Pharmacodynamic evaluation of switching from ticagrelor to clopidogrel in patients with coronary artery disease

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Project overview

The recommended antiplatelet treatment regimen for patients affected by acute coronary syndromes (ACS) and those undergoing percutaneous coronary intervention (PCI) consists in the combination of aspirin and a $P2Y_{12}$ receptor inhibitor. Currently, three $P2Y_{12}$ receptor inhibitors are available for clinical use (clopidogrel, prasugrel, and ticagrelor). Among these, clopidogrel remains the most widely used. However, recent studies have shown that there is a broad variability in platelet-inhibitory response induced by clopidogrel, which in turn is associated with worse outcomes. More potent $P2Y_{12}$ receptor inhibitors (prasugrel and ticagrelor) have been developed which are associated with less response variability than clopidogrel and better clinical outcomes. Ticagrelor use has increased significantly because of its more expanded Food and Drug Administration (FDA) indications compared with prasugrel. However, despite the evidence for sustained efficacy and safety, many physicians limit treatment duration with ticagrelor to the early phases following an ACS (early weeks or months, rather than one-year) mostly due to cost issues and concerns about increased bleeding. Therefore, it is very common in clinical practice to switch patients while on maintenance dosing (MD) with ticagrelor to treatment with clopidogrel. However, the pharmacodynamic (PD) effects of switching from ticagrelor to clopidogrel remain unknown. In addition, it is unknown whether switching from ticagrelor to clopidogrel should occur with or without a loading dose (LD). Therefore, the aim of this investigation is to evaluate the PD effects of switching from ticagrelor to clopidogrel with and without a LD. The present study has a prospective, randomized, open-label design, in which patients will be treated with 4 different strategies to assess PD profiling after switching. This study will provide important insights on PD effects of switching from ticagrelor to clopidogrel.

Background and Significance:

The currently recommended antiplatelet treatment regimen for patients affected by acute coronary syndromes (ACS) and those undergoing percutaneous coronary intervention (PCI) consists in the combination of aspirin and a $P2Y_{12}$ receptor inhibitor [1-3]. Currently, three $P2Y_{12}$ receptor inhibitors are available for clinical use (clopidogrel, prasugrel, and ticagrelor). Among these, clopidogrel remains the most widely used to reduce recurrent ischemic events [1, 4,5,6]. However, several studies have shown that there is a broad variability in platelet-inhibitory response induced by clopidogrel, which in turn is associated with worse outcomes [7]. Variability in clopidogrel response is a multifactorial process [7]. Clopidogrel is a prodrug that requires bioactivation into its active metabolite before targeting the $P2Y_{12}$ receptor on blood platelets. In vivo bioactivation of the drug is a 2-step process that is closely linked to the cytochrome P450 (CYP) system [8]. The most prominent and best established genetic factor is located within the CYP2C19 gene, as the polymorphically expressed isoenzyme CYP2C19 is involved in both metabolic steps of clopidogrel's active metabolite generation [8,9]. In particular, a single-nucleotide polymorphism located within the CYP2C19 gene is a major determinant of clopidogrel responsiveness [9]. The presence of CYP2C19*2 and CYP2C19*3 LOF allelic variants is associated with a loss of enzyme function and comes along with an attenuated response to clopidogrel leading to higher risk for ischemic events [10]. CYP2C19 *2 allele is the most common LOF variant with allele frequencies of ~15% in Caucasians and Africans, and 29-35% in Asians [11].

