Project Title: Pharmacodynamic Effects of Different Ticagrelor Maintenance Dosing Regimens With and Without Aspirin in Patients with Diabetes Mellitus: The OPTIMUS (Optimizing Antiplatelet Therapy in Diabetes Mellitus)-7 Study

1. **Investigators:** Dominick J Angiolillo, MD, PhD, Francesco Franchi, MD, Fabiana Rollini, MD, J. Hope Dover, RN, Latonya Been, AAS

2. **Abstract:** Dual antiplatelet therapy (DAPT) with aspirin and a $P2Y_{12}$ inhibitor is the standard of care for the prevention of thrombotic complications in patients with coronary artery disease (CAD) undergoing percutaneous coronary interventions (PCI). However, such ischemic benefit occurs at the expense of enhanced bleeding, the risk of which increases in a graded fashion with prolonged exposure to DAPT. Recent studies have shown that withdrawing aspirin and maintaining $P2Y_{12}$ inhibitor monotherapy for up to 12 months post-PCI, after a brief period of DAPT, reduces bleeding without increasing ischemic harm. Such effects have shown to of particular benefit in patients with diabetes mellitus (DM). However, if an aspirin-free approach can be considered after this time frame is a matter of debate. In fact, current guidelines recommend maintaining $P2Y_{12}$ inhibiting therapy for high risk patients but which all imply background use of aspirin. $P2Y_{12}$ inhibitors for long-term (beyond 12 months) secondary prevention mainly include clopidogrel and ticagrelor. In particular, the dosing regimen for clopidogrel remains the standard 75 mg qd, whereas ticagrelor dosing is recommended to be reduced from 90 mg bid to 60 mg bid. However, of these regimens the pharmacodynamics (PD) effects of ticagrelor 60 mg in the absence of aspirin has not yet been tested. Because DM patients are likely to continue with long-term

$P2Y_{12}$ inhibitor therapy, defining the optimal antithrombotic approach for these patients is of critical importance. In light of the above made observations, patients with DM represent an ideal population to define the antiplatelet effects of a ticagrelor 60 mg monotherapy regimen. The aim of this study is to assess the PD effects of ticagrelor 60 mg with and without aspirin therapy in CAD patients and to compare this with a standard DAPT regimen of aspirin plus clopidogrel. 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.

3. Background and Significance:

Dual antiplatelet therapy (DAPT) with aspirin and a $P2Y_{12}$ inhibitor is the standard of care for the prevention of thrombotic complications in patients with coronary artery disease (CAD) undergoing percutaneous coronary interventions (PCI) [1]. However, such ischemic benefit occurs at the expense of enhanced bleeding, the risk of which increases in a graded fashion with prolonged exposure to DAPT [1,2]. In light of the adverse prognosis associated with bleeding, there has been much attention toward identifying antithrombotic regimens that can reduce the risk of bleeding while maintaining efficacy post-PCI [3,4]. Among these, maintaining $P2Y_{12}$ inhibitor monotherapy, after a brief period of DAPT, has emerged as a promising bleeding reduction strategy in a number of investigations [5]. Such aspirin-free approach has been postulated based on pharmacodynamic investigations demonstrating that, on background of potent $P2Y_{12}$ inhibiting therapy, including ticagrelor, aspirin offers limited

antiplatelet effect and may therefore mainly contribute to bleeding potential [5]. Recently, the Ticagrelor With Aspirin or Alone in High-Risk Patients after Coronary Intervention (TWILIGHT) trial showed that among high-risk PCI patients, after 3 months of DAPT, $P2Y_{12}$ inhibitor monotherapy with ticagrelor 90 mg bid (without aspirin) reduced bleeding without increasing ischemic harm after 12 months of therapy compared with ticagrelor 90 mg bid used in adjunct to aspirin [6].

