Official Title: A Randomized Comparison of Platelet Inhibition Using a Low Maintenance Dose Ticagrelor Regimen Versus Standard Dose Clopidogrel in Diabetes Mellitus Patients Without Prior Major Cardiovascular Events Undergoing Elective Percutaneous Coronary Intervention: The OPTIMUS (Optimizing Antiplatelet Therapy in Diabetes Mellitus)-6 Study

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A Randomized Comparison of Platelet Inhibition Using a Low Maintenance Dose Ticagrelor Regimen versus Standard Dose Clopidogrel in Diabetes Mellitus Patients without Prior Major Cardiovascular Events Undergoing Elective Percutaneous Coronary Intervention: The OPTIMUS (Optimizing Antiplatelet Therapy in Diabetes Mellitus)-6 Study

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BACKGROUND AND SIGNIFICANCE

Patients with diabetes mellitus (DM) are characterized by platelet hyperreactivity (1,2). Several mechanisms, including hyperglycemia, insulin resistance, associated metabolic conditions and other cellular abnormalities, are involved in the hyperreactive platelet phenotype (1,2). All these metabolic and cellular defects result in intensified platelet adhesion, activation, aggregation and platelet-derived thrombin generation (1,2). Importantly, patients with DM have shown to have reduced pharmacodynamic (PD) effects to several oral antiplatelet agents, including clopidogrel (1-3). In addition to the hyperreactive platelet phenotype, impaired drug metabolism as well as increased platelet turnover rates may contributed to impaired clopidogrel-induced antiplatelet effects in DM patients (3-5). These observations may contribute to the higher ischemic event rates, including stent thrombosis, observed in DM patients compared with non-DM patients treated with clopidogrel (1,2,6). However, clopidogrel remains the most widely used oral $P2Y_{12}$ receptor inhibitor and is the only agent in this class approved for use in patients with stable coronary artery disease (CAD) undergoing percutaneous coronary interventions (PCI) (7,8). These findings underscore the need to identify strategies associated with more effective platelet inhibition in DM patients undergoing PCI.

Ticagrelor is a first in class cyclopentyl triazolo-pyrimidine (CPTP) characterized by more prompt, potent and predictable antiplatelet effects compared with clopidogrel (9). In patients with an acute coronary syndrome (ACS) on a background of aspirin therapy, compared with clopidogrel 75 mg once-daily (od), a 90 mg twice-daily (bid) ticagrelor maintenance dose (MD) regimen was associated with lower one-year ischemic event rates, including cardiovascular mortality (10). Consistent findings were observed in patients with DM (11). In patients who experienced a prior (1-3 years) myocardial infarction (MI), compared with placebo, ticagrelor 60

mg bid on a background of aspirin therapy also reduced long-term ischemic events, with a mortality benefit observed in DM patients (12,13). Although in these studies ticagrelor was associated with increased bleeding, the net benefit still favored the use of ticagrelor, particularly in the DM cohorts (12,13). The advantages of ticagrelor over clopidogrel in patients with DM may be attributed to its enhanced antiplatelet potency, its twice-daily regimen as well as the fact that it does not require metabolism to exert its effects. In fact, studies have shown that twice-daily administration of oral antiplatelet agents may overcome the negative impact of high platelet turnover rates on platelet inhibition in DM patients (5). Moreover, hepatic enzymatic activity may be downregulated in DM patients and may thus affect drugs such as clopidogrel who require hepatic metabolism to exert their PD effects (14).

Aspirin monotherapy is the standard of care for prevention of ischemic events in DM patients without a prior major cardiovascular (CV) event (15). However, these patients remain at high risk for CV events despite aspirin therapy (15). This has prompted the design of the THEMIS (effect of Ticagrelor on Health outcomes in diabEtes Mellitus patients Intervention Study; NCT01991795) trial investigating whether the adjunctive use of ticagrelor 60 mg bid can further reduce major cardiovascular events in type 2 DM patients without a prior major CV event (MI or stroke). Moreover, DM patients are at risk not only for acute atherothrombotic complications but also for chronic CAD progression (16,17). Therefore, these patients frequently undergo PCI for whom clopidogrel, in adjunct to aspirin, remains the guideline recommended $P2Y_{12}$ receptor inhibitor (8). However, to date the PD effects of ticagrelor versus clopidogrel in DM largely derive from post-hoc assessments or in stabilized patients (e.g. >30 days after PCI), and have not been prospectively evaluated in the context of elective PCI procedures (18-21).