More potent $P2Y_{12}$ receptor inhibitors (prasugrel and ticagrelor) have been developed and are associated with less response variability than clopidogrel and better clinical outcomes in

patients with ACS [12,13,14,15]. Ticagrelor use has increased significantly because of its more expanded Food and Drug Administration (FDA) indications compared with prasugrel [1,4,5,14,15]. However, despite the evidence for consistent and sustained efficacy and safety of ticagrelor with up to one-year of treatment, many physicians limit treatment duration with ticagrelor to the early phases following an ACS (early weeks or months) rather than one-year mostly due to cost issues and concerns about increased bleeding [14,16]. The PD profiles after discontinuation of ticagrelor indicate faster recovery of platelet-inhibitory effects than clopidogrel [17], suggesting the need for early overlap of treatment among ticagrelor-treated patients in case of switching antiplatelet therapy. In the SWAP-2 (Switching AntiPlatelet-2) study in which patients were switched from ticagrelor to prasugrel, a loading-dose (LD) appeared to be essential to mitigate a rebound in platelet reactivity due to a drug-interaction after switching [18]. This study also hypothesized that this potential drug-drug interaction could have been attributed to the presence of ticagrelor or its metabolite still on the $P2Y_{12}$ receptor when prasugrel was administered after 12 hours from the last maintenance dose (MD) of ticagrelor. This also suggested that switching should occur after a later time frame (e.g. 24 hours) to enable more time for the receptor to be unbounded by ticagrelor or its metabolite to allow a better switching approach [18]. However, to date, the PD effect of switching from ticagrelor to clopidogrel, and how this may be affected by administering a LD prior to initiating a standard MD regimen, as well as how this may be affected by timing of administration from last MD, has not been explored. Moreover, if such PD response profiles can be affected by CYP2C19 LOF genetic status also remains unknown.

Study aim

The aim of this investigation is to evaluate the PD effects of switching from ticagrelor to clopidogrel with and without a LD., and to evaluate how this might be affected by CYP2C19 LOF genetic status.

Study Population

Patients with known coronary artery disease (CAD) on maintenance aspirin (<100mg qd) and clopidogrel therapy (75mg qd) as a part of their standard-of-care will be screened for this study. Details of inclusion and exclusion criteria are described below:

Inclusion Criteria

1) Patients with angiographically documented CAD
2) On therapy with aspirin(<100mg/day) and clopidogrel (75mg/day) for at least 30 days per standard of care
3) Age between 18 and 80 years old

Exclusion Criteria

1) History of intracranial bleeding
2) Known hepatic impairment (based on clinical judgment)
3) Active bleeding or propensity to bleed or blood dycrasia
4) Platelet count $<80x10^6$/mL
5) Hemoglobin <10g/dL
6) Hemodynamic instability
7) Estimated glomerular filtration rate (eGFR) <30 mL/min
8) On treatment with oral anticoagulants
9) Patients with sick sinus syndrome (SSS) or II or III degree AV block without pacemaker protection

