Adjunctive Vorapaxar Therapy in Patients with Prior Myocardial Infarction Treated with New Generation $P2Y_{12}$ Receptor Inhibitors Prasugrel and Ticagrelor (VORA-PRATIC): A Prospective, Randomized, Pharmacodynamic Study

Dominick J. Angiolillo, MD, PhD
University of Florida College of Medicine-Jacksonville
655 West 8th Street
Jacksonville, Florida, 32209
Tel: +1-904-244-3933
Fax: +1-904-244-3102
E-mail: dominick.angiolillo@jax.ufl.edu

Summary

Dual antiplatelet therapy (DAPT) with aspirin and a $P2Y_{12}$ receptor inhibitor represents the standard of care for the long-term secondary prevention of atherothrombotic events in patients with myocardial infarction (MI). The novel $P2Y_{12}$ receptor inhibitors prasugrel and ticagrelor are characterized by more prompt, potent, and predictable antiplatelet effects compared with clopidogrel and are associated with a greater reduction of ischemic events in acute coronary syndrome patients. However, rates of ischemic recurrences remain high, which may be in part due to the fact that other platelet signaling pathways, such as thrombin-induced platelet aggregation, continue to be activated. Vorapaxar is a novel, orally active, competitive and slowly reversible protease-activated receptor (PAR)-1 inhibitor, which exerts potent inhibition of thrombin-mediated platelet aggregation. It is approved for clinical use by the Food and Drug Administration for the reduction of thrombotic cardiovascular events in patients with a history of MI or with peripheral arterial disease. A large-scale clinical trial showed that the use of vorapaxar (2.5 mg once/daily) in addition to standard antiplatelet therapy (including aspirin and a $P2Y_{12}$ receptor inhibitor) was effective in the secondary prevention of recurrent thrombotic events in patients with previous atherothrombosis, in particular in patients with prior MI, at the expense of an increase in major bleeding. However, to date clinical trial experience with vorapaxar has been almost exclusively with the $P2Y_{12}$ receptor inhibitor clopidogrel and the effects of vorapaxar in combination with state-of-the-art antiplatelet therapy in the post-MI setting, including prasugrel or ticagrelor, is largely unexplored. This may indeed represent a limitation for the uptake of vorapaxar in modern day clinical practice where these agents are being more broadly utilized. Further, the role of vorapaxar as part of a dual antithrombotic treatment regimen, in addition to a novel $P2Y_{12}$ receptor inhibitor,

with withdrawal of aspirin, represents another important area of clinical interest as it has the potential to maximize ischemic protection while reducing the risk of bleeding. The proposed prospective, randomized, parallel-design, open label, study conducted in a real world clinical setting of post-MI patients will aim to assess the pharmacodynamic effects of vorapaxar in addition to antiplatelet therapy with a novel $P2Y_{12}$ receptor inhibitor (prasugrel or ticagrelor) with and without aspirin. Pharmacodynamic assessments will be performed at multiple time points and with different assays exploring multiple pathways of platelet aggregation. Exploratory assessments on the safety of such approach will also be evaluated.

Background and Significance

Dual antiplatelet therapy (DAPT) with aspirin and a $P2Y_{12}$ receptor inhibitor represents the standard of care for the long-term secondary prevention of atherothrombotic events in patients with myocardial infarction (MI) [1]. Clopidogrel is the most widely used $P2Y_{12}$ receptor inhibitor and the use of DAPT with aspirin and clopidogrel has consistently demonstrated to reduce the risk of thrombotic recurrences in patients with acute coronary syndrome (ACS) [2]. However, clopidogrel is a prodrug characterized by high interindividual response variability [3]. The novel $P2Y_{12}$ receptor inhibitors prasugrel and ticagrelor are characterized by more prompt, potent, and predictable antiplatelet effects compared with clopidogrel and are associated with a greater reduction of ischemic events in ACS patients, at the expense of an increase in major bleeding [4,5]. However, despite adequate cyclooxygenase-1 (COX-1) and ADP $P2Y_{12}$-receptor blockade, rates of ischemic recurrences remain high, which may be in part due to the fact that other platelet signaling pathways, such as thrombin-induced platelet aggregation, continue to be activated and can thus contribute to thrombus formation [2,6,7]. In particular, the serine protease thrombin is one of the most potent platelet activators and the surface of activated platelets is the main source of circulating thrombin, especially following an ACS [6-8]. Vorapaxar is a novel, orally active, highly selective, competitive and slowly reversible protease-activated receptor (PAR)-1 inhibitor, which exerts potent inhibition of thrombin-mediated platelet activation and aggregation [9,10]. After oral administration vorapaxar is rapidly absorbed with high bioavailability (>90%) and is metabolized by cytochrome P450 (CYP) 3A4. Pharmacokinetic studies have shown that vorapaxar has a dissociation half-life as long as 20 hours which leads to consistent pharmacodynamic (PD) effects [9,10]. Importantly, there is an

