

Thrombosis Research active studies

A Pharmacodynamic Study Comparing Prasugrel Versus Ticagrelor in Patients With Coronary Artery Disease Undergoing PCI With CYP2C19 Loss-of-function Genotypes: A Feasibility Study With Point-of-care Pharmacodynamic and Genetic Testing

Numerous studies have shown that response profiles vary among clopidogrel treated patients and that individuals with reduced response have an increased risk of recurrent ischemic events. There are multiple factors contributing to clopidogrel response variability, including genetic variations of the hepatic cytochrome P450 (CYP) 2C19 enzyme. In particular, loss-of-function (LOF) alleles of the CYP2C19 enzyme reduce transformation of clopidogrel pro-drug into its active metabolite. Thus, patients carrying LOF alleles have lower levels of clopidogrel's active metabolite as well as diminished platelet inhibition, which translates into an increased rate of adverse cardiovascular events, particularly in the setting of percutaneous coronary intervention (PCI). Prasugrel and ticagrelor are novel generation FDA-approved P2Y12 receptor inhibitors characterized by greater antiplatelet effect and reduced ischemic event rates compared with clopidogrel, and are not affected by CYP2C19 LOF polymorphisms. However, to date there are limited head-to-head comparisons between these two new P2Y12 receptors blockers, and there are no studies assessing how these agents behave among CYP2C19 LOF carriers. The aim of the present study is to compare the antiplatelet effects of prasugrel versus ticagrelor in patients undergoing PCI with CYP2C19 LOF alleles using the novel rapid genetic testing Spartan RX-CYP2C19 which permits accurate and fast (less than 1 hour) identification of CYP2C19 genetic status.

ClinicalTrials.gov Identifier: NCT02065479

Pharmacodynamic Effects of Vorapaxar as an Add-On Antiplatelet Therapy in Post Myocardial Infarction Patients With and Without Diabetes Mellitus: The Optimizing Anti-Platelet Therapy In Diabetes Mellitus (OPTIMUS)-5 Study

Dual antiplatelet therapy (DAPT) with aspirin and a P2Y12 receptor inhibitor, more frequently clopidogrel, represents the standard of care for the long-term secondary prevention of thrombotic events in patients with myocardial infarction. However, rates of ischemic recurrences remain high. Vorapaxar is a protease-activated receptor (PAR)-1 inhibitor, which exerts potent inhibition of thrombin-mediated platelet aggregation. Patients with diabetes mellitus (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. Therefore, vorapaxar is an attractive treatment option for DM patients with a prior MI. The antiplatelet effects of vorapaxar in DM patients and how these may differentiate from non- DM patients has not been explored. Further, 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. The proposed prospective, parallel-design study conducted in post-myocardial infarction patients with and without DM will aim to assess the antiplatelet effects of vorapaxar in addition to standard DAPT with aspirin and clopidogrel, as well as in combination with clopidogrel only, following aspirin withdrawal.

ClinicalTrials.gov Identifier: NCT02548650

Adjunctive Vorapaxar Therapy in Patients With Prior Myocardial Infarction Treated With New Generation P2Y12 Receptor Inhibitors Prasugrel and Ticagrelor (VORA-PRATIC): A Prospective, Randomized, Pharmacodynamic Study

Dual antiplatelet therapy (DAPT) with aspirin and a P2Y12 receptor inhibitor represents the standard of care for the long-term secondary prevention of thrombotic events in patients with myocardial infarction (MI). 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 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. However, to date clinical trial experience with vorapaxar has been almost exclusively with the P2Y12 receptor inhibitor clopidogrel and the effects of vorapaxar in combination with antiplatelet therapy including prasugrel or ticagrelor, is largely unexplored. Further, the role of vorapaxar as part of a dual antithrombotic treatment regimen, in addition to prasugrel or ticagrelor, 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 antiplatelet effects of vorapaxar in addition to antiplatelet therapy with a novel P2Y12 receptor inhibitor (prasugrel or ticagrelor) with and without aspirin.