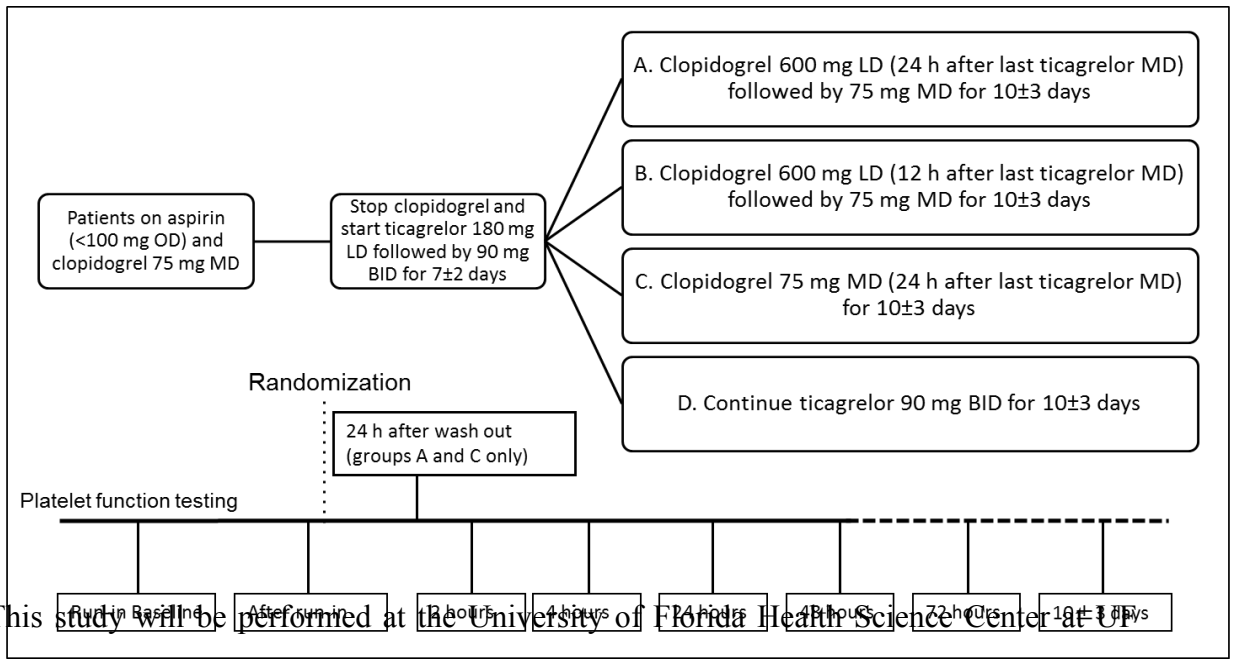
10) Drugs interfering CYP3A4 metabolism (to avoid interaction with ticagrelor): ketoconazole, itraconazole, voriconazole, clarithromicin, nefazodone, ritonavir, saquinavir, nelfinavir, indinavir, atazanavir and telithromizycin
11) Pregnant females [women of childbearing age must use reliable birth control (i.e. oral contraceptives) while participating in the study].

Research design

Patients meeting inclusion criteria will be enrolled in this prospective, randomized, open-label study. Baseline labs obtained within the past 180 days will be considered valid for screening purposes. If baseline labs are not available, these will need to be obtained prior to considering a patient eligible for study entry (patients will have 90 days to enter the study). Eligible patients will undergo a 7±2 day run-in phase with ticagrelor after switching from clopidogrel 75mg/day to ticagrelor 180mg LD followed by 90mg bid MD. Ticagrelor dosing in this study is line with FDA recommendations [15]. After this run-in phase, patients will be randomized (1:1:1:1) into one of the four following groups: A) clopidogrel 600 mg LD 24 hours after last MD of ticagrelor, followed by 75mg daily MD; B) clopidogrel 600 mg LD 12 hours after last MD of ticagrelor, followed by 75mg daily MD; C) clopidogrel 75mg daily MD 24 hours after last MD of ticagrelor; D) continue ticagrelor MD 90mg twice daily. The FDA approved dose for clopidogrel is 300 mg loading dose and 75 mg/qd maintenance dose; however standard of care loading dose is 600 mg which is in line with practice guidelines [1-5].

Blood sampling: Peripheral venous blood samples (20 mL) 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 the following time points: prior to run-in baseline visit (24 hours after last clopidogrel dose in order to assess trough levels of platelet reactivity), after run-in (12 hours after last ticagrelor maintenance dose of run-in period), 24 hours after washout (groups A and C only), and 2, 24, 48, 72 hours and 10±3 days after randomization. For patients randomized to groups A and C, both requiring 24 hours washout from last MD, they will take their morning MD of ticagrelor after blood sample collection for their post-run-in phase and return the following morning to receive the randomized treatment (these groups will have a total of 8 blood sampling time points). Patients randomized to groups B and D will initiate their randomized treatment the same morning of the post-run-in phase visit (these groups will have a total of 7 blood sampling time points). CYP2C19 genetic status will be evaluated at baseline visit. PD assessment will include VerifyNow point-of-care testing (VN-$P2Y_{12}$), light-transmittance aggregometry (LTA) and whole blood vasodilator-stimulated phosphoprotein (VASP) as described below. Time points will have a ±10% window. Results of genetic testing will not be used for clinical decision makings on choice of antiplatelet treatment regimen to be used at the end of the study. This is because we are studying patients in stable clinical conditions who have already on maintenance clopidogrel therapy without experiencing ischemic events, which are more likely to occur in the earlier phases of treatment in the setting of PCI [10]. Moreover, routine genetic testing and modification of treatment based on results of genetic testing is a class III recommendation in practice guidelines [1,2]. An illustration of the study design is provided below. A study table summarizing protocol procedures is provided as an appendix.



