Pharmacodynamic Effects of Vorapaxar as an Add-On Antiplatelet Therapy in Patients with and without Diabetes Mellitus:

the Optimizing anti-Platelet Therapy In diabetes Mellitus (OPTIMUS)-5 Study

NCT02548650
 Protocol version 2, approval date 10/02/2018

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Summary

Dual antiplatelet therapy (DAPT) with aspirin and a P2Y$_{12}$ receptor inhibitor, more frequently clopidogrel, represents the standard of care for the long-term secondary prevention of atherothrombotic events in patients with myocardial infarction (MI) or peripheral arterial disease (PAD). However, rates of ischemic recurrences remain high, 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 PAD. Patients with DM are known to be at increased risk of recurrent atherothrombotic events, which translates into worse outcomes, despite the use of standard of care therapy. This is in part due to the hyperreactive platelet phenotype, which characterizes DM patients, and to inadequate response to oral antiplatelet agents, including clopidogrel. Importantly, in DM patients with prior MI included in the TRA 2P trial, vorapaxar reduced the primary composite end point at 3 years by 27% and led to a greater absolute risk reduction compared with those without DM. Therefore, vorapaxar is an attractive treatment option for DM patients with a prior MI. However, to date the PD effects of vorapaxar in DM patients and how these may differentiate from non-DM patients has not been explored. Further, current trends in clinical practice are seeing many patients discontinue aspirin and maintain clopidogrel. Hence, the role of vorapaxar as part of a dual antithrombotic treatment regimen combined with clopidogrel (and stopping aspirin) represents another important area of clinical
interest, in order to maximize ischemic protection while reducing the risk of bleeding. The proposed prospective, parallel-design study conducted in post-MI and PAD patients with and without DM will aim to assess the pharmacodynamic effects of vorapaxar in addition to standard DAPT with aspirin and clopidogrel as well as in combination with clopidogrel only following aspirin withdrawal. Pharmacodynamic assessments will be performed at multiple time points, with different assays exploring multiple pathways of platelet aggregation.
Background and Significance

Dual antiplatelet therapy (DAPT) with aspirin and a P2Y<sub>12</sub> 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<sub>12</sub> 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, despite this treatment regimen, rates of ischemic recurrences remain elevated, especially in high risk patients, such as those with diabetes mellitus (DM) [2-4]. This is 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 [5,6]. In particular, thrombin is one of the most potent platelet activators, and the surface of activated platelets is the main source of circulating thrombin [5-7]. 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 aggregation [8,9]. Pharmacokinetic studies have shown that vorapaxar has a dissociation half-life as long as 20 hours which leads to consistent pharmacodynamic (PD) effects [8,9]. Importantly, when vorapaxar is added to DAPT, enhanced P2Y<sub>12</sub> inhibition has been shown due to the potential interplay between purinergic and thrombin-mediated platelet signaling pathways [10]. Recently, vorapaxar (2.5 mg once daily) has been approved for clinical use by the US Food and Drug Administration (FDA) and by the European Medicines Agency for the reduction of thrombotic cardiovascular events in patients with a history of MI or with peripheral arterial disease (PAD), and should be used in addition to standard-of-care antiplatelet therapy with aspirin and/or clopidogrel [11,12]. 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 [13]. In particular, the trial showed that the use of vorapaxar in addition to standard antiplatelet therapy was effective in the secondary prevention of recurrent thrombotic events (cardiovascular death, MI, or stroke) in patients with previous atherothrombosis, particularly those with prior MI and PAD, albeit at the cost of increased bleeding [13,14].

Patients with DM are known to be at increased risk of recurrent atherothrombotic events, which translates into worse outcomes, despite the use of standard of care therapy [4,15]. This is in part due to the hyperreactive platelet phenotype with upregulation of multiple platelet signaling pathways, including thrombin, which characterizes patients with DM [4]. Importantly, increased platelet reactivity may account for inadequate response (i.e. reduced platelet inhibitory effects) to oral antiplatelet agents, including the P2Y₁₂ receptor antagonist clopidogrel, contributing to worse outcomes [4]. Notably, in DM patients and prior MI included in the TRA 2P trial, vorapaxar reduced the primary composite end point at 3 years by 27% (p=0.002), and led to a greater absolute risk reduction (absolute risk difference: -3.50%) compared with those without DM (absolute risk difference: -1.36%) with a number needed to treat of 29 [16]. The benefit of vorapaxar was also consistent in patients with PAD, although no specific subgroup data are available based on DM status [17]. Therefore, patients with DM, characterized by diffuse atherothrombotic disease manifestations and enhanced risk of ischemic recurrences, seem particularly attractive for treatment with vorapaxar. However, to date the PD effects of vorapaxar in patients with DM, as well as the comparative effects of DM versus non-DM patients has not yet been explored.