interplay between purinergic and thrombin mediated platelet signaling pathways which may result in enhanced $P2Y_{12}$ inhibition when vorapaxar is added to DAPT [11].

Recently, vorapaxar (2.5 mg once daily) has been approved for clinical use by the US Food and Drug Administration (FDA) for the reduction of thrombotic cardiovascular events in patients with a history of MI or with peripheral arterial disease (PAD), and must be used in addition to standard-of-care antiplatelet therapy with aspirin and/or clopidogrel [12]. Vorapaxar has been also approved by the European Medicines Agency for the treatment of patients with previous MI [13]. These indications are largely attributed to the findings of the TRA 2P-TIMI 50 (Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events - Thrombolysis in Myocardial Infarction 50) trial [14]. In particular, the trial showed that the use of vorapaxar (2.5 mg once/daily) in addition to standard antiplatelet therapy [including aspirin (94% of patients), a thienopyridine, or both (DAPT in 58% of patients; the thienopyridine was clopidogrel in 99.3% of patients)] was effective in the secondary prevention of recurrent thrombotic events (cardiovascular death, MI, or stroke) in patients with previous atherothrombosis, in particular in patients with prior MI, at the cost of increased bleeding [14,15]. However, the effects of vorapaxar in combination with state-of-the-art antiplatelet therapy in the post-MI setting, including prasugrel or ticagrelor, is largely unexplored.

Study Rationale

To date clinical trial experience with vorapaxar has been almost exclusively with the $P2Y_{12}$ receptor inhibitor clopidogrel and the effects of vorapaxar in combination with state-of-the-art antiplatelet therapy in the post-MI setting, including prasugrel or ticagrelor, is largely unexplored.

This may indeed represent a limitation for the uptake of vorapaxar in modern day clinical practice where these agents are being more broadly utilized [1,2]. This knowledge gap represents an important area for exploratory research as it represents how vorapaxar could potentially be used in daily clinical practice. Further, given the potent and comprehensive antiplatelet effects achieved with the novel $P2Y_{12}$ receptor inhibitors, the role of aspirin when added to these agents have been questioned [16,17]. Prasugrel and ticagrelor are effective in inhibiting both ADP $P2Y_{12}$-dependent and thromboxane A2-dependent pathways of platelet aggregation [16,17]. In particular, the platelet inhibition achieved by combining aspirin and a potent P2Y12-receptor blocker was shown to be no greater than that produced by the P2Y12-receptor blocker alone in healthy volunteers [16,17]. Therefore, the role of vorapaxar as part of a dual antithrombotic treatment regimen including prasugrel or ticagrelor and stopping aspirin, represents another important area of clinical interest as it has the potential to maximize ischemic protection while reducing the risk of bleeding.

Study Aims

To assess the pharmacodynamic effects of vorapaxar in addition to antiplatelet therapy with a novel $P2Y_{12}$ receptor inhibitor (prasugrel or ticagrelor) with and without aspirin in a real-world setting of post-MI patients. Exploratory assessments on the safety will also be evaluated.

Research Plan

Study Population

Inclusion criteria:

1. Patients with a prior MI within the previous 12 months.

2. On DAPT with low-dose aspirin (81mg od) and either prasugrel (10mg od) or ticagrelor (90mg bid) as per standard-of-care.
3. Free from bleeding and ischemic events after the index MI event.
4. Age between 18 and 75 years old.