This study will be performed at the University of Florida Health Science Center at UF Health - Division of Cardiology. Patients will be recruited and consented at the inpatient and outpatient services in the UF Health system. Patients will be screened by cardiology research, who will verify that all candidates meet inclusion criteria. Subjects will be identified with a number and data collection sheets will all be stored in a locked area. Data will be kept for 6 years after enrollment ends to comply with HIPAA regulations. Patients will receive a copy of the consent with the names and telephone numbers of the doctors involved in the study.

Study Medications

Study medications will include the ticagrelor doses needed for the run-in phase for all patients enrolled in the study, the clopidogrel 600mg LD needed for Groups A and B, and the ticagrelor MD needed for Groups A and C and D. Study supplies will be obtained by the Department of Cardiology.

Patients will be continued on their prescribed clopidogrel 75mg standard of care dosing at the following time points:

Group A: On the Day after Visit 3

Group B: On the Day after Visit 2

Group C: At Visit 3

Group D: On the Day after Visit 7

Laboratory assessments

1. VerifyNow $P2Y_{12}$ point-of-care testing (VN-$P2Y_{12}$)
2. Light-transmittence aggregometry (LTA)
3. Whole blood vasodilator-stimulated phosphoprotein (VASP)
4. CYP 2C19 Genetic testing

Description of laboratory assays

1) *VerifyNow point-of-care testing (VN-$P2Y_{12}$):* The VN-$P2Y_{12}$ is currently the most widely used point-of-care testing to evaluate platelet aggregation, because is rapid, easy to perform and uses whole blood [19]. The VerifyNow 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 [19]. The assay is based on microbead agglutination and uses specific reagents for the pathways of interest. The VN-$P2Y_{12}$ assay, by combining ADP+PGE1, measures changes in platelet function specific to

$P2Y_{12}$ receptor inhibitors. The assay is based upon the ability of activated platelets to bind fibrinogen. Fibrinogen-coated microparticles aggregate in proportion to the number of GP IIb/IIIa receptors expressed. Microbead aggregation is more rapid and reproducible if platelets are activated; therefore the reagents are incorporated into the assay channel to induce platelet activation without fibrin formation. Light transmittance increases as activated platelets bind and aggregate fibrinogen-coated beads. The instrument measures this change in optical signal and reports results in $P2Y_{12}$ Reaction Units (PRU).

2) *Light transmittance aggregometry (LTA):* Platelet aggregation will be measured 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 [19]. Platelet agonists will include 5 and 20 μM ADP. PRP will be obtained as a supernatant after centrifugation of citrated blood at 1000 rpm for 10 minutes. The isolated PRP will be kept at 37° C before use. Platelet poor plasma (PPP) will be obtained by a second centrifugation of the blood fraction at 2800 rpm for 10 minutes. Light transmission will be adjusted to 0% with the PRP and to 100% for the PPP for each measurement. Curves will be recorded for 6 minutes and platelet aggregation will be determined as the maximal percent change (MPA) in light transmittance from baseline using PPP as a reference.

3) *Whole blood vasodilator-stimulated phosphoprotein (VASP):* VASP phosphorylation (VASP-P) is a marker of $P2Y_{12}$ receptor reactivity, which is the target for ticagrelor. VASP will be assessed according to standard protocol using labeled monoclonal

antibodies by flow cytometry with the Platelet VASP-FCM kit (Biocytex Inc., Marseille, France) as previously described [19]. 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 by inhibitors, addition of ADP will not reduce the PGE1-stimulated VASP-P levels. The platelet reactivity ratio (PRI) will be calculated after measuring VASP-P levels after stimulation with PGE1 (MFI PGE1) and also PGE1 + ADP (MFI PGE1 + ADP). The $P2Y_{12}$ reactivity ratio = ([MFI PGE1] – [MFI PGE1 + ADP]/[MFI PGE1]) x 100%.

