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 Evaluation of Switching From Ticagrelor to Clopidogrel in Patients With Coronary Artery Disease

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 P2Y12 receptor inhibitor. More potent P2Y12 receptor inhibitors, such as 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 acute event 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 with ticagrelor to treatment with clopidogrel. However, the effects on platelet inhibition of switching from ticagrelor to clopidogrel remain unknown. Therefore, the aim of this investigation is to evaluate the effects of switching from ticagrelor to clopidogrel on platelet aggregation.

ClinicalTrials.gov Identifier: NCT02287909

Effect of the Peripheral Opioid Receptor Antagonist Methylnaltrexone on the Pharmacokinetic and Pharmacodynamic Profiles of Ticagrelor in Patients Receiving Morphine: a Prospective, Randomized Placebo-controlled Trial

Ticagrelor is associated with more prompt and potent antiplatelet effects compared with clopidogrel, leading to better clinical outcomes, including reduced cardiovascular mortality, across the spectrum of patients with acute coronary syndrome, including those with ST-elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention. However, in this latter setting a delay in the onset of its antiplatelet effects has been shown. Morphine has been identified as a cause of delayed P2Y12 inhibition in patients with STEMI. Methylnaltrexone is a parenteral peripheral opioid receptor antagonist which has the potential to prevent or reverse opioid-induced peripherally mediated side effects without affecting analgesia. However, whether the use of intravenous methylnaltrexone may overcome the effects of morphine administration on the pharmacokinetic and pharmacodynamics profiles of ticagrelor has not been investigated yet. This investigation will include
patients with coronary artery disease and will have a prospective, randomized, cross-over design where patients will receive morphine, methylnaltrexone (or placebo) and ticagrelor.

**ClinicalTrials.gov Identifier: NCT02403830**

**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 P2Y\textsubscript{12} 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 P2Y\textsubscript{12} Receptor Inhibitors Prasugrel and Ticagrelor (VORA-PRATIC): A Prospective, Randomized, Pharmacodynamic Study**

Dual antiplatelet therapy (DAPT) with aspirin and a P2Y\textsubscript{12} 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 P2Y\textsubscript{12} 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 P2Y\textsubscript{12} 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 P2Y\textsubscript{12} 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

**Effects of Edoxaban on the Cellular and Protein Phase of Coagulation in Patients with Coronary Artery Disease on Dual Antiplatelet Therapy with Aspirin and Clopidogrel: A Prospective Randomized Study**

Dual antiplatelet therapy (DAPT) with aspirin and a P2Y12 receptor antagonist is pivotal for the treatment of patients with coronary artery disease (CAD) undergoing percutaneous coronary intervention (PCI) and in patients following an acute coronary syndrome (ACS). Importantly, it is not uncommon that patients requiring DAPT also need to be treated with oral anticoagulant therapy, such as those with atrial fibrillation (AF). Warfarin and clopidogrel are still the most widely utilized oral anticoagulant and P2Y12 receptor inhibitor, respectively. However, this treatment regimen has shown to be associated with an increased risk of bleeding, as well as ischemic complications. Over the past years, several non-vitamin K antagonist oral anticoagulants (NOACs), including edoxaban, have been studied in the setting of AF showing encouraging safety and efficacy profiles as compared with warfarin. In the phase III ENGAGE AF-TIMI 48 trial, edoxaban (60mg or 30mg once/daily) was non-inferior to warfarin with respect to the prevention of stroke or systemic embolism and was associated with significantly lower rates of bleeding and death from cardiovascular causes, in patients with AF. However, the effects of edoxaban in combination with DAPT in the setting of patients with CAD are unexplored. This may indeed represent a limitation for the uptake of edoxaban in modern day clinical practice where ~10% of patients with AF also have CAD requiring PCI and thus may require TAT. Moreover, the role of edoxaban as part of a dual antithrombotic treatment strategy, including clopidogrel and stopping aspirin, represents another important area of clinical interest as it has the potential reduce the risk of bleeding while preserving protection from ischemic events. This investigation is a prospective, randomized, parallel-design, open label, pharmacodynamic study conducted in patients with CAD on DAPT with aspirin and clopidogrel testing two different edoxaban dosing regimens (60mg or 30mg once/daily) in addition to DAPT with aspirin and clopidogrel, as well as in combination with clopidogrel only (after stopping aspirin).