Exclusion criteria:

1. History of stroke, transient ischemic attack, or intracranial hemorrhage.
2. Active pathological bleeding, history of bleeding events or increased risk of bleeding.
3. Known severe hepatic impairment.
4. Age >75 years.
5. Body weight <60 Kg.
6. Use of strong CYP3A inhibitors (e.g., ketoconazole, itraconazole, posaconazole, clarithromycin, nefazodone, ritonavir, saquinavir, nelfinavir, indinavir, boceprevir, telaprevir, telithromycin and conivaptan) or inducers (e.g., rifampin, carbamazepine, St. John's Wort and phenytoin).
7. On treatment with any oral anticoagulant (vitamin K antagonists, dabigatran, rivaroxaban, apixaban, edoxaban).
8. On treatment with any antiplatelet agent other than aspirin, prasugrel and ticagrelor in the past 14 days.
9. Creatinine clearance <30 mL/minute.
10. Platelet count $<80x10^6$/mL
11. Hemoglobin <10g/dL
12. Hemodynamic instability

13. Pregnant females [women of childbearing age must use reliable birth control (i.e. oral contraceptives) while participating in the study].

Research Design

The proposed investigation will be a prospective, randomized, parallel-design, open label, PD study conducted in a real world clinical setting of post-MI patients. Patients will be required to be on DAPT for at least 2 weeks before randomization. Although vorapaxar is approved for use irrespective of the timing of the MI, the rationale for including patients after 2 weeks is that, given the negative results of the clinical trial with vorapaxar in the acute phase of ACS, it may be reasonable to wait until patients have been stabilized after their index MI [18]. The rationale for the exclusion of elderly patients (aged >75 years) and patients with a low body weight (<60 kg) is that prasugrel is generally not recommended in these patient populations [1,2].

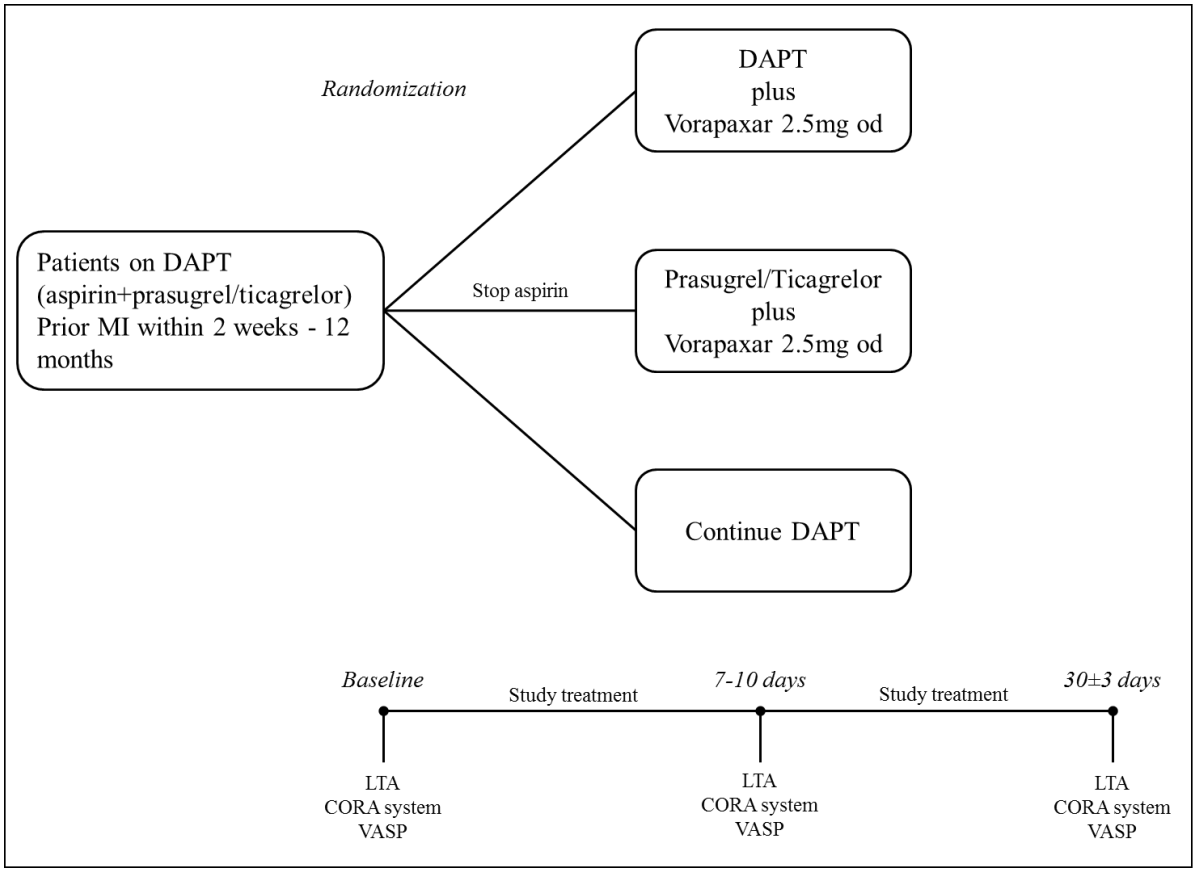
The study will be performed at the University of Florida Health Science Center at UF Health Jacksonville - Division of Cardiology. Patients will be recruited in the Cardiology Clinics of our institution and will be screened by Cardiology Research staff, who will verify that all candidates meet inclusion and exclusion criteria. Results from blood tests performed within the last 90 days will be considered valid for screening purposes. If these are not available, a blood sample will be collected for the screening phase. Although the study has an open-label design, laboratory personnel performing PD testing will be blinded to treatment assignment.