ClinicalTrials.gov Identifier: NCT02545933

Impact of Chronic Kidney Disease on the Pharmacodynamic and Pharmacokinetic Effects of Ticagrelor in Patients With Diabetes Mellitus and Coronary Artery Disease

Patients with diabetes mellitus (DM) are at increased risk of atherothrombotic events. Importantly, DM is a key risk factor for the development of chronic kidney disease (CKD), which further enhances atherothrombotic risk. Clopidogrel is the most widely used platelet P2Y12 receptor inhibitor. However, despite its clinical benefit, patients with DM and CKD frequently experience recurrent atherothrombotic events. Ticagrelor is an oral, reversible, non-competitive P2Y12 receptor inhibitor with more potent and consistent platelet inhibition than clopidogrel. In large-scale clinical investigation, ticagrelor significantly reduced ischemic events to a greater extent than clopidogrel, a finding that was consistent also among DM patients. To date there has been no analysis on the efficacy of ticagrelor in DM patients according to CKD status. Moreover, although PD studies showed enhanced platelet inhibition associated with ticagrelor, it is unknown how this may be affected by CKD status. Ultimately, how PK/PD profiles of different ticagrelor dosing regimens may be affected by DM and CKD status is also unknown. The proposed study is aimed to show the impact of CKD status among patients with DM and CAD on PD and PK profiles of ticagrelor used at 2 doses (90mg bid and 60mg bid) in the setting of a prospective, randomized, cross-over trial.

ClinicalTrials.gov Identifier: NCT02539160

Implementation of CYP2C19 Genotyping to Guide Antiplatelet Therapy for Patients Undergoing Cardiac Catheterization at UF Health Jacksonville

Dual antiplatelet therapy with aspirin and a P2Y₁₂ receptor inhibitor represents the standard of care treatment for the prevention of major adverse cardiovascular events in patients undergoing percutaneous coronary intervention (PCI). Currently, 3 oral P2Y₁₂ receptor inhibitors (clopidogrel, prasugrel, and ticagrelor) are available for clinical use. Clopidogrel remains the most broadly used P2Y₁₂ receptor inhibitor. However, it is well established that clopidogrel-induced antiplatelet effects is suboptimal in many patients who are thus exposed to an increased risk of adverse cardiovascular events. Studies have shown that genotypes of the cytochrome P450 (CYP) 2C19 enzyme, which is a key determinant of clopidogrel metabolism, contribute to these findings. In fact, clopidogrel is a prodrug that requires bioactivation by the CYP2C19 enzyme. Approximately 30-40% of individuals have the loss-of-function (LOF) CYP2C19 genotype and cannot sufficiently convert clopidogrel to its active form, thereby gaining little to no benefit from the drug. Prasugrel and ticagrelor are alternative agents whose effectiveness is not dependent on CYP2C19 genotype. A boxed warning on the Food and Drug Administration (FDA)-approved clopidogrel labeling warns of reduced effectiveness in patients with the LOF genotype and recommends alternative therapies in these patients. Guidelines from the Clinical Pharmacogenetics Implementation Consortium (CPIC) specifically recommend prasugrel or ticagrelor over clopidogrel for patients with a LOF CYP2C19 genotype who undergo PCI. In turn, these recommendations have led to the use in clinical practice of genetic testing of CYP2C19 genotypes as an aid to clinicians in determining therapeutic strategies for patients undergoing PCI. However, the uptake of genetic testing in real-world clinical practice has been limited by the availability of assays able to provide genetic results in a timely fashion. The availability of an assay recently approved by the FDA, SpartanRX, which provides results within one-hour facilitates performing genetic testing as a clinical test in real-world practice. We therefore propose to 1) examine the feasibility of implementing CYP2C19 genotyping using SpartanRX as standard of care for patients undergoing cardiac catheterization at UF Health Jacksonville providing the opportunity for clinicians to embrace genotype-guided antiplatelet therapy in those who proceed to PCI and 2) determine if CYP2C19 genotype-guided antiplatelet therapy reduces the risk for major adverse cardiovascular outcomes after PCI.

