Project Title:

P2Y12 inhibitor utilization in Bifurcation and Chronic Total Occlusion percutaneous coronary intervention with biologically active stents (P2BiTO) registry.

ClinicalTrials.gov Identifier: NCT01967615

- Substudy on Bifurcations -

WHAT IS ALREADY KNOWN ON THE SUBJECT

The newer P2Y12 inhibitors (prasugrel and ticagrelor) were both associated with a significant reduction in the risk of adverse major events in patients undergoing percutaneous coronary interventions (PCI) and receiving aspirin in the setting of an acute coronary syndrome (ACS)[1, 2]. Such a benefit apparently occurs mostly through a reduction in the rate of stent thrombosis. Although independent clinical trials should be compared directly, the 1-year relative risk reduction (RRR) of definite of probable stent thrombosis[3] in patients receiving a drug-eluting stent (DES) were fairly different in TRITON-TIMI 38 and PLATO, with a 67% (P<0.001) RRR for prasugrel[1] and a 10% (P=NS) RRR for ticagrelor[2] – the latter RRR being reported as 25% (P=0.017) when taking into account all coronary stents, either previously implanted or inserted during the course of the trial[4].

The incidence of "biologically active" stent thrombosis is largely variable according to different platforms and lesion settings, being highest when metal struts are inadequately deployed, as after recanalization of a chronic total occlusion (CTO)[5], in bifurcations – mostly after double DES implantation[6, 7] – and after PCI with the recently available bioresorbable vascular scaffolds (BVS)[8].

The "**P2Y12 inhibitor utilization in Bifurcation and Chronic Total Occlusion percutaneous coronary intervention with biologically active stents (P2BiTO) registry**" has been designed with the aim to verify the translation of the supposed benefit of "newer" P2Y12 inhibitors in the setting of PCI with double overlapping DES or BVS in various clinical scenarios, where prasugrel and ticagrelor would be primarily prescribed in patients with an ACS, clopidogrel in patients with stable ischemic heart disease.

The "**Substudy on Bifurcations**" of the P2BiTO registry aims to analyze the outcome of patients treated with single or multiple "biologically active" stents – either DES or BVS – for lesions located in coronary bifurcations, focusing on the relative implication of drugs, platforms and techniques on clinical outcomes.

WHAT DOES THE SUBPROJECT ON BIFURCATIONS ADD TO THE INFORMATION ALREADY AVAILABLE

1. To obtain an up-to-date descriptive analysis (registry) of the real-world attitude of P2Y12 inhibitors utilization for the management of patients with PCI of coronary bifurcation.
2. To verify the translation of the postulated different reduction in the risk of "biologically active" stent thrombosis among various P2Y12 inhibitors (prasugrel and ticagrelor as compared with clopidogrel) in the treatment of a coronary bifurcation.
3. To test the relative risk of adverse outcome for the various double stent techniques and to compare for each strategy the relative risk reduction obtained with newer P2Y12 inhibitors vs. clopidogrel.

DETAILED DESCRIPTION OF THE PROJECT MAIN AND SECONDARY OBJECTIVES

Data on **all patients aged 18-80 who underwent PCI of a bifurcating lesion (all Medina[6] types) with single or multiple "biologically active" stents (DES or BVS) at participating centers in the period January 2012 – December 2014** will be deemed eligible to enter the registry.

PCI access site and technique will be recorded as left at operator's discretion, as well as antithrombotic management. No limitation will be applied for the technique of PCI, for single or double DES or BVS (e.g. T-stenting, coulotte, crush and its modifications).

Patients' data will be entered on a common excel data sheet, and advancement of data collection and analysis will be shared among all study participant centers periodically during study progress.

In-hospital outcomes will be recorded; all patients discharged alive will be followed up with a 30-day and 6-month telephone interview and a 1-year visit.

The **primary end-point will be the occurrence of a cluster of major adverse cardiovascular events (MACE) at 1 year**:

a. Death from any cause.
b. Myocardial infarction (MI).
c. Stent thrombosis, defined as following the Academic Research Consortium[3].

The **secondary endpoints** will be:

1. In-hospital MACE
2. The single 1-year MACE (death, MI and stent thrombosis), as well as target vessel revascularization (TVR)
3. Bleeding as defined by the Bleeding Academic Research Consortium (BARC)[9].

STATISTICAL ANALYSIS AND CALCULATION OF THE SAMPLE SIZE

The primary purpose of the data analysis will be to determine whether the 1-year probability of the occurrence of the primary end-point would significantly differ between patients undergoing newer P2Y12 inhibitors (either prasugrel or ticagrelor) as compared with clopidogrel.

Sample size calculation has been based on the estimation of differences in the rates of occurrence of the primary endpoint between the two groups by use of the 2-sided Fisher exact test, with type I error at 5% and 80% power.

Based on the adverse event rates recently reported by large registries on coronary bifurcations[10, 11], and assuming a cumulative 1-year rate of MACE of 10%, an overall sample size of 1,422 patients in each group would allow to detect a reduction of 30% in the occurrence of the combined primary end-point among patients receiving the newer P2Y12 inhibitors as compared to clopidogrel. By estimating a 10% drop-off rate for incomplete data, data on 1,575 patients will have to be grouped in each arm and therefore a total of 3,150 patients will have to be screened in the study.

GENERAL TRANSFERIBILITY AND POTENTIAL IMPACT OF RESULTS

In the current cost-containment strategy, clopidogrel is still the most used P2Y12 inhibitor prescribed in patients undergoing PCI. Although both prasugrel and ticagrelor have shown a clinical benefit as compared to clopidogrel as adjunctive antiplatelet therapy among patients with ACS undergoing PCI, they are still underused in such clinical scenario. Currently, the use of newer P2Y12 inhibitors is off-label in stable coronary artery disease, and the present registry will obtain a picture of the attitude of physicians.

The present registry gives a unique opportunity to monitor the actual utilization in the “real world” of newer P2Y12 inhibitors and to test their effectiveness in patients with high risk of “biologically active” stent (either DES or BVS) thrombosis.

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