Moreover, PD studies with the ticagrelor 60 mg bid regimen are limited (22,23,24). Although these studies have shown that ticagrelor 60 mg has a similar PD profile than ticagrelor 90 mg, regardless of DM status, and is associated with more potent antiplatelet effects than clopidogrel 75 mg, there are no studies assessing the PD profiles of ticagrelor 60 mg versus clopidogrel 75 mg in DM patients (22,23,24). Therefore, the aim of this investigation will be to compare the PD effects of a ticagrelor 60 mg bid versus clopidogrel 75 mg od MD regimen in DM patients without a prior major CV event undergoing elective PCI.

STUDY RATIONALE

To date there is very little PD and pharmacokinetic (PK) data on the ticagrelor 60 mg bid dosing regimen. In particular, there is no prospective PK/PD study on this dosing regimen in patients with DM who are known to have impaired response to clopidogrel therapy. Since DM patients frequently require elective PCI due to chronic progression of CAD (and not solely because of an acute thrombotic complication), and clopidogrel remains the guideline recommended $P2Y_{12}$ inhibiting therapy for these patients, understanding the PD effects of the ticagrelor 60 mg bid regimen in this setting is an unmet clinical need. This is also in light of the ongoing THEMIS trial which is specifically evaluating the impact of the ticagrelor 60 mg bid dosing regimen in type 2 DM patients without a prior major CV event.