4) *CYP 2C19 Genetic testing:* CYP2C19 genetic status will be performed with the Spartan RX point-of-care rapid genotyping device. Spartan RX (Spartan Bioscience Inc., Ontario, Canada) is a point-of-care determining the CYP2C19 (*1,*2,*3,*17) allele status within 1 hour [20]. This test consisted 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. In particular, this point-of-care assay enables assessment of the following alleles: *1,*2,*3 and *17. The most common LOF alleles are *2 and *3. Therefore, carriers of *2 or *3 LOF carrier status can be homozygotes (*2/*2, *3/*3 or *2/*3) or heterozygotes (*1/*2, *1/*3, *2/*17, *3/*17). Non-carriers of LOF alleles include the following: *1/*1, *1/*17 or *17/*17.

Definitions of high on treatment platelet reactivity

High on-treatment platelet reactivity (HPR) will be defined according to updated expert consensus as following: PRU higher than 208 or 235, MPA-ADP (5 μM) >46%, MPA-ADP (20 μM) >59% and VASP-PRI >50% [21,22].

Study endpoints and sample size calculation

The primary endpoint is the comparison of PRU assessed by VN- $P2Y_{12}$ at 48 hours after switching from ticagrelor 90 mg bid to clopidogrel 600 mg LD given 24 hours after last ticagrelor MD (group A) vs. clopidogrel 75 mg MD given 24 hours after last ticagrelor MD (group C). We hypothesize that switching from ticagrelor to clopidogrel with a loading dose will have less increase in platelet reactivity than that without loading dose and the sample size was determined based on the objective of establishing superiority of this approach. Superiority will be assessed using a 95% confidence interval (CI) of the difference in mean PRU between these two groups. Under the assumption of a mean difference of 60 PRU between groups and a common standard deviation of 50 PRU, a sample size of 16 per group allows for the 95% CI with a 95% power and alpha=0.05. Considering 4 arms of treatment and a possible invalid data in 20-25% of patients due to technical issues or drop-outs, we will randomize up to a total of 80 patients to ensure complete data. We anticipate screening 100 patients to identify these 80 patients to be randomized. Secondary endpoints include comparison of PRU (other than primary endpoint) assessed by VN-$P2Y_{12}$, 5 and 20 μM ADP aggregation assessed by LTA and VASP-PRI in all four groups at each time points; rates of HPR according to each platelet function assay

(VN-P2Y$_{12}$, LTA, and VASP-PRI) in all four groups at each time point; impact of CYP2C19 LOF genetic status on PD parameters.

Statistical analysis plan

Continuous variables will be expressed as a mean ± SD when are normally distributed or median [IQR] when are not normally distributed. Categorical variables will be expressed as frequencies and percentages. The Kolmogorov-Smirnov test will be used to examine data distribution normality. Comparisons between categorical variables will be performed using two-tailed Fisher's exact test or the Pearson's chi-square test. Student´s t test, Mann-Whitney U-test and Wilcoxon test will be used to compare continuous variables when appropriate. A repeated measures analysis of variance (ANOVA) model will be used to evaluate intra-group comparisons and the overall difference between groups. An analysis of covariance (ANCOVA) method with a general linear model, using the baseline value of platelet reactivity as a covariate, will be used to evaluate all between-groups comparisons. Missing data will not be imputed. A 2-tailed p value of < 0.05 is considered to indicate a statistically significant difference for all the analyses performed. Statistical analysis will be performed by our group using SPSS v22.0 software (SPSS Inc. Chicago, IL).