Although the TWILIGHT trial provides important insights on the benefits of an aspirin-free approach within the first year after undergoing PCI, it does not address how to manage patients after this time frame. Current guidelines recommend maintaining $P2Y_{12}$ inhibiting therapy for high risk patients but which all imply background use of aspirin [1]. $P2Y_{12}$ inhibitors for long-term (beyond 12 months) secondary prevention mainly include clopidogrel and ticagrelor [1]. In particular, the dosing regimen for clopidogrel remains the standard 75 mg qd, whereas ticagrelor dosing is recommended to be reduced from 90 mg bid to 60 mg bid [1]. In light of the improved outcomes associated with a ticagrelor 90 mg bid regimen without aspirin during the first year after PCI demonstrated in the TWILIGHT trial, understanding the differential effects of different antiplatelet combinations, in particular the effects of long-term ticagrelor at a 60 mg bid regimen without aspirin, is of utmost clinical interest. Importantly, pharmacodynamic (PD) studies have shown that the 90 and 60 mg ticagrelor regimens provide similar platelet inhibitory effects [7-9]. However, the 60 mg regimen has been associated with an overall more favorable safety profile which is the rationale for it being recommended for long-term secondary prevention in patients with CAD, irrespective of whether they underwent PCI [10]. However, the PD effects of ticagrelor 60 mg in the absence of aspirin have not yet been tested.

Patients with diabetes mellitus (DM) are known to be at high-risk for both ischemic and bleeding complications post-PCI [11,12]. A number of factors which commonly affect patients with DM contribute to these observations, including the complexity of coronary interventions, endothelial dysfunction, concomitant comorbidities, and dysregulation of hemostatic and thrombotic processes [11,12]. Importantly, the prevalence of DM (mostly type 2) in the past decade has increased by 30% globally, an observation also reflected in PCI trials wherein DM is a more frequently encountered risk factor, and is projected to markedly increase in the upcoming decades [13]. These observations highlight the importance of defining optimal post-PCI pharmacotherapy in patients with DM. Of note, a pre-defined subgroup analysis of the TWILIGHT trial showed that among patients with DM patients undergoing PCI, ticagrelor monotherapy significantly reduced clinically relevant bleeding compared with ticagrelor plus aspirin, without increasing the risk of ischemic events [14]. In particular, the reduction in net adverse cardiac events in DM patients treated with a ticagrelor monotherapy strategy was markedly greater than that observed in non-DM patients [14]. While the potent level of $P2Y_{12}$ blockade achieved with ticagrelor limits the adjunctive benefits associated with aspirin therapy, the synergism on platelet inhibitory effects with the use aspirin in the presence of more modest levels of $P2Y_{12}$ blockade induced by clopidogrel may be more relevant particularly in patients with DM [15]. Because DM patients are likely to continue with more potent antithrombotic treatment regimens for long-term secondary prevention beyond 12 months [1,16], defining the optimal antithrombotic approach for these patients is of critical importance. In light of the above made observations, patients with DM represent an ideal population to define the antiplatelet effects of a ticagrelor 60 mg monotherapy regimen.

4. Specific Aims:

The aim of this study is to assess the PD effects of ticagrelor 60 mg with and without aspirin therapy in CAD patients and to compare this with a standard DAPT regimen of aspirin plus clopidogrel. We hypothesize that withdrawal of aspirin therapy among ticagrelor treated patients will not result in significant changes in ADP-induced platelet reactivity and will provide more effective platelet inhibition compared with aspirin plus clopidogrel. The results of the study will allow defining the best antiplatelet strategy when transitioning patients to long-term antiplatelet treatment.