ClinicalTrials.gov Identifier: NCT02724319

Pharmacodynamic Comparison of Prasugrel versus Ticagrelor in Patients With CYP2C19 Loss-of-Function Genotype: A Validation Study in Patients With Stable Coronary Artery Disease

Therapeutic inhibition of platelet activation is essential for the management of ischemic cardiovascular disease. The use of platelet adenosine diphosphate (ADP) P2Y₁₂ receptor antagonists (clopidogrel, prasugrel, and ticagrelor) in addition to aspirin are associated with a decrease in cardiovascular events in high-risk coronary artery disease (CAD) patients. Clopidogrel is the most broadly utilized P2Y₁₂ receptor antagonist. However, among clopidogrel treated patients, there is broad variability in antiplatelet drug response which is known carry prognostic implications. Polymorphisms of the cytochrome P450 (CYP) 2C19 enzyme has been consistently shown to modulate clopidogrel response. Accordingly, the Food and Drug Administration (FDA) has issued a warning on the potential for reduced efficacy of clopidogrel among carriers of loss-of-function alleles (LOF) for CYP2C19 and suggest considering alternative antiplatelet therapies for these individuals.

The pharmacodynamic (PD) effects of prasugrel and ticagrelor are not affected by CYP2C19 genetic polymorphisms. However, to date there are no head-to-head PD comparisons between these agents among patients with different CYP2C19 genetic polymorphisms which is currently under investigation in CAD patients undergoing PCI at UF Health-Jacksonville (UFJ 2014-12, NCT 02065479). In order to rule out play of chance findings, pharmacogenetic investigations require external validation cohorts to support the study findings. Therefore, the present randomized study is designed to serve as an external validation cohort conducted in patients with established CAD not undergoing PCI testing the non-inferiority in platelet reactivity of prasugrel versus ticagrelor among CYP2C19 LOF allele carriers.

ClinicalTrials.gov Identifier: NCT03489863

Impact of the PCSK9 Inhibitor Evolocumab on the Pharmacodynamic Effects of Clopidogrel in Patients with Atherosclerotic Cardiovascular Disease and High On-Treatment Platelet Reactivity

Clopidogrel is the most widely used P2Y₁₂ receptor inhibitor and is the only agent of this class currently recommended in patients with stable coronary artery disease (CAD) undergoing PCI, and for the treatment of stroke or PAD. Pharmacodynamic (PD) studies have shown that approximately 30-40% of patients experience high on-treatment platelet reactivity (HPR) while receiving clopidogrel treatment. Importantly HPR status has been strongly associated with an increased risk of ischemic events. Multiple approaches have been advocated to reduce HPR rates. In a previous study treatment with high-dose atorvastatin in addition to double-dose clopidogrel reduced platelet reactivity significantly more than double-dose clopidogrel alone in statin-naïve patients with stable CAD and HPR. To date, the exact biological mechanisms involved in the statin modulation of platelet function are not fully understood, although likely attributed to both its lipid-lowering and non-lipid-related effects.

Evolocumab is a monoclonal antibody targeting proprotein convertase subtilisin/kexin type 9 (PCSK9). The use of evolocumab plus standard therapy, as compared with standard therapy alone, significantly reduced the incidence of cardiovascular events. Whether the reduction in cardiovascular events is simply due to LDL reduction or might be related to other mechanisms is currently subject of investigation. Although LDL reduction with statin therapies has been associated with reduction in platelet reactivity, to date the effects on platelet aggregation of adjunctive lipid lowering with evolocumab has not been explored.

The aim of the present study is to investigate the effects of evolocumab in addition to statin therapy on HPR rates and platelet reactivity in patients with atherosclerotic cardiovascular disease (ASCVD) and HPR while on clopidogrel treatment.

ClinicalTrials.gov Identifier: NCT03096288

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

Patients with diabetes mellitus (DM) are characterized by platelet hyperreactivity and reduced pharmacodynamic (PD) effects to several oral antiplatelet agents, including clopidogrel. In addition to the hyperreactive platelet phenotype, impaired drug metabolism as well as increased platelet turnover rates may contribute to impaired clopidogrel-induced antiplatelet effects in DM patients. 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.

Ticagrelor is characterized by more prompt, potent and predictable antiplatelet effects compared with clopidogrel and lower ischemic events in patients with an acute coronary syndrome (ACS) on a background of aspirin therapy. 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.

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. Moreover, PD studies with the ticagrelor 60 mg bid regimen are limited. 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.

ClinicalTrials.gov Identifier: NCT03437044