REASERCH PLAN

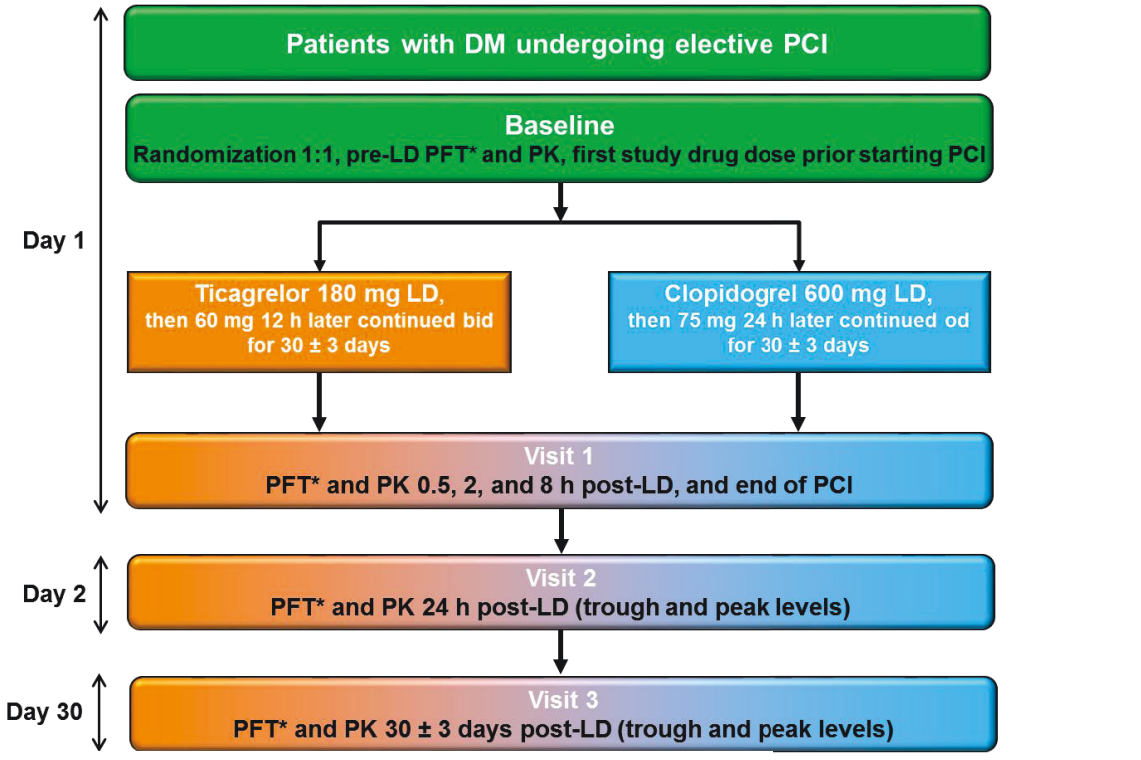
Study design

The proposed investigation will be a prospective, randomized, open-label, PK/PD study conducted in DM patients undergoing elective PCI. Figure 1 illustrates the overall study design. After providing written informed consent and following diagnostic angiography, patients meeting study entry criteria (see inclusion and exclusion criteria below) undergoing PCI will be randomly assigned in a 1:1 ratio to treatment with either ticagrelor or clopidogrel. Patients randomized to ticagrelor will receive ticagrelor 180 mg loading dose (LD) followed by a 60 mg bid MD starting 12 h (± 1 h) after the LD. Patients randomized to clopidogrel will receive a 600 mg LD followed by a 75 mg od MD starting 24 hours (± 1 h) after the LD. Maintenance dose therapy will be maintained for 30±3 days. All patients will receive a 325 mg LD of aspirin prior to the procedure and then 81 mg daily. Afterwards, antiplatelet treatment will be left to the discretion of the treating physician.

The randomized treatment will be administered in the catheterization laboratory after defining coronary anatomy and before starting PCI (defined as before guide wire passing the target coronary lesion). Blood samples for PK/PD testing will be obtained at a total of 9 time points: immediately before the LD, and then at 0.5 h, 2 h, 8 h, 24 h (trough and peak), and 30 (±3) days (trough and peak) following LD; an additional sample will be collected at the end of PCI. The end of PCI is defined as when the guide catheter is removed from the body at the completion of the procedure. Access site, choice of anticoagulant (i.e., heparin or bivalirudin), stent type and procedural technique will be at the discretion of the physician. Staff performing PK/PD assessments will remain blinded to treatment assignment.

The study will be performed at the University of Florida Health Science Center at UF Health Jacksonville - Division of Cardiology. Patients will be recruited prior to undergo diagnostic angiography at the inpatient and outpatient facilities of our institution and 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 30 days will be considered valid for screening purposes. If these are not available, a blood sample will be collected for the screening phase.

Figure 1



Study Population

Specific inclusion and exclusion criteria are described below and have been considered to closely reflect study entry criteria of the THEMIS trial (NCT01991795).

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 drug (oral medications and / or insulin) treatment for at least 1 month
4. Presence of CAD undergoing elective PCI*

* Patients will need to be cardiac enzyme-negative prior to undergoing coronary angiography. Patient will need to be on a background of aspirin therapy (treated with a 325 mg LD prior to coronary angiography unless already on chronic low-dose aspirin therapy). Patients on maintenance clopidogrel 75 mg therapy for at least 1 week due to a prior vascular intervention will also be eligible. However, patients on clopidogrel, ticagrelor or prasugrel due to a prior acute major cardiovascular event (MI or stroke) will not be eligible.

Exclusion criteria

Patients should not enter the study if any of the following exclusion criteria are fulfilled:

1. Previous MI (with the exception of definite non-type 1 MI [eg, due to coronary revascularization procedure, profound hypotension, hypertensive emergency, tachycardia, or profound anemia])

2. Previous stroke (transient ischemic attack [TIA] is not included in the stroke definition)
3. Use of an intravenous antiplatelet therapy (i.e., cangrelor or GPI) during PCI
4. On treatment with clopidogrel, prasugrel, or ticagrelor due to a prior acute major CV event (MI or stroke) (on treatment with clopidogrel due to prior vascular intervention not secondary to a major CV event is allowed)
5. Planned use of aspirin treatment at doses >100 mg od
6. 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
7. Need for chronic oral anticoagulant therapy or chronic low-molecular-weight heparin (at venous thrombosis treatment not prophylaxis doses)
8. Patients with known bleeding diathesis or coagulation disorder
9. 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
10. Active pathological bleeding
11. Hypersensitivity to ticagrelor and clopidogrel or any of the excipients

12. 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
13. Known severe liver disease (eg, ascites and/or clinical signs of coagulopathy)
14. Renal failure requiring dialysis
15. Known platelet count $<80x10^6$/mL
16. Known hemoglobin <9 g/dL
17. Women of child-bearing potential (ie, those who are not chemically or surgically sterilized or who are not post-menopause) who are not willing to use a medically accepted method of contraception that is considered reliable in the judgment of the investigator OR who have a positive pregnancy test at enrolment or randomization OR women who are breast-feeding. If a subject becomes pregnant during the course of the study the investigational product should be discontinued immediately [the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) will be followed up and documented even if the subject was discontinued from the study].
18. Inability of the patient to understand and/or comply with study procedures and/or follow up, in the opinion of the investigator, OR any conditions that, in the opinion of the investigator, may render the patient unable to complete the study
19. Life expectancy of less than 1 month based on investigator's judgement
20. Participation in another clinical study with an investigational (defined as non-FDA approved) product within 28 days prior to enrolment
21. Previous randomization in the present study

