29]. Ischemic stroke will be defined as

an ischemic cerebral infarction caused by an embolic or thrombotic occlusion of a major intracranial artery. Death will be considered cardiac in origin unless obvious non-cardiac causes can be identified.

7. Possible Discomforts and Risks

In clinical trials, the most important adverse effect associated with the use of ticagrelor 60 mg was bleeding. The risk of major bleeding with ticagrelor 60 mg was 2.3%; the combined risk of intracranial hemorrhage or fatal bleeding was 0.7% [30]. However, such bleeding prevalence occurred in the setting of long-term trial (median follow-up of 33 months) with bleeding events that accrued over time, while our study is limited to only 30 ± 3 days of therapy. Moreover, these bleeding rates occurred versus placebo, while in our investigation which is being conducted in patients undergoing PCI which mandates the use of a P2Y12 inhibitor per standard of care. Ticagrelor will be compared with clopidogrel, which is also associated with an increased risk of bleeding compared with placebo [31]. However, the rates of bleeding are lower with clopidogrel than with ticagrelor [32]. Dyspnea has been reported as the main non-bleeding side effect with ticagrelor and occurs in up to 15.8% of patients [30]. Dyspnea has been associated with drug discontinuation in 4.6% of patients [30]. Below is a complete lists of potential medication risks:

- Bleeding
- Dyspnea (shortness of breath)
- Headache
- Cough

- Atrial fibrillation
- Mild to moderate diarrhea
- Nausea
- Hypotension (low blood pressure)
- Hypertension
- Dizziness
- Non-cardiac chest pain
- Back Pain
- Fatigue
- Cardiac (heart) chest pain

Patients who discontinue ticagrelor therapy will be switched to clopidogrel. Ultimately, although a 60 mg dosing regimen has not been specifically tested in patients undergoing PCI treated with an OAC, this dosing regimen has shown to be associated with more potent antiplatelet effects than clopidogrel and has not been associated with any increase in thrombotic complications in elective PCI patients conducted in an unselected cohort of subjects [20]. Overall, these considerations limit any safety concerns associated with the conduct of this study.

The risks of the blood draw may include faintness, inflammation of the vein, pain, bruising or bleeding at the site of the puncture.There is also a slight risk of infection from the blood draw.

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. Clinical events will be evaluated by a local data safety monitoring board (DSMB) 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 (as defined below) the DSMB will meet and antiplatelet treatment management will be managed, including stopping if of clinical concern, according to physician recommendation.

8. Possible benefits

The present investigation is aimed to evaluate the PD effects of ticagrelor 60 mg bid compared with a standard dosing regimen of clopidogrel in PCI patients requiring OAC presenting with an ABCD-GENE score ≥10. This study is not designed to evaluate differences in clinical benefit. However, differences in antiplatelet profiles may potentially prompt further investigations of the clinical implication of this difference by means of a larger scale clinical study.

9. Conflict of Interest

Dr. Angiolillo is a consultant for Sanofi, the maker of clopidogrel (Plavix) and Astra Zeneca, the makers of ticagrelor (Brilinta). Dr. Franchi is a consultant for Sanofi, the maker of clopidogrel (Plavix) and Astra Zeneca, the maker of ticagrelor (Brilinta).

10. Publication Strategy/Additional Information

Study subjects will be identified first (months 1-21): we expect to enroll approximately 4 subjects monthly and complete enrollment in 21 months (total: 84

subjects enrolled). Months 22-24 will be implied for completion of follow-up, statistical analysis and abstract or manuscript preparation. We intend to present data at a major scientific meeting at completion of the study. We anticipate no major problems with the described protocol since the approach is a straightforward prospective study and is based on well-established methods.

11. Potential Financial Risks or Benefits

None

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Abbreviation List (alphabetical order)

AA: arachidonic acid

ADP: adenosine diphosphate

BARC: Bleeding Academic Research Consortium

CAD: coronary artery disease

CAT: Collagen, Adenosine Diphosphate, Thrombin receptor activator for peptide 6

DAPT: dual antiplatelet therapy

HPR: high platelet reactivity

LOF: loss of function

LTA: light transmittance aggregometry

MPA: maximal percent change

PCI: percutaneous coronary intervention

PD: pharmacodynamics

PGE1: Prostaglandin E1

PPP: platelet-poor plasma

PRU: $P2Y_{12}$ Reaction Units

TMB: 3,3',5,5'-tetramethylbenzidine

TRAP: thrombin receptor activating peptide

VASP: vasodilator-stimulated phosphoprotein

VN: VerifyNow