Possible Discomforts and Risk

The study entails blood draws at multiple time points as indicated above. 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. In clinical trials, the

most common clinical side effects of ticagrelor were dyspnea (13.8%), headache (6.5%), cough (4.9%), dizziness (4.5%), nausea (4.3%), bradycardia (4.4%) principally. Infrequent events included intracranial hemorrhage (0.3%) and severe bradycardia requiring pacemaker insertion (0.9%). Patients considered to be at high risk of bradyarrhythmic events will be excluded. The most important adverse effect associated with the use of ticagrelor is bleeding. The risk of major spontaneous bleeding with ticagrelor is 2.8% [9]. However, such bleeding prevalence occurred in the setting of long-term (12 months) trials, while our study is limited only to approximately 1-week of ticagrelor therapy, thus reducing the risk of bleeding complications. All clinical events described above, if they were to occur, as well as death, myocardial infarction, stroke, and urgent revascularization procedure with PCI or coronary artery bypass grafting will be recorded. Bleeding data will be collected using PLATO definitions [14]. Clinical events will be evaluated by a local committee, comprised of 2 faculty members (2 cardiologists), not directly involved in the research. In the event of a report of a serious adverse event (major bleeding – defined as life-threatening: fatal, symptomatic intracranial hemorrhage, leading to a drop in hemoglobin of at least 5 g/dL, significant hypotension requiring intravenous inotropes, requiring surgical intervention, or requiring transfusion of 4 or more units of blood; non–life-threatening: substantially disabling, intraocular bleeding leading to vision loss, or requiring at least 2 units of blood; thrombocytopenia <50,000) the local committee will meet and antiplatelet treatment management will be managed 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 adverse event occurring while on study and considered related (reasonable possibility that the study treatment caused the adverse experience) to the study treatment 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.

Possible benefits

The present investigation is aimed to evaluate the PD effects of switching from ticagrelor to clopidogrel. This study is not designed to evaluate differences in clinical benefit. However, differences in antiplatelet profiles may potentially prompt further investigation of the clinical implication of this difference by means of a larger scale clinical study.

Potential Financial Risks or Benefits

None

Conflict of Interest

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

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Table S1. Summary of protocol procedures

	Screening		**V1** *Run-in Baseline*			**V2** *After 7±2 days Run-in$*				**V3** *After 24 hours wash-out$$*			**V4**	**V5**	**V6**	**V7**
	Consent	Baseline Labs*	PD testing	Genetic Testing	Study drug^	Baseline PD	Randomi-zation	Study drug	2 hrs PD†	Baseline PD†	Study drug	2 hrs PD†	24 hrs PD†	48 hrs PD†	72 hrs PD†	10±3 days PD†
Group A	X	X	X	X	X	X	X	X**		X	X***	X	X	X	X	X
Group B	X	X	X	X	X	X	X	X***	X				X	X	X	X
Group C	X	X	X	X	X	X	X	X**		X		X	X	X	X	X
Group D	X	X	X	X	X	X	X	X++	X				X	X	X	X

* Baseline labs obtained within the past 180 days will be considered valid for screening purposes. If baseline labs are not available, these will need to be obtained prior to considering a patient eligible for study entry and start the run-in phase (patients will have 90 days to enter the study).
^ Ticagrelor LD 180mg followed by 90mg BID MD for 7±2 days
† After Study Drug administration.
$ 12 hours after last ticagrelor 90-mg dose.
$$ 24 hours after last ticagrelor 90-mg dose.
Screening visit, V1, V2 and V4-V7 are common for all groups.
**At V2, group A and C will receive a 90-mg maintenance dose of ticagrelor.
*** Clopidogrel 600 LD
++ Ticagrelor 90mg BID for 10±3days
V3 will be needed only for group A and group C.

Group A: clopidogrel 600mg LD 24 hours after last MD of ticagrelor, followed by 75mg daily MD;
Group B: clopidogrel 600mg LD 12 hours after last MD of ticagrelor, followed by 75mg daily MD;
Group C: clopidogrel 75mg daily MD 24 hours after last MD of ticagrelor;
Group D: continue ticagrelor MD 90mg twice daily.
PD: pharmacodynamic; V: visit.