Patients on DAPT with aspirin and prasugrel/ticagrelor as part of their standard of care for at least 2 weeks and who are meeting study entry criteria will be randomly assigned in a 1:1:1 fashion to one of the following 3 treatment regimens: 1) DAPT (aspirin and prasugrel/ticagrelor) plus

vorapaxar 2.5mg od; 2) prasugrel/ticagrelor plus vorapaxar 2.5mg od; 3) continue DAPT with aspirin and prasugrel/ticagrelor. Randomized treatment will be administered for 30 ± 3 days; prasugrel and ticagrelor will be administered at their standard maintenance dose (10mg od and 90mg bid, respectively). Randomization will be stratified according to type of $P2Y_{12}$ inhibitor, in order to include at least 35% of patients on prasugrel. The rationale for predicting a higher number of randomized patients on ticagrelor derives from the more broad clinical indications of ticagrelor compared with prasugrel. Patient who entered the study before being on DAPT for 2 weeks will be required to complete 2 weeks of DAPT with aspirin and prasugrel/ticagrelor before randomization.

Blood sampling for PD testing will be conducted at 3 time-points: a) baseline (while patients will be on standard DAPT prior to initiating randomized treatment); b) after 7-10 days of randomized study treatment; c) after 30 ± 3days of randomized study treatment. At each time point, blood will be collected before the morning dose of prasugrel/ticagrelor and vorapaxar, in order to measure trough levels of platelet inhibition. During study treatment in-hospital major adverse cardiac events (death, MI, stroke, and urgent revascularization procedures) and serious adverse events (bleeding and other adverse events) will be collected. Bleeding will be defined by the BARC (Bleeding Academic Research Consortium) definition [19].

After study completion, patients will resume antiplatelet treatment regimen at the discretion of the treating physician. A flow diagram of the study design is illustrated below.



Laboratory assessments

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 3 time points as indicated above in the study design section. Various PD assays will be performed as described below. Given the potential interplay between PAR-1 and $P2Y_{12}$ mediated signaling, assessments specific for both pathways will be conducted [11]:

1. Light transmittance aggregometry (LTA)
2. Thrombelastograph Coagulation Analyzer TEG 6s Series system (CORA® system)
3. Whole blood vasodilator-stimulated phosphoprotein (VASP)
4. Serum thromboxane B2

Description of laboratory assays

1) 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 [20,21]. Platelet agonists will include AA (1 mM), collagen (3µg/ml), ADP (5 and 20 µM), 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. 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.