Blood sampling and PK/PD Assessments

Blood samples for screening procedures if needed will be obtained via antecubital vein puncture using a 21-gauge needle. Blood samples for PK/PD testing at baseline (before the LD), at 0.5 h, and at the end of the PCI will be collected from the arterial access site sheet; blood samples for the 2 h, 8 h, 24 h (trough and peak), and 30±3 days (trough and peak) time points will be collected via antecubital vein puncture using a 21-gauge needle. The last dose intake of study drug will be 12±2 h and 24±2 h prior to blood sampling in order to guarantee assessment of trough level of platelet inhibition for ticagrelor and clopidogrel, respectively, while peak levels of platelet inhibition will be assessed by obtaining blood samples 2 h after MD administration (22). The first few mL of blood will be discharged in order to avoid spontaneous platelet activation. Whole blood samples will be collected into 3.2% 9NC Coagulation Sodium Citrate, 2mL (Vacuette, Kremsmünster, Austria) and 3.2% Buffered Sodium Citrate, 4.5mL (BD, Franklin Lakes, NJ, USA) tubes as appropriate for the specific assays being conducted.

PD assessments

A total of 3 different PD assays will be used for this study:

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 (Accumetrics, San Diego, CA) and will be utilized according to manufacturer's instructions, as previously described (3). 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).

2) Whole blood vasodilator-stimulated phosphoprotein (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.

3) Light transmittance aggregometry (LTA): Platelet aggregation will be performed using LTA according to standard protocols. 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 (3). Platelet agonists will include arachidonic acid (AA; 1 mM), collagen (3µg/ml) and ADP (5 and 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) and late platelet aggregation (LPA) in light transmittance from baseline using PPP as a reference.

PK assessments

PK assessments will include determination of plasma concentration of clopidogrel active metabolite, ticagrelor and its active metabolite (AR-C124910XX), as previously described (3,26). Time for the maximum plasma concentration (T_{max}), maximum observed plasma concentration (C_{max}) and the area under the plasma concentration vs. time curve from time 0 to the last measurable concentration (AUC_{0-t}) will be calculated.

Other laboratory assessments

Blood samples will also be collected to assess the following parameters: a) HbA1c at baseline; b) reticulated platelets at baseline and 30 days; c) troponin levels at baseline, and 6 h and 24 h post PCI.

Study endpoints, sample size calculation and statistical analysis

The primary endpoint of our study will be platelet reactivity, measured as PRU level using VN, of ticagrelor versus clopidogrel MD at 30 days after PCI, immediately pre-dosing dosing (trough levels). Based on previous studies (22,24,27), assuming a standard deviation of 55 and 100 PRU for ticagrelor and clopidogrel, respectively, a sample size of 34 patients (17 per treatment group) will be needed to detect an absolute difference of 95 PRU between ticagrelor and clopidogrel (corresponding to means of 170 versus 75) 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 approximately 42 patients is expected to be randomized.

Conformity to the normal distribution will be evaluated for continuous variables with the Shapiro-Wilk test. For baseline characteristics, continuous variables will be expressed as mean (standard deviation [SD]) and categorical variables as frequencies and percentages. Chi-squared test or Fisher's exact test will be used where appropriate to compare categorical variables between 2 groups.

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.

The primary analysis of the difference between ticagrelor and clopidogrel in PRU will be analyzed using analysis of variance. Treatment level means and 2-sided 95% confidence intervals (CIs) will be estimated. Analysis of variance will also used to evaluate other intergroup comparisons. Repeated measures of analysis of variance, taking into account between- and within-subject variations, will be conducted to evaluate the impact of the 2 different treatments on platelet reactivity across time points. A p-value < 0.05 will be considered statistically significant. Statistical analysis will be performed with SPSS version 24 software (SPSS Inc.).

Secondary endpoints will include comparisons of measures of platelet reactivity using VN, VASP, and LTA at all other time points [0.5 h, 8 h, 24 h (trough and peak), 30 days (trough and peak) following LD, and end of PCI] as well as rates of high on-treatment platelet reactivity (HPR). In line with recent expert consensus definitions, HPR will be defined as a PRU >208, VASP-PRI> 50%, maximum LTA response to 20 μM ADP > 59 %, maximum LTA response to 5 μM ADP > 46 % (28). In addition, time for the maximum plasma concentration (T_{max}), maximum observed plasma concentration (C_{max}) and the area under the plasma concentration vs. time curve from time 0 to the last measurable concentration (AUC_{0-t}) of plasma concentration of clopidogrel active metabolite, ticagrelor and its active metabolite (AR-C124910XX) will be calculated.