5. Research Plan:

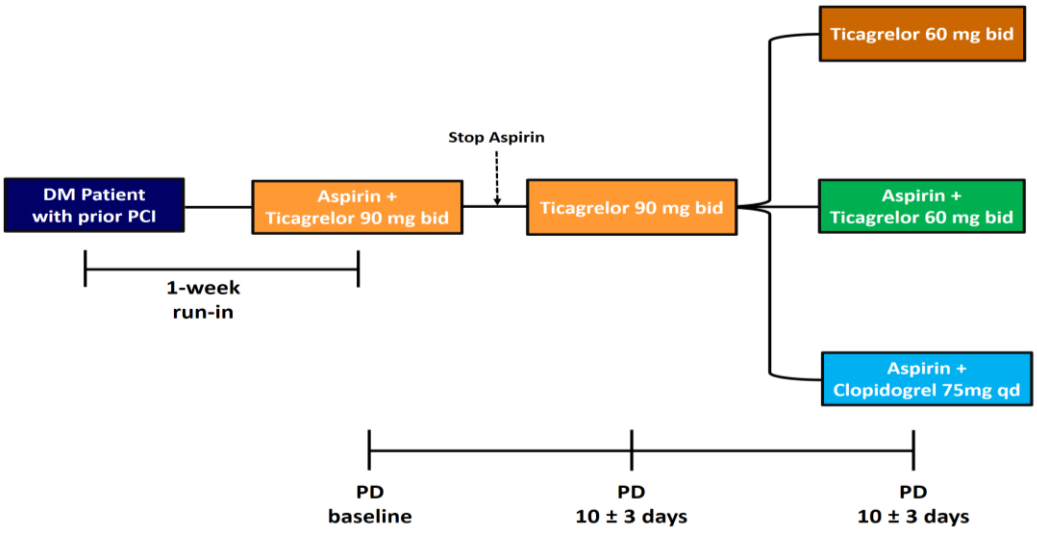
Research Design

This will be a prospective, randomized, open-label study conducted in patients with CAD and diagnosis of DM. Patients can be on any background antiplatelet therapy, including aspirin or any $P2Y_{12}$ inhibitor (clopidogrel, ticagrelor or prasugrel). The study will be performed at the Division of Cardiology of University of Florida Health, Jacksonville, Florida and patients will be recruited within the Cardiovascular services of our Institution. Patients will be screened by Cardiology Research staff, who will verify that all candidates meet inclusion and exclusion criteria. 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 the patient has signed informed consent.

Eligible patients will enter a 7-10 day run-in phase with aspirin 81 mg/ qd plus ticagrelor 90 mg bid after which they will discontinue aspirin and maintain ticagrelor 90 mg bid

monotherapy for 10±3 days. After this period, patients will be randomized using a randomly generated computer sequence in a 1:1:1 fashion to one of three treatment groups: a) ticagrelor 60 mg bid monotherapy; b) aspirin 81 mg qd plus ticagrelor 60 mg bid; c) aspirin 81 mg qd plus clopidogrel 75 mg qd. Randomized treatment will be maintained for 10±3 days. The approach of having a run-in phase with aspirin plus ticagrelor 90 mg followed by ticagrelor 90 mg monotherapy is in line with the TWILIGHT trial to assess for tolerability and compliance with ticagrelor therapy [6, 17]. The approach of having an aspirin plus ticagrelor 60 mg regimen as well as an aspirin plus clopidogrel regimen is reflective of guideline recommendations for long-term secondary prevention [1,16]. The current investigation will test the hypothesis that the experimental strategy of ticagrelor 60 mg monotherapy will not result in significant changes in $P2Y_{12}$ inhibitory effects compared with aspirin plus ticagrelor 60 mg and will provide more effective platelet inhibition compared with aspirin plus clopidogrel. The study design is illustrated in Figure 1 and a further breakdown of what will occur during the course of the study:

Figure 1. OPTIMUS-7 study design.



- Potential subjects will first be screened by research personnel to see if they are eligible for the study. Results from blood tests performed within the last 90 days which they would have performed as part of their standard of care will be considered valid for screening purposes.
- If the potential subject is a woman of childbearing potential, a pregnancy test will be done. If subject is found to be pregnant, the participation in this study will end.
- If subject is eligible for the study based on the screening results, the subject will start the study procedures as outlined below:
    - Every participant will start a so called run-in phase during and will be treated with aspirin 81mg once a day, and Ticagrelor 90mg twice a day for 7-10 days. After that, the participant will stop taking the aspirin and only take the Ticagrelor 90mg for 10±3 days. This run-in phase is to make sure that subjects are able to take the medication without side effects.