2) TEG 6s Series system (CORA® system): the TEG 6s system (Haemonetics Corporation, Braintree, MA, USA) will be used according to manufacture instructions [22]. In brief, the CORA®

system is a new generation portable thrombelastography technology able to evaluate all phases of hemostasis, including time to clot formation, rate of clot formation, strength of clot and residual clot strength due to antiplatelet drugs, rate of clot lysis. Disposable assay cartridges contain all of the components necessary to allow the analyzer to prepare samples and perform hemostasis tests. The analyzer automatically draws the blood into the active area of the cartridge, meters the exact amount required for the test, and mixes it with the reagents spotted in the cartridge. The analyzer then monitors the harmonic motion of a pendant drop of blood in response to external vibration. As the sample transitions from a liquid state to a gel-like state during clotting, the modulus of elasticity and resonant frequency increase. The instrument measures these variations in resonant frequency during clotting and lysis. The results are displayed in a table and on a graphical tracing that reflects a hemostasis profile of clot formation. The resulting hemostasis profile is a measure of the time it takes for the first measurable clot to be formed, the kinetics of clot formation, the strength of the clot, and the breakdown of the clot, or fibrinolysis. In particular, the PlateletMapping Cartridge are used to assess platelet function in patients who have received platelet inhibiting drugs. The PlateletMapping assay consists of a set of agonists, ADP and arachidonic acid (AA) platelet agonists together with ActivatorF, which can measure the inhibition of platelet function. This assay specifically determines the MA (Maximum Amplitude, a measure of clot strength) and the reduction in MA due to antiplatelet therapy and reports it as a percentage of reduction in clot strength. The assay uses AA and ADP agonists to generate test results that reflect the inhibiting effects of antiplatelet agents such as TxA2 Inhibitors (e.g., aspirin) and ADP $P2Y_{12}$ inhibitors (e.g., ticagrelor). Since thrombin (present in blood samples) is the primary and most potent activator of platelets, its activity must be inhibited with heparin so that the platelet activating effects of ADP and

AA can be measured. Since thrombin has been rendered inactive by heparin, activatorF is used to replace thrombin's role in the conversion of fibrinogen to fibrin and Factor XIII to Factor XIIIa. Thus, with this cross-linked fibrin network as the foundation, additional clot strength due to platelet-fibrin bonding related to ADP and AA platelet receptor activation can be measured. The HKH reagent, a combination of kaolin and heparinase, generates test data for the uninhibited MA resulting from thrombin activation of the blood sample, while the heparinase neutralizes the effects of heparin. The HKH test provides measures of R (Reaction time; the amount of time between the start of the test and the beginning of coagulation), K (the speed of formation of the clot from R time to a specific clot strength), Angle (the speed of clot strengthening), LY30 (Percent lysis 30 minutes after MA is finalized) and MA parameters; The activatorF test provides the contribution of fibrin to the overall strength of the clot. This test value is used in the calculation of aggregation/inhibition for MA ADP and MA AA. The AA and ADP test provide measures of MA, percent inhibition and percent aggregation.

3) Whole blood vasodilator-stimulated phosphoprotein (VASP): VASP phosphorylation (VASP-P) is a marker of $P2Y_{12}$ receptor reactivity. 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 [23]. 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 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 P2Y12 reactivity ratio = ([MFI PGE1] – [MFI PGE1 + ADP]/[MFI PGE1]) x 100%.

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) according to the instructions of the manufacturer, as previously described [24]. Briefly, samples will be diluted with EIA buffer to bring their concentrations within the range of the standard curve. No other purification will be performed on any of the samples. 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.

Study endpoints and sample size calculation

The primary end point of our study is the comparison of CAT-induced MPA between DAPT and DAPT plus vorapaxar after 30 ± 3 days of treatment. We hypothesize that adjunctive vorapaxar will result into a significant reduction of platelet aggregation. Assuming a 10% absolute reduction in CAT-induced MPA with a common standard deviation of 13%, 37 patients per group will be needed to detect a significant difference between DAPT and DAPT plus vorapaxar with a 90% power and 2-sided alpha=0.05. Considering a possible 30-35% rate of invalid results due to hemolysis or drop-out and the three arms of treatment up to 146 patients will need to be randomized. Since there are no preliminary data in this particular setting, the sample size of our study was calculated based on previous data of vorapaxar in addition to DAPT with aspirin and clopidogrel [21]. This approach is in agreement with recommendations for pilot investigations [25].