**Study Rationale and aims**

Despite the encouraging clinical findings from TRA-2P and the potential for an uptake of vorapaxar in daily practice, there is limited data on the PD effects of vorapaxar as an add-on therapy in key high-risk settings, such as prior MI or PAD patients with DM, where enhanced platelet
inhibition by means of PAR-1 blockade, may be more clinically beneficial. Further, given the length of the TRA-2P trial (median follow-up of 30 months), many patients were enrolled in the trial while on standard DAPT with aspirin and clopidogrel, but then interrupted one antiplatelet agent as per standard of care [13]. Although most patients discontinue clopidogrel therapy and continue aspirin, current trends in clinical practice are seeing many patients discontinue aspirin and maintain clopidogrel, which provides more comprehensive platelet inhibition compared with aspirin [18]. Hence, the role of vorapaxar as part of a dual antithrombotic treatment regimen combined with clopidogrel (and stopping aspirin) represents another important area of clinical interest, in order to maximize ischemic protection while reducing the risk of bleeding. Further, the comparative PD effects of vorapaxar in addition to different combination of antiplatelet therapy in patients with DM versus those without DM is currently unknown. A comprehensive understanding of the PD effects of vorapaxar as an add-on therapy will thus be informative to the practicing clinician. Therefore, the aim of the proposed investigation is to assess the PD effects of vorapaxar in addition to DAPT with aspirin and clopidogrel as well as to antiplatelet therapy with clopidogrel, in the setting of post-MI or PAD patients with and without DM.

**Research Plan**

**Study Population**

*Inclusion criteria:*

1. Patients with a prior MI between 2 weeks and 24 months or with PAD.
2. On DAPT with low-dose aspirin (81mg od) and clopidogrel (75mg od) as per standard-of-care for at least 14 days.
3. Age ≥ 18 years old.
4. Patients entering the DM cohort will need to have diagnosis of type 2 DM defined according to the WHO definition [19], on treatment with oral hypoglycemic agents and/or insulin for at least two months, without any changes in regimen.

Exclusion criteria:

1. History of ACS in the previous 2 weeks.
2. History of stroke, transient ischemic attack, or intracranial hemorrhage.
3. Active pathological bleeding, history of bleeding events or increased risk of bleeding.
4. Known severe hepatic impairment.
5. Type 2 DM on dietary control.
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 and clopidogrel 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 parallel-design PD study conducted in post-MI or PAD patients with and without DM. Although vorapaxar is approved for use irrespective of the timing of the MI, the rationale for including patients after 2 weeks is that this time frame allows clopidogrel to exert its full antiplatelet effects [20,21].

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.

After providing written informed consent, patients on DAPT with aspirin and clopidogrel meeting study entry criteria will be divide in two groups according to DM status and will receive vorapaxar 2.5mg od in addition to DAPT. Triple therapy (vorapaxar 2.5mg od plus clopidogrel 75 mg od and aspirin 81 mg od) will be administered for 30±5 days; then patients will stop aspirin and will take dual treatment (vorapaxar 2.5mg od plus clopidogrel 75 mg od) for other 30±5 days. Blood sampling for PD testing will be conducted at 3 time-points: baseline (while patients will be on standard DAPT); after 30±5 days of triple therapy; 30±5 days after dual treatment. At each time point, blood will be collected before the morning dose of clopidogrel and vorapaxar, in order to measure trough levels of platelet inhibition. Although no wash-out period will be performed, the risk of carry-over effect is considered low, as the treatment period will be significantly longer than the offset of aspirin antiplatelet effect (7-10 days). During study treatment major adverse cardiac events (death, MI, stroke, and urgent revascularization procedures) and serious adverse events
(bleeding and other adverse events) will be collected in each group. Bleeding will be defined by the BARC (Bleeding Academic Research Consortium) definition [22].