- After completing the run-in part of the study, subjects will be randomized to one of three medication groups and take study medication for 10 ± 3 days:
    a) Ticagrelor 60mg twice daily (without aspirin)
    b) Ticagrelor 60mg twice daily, plus aspirin 81mg once daily
    c) Clopidogrel 75mg once daily, plus aspirin 81mg once daily

Blood sampling for PD testing will be performed at 4 time points: a) after completing 1-week aspirin plus ticagrelor 90 mg run-in phase; b) after completing 10±3 days of treatment with ticagrelor 90 mg monotherapy; c) after completing 10±3 days of randomized treatment. At each time point PD assessments will be performed 12 ± 2 hours after last ticagrelor dose and 24 hours after last clopidogrel dose in order to define trough levels of platelet inhibition. At the last time point (after 10±3 days of randomized treatment) blood samples will also be collected 2 hours after administration of the antiplatelet regimen in order to assess for peak levels of platelet inhibition. The Ticagrelor (Brilinta) tablets are being provided by AstraZeneca. The Clopidogrel and aspirin will be provided by the Cardiovascular Research Department. All medications will dispensed by the Cardiovascular Research Department and will be packaged using supplies and guidelines provided by UF Health Research Pharmacy.

Study Population

Inclusion criteria:

For inclusion in the study patients should fulfill the following criteria:

1. Provision of informed consent prior to any study specific procedures
2. Men or women ≥18 years of age

3. Diagnosed with type 2 DM defined by ongoing glucose lowering therapy (oral medications and/or insulin) treatment for at least 1 month

4. Known angiographically defined CAD (including a history of previous PCI, CABG, or >50% stenosis in a major epicardial vessel) on standard of care antiplatelet therapy*

*Patients can be treated with any background antiplatelet treatment regimen as part of their standard of care, including aspirin and/or any $P2Y_{12}$ inhibitor (clopidogrel, ticagrelor, prasugrel).

Exclusion criteria:

1. PCI < 6 months prior
2. Recent (< 6 months) type I myocardial infarction
3. Anticipated concomitant oral or intravenous therapy with strong cytochrome P450 3A4 (CYP3A4) inhibitors or CYP3A4 substrates with narrow therapeutic indices that cannot be stopped for the course of the study:
    - Strong inhibitors: ketoconazole, itraconazole, voriconazole, telithromycin, clarithromycin (but not erythromycin or azithromycin), nefazadone, ritonavir, saquinavir, nelfinavir, indinavir, atanazavir
    - CYP3A4 substrates with narrow therapeutic index: quinidine, simvastatin at doses >40 mg daily or lovastatin at doses >40 mg daily
4. Anticipated concomitant oral or intravenous therapry of strong CYP3A inducers (phenytoin, rifampin, phenobarb, carbamazepine)
5. Need for chronic oral anticoagulant therapy or chronic low-molecular-weight heparin (at venous thrombosis treatment not prophylaxis doses)
6. Patients with known bleeding diathesis or coagulation disorder

7. History of previous intracerebral bleed at any time, gastrointestinal (GI) bleed within the past 6 months prior to randomization, or major surgery within 30 days prior to randomization
8. Active pathological bleeding
9. Hypersensitivity to aspirin, ticagrelor or clopidogrel
10. Increased risk of bradycardic events (eg, known sick sinus syndrome, second or third degree AV block or previous documented syncope suspected to be due to bradycardia) unless treated with a pacemaker
11. Known severe liver disease
12. Renal failure requiring dialysis
13. Known platelet count $<80x10^6$/mL
14. Known hemoglobin <9 g/dL
15. Pregnant or breastfeeding women.

*Women of childbearing age must use reliable birth control (i.e. oral contraceptives) while participating in the study.

Laboratory assessments

Laboratory assessments will be the same for all time points and will include:

1. VerifyNow PRU assay
2. Whole blood vasodilator-stimulated phosphoprotein (VASP)
3. Light transmittance aggregometry (LTA)
4. Serum thromboxane B2
5. Total Thrombus-Formation Analysis System (T-TAS)

Blood sampling: Peripheral venous 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 PD assessments. The first 2-4 mL of blood will be discarded to avoid spontaneous platelet activation.