Our secondary outcome will be the comparison of CAT-induced MPA between vorapaxar in addition to a new generation $P2Y_{12}$ receptor inhibitor (prasugrel or ticagrelor) and vorapaxar in addition to standard DAPT (aspirin and prasugrel/ticagrelor). We hypothesize that stopping aspirin will not lead to significant differences in CAT-induced MPA after 30 ± 3 days of treatment.

Other objectives will include the comparisons among the 3 groups of all PD parameters measured by multiple assays at every time point, as well as intragroup comparisons of PD parameters in order to evaluate the variability over time of vorapaxar PD effects, as well as how PD measures will be affected by aspirin withdrawal.

Statistical analysis plan

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 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. An analysis of covariance (ANCOVA) method with a general linear model, using baseline variables significantly different between groups as covariates, will be used to evaluate the overall difference between groups and all between-groups comparisons, in line with other PD studies [23]. Analysis of variance (ANOVA) will be used to evaluate intragroup comparisons. 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).

Publication Strategy/Additional Information

Study subjects will be identified first (months 1-24): we expect to enroll approximately 5-6 subjects monthly and complete enrollment in 24 months (total: 126 subjects enrolled). Months 25-26 will be implied for statistical analysis and months 27-28 for 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 straight forward prospective study and is based on well-established methods. However, since there is limited experience with vorapaxar to define platelet function, variability may be higher than expected and we cannot currently perform a detailed sample size calculation. We anticipate adding this to the protocol after inclusion of the study population has been completed. If the sample size after one year is estimated to be too small, additional patients will be included. This approach is in agreement with recommendations for pilot investigations [25].

Possible Discomforts and Risk

In clinical trials, the most common clinical side effects of vorapaxar were anemia (5%), depression (2.4%) and rash (2.2%) [14, 18]. The most important adverse effect associated with the use of vorapaxar is bleeding. The risk of TIMI clinically significant bleeding with vorapaxar is 15.8% and 11.1% with placebo (HR 1.46; 95% CI, 1.36-1.57, $p<0.001$); the risk of TIMI non-CABG-related major bleeding with vorapaxar is 2.8% and 1.8% with placebo (HR 1.46; 95% CI, 1.22-1.75, $p<0.001$); the risk of intracranial bleeding (intracerebral, subdural or epidural) with vorapaxar is 1% vs 0.5% with placebo (HR 1.94; 95% CI 1.39-2.70; $p <0.001$) [14]. However, such

bleeding prevalence occurred in the setting of long-term (3 years) trial, while our study is limited to only approximately 30 days of vorapaxar therapy. We have also excluded from the study patients at increased risk of bleeding complications [12-14]. Moreover, the use of vorapaxar in this study is limited to the intended for use population at low risk of bleeding. All clinical events described above, if they were to occur, as well as death, myocardial infarction, stroke, and urgent revascularization procedure with PCI or coronary artery bypass grafting will be recorded. Bleeding data will be collected using BARC definitions [20]. 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 vorapaxar as an add-on therapy to standard antiplatelet treatment in patients with previous MI. 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

Conflict of Interest

Dr. Angiolillo is a consultant for Merck, the maker of vorapaxar.