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), serious adverse events, physical examination, and vital signs. Adverse events will collected up to 7 days after the completion of the study. Bleeding events will be classified according to BARC (Bleeding Academic Research Consortium) criteria (29). Stent thrombosis

will be classified according to ARC (Academic Research Consortium) definitions (30). MI, including peri-procedural MI, will be defined according to the universal definition (31). 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.

Possible Discomforts and Risk

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% (12). 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 $P2Y_{12}$ inhibitor, ticagrelor will be compared with clopidogrel, which is also associated with an increased risk of bleeding compared with placebo (9). Therefore, 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 (10,12). Dyspnea has been associated with drug discontinuation in 4.6% of patients (10,12). Patients who discontinue ticagrelor therapy will be switched to clopidogrel. Ultimately, although a 60 mg dosing regimen has not been specifically tested in DM patients undergoing PCI, 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, which included patients with DM (27). Overall, these considerations limit any safety concerns associated with the conduct of this study.

All clinical events described above, if they were to occur, as well as death, myocardial infarction, stroke, and urgent revascularization procedure with PCI or coronary artery bypass grafting will be recorded. 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.

Definition of Adverse Events

An adverse event is any unintended or undesirable experience that occurs during the course of the clinical investigation whether or not it is considered to be therapy related. This includes any newly occurring event or previous condition that has increased in severity or frequency since the initiation of study treatment. Adverse events will be followed until resolution while the patient remains on-study. Once the patient is removed from study, events thought to be related to the study therapy will be followed until resolution or until the patient starts a new treatment regimen.

Serious Adverse Events (SAE)- an immediately life-threatening adverse experience: An adverse event occurring while on study that results in any of the following outcomes:

- Death

- A life-threatening adverse experience.
- A persistent or significant disability, incapacity, or is a congenital anomaly, or birth defect.
- Requires inpatient hospitalization, or prolongation of existing hospitalization.

The definition of serious adverse event also includes 'important medical event'. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient and/or may require medical or surgical intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse. Study related SAE will be defined as a SAE considered related (reasonable possibility that the study treatment caused the adverse experience) to the study treatment.

Reporting of serious adverse events

A copy of the MedWatch/AdEERs report must be faxed to AstraZeneca at the time the event is reported to the FDA. It is the responsibility of the investigator to compile all necessary information and ensure that the FDA receives a report according to the FDA reporting requirement timelines and to ensure that these reports are also submitted to AstraZeneca at the same time.

Serious adverse events that do not require expedited reporting need to be reported to AstraZeneca quarterly either as individual case reports or as line-listings. When reporting to AstraZeneca, a cover page should accompany the MedWatch/AdEERs form indicating the following:

- External Sponsored Research (ESR)
- The investigator IND number assigned by the FDA
- The investigator's name and address
- The trial name/title and AstraZeneca ESR reference number

Investigative site must also indicate, either in the SAE report or the cover page, the causality of events in relation to all study medications.

To meet data privacy and confidentiality requirements, Adverse Event (AE) information (both individual case reports and listings) must be sent from the Sponsor/Sponsor-Investigator by secure e-mail, if secure email is not available AE information must be sent by fax. Send SAE report and accompanying cover page to AstraZeneca by Email: AEMailboxClinicalTrialTCS@astrazeneca.com) or Fax to AstraZeneca's designated fax line: +1 302 886 4114). Serious adverse events that do not require expedited reporting to the FDA need to be reported to AstraZeneca preferably using the MedDRA coding language for serious adverse events.

All SAEs have to be reported to AstraZeneca, whether or not considered causally related to the investigational product. All SAEs will be documented. The investigator is responsible for informing the IRB and/or the Regulatory Authority of the SAE as per local requirements. All

pregnancies and outcomes of pregnancy should be reported to AstraZeneca's designated e-mail or fax line (noted above)

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 DM patients with CAD undergoing elective PCI. 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.

Potential Financial Risks or Benefits

None

Publication Strategy/Additional Information

Study subjects will be identified first (months 1-12): we expect to enroll approximately 3-4 subjects monthly and complete enrollment in 12 months (total: 42 subjects enrolled). Months 13-14 will be implied for statistical analysis and months 15-16 for 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.

Conflict of Interest

Dr. Angiolillo is a consultant for Astra Zeneca, the maker of ticagrelor.

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