Description of laboratory assays

1) VerifyNow PRU assay: 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 [15]. The assay is based on microbead agglutination and uses specific reagents for the pathways of interest. 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 [15]. 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) Light transmittance aggregometry (LTA): Platelet aggregation will be performed using LTA according to standard protocols. Blood will be collected in citrated (3.8%) 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) as previously described [15]. Platelet agonists will include ADP (20 µM), arachidonic acid (1 mM), collagen (3µg/ml), TRAP (15 µM), and a combination of 2 µg/ml collagen-related peptide + 5 µM ADP + 15 µM TRAP (CAT). The reagent cocktail CAT will allow to assess the overall platelet response to a combination of agonists that leads to activation of multiple platelet pathways (platelet-mediated global 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 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.

4) *Serum thromboxane B2*: The concentration of serum thromboxane B2 (TXB2) will be measured by using the TXB2 EIA kit (Cayman Chemical Company, Ann Arbor, MI), as previously described [15]. Briefly, samples will be diluted with EIA buffer to bring their concentrations within the range of the standard curve. A standard curve will be established by

serial dilution of TXB2 between 1000 pg/mL and 7.8 pg/mL using EIA buffer as the matrix. The concentration of TXB2 in the samples will be calculated from a logistic 4-parameter fit of the standard concentrations versus percentage bound/maximum bound.

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-chip (Diapharma, West Chester Township, OH) [18]. 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.

Study endpoints, sample size calculation and statistical analysis

The primary end-point of the study is the comparison of the PRU determined by VerifyNow PRU between between aspirin plus ticagrelor 60 mg and ticagrelor 60 mg monotherapy at 10 ± 3 days (trough effect). We hypothesize that ticagrelor monotherapy will be non-inferior to aspirin plus ticagrelor. Under the assumption of 0 difference in mean PRU between the 2 groups and a common standard deviation of 55 PRU, a sample size of 25 patients

per group will allow for the 95% confidence interval (CI) to stay within 45 PRU with a 80% power and alpha=0.025. Considering ~15% of invalid samples due to haemolysis, technical issues or drop out, and the 3 arms of treatment a total of 87 patients will need to be included. Non-inferiority will be assessed using a 95% CI of the difference in mean PRU between the 2 strategies. The sample size has been calculated according to data previously published [19]. A PRU of 45 was arbitrarily chosen for the noninferiority margin for the upper 95% CI limit of the difference in line with prior similar investigations [20-22]. Secondary end points will include 1) the comparisons of platelet reactivity, measured by the different assays and agonists (see Description of laboratory assays for details) between the different randomized treatments; 2) the comparisons between ticagrelor 90 mg monotherapy and the randomized treatments; 3) the comparisons between groups of rates of high on-treatment platelet reactivity, defined according to consensus definitions [23]. Continuous variables will be expressed as a mean ± SD or median [IQR]. Categorical variables will be expressed as frequencies and percentages. An analysis of variance method with a general linear model, with treatment as the main effect will be used to evaluate the primary non-inferiority endpoint as well as all superiority between-group comparisons at each time point. Least squares mean (LSM) differences in PRU between groups and the corresponding 2-sided 95% CI for the difference will be obtained based on the analysis of variance model and used to assess non-inferiority. Chi-square test and McNemar test will be used to compare categorical variables between groups. Statistical analysis will be performed using a SPSSv24.0 software (SPSS Inc. Chicago, IL).

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 will receive 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 collected up to completion of the study. Bleeding events will be classified according to BARC (Bleeding Academic Research Consortium) criteria [24]. Stent thrombosis will be classified according to ARC (Academic Research Consortium) definitions [25]. MI, including peri-procedural MI, will be defined according to the universal definition [26]. 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.

6. Possible Discomforts and Risk:

In clinical trials, the most important adverse effect associated with the use of ticagrelor was bleeding. The risk of major bleeding with ticagrelor 90 and 60 mg was 2.8% and 2.3%, respectively; the combined risk of intracranial hemorrhage or fatal bleeding was <1% [7,27]. However, such bleeding prevalence occurred in the setting of long-term trial (median follow-up of 9 and 33 months in PLATO and PEGASUS) with bleeding events that accrued over time, while our study is limited to only 30 ± 3 days of therapy. Ticagrelor will be compared with clopidogrel, which is also associated with an increased risk of bleeding compared with placebo [28]. We do not anticipate that ticagrelor will significantly increase the risk of bleeding compared with clopidogrel. Dyspnea has been reported as the main non-bleeding side effect with

ticagrelor and occurs in up to 15.8% of patients [7,27]. Below is a complete lists of potential medication risks:

- Bleeding
- Dyspnea (shortness of breath)
- Headache
- Cough
- 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 back to their standard of care treatment regimen.