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 [10]:

1. Light transmittance aggregometry (LTA)
2. Whole blood vasodilator-stimulated phosphoprotein (VASP)
3. VerifyNow P2Y12
4. Thrombelastograph Coagulation Analyzer TEG 6s Series system (CORA® system)
5. 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 [23,24]. 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) Whole blood vasodilator-stimulated phosphoprotein (VASP): VASP phosphorylation (VASP-P) is a marker of P2Y12 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 [25]. 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 = \([\text{MFI PGE1} – \text{MFI PGE1 + ADP}] / \text{MFI PGE1}\) x 100%.

3) VerifyNow (VN) P2Y12: 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 [25]. The assay is based on microbead agglutination and uses specific reagents for the pathways of interest. The VN-P2Y12 assay, by combining ADP+PGE1, measures changes in platelet function specific to P2Y12 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 P2Y12 Reaction Units (PRU).
4) TEG 6s Series system (CORA® system): the TEG 6s system (Haemonetics Corporation, Braintree, MA, USA) will be used according to manufacture instructions [26]. 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 P2Y₁₂ inhibitors (e.g., clopidogrel). 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.

5) 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 [27]. 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 measured by LTA between vorapaxar plus DAPT and vorapaxar plus clopidogrel. We hypothesize that vorapaxar in addition to single antiplatelet therapy with clopidogrel will be non-inferior to vorapaxar in addition to DAPT with aspirin and clopidogrel in MPA after 30±5 days of treatment in both DM and non-DM patients. Under the assumption of 0 difference in mean CAT-induced MPA between vorapaxar plus clopidogrel and vorapaxar plus DAPT and a common standard deviation of 13%, a sample size of 28 patients per group allows for the 95% confidence interval (CI) to stay within ± 10% with a 80% power and alpha=0.025. Considering the two groups (DM and non-DM), a total of 56 patients with valid primary end point data will need to be included. Assuming up to 40% rate of invalid results due to haemolysis or drop-out, up to 79 patients will need to be enrolled. Non-inferiority will be assessed using a 95% CI of the difference in mean MPA between the 2 arms. As there are no preliminary data in this setting, the 10% non-inferiority margin was arbitrarily defined. Mean values of platelet aggregation and variability were estimated based on previous data of vorapaxar in addition to DAPT with aspirin and clopidogrel [24]. This approach is in agreement with recommendations for pilot investigations [28].

Other objectives will include the comparisons between DM and non-DM patients of all PD parameters measured by multiple assays, and the comparisons between levels of platelet inhibition achieved by DAPT (baseline therapy) versus levels achieved by antiplatelet therapy including vorapaxar. The effects of additive inhibition of the thrombin-mediated platelet activation pathway, with or without aspirin therapy, on serum thromboxane levels will also be evaluated.

**Statistical analysis plan**

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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 [25]. Student’s t test or Wilcoxon test will be used to evaluate intragroup comparisons. Non-inferiority will be assessed using a 95% CI of the difference in mean MA between vorapaxar plus prasugrel/ticagrelor and vorapaxar plus DAPT.

A p-value of <0.025 will be considered to be statistically significant for the non-inferiority analysis. A 2-tailed p value of < 0.05 is considered to indicate a statistically significant difference for all the other 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 1-16): we expect to enroll 4 subjects monthly and complete enrollment in 16 months (total: 64 subjects enrolled). Months 17-18 will be implied for statistical analysis and months 19-20 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 straightforward 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 [28].

**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%) [13,20]. 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) [13]. However, such bleeding prevalence occurred in the setting of long-term (3 years) trial, while our study is limited to only approximately 60 days of vorapaxar therapy. We have also excluded from the study patients at increased risk of bleeding complications [11,12,29]. 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 [22]. 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 or PAD. 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


11. FDA Vorapaxar prescribing information [online]

12. EMA Vorapaxar prescribing information [online]


26. FDA TEG 6s Series system indications for use and 510(k) summary [online] 