References

1. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC Guideline for the Management of Patients with Non-ST-Elevation Acute Coronary Syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;64:e139-228.
2. Franchi F, Angiolillo DJ. Novel antiplatelet agents in acute coronary syndrome. Nat Rev Cardiol. 2015;12:30-47.
3. Angiolillo DJ, Fernandez-Ortiz A, Bernardo E, et al. Variability in individual responsiveness to clopidogrel: clinical implications, management, and future perspectives. J Am Coll Cardiol. 2007;49:1505-16.
4. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2007;357:2001-15.
5. 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.
6. Davì G, Patrono C. Platelet activation and atherothrombosis. N Engl J Med. 2007; 357:2482-94.
7. Angiolillo DJ, Ueno M, Goto S. Basic principles of platelet biology and clinical implications. Circ J. 2010; 74:597-607.
8. Brummel-Ziedins K, Undas A, Orfeo T, et al. Thrombin generation in acute coronary syndrome and stable coronary artery disease: dependence on plasma factor composition. J Thromb Haemost. 2008;6:104-10.
9. Cho JR, Rollini F, Franchi F, et al. Unmet needs in the management of acute myocardial infarction: role of novel protease-activated receptor-1 antagonist vorapaxar. Vasc Health Risk Manag. 2014; 10:177-88.
10. Angiolillo DJ, Capodanno D, Goto S. Platelet thrombin receptor antagonism and atherothrombosis. Eur Heart J. 2010; 31:17-28.
11. Nylander S, Mattsson C, Ramström S, Lindahl TL. Synergistic action between inhibition of P2Y12/P2Y1 and P2Y12/thrombin in ADP- and thrombin-induced human platelet activation. Br J Pharmacol. 2004;142:1325-31.

12. FDA Vorapaxar prescribing information [online] http://www.fda.gov/drugs/informationondrugs/ucm423935.htm Accessed on March 2015.
13. EMA Vorapaxar prescribing information [online] http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002814/human_med_001839.jsp&mid=WC0b01ac058001d124 Accessed on March 2015.
14. Morrow DA, Braunwald E, Bonaca MP, et al. Vorapaxar in the secondary prevention of atherothrombotic events. N Engl J Med. 2012; 366:1404-13.
15. Scirica BM, Bonaca MP, Braunwald E, et al. Vorapaxar for secondary prevention of thrombotic events for patients with previous myocardial infarction: a prespecified subgroup analysis of the TRA 2°P-TIMI 50 trial. Lancet. 2012; 380:1317-24.
16. Armstrong PC, Leadbeater PD, Chan MV, et al. In the presence of strong P2Y12 receptor blockade, aspirin provides little additional inhibition of platelet aggregation. J Thromb Haemost. 2011;9:552-61.
17. Kirkby NS, Leadbeater PD, Chan MV, et al. Antiplatelet effects of aspirin vary with level of $P2Y_{12}$ receptor blockade supplied by either ticagrelor or prasugrel. J Thromb Haemost. 2011;9:2103-5.
18. Tricoci P, Huang Z, Held C, et al. Thrombin-receptor antagonist vorapaxar in acute coronary syndromes. N Engl J Med. 2012;366:20-33.
19. 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.
20. Angiolillo DJ, Badimon JJ, Saucedo JF, et al. A pharmacodynamic comparison of prasugrel vs. high-dose clopidogrel in patients with type 2 diabetes mellitus and coronary artery disease: results of the Optimizing anti-Platelet Therapy In diabetes MellitUS (OPTIMUS)-3 Trial. Eur Heart J. 2011;32:838-46.
21. Storey RF, Kotha J, Smyth SS, et al. Effects of vorapaxar on platelet reactivity and biomarker expression in non-ST-elevation acute coronary syndromes. The TRACER Pharmacodynamic Substudy. Thromb Haemost. 2014;111:883-91.

22. FDA TEG 6s Series system indications for use and 510(k) summary [online] www.accessdata.fda.gov/cdrh_docs/pdf14/k140893.pdf Accessed on April 2015
23. Rollini F, Franchi F, Tello-Montoliu A, et al. Pharmacodynamic effects of cangrelor on platelet P2Y12 receptor-mediated signaling in prasugrel-treated patients. JACC Cardiovasc Interv. 2014;7:426-34.
24. Capodanno D, Patel A, Dharmashankar K, et al. Pharmacodynamic effects of different aspirin dosing regimens in type 2 diabetes mellitus patients with coronary artery disease. Circ Cardiovasc Interv. 2011;4:180-7.
25. Lancaster GA, Dodd S, Williamson PR. Design and analysis of pilot studies: recommendations for good practice. J Eval Clin Pract. 2004; 10:307-12.