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. All serious adverse events will be submitted to the AstraZeneca Product Safety mailbox. Bleeding data will be collected using BARC definitions [24]. The study will have a DSMB, 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.

7. Possible benefits:

The present investigation is aimed to evaluate the PD effects of ticagrelor 60 mg bid with and without aspirin compared with a standard dosing regimen of aspirin and clopidogrel. 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.

8. Conflict of Interest:

Dr. Angiolillo is a consultant for Bristol Myers Squibb/Sanofi-Aventis, the makers of clopidogrel (Plavix) and Astra Zeneca, the makers of ticagrelor (Brilinta).

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

9. Publication Strategy/Additional Information:

Study subjects will be identified first (months 1-21): we expect to enroll approximately 3 subjects monthly and complete enrollment in 21 months (total: 87 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.

10. Potential Financial Risks or Benefits

None

REFERENCES

1. Capodanno D, Alfonso F, Levine GN, Valgimigli M, Angiolillo DJ. ACC/AHA Versus ESC Guidelines on Dual Antiplatelet Therapy: JACC Guideline Comparison. *J Am Coll Cardiol.* 2018;72:2915-31.
2. Bittl JA, Baber U, Bradley SM, Wijeysundera DN. Duration of Dual Antiplatelet Therapy: A Systematic Review for the 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2016;68:1116-39.
3. Genereux P, Giustino G, Witzenbichler B, et al. Incidence, Predictors, and Impact of Post-Discharge Bleeding After Percutaneous Coronary Intervention. *J Am Coll Cardiol.* 2015;66:1036-45.
4. Buccheri S, Capodanno D, James S, Angiolillo DJ. Bleeding after antiplatelet therapy for the treatment of acute coronary syndromes: a review of the evidence and evolving paradigms. *Expert Opin Drug Saf.* 2019;18:1171-89.
5. Capodanno D, Mehran R, Valgimigli M, et al. Aspirin-free strategies in cardiovascular disease and cardioembolic stroke prevention. *Nat Rev Cardiol.* 2018;15:480-96.
6. Mehran R, Baber U, Sharma SK, et al. Ticagrelor with or without Aspirin in High-Risk Patients after PCI. *N Engl J Med*. 2019;381:2032-42.
7. Storey RF, Angiolillo DJ, Bonaca MP, et al. Platelet Inhibition With Ticagrelor 60 mg Versus 90 mg Twice Daily in the PEGASUS-TIMI 54 Trial. *J Am Coll Cardiol.* 2016;67:1145-1154.

8. Thomas MR, Angiolillo DJ, Bonaca MP, et al. Consistent platelet inhibition with ticagrelor 60 mg twice-daily following myocardial infarction regardless of diabetes status. *Thromb Haemost*. 2017;117:940-947.
9. Orme RC, Parker WAE, Thomas MR, et al. Study of Two Dose Regimens of Ticagrelor Compared with Clopidogrel in Patients Undergoing Percutaneous Coronary Intervention for Stable Coronary Artery Disease (STEEL-PCI). *Circulation.* 2018; 138: 1290–1300.
10. Bonaca MP, Bhatt DL, Cohen M, et al. Long-term use of ticagrelor in patients with prior myocardial infarction. *N Engl J Med*. 2015;372:1791-800.
11. Ferreiro JL, Angiolillo DJ. Diabetes and antiplatelet therapy in acute coronary syndrome. *Circulation.* 2011;123:798-813.
12. Rivas Rios JR, Franchi F, Rollini F, Angiolillo DJ. Diabetes and antiplatelet therapy: from bench to bedside. *Cardiovasc Diagn Ther.* 2018;8:594-609.
13. Ogurtsova K, da Rocha Fernandes JD, Huang Y, et al. IDF Diabetes Atlas: Global estimates for the prevalence of diabetes for 2015 and 2040. *Diabetes Res Clin Pract.* 2017;128:40-50.
14. Angiolillo DJ, Baber U, Sartori S, et al. Ticagrelor with or without Aspirin in High-Risk Patients with Diabetes Mellitus undergoing Percutaneous Coronary Intervention. *J Am Coll Cardiol.* 2020 (in press) Mar 19. pii: S0735-1097(20)34530-7.
15. Franchi R, Rollini F, Kairouz V, et al. Pharmacodynamic Effects of Vorapaxar in Patients with and without Diabetes Mellitus treated with Dual Antiplatelet Therapy: Results of the Optimizing anti-Platelet Therapy In diabetes MellitUS (OPTIMUS)-5 Study. *J Am Coll Cardiol Basic Trans Science* 2019;4:763-75.

16. Knuuti J, Wijns W, Saraste A, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J*. 2020;41:407-477.
17. Baber U, Dangas G, Cohen DJ, et al. Ticagrelor with aspirin or alone in high-risk patients after coronary intervention: Rationale and design of the TWILIGHT study. *Am Heart J.* 2016;182:125-34.
18. Kikuchi S, Tsukahara K, Ichikawa S, Abe T, Minamimoto Y, Kimura Y, Akiyama E, Nakayama N, Okada K, Matsuzawa Y, Konishi M, Maejima N, Iwahashi N, Hibi K, Kosuge M, Ebina T, Tamura K, Kimura K. Platelet-Derived Thrombogenicity Measured by Total Thrombus-Formation Analysis System in Patients With ST-Segment Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention. Circ J. 2020;84:975-984.
19. http://www.clinicaltrials.gov Unique Identifier: NCT03437044 - Low Maintenance Dose Ticagrelor Versus Clopidogrel in Diabetes Patients Undergoing PCI (OPTIMUS-6)
20. Angiolillo DJ, Curzen N, Gurbel P, et al. Pharmacodynamic evaluation of switching from ticagrelor to prasugrel in patients with stable coronary artery disease: Results of the SWAP-2 Study (Switching Anti Platelet-2). *J Am Coll Cardiol*. 2014;63:1500-9.
21. Franchi F, Faz GT, Rollini F, et al. Pharmacodynamic Effects of Switching From Prasugrel to Ticagrelor: Results of the Prospective, Randomized SWAP-3 Study. *JACC Cardiovasc Interv*. 2016;9:1089-98.
22. Franchi F, Rollini F, Rivas J, Rivas A, Agarwal M, Briceno M, Wali M, Nawaz A, Silva G, Shaikh Z, Maailiki N, Been L, Pineda AM, Suryadevara S, Soffer D, Zenni MM, Bass TA, Angiolillo DJ. Prasugrel Versus Ticagrelor in Patients With CYP2C19 Loss-of-Function Genotypes: Results of a Randomized Pharmacodynamic Study in a Feasibility Investigation of Rapid Genetic Testing. *JACC: Basic to Translational Science* 2020 (in press). doi: 10.1016/j.jacbts.2020.02.009.

23. Sibbing D, Aradi D, Alexopoulos D, et al. Updated Expert Consensus Statement on Platelet Function and Genetic Testing for Guiding P2Y12 Receptor Inhibitor Treatment in Percutaneous Coronary Intervention. *JACC Cardiovasc Interv*. 2019;12:1521-1537.
24. Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. *Circulation* 2011;123: 2736-47.
25. Cutlip DE, Windecker S, Mehran R, et al. Academic Research Consortium. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation* 2007; 115: 2344-51.
26. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD. Third universal definition of myocardial infarction. *J Am Coll Cardiol* 2012; 60:1581-98.
27. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2009;361:1045-57.
28. Yusuf S, Zhao F, Mehta SR, et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med*. 2001;345:494-502.

Abbreviation List (alphabetical order)

AA: arachidonic acid

CAD: coronary artery disease

DAPT: dual antiplatelet therapy

LTA: light transmittance aggregometry

MPA: maximal percent change

PCI: percutaneous coronary intervention

PD: pharmacodynamics

PGE1: Prostaglandin E1

PRU: P2Y12 Reaction Units

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

TRAP: thrombin receptor activating peptide

VASP: vasodilator-stimulated phosphoprotein

VN: VerifyNow